DESCRIPTION

IMMUNOSUPPRESSANT

Technical Field

The present invention relates to a pharmaceutical composition, more specifically to an immunosuppressant useful in the prevention or treatment of diseases assumed to be associated with immunity, including autoimmune diseases, or in the prevention of graft rejection following organ transplantation.

Background Art

In diseases assumed to be associated with immune reaction, including autoimmune diseases, accentuation of immune reaction or accentuation of body defence reaction based on immune reaction may be involved in their pathology, whose site is affected varies among diseases. Traditionally, these diseases have been treated using steroids or certain immunosuppressants (e.g., azathioprine, cyclophosphamide, methotrexate, mizoribine, cyclosporine A, Tacrolimus (FK506; THE MERCK INDEX 12th Edition, p1546, No. 9200 (1996)). All these agents have severe side effects; immunosuppressants mentioned above, in particular, have side effects characteristic to respective agents, as well as leukopenia and thrombocytopenia due to bone marrow suppression [The New England Journal of Medicine, Vol. 330(19), p. 1368 (1994)]. The same applies in the prevention of graft rejection following organ transplantation; to cope with this situation, such immunosuppressants as cyclosporine A and Tacrolimus (FK506) have been developed, but all have problems to be resolved, including severe renal toxicity.

The diseases associated with immune reaction, including autoimmune diseases are chronic and their cases are complicated. Therefore, the most suitable agent for

the each condition of a patient should be chosen. But, it is usually difficult to chose a proper agent in a chlinical use because of several problems such as side effects due to the increase of dose and the long-term administration, since the treatment of the diseases associated with immune reaction takes long time. And all these agents, which have been used for the treatment of those diseases and for the prevention of graft rejection following organ transplantation, have severe side effects as mentioned above. Therefore there is strong demand for the development of a drug of very low prevalence of side effects.

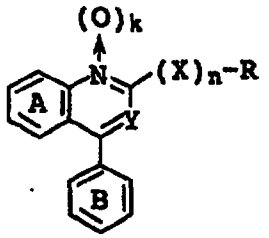
Against this background, the present inventors investigated in search of a new agent possessing immunosuppressing activity, and discovered a safe quinoline- or quinazoline-series compound with low toxicity.

Disclosure of Invention

The present inventors found that a quinoline or quinazoline compound or a pharmaceutically acceptable salt thereof possesses immune cytokine production-suppressing activity, and that it is effective in the prevention or treatment of diseases assumed to be associated with immunity, or in the prevention of graft rejection following organ transplantation. The present inventors also found unexpectedly that a combination comprising the quinoline or qunazoline compound and the traditionally used immunosappressant has a remarkable immunosuppressing activity. The inventors made further investigation based on these finding, and developed the present invention.

Accordingly, the present invention relates to:

(1) an immunosuppressant containing as an active ingredient a compound represented by the formula (I):



(I)

wherein Y is a nitrogen atom or C-G (G is an optionally esterified or amidated carboxyl group, an acyl group, an optionally protected hydroxyalkyl group, or a halogen atom); R is an optionally substituted hydrocarbon residue or an optionally substituted heterocyclic group; X is an oxygen atom or an optionally oxidized sulfur atom; n is 0 or 1; k is 0 or 1; G and R may bind together to form a ring; rings A and B may each have a substituent; or a pharmaceutically acceptable salt thereof,

(2) the immunosuppressant of the above item (1), wherein n is 0, and wherein the optionally substituted hydrocarbon residue represented by R is a group represented by the formula:

$-CH_2-X^1-Z^1$

wherein X^1 is an oxygen atom, an optionally oxidized sulfur atom, or $-(CH_2)_m-$ (m is an integer from 0 to 5); Z^1 is a hydrogen atom, an optionally substituted hydrocarbon residue, an optionally substituted heterocyclic group, or an optionally substituted amino group,

(3) the immunosuppressant of the above item (2), wherein m is 0, provided that X^1 is $-(CH_2)_m-$,

(4) the immunosuppressant of the above item (1), wherein the optionally substituted heterocyclic group represented by Z^1 is an aromatic 5-membered heterocyclic group containing 2 or 3 hetero atoms,

(5) the immunosuppressant of the above item (1), wherein Y is C-G,

(6) the immunosuppressant of the above item (5), wherein G is a C_{1-6} alkyloxycarbonyl group,

(7) the immunosuppressant of the above item (1), wherein G is an ethoxycarbonyl group,

(8) the immunosuppressant of the above item (1), wherein ring A is substituted for by at least 1 alkoxy group,

(9) the immunosuppressant of the above item (1), wherein ring A is substituted for by 2 methoxy groups,

(10) the immunosuppressant of the above item (1), wherein ring A is substituted for by 2 methoxy groups respectively at the 6- and 7-positions of the quinoline ring or quinazoline ring,

(11) the immunosuppressant of the above item (1), wherein ring B is substituted for by at least 1 alkoxy group,

(12) the immunosuppressant of the above item (1), wherein ring B is substituted for by 2 identical or different alkoxy groups,

(13) the immunosuppressant of the above item (1), wherein k is 0,

(14) the immunosuppressant of the above item (1), wherein the compound represented by the formula (I) is

methyl 4-(3,4-dimethoxyphenyl)-2-ethyl-6,7-dimethoxyquinoline-3-carboxylate;

ethyl 6-chloro-2-methyl-4-(3,4-dimethoxyphenyl)quinoline-3-carboxylate;

6,7-dimethoxy-9-phenylfuro[3,4-b]quinoline-1(3H)-one;

ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-[(1-methylimidazol-2-yl)thiomethyl]quinoline-3-carboxylate;

4-(3,4-dimethoxyphenyl)-2-(2-hydroxyethylthiomethyl)-6,7-dimethoxyquinazoline;

4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-[(4-methyl-1,2,4-triazol-3-yl)thiomethyl]quinazoline;

ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-[(1-methylimidazol-2-yl)ethyl]quinoline-3-carboxylate;

methyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonylquinoline-2-acetate;

ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate;

ethyl 4-(3-isopropoxy-4-methoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate;

ethyl 4-(3-hydroxy-4-methoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate;

ethyl 4-(4-hydroxy-3-methoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate;

ethyl 7-hydroxy-6-methoxy-4-(3,4-dimethoxyphenyl)-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate;

ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate 1-oxide; or

ethyl 2-(N,N-diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline-3-carboxylate,

(15) the immunosuppressant of the above item (1) possessing immune cytokine production-suppressing activity,

(16) the immunosuppressant of the above item (1) for the prophylaxis or therapy of autoimmune diseases,

(17) the immunosuppressant of the above item (1) for the prophylaxis or therapy of systemic lupus erythematosus, chronic hepatitis, interstitial liver diseases, asthma, psoriasis, ulcerative colitis, Crohn disease, regional ileitis or multiple sclerosis,

(18) the immunosuppressant of the above item (1) for the prophylaxis of graft rejection following organ transplantation,

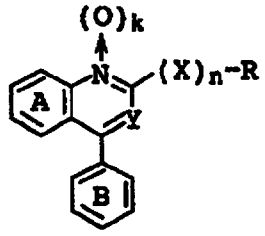
(19) a method of preventing or treating autoimmune diseases in mammals which comprises administering to the mannals a therapeutically effective amount of a compound represented by the formula (I) of the above item (1) or a pharmaceutically acceptable salt thereof,

(20) the method of the above item (19), wherein autoimmune diseases is systemic lupus erythematosus, chronic hepatitis, interstitial liver diseases, asthma, psoriasis, ulcerative colitis, Crohn disease, regional ileitis or multiple sclerosis,

(21) a method of preventing graft rejection following organ transplation in mammals which comprises administering to the mannals a therapeutically effective amount of a compound represented by the formula (I) of the above item (1) or a pharmaceutically acceptable salt thereof,

(22) use of a compound represented by the formula (I) of the above item (1) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament to be used as an immunosuppressant,

(23) a pharmaceutical composition which comprises a quinoline or quinazoline compound represented by the formula (I):



(I)

wherein Y is a nitrogen atom or C-G (G is an optionally esterified or amidated carboxyl group, an acyl group, an optionally protected hydroxyalkyl group, or a halogen atom); R is an optionally substituted hydrocarbon residue or an optionally substituted heterocyclic group; X is an oxygen atom or an optionally oxidized sulfur atom; n is 0 or 1; k is 0 or 1; G and R may bind together to form a ring; rings A and B may each have a substituent; or a pharmaceutically acceptable salt thereof; and an immunosuppressant except for a quinoline or quinazoline compound mentioned above,

(24) the pharmaceutical composition of the above item (23), wherein n is 0, and wherein the optionally substituted hydrocarbon residue represented by R is a group represented by the formula:

$-CH_2-X^1-Z^1$

wherein X^1 is an oxygen atom, an optionally oxidized sulfur atom, or $-(CH_2)_m-$ (m is an integer from 0 to 5); Z^1 is a hydrogen atom, an optionally substituted hydrocarbon residue, an optionally substituted heterocyclic group, or an optionally substituted amino group,

(25) the pharmaceutical composition of the above item (24), wherein m is 0, provided that X^1 is $-(CH_2)_m-$,

(26) the pharmaceutical composition of the above item (23), wherein the optionally substituted heterocyclic group represented by Z^1 is an aromatic 5-membered heterocyclic group containing 2 or 3 hetero atoms,

(27) the pharmaceutical composition of the above item (23), wherein Y is C-G,

(28) the pharmaceutical composition of the above item (23), wherein G is a C_{1-6} alkyloxycarbonyl group,

(29) the pharmaceutical composition of the above item (23), wherein G is an ethoxycarbonyl group,

(30) the pharmaceutical composition of the above item (23), wherein ring A is substituted for by at least 1 alkoxy group,

(31) the pharmaceutical composition of the above item (23), wherein ring A is substituted for by 2 methoxy groups,

(32) the pharmaceutical composition of the above item (23), wherein ring A is substituted for by 2 methoxy groups respectively at the 6- and 7-positions of the quinoline ring or quinazoline ring,

(33) the pharmaceutical composition of the above item (23), wherein ring B is substituted for by at least 1 alkoxy group,

(34) the pharmaceutical composition of the above item (23), wherein ring B is substituted for by 2 identical or different alkoxy groups,

(35) the pharmaceutical composition of the above item (23), wherein k is 0,

(36) the pharmaceutical composition of the above item (23), wherein the compound represented by the formula (I) is

methyl 4-(3,4-dimethoxyphenyl)-2-ethyl-6,7-dimethoxyquinoline-3-carboxylate;

ethyl 6-chloro-2-methyl-4-(3,4-dimethoxyphenyl)quinoline-3-carboxylate;

6,7-dimethoxy-9-phenylfuro[3,4-b]quinoline-1(3H)-one;

ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-[(1-methylimidazol-2-yl)thiomethyl]quinoline-3-carboxylate;

4-(3,4-dimethoxyphenyl)-2-(2-hydroxyethylthiomethyl)-6,7-dimethoxyquinazoline;

4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-[(4-methyl-1,2,4-triazol-3-yl)thiomethyl]quinazoline;

ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-[(1-methylimidazol-2-yl)ethyl]quinoline-3-carboxylate;

methyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonylquinoline-2-acetate;

ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate;

ethyl 4-(3-isopropoxy-4-methoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate;

ethyl 4-(3-hydroxy-4-methoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate;

ethyl 4-(4-hydroxy-3-methoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate;

ethyl 7-hydroxy-6-methoxy-4-(3,4-dimethoxyphenyl)-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate;

ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate 1-oxide; or

ethyl 2-(N,N-diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline-3-carboxylate,

(37) the pharmaceutical composition of the above item (23) possessing immune cytokine production-suppressing activity,

(38) the pharmaceutical composition of the above item (23) for the prophylaxis or therapy of autoimmune diseases,

(39) the pharmaceutical composition of the above item (23) for the prophylaxis or therapy of systemic lupus erythematosus, chronic hepatitis, interstitial liver diseases, asthma, psoriasis, ulcerative colitis, Crohn disease, regional ileitis or multiple sclerosis,

(40) the pharmaceutical composition of the above item (23) for the prophylaxis of graft rejection following organ transplantation,

(41) the pharmaceutical composition of the above item (23) wherein the immunosuppressant is Tacrolimus (FK506), cyclosporm or methotrexate,

(42) a method of preventing or treating autoimmune diseases in mammals which comprises administering to the mammals a therapeutically effective amount of a pharmaceutical composition of the above item (23),

(43) the method of the above item (42), wherein autoimmune diseases is systemic lupus erythematosus, chronic hepatitis, interstitial liver diseases, asthma, psoriasis, ulcerative colitis, Crohn disease, regional ileitis or multiple sclerosis,

(44) a method of preventing graft rejection following organ transplantation in mammals which comprises administering to the mammals a therapeutically effective amount of a pharmaceutical composition of the above item (23), and

(45) use of a pharmaceutical composition of the above item (23) for the manufacture of a medicament to be used as an immunosuppressant.

The immunosuppressant in the present invention generically refers to the class of immunosuppressants possessing a quinoline or quinazoline skeleton. Their active ingredients, along with production methods, are described in detail in Japanese Patent Unexamined Publication Nos. 306052/1994 (EP-A-0567107), 118266/1995 (EP-A-0608870),

069890/1995 (EP-A-0634169), WO 95/24394 and 53419/1996 (EP-A-0686630), for instance. The compounds described in these documents all possess immunosuppressing activity and are advantageously used for the present invention.

In the above formula (I), the optionally substituted hydrocarbon residue represented by R is exemplified by aliphatic hydrocarbon residues, alicyclic hydrocarbon residues, alicyclic-aliphatic hydrocarbon residues, aromatic carbon ring-aliphatic hydrocarbon residues and aromatic hydrocarbon residues.

Such aliphatic hydrocarbon residues include C_{1-8} saturated aliphatic hydrocarbon residues (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, hexyl, isohexyl, heptyl, octyl) and C_{2-8} unsaturated aliphatic hydrocarbon residues (e.g., vinyl (ethenyl), 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl, 1-heptenyl, 1-octenyl, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 3-hexynyl, 2,4-hexadynyl, 5-hexynyl, 1-heptynyl, 1-octynyl).

Such alicyclic hydrocarbon residues include C_{3-7} saturated alicyclic hydrocarbon residues (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl) and C_{5-7} unsaturated alicyclic hydrocarbon residues (e.g., 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-cycloheptenyl, 2-cycloheptenyl, 3-cycloheptenyl and 2,4-cycloheptadienyl).

Such alicyclic-aliphatic hydrocarbon residues include those C_{4-9} ones comprising a combination of one of the above-mentioned alicyclic hydrocarbon residues and one of the above-mentioned aliphatic hydrocarbon residues, (e.g., cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl,

cyclopentylmethyl, 2-cyclopentenylmethyl, 3-cyclopentenylmethyl, cyclohexylmethyl, 2-cyclohexenylmethyl, 3-cyclohexenylmethyl, cyclohexylethyl, cyclohexylpropyl, cycloheptylmethyl, cycloheptylethyl).

Such aromatic carbon ring-aliphatic hydrocarbon residues include C_{7-9} phenylalkyls (e.g., benzyl, phenethyl, 1-phenylethyl, 3-phenylpropyl, 2-phenylpropyl, 1-phenylpropyl) and C_{11-13} naphthylalkyls (e.g., α-naphthylethyl, β-naphthylmethyl, β-naphthylethyl).

Such aromatic hydrocarbon residues include phenyl, naphthyl (e.g., α-naphthyl, β-naphthyl).

In the above formula (I), the optionally substituted heterocyclic group represented by R is exemplified by (i) 5- to 7-membered heterocyclic groups containing 1 sulfur atom, 1 nitrogen atom or 1 oxygen atom; (ii) 5- or 6-membered heterocyclic groups containing 2 to 4 nitrogen atoms; (iii) 5- or 6-membered heterocyclic groups containing 1 or 2 nitrogen atoms and 1 sulfur atom or 1 oxygen atom; (iv) these heterocyclic groups may be condensed with a 6-membered ring containing 2 or fewer nitrogen atoms, a benzene ring, or a 5-membered ring containing 1 sulfur atom.

Examples of such heterocyclic groups include 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrazinyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, isothiazolyl, isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 1,2,4-triazol-3-yl, 1,2,3-triazol-4-yl, tetrazol-5-yl, benzimidazol-2-yl, indol-3-yl, 1H-indazol-3-yl, 1H-pyrrolo[2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-b]pyridin-6-yl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl and 1H-imidazo[4,5-b]pyrazin-2-yl.

In the above formula (I), the optionally substituted heterocyclic group for R is preferably 2-imidazolyl or 1,2,4-triazol-3-yl.

In the above formula (I), the hydrocarbon residue for R is preferably a group represented by the formula: $-CH_2-X^1-Z^1$ wherein X^1 is an oxygen atom, an optionally oxidized sulfur atom, or $-(CH_2)_m-$ (m is an integer from 0 to 5); Z^1 is an optionally substituted a hydrocarbon residue, an optionally substituted heterocyclic group, or an optionally substituted amino group.

The optionally oxidized sulfur atom for X^1 is exemplified by thio group, sulfinyl group and sulfonyl group, with preference given to thio group.

X^1 is preferably $-(CH_2)_m-$ (m is an integer from 0 to 2, preferably 0).

The optionally substituted hydrocarbon residue for Z^1 is exemplified by the same hydrocarbon residues as those exemplifying the optionally substituted hydrocarbon residue for R mentioned above.

In the above formula (I), the optionally substituted heterocyclic group for Z^1 is exemplified by the same heterocyclic groups as those exemplifying the optionally substituted heterocyclic group for R mentioned above. Of such heterocyclic groups, aromatic 5-membered heterocyclic groups containing 2 or 3 hetero atoms (e.g., oxygen atom, nitrogen atom, sulfur atom) are preferred, with greater preference given to 2-imidazolyl or 1,2,4-triazol-3-yl.

In the above formula (I), the hydrocarbon residue and heterocyclic group each represented by R or Z^1 mentioned above may have 1 to 3 substituents at any substitutable positions on the chain or the ring thereof. Such substituents include aliphatic chain hydrocarbon groups, alicyclic hydrocarbon groups, aryl groups, aromatic heterocyclic groups, non-aromatic heterocyclic groups, halogen atoms, nitro groups, optionally substituted amino

groups, optionally substituted acyl groups, optionally substituted hydroxyl groups, optionally substituted thiol groups, optionally esterified carboxyl groups and so on.

Aliphatic chain hydrocarbon groups mentioned as substituents for the hydrocarbon residue and heterocyclic group each represented by R or Z^1 include linear or branched aliphatic hydrocarbon groups such as alkyl groups (preferably C_{1-10} alkyl), alkenyl groups (preferably C_{2-10} alkenyl), and alkinyl groups (preferably C_{2-10} alkinyl).

Preferable alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, hexyl, pentyl, octyl, nonyl and decyl.

Preferable alkenyl groups include vinyl, allyl, isopropenyl, 1-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-ethyl-1-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl and 5-hexenyl.

Preferable alkinyl groups include ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl.

Alicyclic hydrocarbon groups mentioned as substituents for the hydrocarbon residue and heterocyclic group each represented by R or Z^1 include saturated or unsaturated C_{3-8} alicyclic hydrocarbon groups such as C_{3-8} cycloalkyl groups, C_{3-8} cycloalkenyl groups and C_{4-8} cycloalkadienyl groups.

Preferable examples of the C_{3-8} cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl,

bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl and bicyclo[4.3.1]decyl.

Preferable examples of the C_{3-8} cycloalkenyl groups include those having 5 to 7 carbon atoms, such as 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl and 3-cyclohexen-1-yl.

Preferable examples of the C_{4-8} cycloalkadienyl groups include those having 5 to 7 carbon atoms, such as 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl and 2,5-cyclohexadien-1-yl.

Aryl groups mentioned as substituents for the hydrocarbon residue and heterocyclic group each represented by R or Z^1 are monocyclic or condensed polycyclic aromatic hydrocarbon groups, preferably phenyl, naphthyl, anthryl, phenanthryl, acenaphthylenyl and others, with greater preference given to phenyl, 1-naphthyl, 2-naphthyl and others.

Preferable examples of aromatic heterocyclic groups mentioned as substituents for the hydrocarbon residue and heterocyclic group each represented by R or Z^1 include aromatic monocyclic heterocyclic groups (e.g., furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl) and aromatic condensed heterocyclic groups (e.g., benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthylizinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenathridinyl,

phenathrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl, 1,2,4-triazolo[4,3-b]pyridazinyl).

Preferable examples of non-aromatic heterocyclic groups mentioned as substituents for the hydrocarbon residue and heterocyclic group each represented by R or Z^1 include oxylanyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperizinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl and piperazinyl.

Examples of halogens mentioned as substituents for the hydrocarbon residue and heterocyclic group each represented by R or Z^1 include fluorine, chlorine, bromine and iodine, with preference given to fluorine and chlorine.

Examples of the optionally substituted amino groups mentioned as substituents for the hydrocarbon residue and heterocyclic group each represented by R or Z^1 include (i) amino group and (ii) substituted amino groups having 1 or 2 substituents selected from C_{1-10} alkyl groups, C_{2-10} alkenyl groups, C_{2-10} alkinyl groups, C_{1-10} acyl groups, C_{6-12} aromatic groups, heterocyclic groups and so on (e.g., methylamino, dimethylamino, ethylamino, diethylamino, dibutylamino, diallylamino, cyclohexylamino, phenylamino, N-methyl-N-phenylamino, acetylamino, propionylamino, benzoylamino, nicotinoylamino).

Examples of the optionally substituted acyl groups, mentioned as substituents for the hydrocarbon residue and heterocyclic group each represented by R or Z^1 include (i) formyl and (ii) groups resulting from binding of an C_{1-10} alkyl group, C_{2-10} alkenyl group or aromatic group and a carbonyl group (e.g., acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl, octanoyl, cyclobutanecarbonyl, cyclopentane-

carbonyl, cyclohexanecarbonyl, cycloheptanecarbonyl, crotonyl, 2-cyclohexenecarbonyl, benzoyl, nicotinoyl).

Examples of the optionally substituted hydroxyl groups mentioned as substituents for the hydrocarbon residue and heterocyclic group each represented by R or Z^1 include (i) hydroxyl group and (ii) substituted hydroxyl groups having an appropriate substituent, particularly a substituent for use as a hydroxyl group protecting group, such as alkoxy, alkenyloxy, alkinyloxy, aralkyloxy, acyloxy and aryloxy.

Said alkoxy is preferably C_{1-10} alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, isopentyloxy, neopentyloxy, hexyloxy, heptyloxy, nonyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy).

Said alkenyloxy is exemplified by C_{2-10} alkenyloxy (e.g., allyloxy, crotyloxy, 2-pentenyloxy, 3-hexenyloxy, 2-cyclopentenylmethoxy, 2-cyclohexenylmethoxy).

Said alkinyloxy is preferably C_{2-10} alkinyloxy (e.g., ethynyloxy, 2-propinyloxy).

Said aralkyloxy is exemplified by phenyl-C_{1-4} alkyloxy (e.g., benzyloxy, phenethyloxy).

Said acyloxy is preferably C_{2-4} alkanoyloxy (e.g., acetyloxy, propionyloxy, n-butyryloxy, isobutyryloxy).

Said aryloxy is exemplified by phenoxy and 4-chlorophenoxy.

Examples of the optionally substituted thiol groups mentioned as substituents for the hydrocarbon residue and heterocyclic group each represented by R or Z^1 include the (i) thiol group and (ii) substituted thiol groups having an appropriate substituent, particularly a substituent for use as a thiol group protecting group, such as alkylthio, alkenylthio, alkinylthio, aralkylthio, acylthio and arylthio.

Said alkylthio is preferably C_{1-10} alkylthio (e.g., methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio,

pentylthio, isopentylthio, neopentylthio, hexylthio, heptylthio, nonylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio).

Said alkenylthio is exemplified by C_{2-10} alkenylthio (e.g., allylthio, crotylthio, 2-pentenylthio, 3-hexenylthio, 2-cyclopentenylmethylthio and 2-cyclohexenylmethylthio).

Said alkinylthio is preferably C_{2-10} alkinylthio (e.g., ethynylthio, 2-propinylthio).

Said aralkylthio is exemplified by phenyl-C_{1-4} alkylthios (e.g., benzylthio, phenethylthio).

Said acylthio is preferably an alkanoylthio having 2 to 4 carbon atoms (e.g., acetylthio, propionylthio, butyrylthio, isobutyrylthio).

Said arylthio is exemplified by phenylthio and 4-chlorophenylthio.

Examples of the optionally esterified carboxyl groups mentioned as substituents for the hydrocarbon residue and heterocyclic group each represented by R or Z^1, include (i) carboxyl group, (ii) groups resulting from binding of a carboxyl group and a C_{1-6} alkyl group (i.e., alkoxycarbonyl, e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl), (iii) groups resulting from binding of a carboxyl group and a C_{3-6} alkenyl group (i.e., alkenyloxycarbonyl e.g., allyloxycarbonyl, crotyloxycarbonyl, 2-pentenyloxycarbonyl, 3-hexenyloxycarbonyl), and (iv) groups resulting from binding of a carbonyl group and an aralkyl group (i.e., aralkyloxycarbonyl, e.g., benzyloxycarbonyl, phenethyloxycarbonyl).

In the above formula (I), the substituent on the hydrocarbon residue and heterocyclic group each represented by R or Z^1 may optionally have further 1 or more, preferably 1 to 3, substituents at any substitutable

positions. Examples of such substituents include C_{1-10} lower alkyl groups, C_{2-10} lower alkenyl groups, C_{2-10} lower alkinyl groups, C_{3-8} cycloalkyl groups, C_{3-8} cycloalkenyl groups, C_{4-8} cycloalkadienyl groups, aryl groups, aromatic heterocyclic groups, non-aromatic heterocyclic groups, aralkyl groups (e.g., aryl-C_{1-6}-alkyl groups etc.), amino groups, N-mono-substituted amino groups, N,N-di-substituted amino groups, amidino groups, acyl groups, carbamoyl groups, N-mono-substituted carbamoyl groups (e.g., methylcarbamoyl, ethylcarbamoyl, phenylcarbamoyl), N,N-di-substituted carbamoyl groups (e.g., N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, piperidinocarbamoyl, morpholinocarbamoyl), sulfamoyl groups, N-mono-substituted sulfamoyl groups (e.g., methylsulfamoyl, ethylsulfamoyl, phenylsulfamoyl, p-toluenesulfamoyl), N,N-di-substituted sulfamoyl groups (e.g., N,N-dimethylsulfamoyl, N-methyl-N-phenylsulfamoyl, piperidinosulfamoyl, morpholinosulfamoyl), carboxyl groups, C_{1-10} lower alkoxycarbonyl groups (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, isobutoxycarbonyl, sec.-butoxycarbonyl, tert.-butoxycarbonyl), hydroxyl groups, C_{1-10} lower alkoxy groups, C_{2-10} lower alkenyloxy groups, C_{3-7} cycloalkyloxy groups, aralkyloxy groups, aryloxy groups, mercapto groups C_{1-10} lower alkylthio groups, aralkylthio groups, arylthio groups, sulfo groups, cyano groups, azide groups, halogen atoms, nitro groups and nitroso groups. These substituents are exemplified by the same substituents as those for the hydrocarbon residue and heterocyclic group each represented by R or Z^1.

In the above formula (I), provided that R is $-CH_2-X^1-Z^1$, the optionally substituted amino group for Z^1, is represented by $-N(R^1)(R^2)$ (R^1 and R^2, whether identical or not, represent a hydrogen atom, an optionally substituted hydrocarbon, or an optionally substituted heterocyclic group; or R^1 and R^2 may bind together to form a ring).

The optionally substituted hydrocarbon residue or the optionally substituted heterocyclic group represented by R^1 or R^2 is exemplified by the same optionally substituted hydrocarbon residues or optionally substituted heterocyclic groups as those mentioned to exemplify the group for R above.

R^1 and R^2 may bind together to form a ring. Examples of such $-N(R^1)(R^2)$ rings include 1-pyrrolidinyl, 1-imidazolidinyl, 1-pyrazolidinyl, 1-piperidyl, piperazinyl, 4-morpholinyl, 4-thiomorpholinyl, homopiperazin-1-yl, 1,2,4-triazol-1-yl, 1,3,4-triazol-1-yl, pyrazol-1-yl, imidazol-1-yl, 1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, tetrazol-1-yl, benzimidazol-1-yl, indol-1-yl and 1H-indazol-1-yl.

The hydrocarbon residue and heterocyclic group each represented by R^1 or R^2 may have 1 to 3 substituents at any substitutable positions on the chain or the ring thereof. Such substituents are exemplified by the same substituents as those for the optionally substituted hydrocarbon residue and optionally substituted heterocyclic group each represented by R. These substituents on the hydrocarbon residue and heterocyclic group each represented by R^1 or R^2 may have 1 or more, preferably 1 to 3, substituents at any substitutable positions. Examples of such substituents include C_{1-10} lower alkyl groups, C_{2-10} lower alkenyl groups, C_{2-10} lower alkinyl groups, C_{3-7} cycloalkyl groups, aryl groups, aromatic heterocyclic groups, non-aromatic heterocyclic groups, aralkyl groups, amino groups, N-mono-substituted amino groups, N,N-di-substituted amino groups, amidino groups, acyl groups, carbamoyl groups, N-mono-substituted carbamoyl groups, N,N-di-substituted carbamoyl groups, sulfamoyl groups, N-mono-substituted sulfamoyl groups, N,N-di-substituted sulfamoyl groups, carboxyl groups, lower alkoxycarbonyl groups, hydroxyl groups, lower alkoxy groups, lower alkenyloxy groups, cycloalkyloxy groups, aralkyloxy groups, aryloxy groups, mercapto groups,

lower alkylthio groups, aralkylthio groups, arylthio groups, sulfo group, cyano group, azide group, nitro group, nitroso group and halogens. These substituents are exemplified by the same substituents as those for the optionally substituted hydrocarbon residue and the optionally substituted heterocyclic group each represented by R.

In the above formula (I), rings A and B may each have substituents. Such substituents include halogen atoms, nitro group, optionally substituted C_{1-10} alkyl groups, optionally substituted C_{2-10} alkenyl groups, optionally substituted C_{2-10} alkinyl groups, optionally substituted hydroxyl groups, optionally substituted thiol groups, optionally substituted amino groups, optionally substituted acyl groups (e.g., C_{1-10} alkanoyl, C_{2-10} alkenoyl, C_{2-10} alkinoyl), optionally esterified carboxyl groups, and optionally substituted aromatic ring groups.

Examples of halogens mentioned as substituents for rings A and B include fluorine, chlorine, bromine and iodine, with preference given to fluorine and chlorine.

Examples of the optionally substituted C_{1-10} alkyl groups, mentioned as substituents for rings A and B, may be C_{1-10} linear alkyl, C_{3-10} branched alkyl or C_{3-10} cyclic alkyl, including methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. These C_{1-10} alkyl gorups, C_{2-10} alkenyl groups or C_{2-10} alkinyl groups, respectively may have 1 to 3 substituents exemplified by the same substituents as those for the optionally substituted hydrocarbon residue and the optionally substituted heterocyclic gorup each represented by R or Z^1.

Examples of the optionally substituted hydroxyl groups mentioned as substituents for rings A and B, include (i) hydroxyl group and (ii) substituted hydroxyl groups having

an appropriate substituent, particularly a substituent for use as a hydroxyl group protecting group, such as alkoxy, alkenyloxy, alkinyloxy, aralkyloxy and acyloxy, as well as aryloxy.

Said alkoxy is preferably an C_{1-10} alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, isopentyloxy, neopentyloxy, hexyloxy, heptyloxy, nonyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy).

Said alkenyloxy is exemplified by C_{2-10} alkenyloxys (e.g., allyloxy, crotyloxy, 2-pentenyloxy, 3-hexenyloxy, 2-cyclopentenylmethoxy, 2-cyclohexenylmethoxy).

said alkinyloxy is exemplified by C_{2-10} alkinyloxys (e.g., propinyloxy).

Said aralkyloxy is exemplified by phenyl-C_{1-4} alkoxys (e.g., benzyloxy, phenethyloxy).

Said acyloxy is preferably a C_{2-4} alkanoyloxy (e.g., acetyloxy, propionyloxy, butyryloxy, isobutyryloxy).

Said aryloxy is exemplified by phenoxy and 4-chlorophenoxy.

Examples of the optionally substituted thiol groups mentioned as substituents for rings A and B include (i) thiol group and (ii) substituted thiol groups having an appropriate substituent, particularly a substituent for use as a thiol group protecting group, such as alkylthio, alkenylthio, alkinylthio, aralkylthio, acylthio, arylthio and so on.

Said alkylthio is preferably C_{1-10} alkylthio (e.g., methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio, pentylthio, isopentylthio, neopentylthio, hexylthio, heptylthio, nonylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio).

Said alkenylthio is exemplified by C_{2-10} alkenylthio (e.g., allylthio, crotylthio, 2-pentenylthio, 3-

hexenylthio, 2-cyclopentenylmethylthio and 2-cyclohexenylmethylthio).

Said alkinylthio is preferably C_{2-10} alkinylthio (e.g., ethynylthio, 2-propinylthio).

Said aralkylthio is exemplified by phenyl-C_{1-4} alkylthios (e.g., benzylthio, phenethylthio).

Said acylthio is preferably an alkanoylthio having 2 to 4 carbon atoms (e.g., acetylthio, propionylthio, butyrylthio, isobutyrylthio).

Said arylthio is exemplified by phenylthio and 4-chlorophenylthio.

Examples of the optionally substituted amino groups mentioned as substituents for rings A and B, include (i) amino group and (ii) substituted amino groups having 1 or 2 substituents selected from C_{1-10} of alkyl groups, C_{2-10} alkenyl groups, C_{2-10} alkinyl groups, C_{1-10} acyl groups, C_{6-12} aromatic groups, heterocyclic groups and so on (e.g., methylamino, dimethylamino, ethylamino, diethylamino, dibutylamino, diallylamino, cyclohexylamino, phenylamino, N-methyl-N-phenylamino, acetylamino, propionylamino, benzoylamino, nicotinoylamino).

Examples of the optionally substituted acyl groups mentioned as substituents for rings A and B, include (i) formyl and (ii) groups resulting from binding of a C_{1-10} alkyl group, a C_{2-10} alkenyl group, a C_{2-10} alkinyl or a C_{6-12} aromatic group and a carbonyl group (e.g., acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl, octanoyl, cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, cycloheptanecarbonyl, crotonyl, 2-cyclohexenecarbonyl, benzoyl, nicotinoyl).

Examples of the optionally esterified carboxyl groups mentioned as substituents for rings A and B, include the (i) carboxyl group, (ii) groups resulting from binding of a carboxyl group and a C_{1-6} alkyl group (i.e., alkoxycarbonyl, e.g., methoxycarbonyl, ethoxycarbonyl,

propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl), (iii) groups resulting from binding of a carboxyl group and a C_{3-6} alkenyl group (i.e., alkenyloxycarbonyl, e.g., allyloxycarbonyl, crotyloxycarbonyl, 2-pentenyloxycarbonyl, 3-hexenyloxycarbonyl), and (iv) groups resulting from binding of a carbonyl group and an aralkyloxy group (i.e., aralkyloxycarbonyl, e.g., benzyloxycarbonyl and phenethyloxycarbonyl).

Examples of the optionally substituted aromatic ring groups mentioned as substituents for rings A and B include C_{6-14} aromatic hydrocarbon residues (e.g., phenyl, naphthyl, anthryl) and heterocyclic aromatic residues (e.g., pyridyl, furyl, thienyl, imidazolyl, thiazolyl).

Such substituents for rings A and B may each be present at any substitutable position of the ring thereof; 1 to 4 identical or different substituents may be present. Provided that substituents on ring A or B are mutually adjoining, they may bind together to form a ring represented by $-(CH_2)_t-$ or $-O-(CH_2)_l-O-$ (t is an integer from 3 to 5; l is an integer from 1 to 3); such rings include 5- to 7-membered rings formed in cooperation with carbon atoms of the benzene ring.

Preferably, ring A is substituted for by at least 1 alkoxy group (preferably C_{1-3} alkoxy gorup), more preferably at least 1 methoxy group. Still more preferably, ring A is substituted for by 2 identical or different alkoxy groups (preferably C_{1-3} alkoxy gorup), more preferably by methoxy groups. Most preferably, ring A is substituted for by 2 methoxy groups respectively at the 6- and 7-positions of the quinoline ring or quinazoline ring.

Preferably, ring B is substituted for by at least 1 alkoxy group (preferably C_{1-3} alkoxy gorup), more preferably at least 1 methoxy or isopropoxy group. Still

more preferably, ring B is substituted for by 2 identical or different alkoxy groups (preferably C_{1-3} alkoxy gorup). Most preferably, ring B is substituted for by a methoxy or isopropoxy group at the 3-position and by a methoxy gorup at the 4-position of the quinoline ring or quinazoline ring.

The optionally oxidized sulfur atom represented by X is exemplified by the thio group, sulfinyl group and sulfonyl group, with preference given to the thio group.

In the above formula (I), provided that Y is C-G, the optionally esterified carboxyl group for G include the (i) carboxyl group, (ii) groups resulting from binding of a carboxyl group and a C_{1-6} alkyl group (i.e., alkoxycarbonyl e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl), (iii) groups resulting from binding of a carboxyl group and a C_{3-6} alkenyl group (i.e., alkenyloxycarbonyl e.g., allyloxycarbonyl, crotyloxycarbonyl, 2-pentenyloxycarbonyl and 3-hexenyloxycarbonyl), and (iv) groups resulting from binding of a carbonyl group and an aralkyloxy group (i.e., aralkyloxycarbonyl, e.g., benzyloxycarbonyl and phenethyloxycarbonyl). The aralkyl group in said aralkyloxycarbonyl groups is an alkyl group having an aryl group as a substituent (arylalkyl group). Said aryl group is exemplified by phenyl and naphthyl, each of which may have the same substituents as those for ring A above. Said alkyl group is preferably a lower C_{1-6} alkyl group. Preferable aralkyl groups include benzyl, phenethyl, 3-phenylpropyl, (1-naphthyl)methyl and (2-naphthyl)methyl, with preference given to benzyl, phenetyl and others.

In the above formula (I), provided that Y is C-G, the amidated carboxyl group for G is represented by -$CON(R^1)(R^2)$ (R^1 and R^2 have the same definitions as those given above).

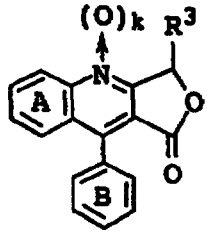
In the above formula (I), provided that Y is C-G, the acyl group for G is represented by $-CO-R^4$ (R^4 is a C_{1-5} alkyl group or an aryl group). The C_{1-5} alkyl group for R^4, is exemplified by methyl, ethyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl and 1-ethylpropyl, preferably methyl, butyl, isobutyl and pentyl. The aryl group for R^4 is a monocyclic or condensed polycyclic aromatic hydrocarbon group, preferably examples including C_{6-14} monocyclic or condensed polycyclic aromatic hydrocarbon group such as phenyl, naphthyl, anthryl and phenanthryl. In particular, phenyl, 1-naphtyl and 2-naphtyl are more preferred.

Provided that G is a hydroxyalkyl group, the alkyl group thereof is exemplified by the C_{1-8} saturated aliphatic hydrocarbon residues, mentioned to exemplify the hydrocarbon residue represented by R above. Said hydroxyalkyl group is preferably represented by $-CH_2OH$ or $-CH(OH)-R^4$ (R^4 has the same definition as that given above), wherein R^4 is preferably methyl, ethyl, or the like.

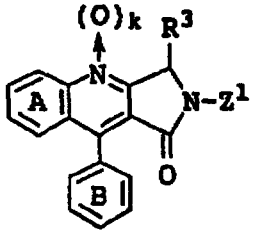
Provided that G is a protected hydroxyalkyl group, said protected hydroxyalkyl group is represented by $-CH_2OCOR^5$ or $-CH(OCOR^5)-R^4$ (R^4 has the same definition as that given above; R^5 represents an alkyl group, aralkyl group or aryl group each of which may have a substituent). The alkyl group represented by R^5 is exemplified by C_{1-6} alkyl groups, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl. The aralkyl group represented by R^5 is a C_{1-4} alkyl group having an C_{6-14} aryl group as a substituent (arylalkyl group), or the like. Said aryl group is exemplified by phenyl and naphthyl. Said aralkyl group is exemplified by benzyl, phenethyl, 3-phenylpropyl, (1-naphthyl)methyl and (2-naphthyl)methyl. The aryl group for R^5 is exemplified by phenyl and naphthyl.

Provided that G is a halogen atom, said halogen atom is an atom of chlorine, bromine, iodine or fluorine, with preference given to chlorine or bromine.

In the above formula (I), provided that Y is C-G, R and G may bind together to form a 5-membered ring. Such a structure is represented by the following formula (II) or (III).



(II)



(III)

In these formulas, R^3 represents a hydrogen atom, an optionally substituted hydrocarbon residue, or an optionally substituted heterocyclic group; the other symbols have the same definitions as those given above.

In the above formulas (II) and (III), the optionally substituted hydrocarbon residue and the optionally substituted heterocyclic group for R^3 are exemplified by the same optionally substituted hydrocarbon residues and optionally substituted heterocyclic groups mentioned to exemplify R and Z^1 above.

In the above formula (I), Y is preferably C-G, with greater preference given to a C_{1-6} alkyloxycarbonyl group for G, and greatest preference given to an ethoxycarbonyl group for G.

n in the above formula (I) is preferably 0.

k in the above formula (I) is preferably 0.

Of the compounds represented by the above formula (I), preference is given to those wherein Y is C-G (G is ethoxycarbonyl), R is $-CH_2-Z^1$, Z^1 is 1,2,4-triazol-1-yl,

the substituents for ring A are methoxy groups each present at the 6- or 7-position of the quinoline ring, each substituent for ring B is methoxy or isopropoxy group present at the 3- position and methoxy group present at the 4-position thereof, n is 0, and k is 0.

Preferable examples of compounds represented by the formula (I) is

methyl 4-(3,4-dimethoxyphenyl)-2-ethyl-6,7-dimethoxyquinoline-3-carboxylate;

ethyl 6-chloro-2-methyl-4-(3,4-dimethoxyphenyl)quinoline-3-carboxylate;

6,7-dimethoxy-9-phenylfuro[3,4-b]quinoline-1(3H)-one;

ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-[(1-methylimidazol-2-yl)thiomethyl]quinoline-3-carboxylate;

4-(3,4-dimethoxyphenyl)-2-(2-hydroxyethylthiomethyl)-6,7-dimethoxyquinazoline;

4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-[(4-methyl-1,2,4-triazol-3-yl)thiomethyl]quinazoline;

ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-[(1-methylimidazol-2-yl)ethyl]quinoline-3-carboxylate;

methyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonylquinoline-2-acetate;

ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate (hereinafter reffered to as compound (A));

ethyl 4-(3-isopropoxy-4-methoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate;

ethyl 4-(4-hydroxy-3-methoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate (hereinafter reffered to as compound (B));

ethyl 4-(3-hydroxy-4-methoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate;

ethyl 7-hydroxy-6-methoxy-4-(3,4-dimethoxyphenyl)-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate;

ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate 1-oxide; or

ethyl 2-(N,N-diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline-3-carboxylate.

The salt of compound (I) for the present invention is preferably a pharmaceutically acceptable salt, exemplified by salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids and salts with basic or acidic amino acids.

Preferable salts with inorganic bases include alkali metal salts such as sodium salt and potassium salt; alkaline earth metal salts such as calcium salt and magnesium salt; aluminum salt and ammonium salt.

Preferable salts with organic bases include salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine and N,N'-dibenzylethylenediamine.

Preferable salts with inorganic acids include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid and phosphoric acid.

Preferable salts with organic acids include salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid and p-toluenesulfonic acid.

Preferable salts with basic amino acids include salts with arginine, lysine and ornithine. Preferable salts with acidic amino acids include salts with aspartic acid and glutamic acid. Among these salts, sodium or potassium salts are most preferable. Compound (I) or a pharmaceutically acceptable salt thereof for the present invention may be a hydrate.

Compound (I) for the present invention can, for example, be produced by or according to the methods described in Japanese Patent Unexamined Publication Nos. 306052/1994 (EP-A-0567107), 118266/1995 (EP-A-0608870) and 069890/1995 (EP-A-0634169), 53419/1996 (EP-A-0686630) and WO95/24394.

These dosage forms can be manufactured by the per se known technique conventionally used in pharmaceutical procedures.

Compound (I) for the present invention can be administered orally or non-orally to mammals, including humans, as formulated with a pharmaceutically acceptable carrier, in the form of solid preparations such as tablets, capsules, granules, powders or suppositories, or liquid preparations such as syrups and injectable preparations.

Pharmaceutically acceptable carriers are various organic or inorganic carrier substances in common use as pharmaceutical materials, including excipients, lubricants, binders and disintegrating agents for solid preparations, and solvents, dissolution aids, suspending agents, isotonizing agents, buffers and soothing agents for liquid preparations. Other pharmaceutical additives such as preservatives, antioxidants, coloring agents and sweetening agents may be used as necessary.

Preferable excipients include lactose, sucrose, D-mannitol, erythritol, starch, crystalline cellulose and light silicic anhydride.

Preferable lubricants include magnesium stearate, calcium stearate, talc and colloidal silica.

Preferable binders include crystalline cellulose, sucrose, D-mannitol, dextrin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose and polyvinylpyrrolidone.

Preferable disintegrating agents include starch, carboxymethyl cellulose, carboxymethyl cellulose calcium, crosscarmellose sodium and carboxymethyl starch sodium.

Preferable solvents include water for injection, alcohol, propylene glycol, macrogol, sesame oil and corn oil.

Preferable dissolution aids include polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, tris-aminomethane, cholesterol, triethanolamine, sodium carbonate and sodium citrate.

Preferable suspending agents include surfactants such as stearyltriethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride and monostearic glycerol; and hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethyl cellulose sodium, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose and hydroxypropyl cellulose.

Preferable isotonizing agents include sodium chloride, glycerol and D-mannitol.

Preferable buffers include buffer solutions of phosphates, acetates, carbonates and citrates.

Preferable soothing agents include benzyl alcohol.

Preferable preservatives include p-oxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid and sorbic acid.

Preferable antioxidants include sulfites and ascorbic acid.

Compound (I) for the present invention is of low toxicity; no deaths occurred during a 1-week observation period following oral administration of compound (A), for instance, to female F344/Jcl rats at 6 weeks of age at a dose of 2,000 mg/kg. As such, compound (I) for the present invention is useful as an immunosuppressant for mammals (e.g., humans, horses, bovines, pigs, dogs, cats).

Although the dose of compound (I) for the present invention can be chosen over a wide range, depending on target disease, route of administration, and patient condition to be treated, it can normally be chosen over the range from 1 mg to 2,000 mg a day, preferably 10 mg to 400 mg, for oral administration, and from 1 mg to 1,000 mg, preferably from 1 mg to 100 mg, for non-oral administration, per adult. These doses can be administered in about 1 to 3 portions a day.

In the present invention, examples of the drug which is used in combination with the quinoline or quinazoline

compound represented by the formula (I) or a pharmaceutically acceptable salt thereof include immunosuppressants ecept for a quinoline or quinazoline compound mentioned above, for example, (i) T cell inhibitors, (ii) cytotoxic chemicals, (iii) anti-tumor antibiotics, (iv) anti-lymphocyte immunoglobulins, and so on.

(i) T cell inhibitors are drugs having the property to suppress the immune response of T cells by inhibiting the production of both Th1 and Th2 cytokines which are derived from the T cells (e.g., Tacrolimus (FK506), cyclosporin A, cyclosporin G), or drugs having the property to inhibit the activity of cytokines produced by T cells (e.g., rapamycin). Consequently, these drugs suppress the immune reaction.

(ii) Cytotoxic chemicals are drugs, which are also used as anticancer drugs, having the property to act nonspecifically on actively proliferating cells, i.e. hematopoietic stem cells, germ cells, malignant cells or lymphocytes (T lymphocytes and B lymphocytes), which inhibit both responses of cellular immunity and humoral immunity as a result of the suppression of both T lymphocytes and B lymphocytes. Accordingly, these drugs always have both activities of myelosuppression and hypofertility as well as immunosuppressing activity. Examples of the cytotoxic chemicals include ① alkylating agents, ② nucleic acid metabolic antagonists, ③ folic acid metabolic antagonists and so on. ① The alkylating agents are drugs having the property to suppress the immune response by damaging T cells or B cells, mainly through the inhibition of DNA symthesis or DNA replication. Examples of the alkylating agents include cyclophosphamide, ifosfamide, chlorambucil and the like. ② The nucleic acid metabolic antagonists, which inhibit the metabolism of nucleic acid, are drugs having the property to suppress the antibody production by damaging mainly T cells. Examples

of the nucleic acid metabolic antagonists include 6-mercaptopurine, azathiopurine, 6-thioguanine, 5-fluorouracil, cytosine arabinoside, mizoribine and the like. ③ The folic acid metabolic antagonists, which inhibit the metabolism of folic acid, are drugs having the property to suppress the antibody production by damaging mainly T cells. Examples of the folic acid metabolic antagonists include methotrexate and the like.

(iii) Anti-tumor antibiotics are drugs having the property to inhibit DNA or RNA synthesis by intercalating therein, as a result of damaging T cells or B cells. Examples of the anti-tumor antibiotics include adriamycin, daunomycin and the like.

(iv) Anti-lymphocyte immunoglobulins are drugs having the property to suppress the immune response by damaging mainly T cells. Examples of the anti-lymphocyte immunoglobulins include anti-CD3 antibody, anti-CD4 antibody, anti-CD5 antibody, anti-IL-2 receptor antibody and the like.

On the other hand, a quinoline or quinazoline compound represented by the formula (I) of the present invention, are the drugs having the property to suppress the immune response of T cells by specific inhibition of the production of Th1 cytokines such as interferon-γ (IFN-γ) and interleukin-2 (IL-2) among the cytokines which are derived from the T cells. Therefore, the inhibition mechanism of the quinoline or quinazoline compound represented by the formula (I) is different from those of the immunosuppressants mentioned above.

In the present invention, especially preferred is the pharmaceutical composition which comprises a quinoline or quinazoline compound represented by the formula (I) or a pharmaceutically acceptable salt thereof (e.g., compound A or compound B) in combination with Tacrolimus (FK506), methotrexate or cyclosporin A, particularlly Tacrolimus (FK506).

The pharmaceutical composition of the present invention comprising the quinoline or quinazoline compound represented by the formula (I) or pharmaceutically acceptable salt thereof in combination with an immunosuppressant except for a quinoline or quinazoline compound mentioned above, which is provided in accordance with the present invention, can be respectively put to use by mixing the respective active components either all together or independently with a physiologically acceptable carrier, excipient, binder, diluent, etc. and administering the mixture or mixtures either orally or non orally as a pharmaceutical composition. When the active components are formulated independently, the respective formulations can be extemporaneously admixed using a diluent or the like and aministered or can be administered independently of each other, either concurrently or at staggered times to the same subject.

The dosage form for said pharmaceutical composition includes such oral dosage forms as granules, powders, tablets, capsules, syrups, emulsions, suspensions, etc. and such non-oral dosage forms as injections (e.g. subcutaneous, intravenous, intramuscular and intraperitoneal injections), drip infusions, external application forms (e.g. nasal spray preparations, transdermal preparations, ointments, etc.), and suppositories (e.g. rectal and vaginal suppositories).

These dosage forms can be manufactured by the per se known technique conventionally used in pharmaceutical procedures.

To manufacture an oral dosage form, an excipient (e.g. lactose, sucrose, starch, mannitol, etc.), a dis-integrator (e.g. calcium carbonate, carboxymethylcellulose calcium, etc.), a binder (e.g. α-starch, gum arabic, carboxymethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose, trehalose etc.), and a lubricant (e.g. talc, magnesium stearate, polyethylene glycol 6000,

etc.), for instance, are added to the active component or components and the resulting composition is compressed. Where necessary, the compressed product is coated, by the per se known technique, for masking the taste or for enteric dissolution or sustained release. The coating material that can be used includes, for instance, ethylcellulose, hydroxymethylcellulose, polyoxyethyleneglycol, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, and Eudragit (Rohm & Haas, Germany, methacrylic-acrylic copolymer).

Injections can be manufactured typically by the following procedure. The active component or components are dissolved, suspended or emulsified in an aqueous vehicle (e.g. distilled water, physiological saline, Ringer's solution, etc.) or an oily vehicle (e.g. vegitable oil such as olive oil, sesame oil, cottonseed oil, corn oil, etc. or propylene glycol) together with a dispersant (e.g. Tween 80 (Atlas Powder, U.S.A.), HCO 60 (Nikko Chemicals), polyethylene glycol, carboxymethylcellulose, sodium alginate, etc.), a preservative (e.g. methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, benzyl alcohol, chlorobutanol, phenol, etc.), an isotonizing agent (e.g. sodium chloride, glycerol, sorbitol, glucose, inverted sugar, etc.) and other additives. If desired, a solubilizer (e.g. sodium salicylate, sodium acetate, etc.), a stabilizer (e.g. human serum albumin), a soothing agent (e.g. benzalkonium chloride, procaine hydrochloride, etc.) and other additives can also be added.

A dosage form for external application can be manufactured by processing the active component or components into a solid, semi-solid or liquid composition. To manufacture a solid composition, for instance, the active component or components, either as they are or in admixture with an excipient (e.g. lactose, mannitol, starch, microcrystalline cellulose, sucrose, etc.), a thickener (e.g. natural gums, cellulose derivatives,

acrylic polymers, etc.), etc., are processed into powders. The liquid composition can be manufactured in substantially the same manner as the injections mentioned above. The semi-solid composition is preferably provided in a hydrous or oily gel form or an ointment form. These compositions may optionally contain a pH control agent (e.g. carbonic acid, phosphoric acid, citric acid, hydrochloric acid, sodium hydroxide, etc.), and a preservative (e.g. p-hydroxybenzoic acid esters, chlorobutanol, benzalkonium chloride, etc.), among other additives.

Suppositories can be manufactured by processing the active component or components into an oily or aqueous composition, whether solid, semi-solid or liquid. The oleaginous base that can be used includes, for instance, higher fatty acid glycerides [e.g. cacao butter, Witepsols (Dynamite-Nobel), etc.], medium-chain fatty acids [e.g. Migriols (Dynamite-Nobel), etc.], vegetable oils (e.g. sesame oil, soybean oil, cotton-seed oil, etc.), etc. Ther water-soluble base includes, for instance, polyethylene glycols, propylene glycol, etc. The hydrophilic base includes, for instance, natural gums, cellylose derivatives, vinyl polymers, and acrylic polymers, etc.

The pharmaceutical composition of the present invention is low in toxicity and can be safely used in mammals (e.g. humans, mice, rats, rabbits, dogs, cats, bovines, horses, swines, monkeys).

The dosage of the pharmaceutical composition of the present invention may be appropriately determined with reference to the dosages recommended for the respective active components and can be selected appropriately according to the recipient, the recipient's age and body weight, current clinical status, administration time, dosage form, method of administration, and combination of the active components, among other factors. The preferred frequency of administration is 1 to 3 times a day.

The proportions of the active components in the pharmaceutical composition of the present invention can be appropriately selected according to the recipient, the recipient's age and body weight, current clinical status, administration time, dosage form, method of administration, and combination of active components, among other factors. When, for example, the compound represented by the formula (I) or a pharmaceutically acceptable salt thereof (e.g. compound A or B) and Tacrolimus (FK506), which is an example of T cell inhibiting agents, are to be administered in combination to a human subject, Tacrolimus (FK506) is used in a proportion of usually about 0.001 to 10 weight parts and preferably about 0.01 to 1 weight parts relative to 1 weight part of the compound or a salt thereof. When, for example, the compound represented by the formula (I) or a pharmaceutically acceptable salt thereof (e.g. compound A or B) and cyclosporin A, which is an example of T cell inhibiting agent, are to be administered in combination to a human subject, cyclosporin A is used in a proportion of usually about 0.01 to 100 weight parts and preferably about 0.1 to 10 weight parts relative to 1 weight part of the compound or a salt thereof. When, for example, the compound represented by the formula (I) or a pharmaceutically acceptable salt thereof and methotrexate which is a metabolic antagonist for a folic acid are to be administered in combination to a human subject, methotrexate is used in a proportion of usually about 0.0001 to 1 weight parts and preferably about 0.001 to 0.1 weight parts, relative to 1 weight part of the compound or a pharmaceutically acceptable salt thereof.

The pharmaceutically composition of the present invention shows a marked synergistic effect compared with administration of either active component alone. For example, compared with cases in which each of these active components was administered to patients with the diseases associated with immunity, administration of these active

components in combination resulted in marked improvements in both efficacy and toxicity. Thus, the pharmaceutical composition of the present invention improves the disorder of immune response more effectively than it is the case with administration of each component drug alone and, therefore, can be used advantageously for the prophylaxis and treatment of diseases assumed to be associated with immunity including autoimmunity, and the prevention of graft rejection following transplantation.

Furthermore, since the pharmaceutical composition of the present invention develops sufficient efficacy with reduced doses as compared with the administration of any one of the active components alone, the side effects of the respective components (e.g. nephrotoxicity, myelosuppression, pneumonitis, etc.) can be reduced.

The immunosuppressant of the present invention specifically suppresses the production of immune cytokines [e.g., interleukin-2 (IL-2), interferon-γ (IFN-γ)], and is useful in treating or preventing diseases assumed to be associated with immunity, including autoimmune diseases, in mammals, including humans. Such target diseases include systemic lupus erythematosus, ulcerative colitis, Crohn disease, multiple sclerosis, psoriasis, chronic hepatitis, gallbladder cancer, breast cancer, uterine cervical cancer, chronic lymphatic leukemia, chronic myelocytic leukemia, large intestine cancer, colic cancer, rectal cancer, Helicobacter pylori infection, Hodgkin's disease, insulin-dependent diabetes mellitus, malignant melanoma, multiple myeloma, non-Hodgkin lymphoma, non-small cell lung cancer, ovarian cancer, digestive ulcer, prostatic cancer, septic shock, tuberculosis, infertility, arteriosclerosis, Behcet's disease, asthma, atopic dermatitis, nephritis, systemic fungal infection, acute bacterial meningitis, acute myocardial infarction, acute pancreatitis, acute viral encephalitis, adult respiratory distress syndrome, bacterial pneumonia, chronic pancreatitis, herpes simplex

viral infection, varicella-zoster viral infection, AIDS, human papilloma viral infection, influenza, invasive staphylococcal infection, peripheral vascular disease, sepsis, interstitial liver diseases, regional ileitis and multiple sclerosis, especially systemic lupus erythematosus, chronic hepatitis, interstitial liver diseases, asthma, psoriasis, ulcerative colitis, Crohn disease, regional ileitis and multiple sclerosis. The immunosuppressant of the present invention is also useful in the prevention of graft rejection following organ transplantation.

Brief Description of Drawings

Fig. 1 shows the effect of concomitant administration of compound A and Tacrolimus (FK506) on body weight change in adjuvant arthritic rats.

Fig. 2 shows the effect of concomitant administration of compound A and methotrexate on body weight change in adjuvant arthritic rats.

Best modes for carrying out the invention

The immunosuppressing activity of the pharmaceutical composition of the present invention is hereinafter described with reference to experimental examples.

Experimental Example 1

Action on interleukin-2 and interferon-γ production by rat splenocytes

Interleukin-2 (IL-2) and interferon-γ (IFN-γ), both cytokines produced by T-cells, show diverse actions, including T-cell growth and macrophage activation, respectively, and play key roles in immune reaction. Suppression of production of these cytokines serves as a good index of immunosuppressing activity.

i) Experimental materials and methods

Splenocytes were isolated from the spleen of a Lewis rat (male, 8 weeks of age), and suspended in RPMI-1640 (containing penicillin, streptomycin and 2-mercaptoethanol) supplemented with 5% fetal bovine serum), followed by cultivation of 1×10^7 splenocytes in the presence of 2 μg/ml concanavalin A for 24 hours. After completion of the cultivation, the supernatant was collected. The IL-2 content in the supernatant was determined with ^{3}H-thymidine incorporation as an index, by 50 fold diluting the culture supernatant, and carrying out a reaction for growing CTLL-2 cells, an IL-2 dependent cell line. The IFN-γ content was determined by a commonly known method using an ELISA kit (GIBCO PBL, USA).

ii) Results

Compounds (A) and (B) both suppressed IL-2 and IFN-γ production dose dependently (Table 1).

Table 1

	Concentration μM	Interleukin-2 cpm	%Inh.	Interferon-γ ng/ml	%Inh.
Medium		39,093 ± 4,755		54.8 ± 2.9	
Compound (A)	1	32,202 ± 752	18%	36.6 ± 2.7**	33%
	10	22,273 ± 1,088**	43%	27.9 ± 0.7**	49%
	100	446 ± 78**	99%	1.1 ± 0.6**	98%
Compound (B)	1	34,355 ± 1,744	12%	53.2 ± 4.0	3%
	10	18,955 ± 661**	52%	36.6 ± 1.7**	33%
	100	248 ± 14**	100%	1.0 ± 0.8**	98%

Data are shown mean for 3 cases ± standard error.

*: $p < 0.05$ versus drug-free control group

**: $p < 0.01$ versus drug-free control group

Experimental Example 2

Action on interleukin-2 and interferon-γ production by antigen-stimulated mouse T-lymphocytes

i) Experimental materials and methods

Lymphocytes were isolated from a lymph node of a Balb/c mouse at 10 days after sensitization with ovalbumin (OVA, 100 μg), and suspended in RPMI-1640 (containing penicillin and streptomycin) supplemented with 10% fetal bovine serum). Lymph node cells were subjected to alternative cultivation in the presence of splenocytes from an X-ray-irradiated mouse of the same line and 50 μg/ml OVA, and in the presence of 20 ng/ml IL-2, to yield an OVA-reactive T cell line, from which an OVA-reactive T cell clone was established by the limiting dilution analysis method. An allo-reactive T-cell line was prepared by subjecting Balb/c mouse splenocytes to alternative cultivation in the presence of splenocytes from an X-ray-irradiated A/J mouse, and in the presence of 20 ng/ml IL-2.

To assess drug effect, subject cells were cultured with each drug in the presence of splenocytes from an X-ray-irradiated mouse of the same line and 50 μg/ml OVA for 48 hours for the OVA-reactive T cells, and in the presence of splenocytes from an X ray-irradiated A/J mouse for 24 hours for the allo-reactive T-cells, after which the IFN-γ and IL-2 contents in the supernatant were determined by ELISA (according to the same method mentioned in Experimental Example 1).

ii) Results

Compound (A) significantly suppressed IFN-γ production by the OVA-reactive T cell line, OVA-reactive T cell clone and allo-reactive T cell line at concentrations exceeding 1 μM, and also significantly suppressed IL-2 production by the allo-reactive T cell line at concentrations exceeding 1 μM (Table 2).

Table 2

	Cytokine	Compound (A) (μM) 0.1	1	10
OVA-reactive T cell line A	IFN-γ	27	43*	72**
OVA-reactive T cell line B	IFN-γ	17	36*	98**
OVA-reactive T cell clone 5A7	IFN-γ	ND	35*	71**
OVA-reactive T cell clone 5E3	IFN-γ	ND	38*	69**
Allo-reactive T cell line A	IFN-γ	ND	28*	38*
	IL-2	ND	25*	63*
Allo-reactive T cell line B	IFN-γ	11	22*	30**
	IL-2	ND	26*	45**

Data are shown in suppression rate (%).

*: $p < 0.05$ versus drug-free control group

**: $p < 0.01$ versus drug-free control group

ND: Not done

Experimental Example 3

Action on rat adjuvant arthritis

Male Lewis rats (7 weeks of age), 6 per group, were sensitized by intradermally injecting 0.05 ml of Freund's complete adjuvant (0.5% liquid paraffin suspension of dead tubercle bacillus cells) to the right hind leg paw (0 day). Five to 6 times weekly from just before sensitization (0 day) to 30 days, Compound A (3.13 mg/kg/day or 12.5 mg/kg/day), Tacrolimus (FK506) (0.63 mg/kg/day) and methotraxate (0.05 mg/kg/day), in suspension in 0.5% methyl cellulose, singly or concomitantly, were orally administered. Just before sensitization (0 day) and at 14 and 18 days, the left hind leg paw volume was measured to obtain the paw swelling suppression rate, in comparison with non-sensitized rats (see Table 3). Body weight was

measured just before administration; the body weight increase was obtained in comparison with non-sensitized rats (see Fig. 1 and Fig. 2).

The results are shown in mean ± standard error for each group (N = 6) and compared by Student's t-test at a significance level of < 5%.

As shown in Table 3, concomitant administrations of Compound A and Tacrolimus (FK506), or compound A and methotratate showed more potent action in terms of edema suppression, in comparison with either drug administered alone.

Particularly, with respect to the action in terms of edema suppression, the result of concomitant administration of compound A and Tacrolimus (FK506) at 18 days, also of compound A and methotrexate at 18 days, showed a remarkable effect beyond the sum effect of both agents. As is clear from Fig. 1 and Fig. 2, concomitant administrations of Compound A and Tacrolimus (FK506), or Compound A and methotraxate showed more potent effect in terms of body weight change (increase), in comparison with either drug administration alone.

Table 3

Manner of Administration (mg/kg)		Swelling Suppression Rate (%)	
		14 days	18 days
I) Compound A	3.13	34*	31*
FK506	0.63	55**	42**
Concomitant use (Compound A + FK506)		98**	100**
II) Compound A	12.5	40	37
Methotrexate	0.05	83**	37
Concomitant use (Compound A + Methotrexate)		100**	88**

*: $p < 0.05$ versus drug-free control group

**: $p < 0.01$ versus drug-free control group

Examples

The present invention is hereinafter described in more detail by means of, but are not limited to, the following working examples and reference examples.

Reference Example 1

Production of N-(3,4-dimethoxyphenyl)acetamide

3,4-dimethoxyaniline (100 g) was suspended in H_2O (800 ml); after an aqueous solution of NaOH (34.0 g/200 ml) and acetic anhydride (86.6 g) were alternatively added in one-fifth portions at under 65°C, the mixture was stirred at 55-60°C for about 20 minutes. After the reaction mixture was cooled to about 5°C and stirred for 1 hour, the resulting crystal was collected by filtration and dried under reduced pressure to yield 119 g (recovery 93.2%) of N-(3,4-dimethoxyphenyl)acetamide as a brown crystal.

A sample for IR and ^{1}H-NMR determination was obtained by recrystallization from ethyl acetate.

IR (cm^{-1}, KBr): 3276, 1653, 1606, 1575, 1520, 1462
^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.15 (3H, s), 3.84 (6H, s), 6.78 (1H, d, J=8.6 Hz), 6.88 (1H, dd, J=8.6, 2.4 Hz), 7.30 (1H, d, J=2.4 Hz), 7.55 (1H, brs)

Reference Example 2

Production of 2-acetylamino-3',4,4',5-tetramethoxybenzophenone

A mixture of N-(3,4-dimethoxyphenyl)acetamide (114 g), 3,4-dimethoxybenzoic acid (117 g) and polyphosphoric acid (1,203 g) was stirred at 95-110°C for 3 hours. After cold water (3 l) was added, the reaction mixture was extracted with ethyl acetate (3 l); the extract was washed with a 2 N aqueous solution of NaOH (3 l), then with water (3 l). After the reaction mixture was concentrated under reduced pressure, n-hexane (1.2 l) was added to the residue, followed by stirring at about 5°C for 30 minutes. The resulting crystal was collected by filtration, then dried under reduced pressure to yield 129 g (recovery 61.3%) of 2-acetylamino-3',4,4',5-tetramethoxybenzophenone as a yellow crystal.

A sample for IR and ^{1}H-NMR determination was obtained by recrystallization from ethyl acetate.
IR (cm^{-1}, KBr): 2947, 1695, 1678, 1616, 1595
^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.22 (3H, s), 3.76 (3H, s), 3.94 (3H, s), 3.98 (3H, s), 4.00 (3H, s), 6.93 (1H, d, J=7.7 Hz), 7.09 (1H, s), 7.28 (1H, dd, J=7.7, 1.9 Hz), 7.32 (1H, s), 8.38 (1H, s), 11.0 (1H, brs)

Reference Example 3

Production of 2-amino-3',4,4',5-tetramethoxybenzophenone hydrochloride

To a solution of 2-acetylamino-3',4,4',5-tetramethoxybenzophenone (129 g) in isobutanol (1.49 l), concentrate hydrochloric acid (446 ml) was added, followed by thermal refluxing for 2 hours. After the reaction mixture was

cooled and stirred at about 5°C for 2 hours, the resulting crystal was collected by filtration, then dried under reduced pressure to yield 117 g (recovery 92.3%) of 2-amino-3',4,4',5-tetramethoxybenzophenone hydrochloride as a yellowish white crystal.

A sample for IR and ^{1}H-NMR determination was obtained by recrystallization from EtOH.

IR (cm^{-1}, KBr): 3618, 2839, 2567, 1657, 1628, 1583

^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 3.58 (3H, s), 3.80 (6H, s), 3.85 (3H, s), 3.61 (1H, brs), 6.93 (1H, s), 7.06 (1H, d, J=8.6 Hz), 7.20-7.22 (2H, m)

Reference Example 4

36.0 g of 2-amino-3',4,4',5-tetramethoxybenzophenone hydrochloride and 21.4 g of the ethyl ester of 4-chloroacetoacetic acid were thermally refluxed in 350 ml of ethanol for 7 hours during stirring. After completion of the reaction, 10.6 g of triethylamine was added drop by drop at under 20°C, followed by stirring at 5°C for 1 hour. The resulting crystal was filtered, twice washed with 50 ml of ethanol, then dried under reduced pressure to yield 41.0 g (recovery 92%) of the ethyl ester of 2-chloromethyl-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline-3-carboxylic acid.

Reference Example 5

Production of 4-amino-1-[4-(3,4-dimethoxyphenyl)-3-ethoxycarbonyl-6,7-dimethoxyquinolin-2-ylmethyl]-4H-1,2,4-triazolium bromide

The ethyl ester of 2-chloromethyl-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline-3-carboxylic acid (22.5 g, content ratio 99.1%, 50.0 mmol), sodium bromide (5.81 g, 56.5 mmol) and 4-amino-1,2,4-triazole (5.47 g, 65.1 mmol) were suspended in DMF (50 ml) and stirred at 65°C for 3 hours.

After ethyl acetate (100 ml) was added to the reaction mixture, the resulting crystal was collected by filtration and dried to yield 4-amino-1-[4-(3,4-dimethoxyphenyl)-3-ethoxycarbonyl-6,7-dimethoxyquinolin-2-ylmethyl]-4H-1,2,4-triazolium bromide as a white crystal (31.1 g, content ratio 83.6%, recovery 90.6%).

A sample for structural identification was purified by silica gel column chromatography (mobile phase CH_2Cl_2:MeOH = 5:1) and recrystallization (4.8% hydrated EtOH).

IR (cm^{-1}, KBr): 3196, 1706, 1518, 1472

^{1}H-NMR (DMSO-d_6, 90 MHz) δ: 0.92 (3H, t, J=6.9 Hz, $CO_2CH_2CH_3$), 3.72 (3H, s, OMe), 3.77 (3H, s, OMe), 3.86 (3H, s, OMe), 3.96 (3H, s, OMe), 3.72-4.09 (2H, m, CO_2CH_2), 5.94 (2H, s, CH_2N), 6.93-7.31 (7H, m), 9.28 (1H, s, CH=N), 10.41 (1H, s, CH=N)

Anal. Calcd for $C_{25}H_{28}N_5O_5Br(0.73\ H_2O)$: C, 51.10; H, 5.05; N, 11.92; Br, 13.60

Found: C, 51.10; H, 4.91; N, 11.88; Br, 13.55

mp: 183.8-184.4°C

Reference Examples 6 through 12

Reaction was carried out using the same starting quinoline and triazole compounds as those used in Reference Example 5 in a 1:1.3 molar ratio and the same procedure, but different reaction solvents and additives were used. The results are shown in Table 4 (percent areal ratios for HPLC peaks confirmed with the reaction mixture).

Table 4

Reference Example Number	Reaction Solvent [Molar Concentration (M)]	Additive	Reaction Conditions		Percent Areal Ratios for HPLC Peaks (%)		Recovery (%)
			Temperature (°C)	Duration (h)	Desired Product	Starting Material	
6	CH_3CN [0.5]	—	100	15	87.5	6.6	93.7
7	CH_3CN [0.6]	NaBr	70	3.0	61.2	34.8	93.9
8	EtOH [0.2]	—	100	15	48.7	46.4	90.9
9	i-PrOH [0.2]	—	80-100	7-12	38.6	58.1	92.1
10	DMF [1.0]	—	80-100	8-12	88.6	0.2	88.8
11	DMF [1.0]	NaI	70	1.5	88.1	—	88.1
12	DMF [1.0]	NaBr	70	3.0	94.1	0.01	94.1

Reference Example 13

Production of ethyl ester of 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylic acid

4-amino-1-[4-(3,4-dimethoxyphenyl)-3-ethoxycarbonyl-6,7-dimethoxyquinolin-2-ylmethyl]-4H-1,2,4-triazolium bromide (10.31 g, content ratio 83.6%, 15.0 mmol) was suspended in H_2O (37.5 ml); under ice cooling conditions, concentrate hydrochloric acid (3.8 ml, 45 mmol) and a 5.6 M aqueous solution of $NaNO_2$ (4.00 ml, 22.5 mmol) were added, followed by stirring at room temperature for 2 hours.

After a 5 N aqueous solution of NaOH (8.7 ml) was added to neutralize the reaction mixture, the resulting crystal was collected by filtration and washed with water to yield 6.66 g (recovery 92.8%) of the ethyl ester of 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylic acid as a white crystal.

IR (cm^{-1}, KBr): 1720, 1504, 1468, 1430

^1H-NMR ($CDCl_3$, 90 MHz) δ: 0.89 (3H, t, J=7.1 Hz, $CO_2CH_2CH_3$), 3.79 (3H, s, OMe), 3.86 (3H, s, OMe), 3.96 (3H, s, OMe), 4.04 (3H, s, OMe), 3.86-4.13 (2H, q, J=7.1 Hz, CO_2CH_2), 5.72 (2H, s, CH_2N), 6.86-6.95 (4H, m), 7.41 (1H, s), 7.93 (1H, s), 8.23 (1H, s)

mp: 175.4-176.0°C

Reference Example 14

Production of ethyl ester of 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylic acid

4-amino-1-[4-(3,4-dimethoxyphenyl)-3-ethoxycarbonyl-6,7-dimethoxyquinolin-2-ylmethyl]-4H-1,2,4-triazolium bromide (503 g, content ratio 80.9%, 0.709 mol) was suspended in H_2O (5.44 l); under ice cooling conditions, concentrate hydrochloric acid (159 g, 1.56 mol) and a 0.63 M aqueous

solution of $NaNO_2$ (1.46 l, 0.920 mol) were added, followed by stirring at room temperature for 3 hours.

After a 5 N aqueous solution of NaOH (295 ml) was added to neutralize the reaction mixture, the resulting crystal was collected by filtration and washed with water to yield 329 g (recovery 97.0%) of the ethyl ester of 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylic acid as a white crystal.

Example 1

Table 5

Composition (per Tablet)	12.5 mg Tablet	25 mg Tablet	50 mg Tablet	100 mg Tablet
(1) Compound (A)	12.5 mg	25.0 mg	50.0 mg	100.0 mg
(2) Lactose	133.13	120.63	95.63	45.63
(3) Corn starch	26.7	26.7	26.7	26.7
(4) Hydroxypropyl cellulose	5.7	5.7	5.7	5.7
(5) Crosscarmellose sodium	9.5	9.5	9.5	9.5
(6) Macrogol 6000	1.9	1.9	1.9	1.9
(7) Magnesium stearate	0.57	0.57	0.57	0.57
Total	190.0 mg	190.0 mg	190.0 mg	190.0 mg

In a granulating machine (Powrex Co., model FD-5S, FV-25: Japan), 75 g of the above component (1), 798.8 g of component (2) and 160.2 g of component (3) were granulated with an aqueous solution of 34.2 g of component (4) as a binder solution. After drying and size reduction, 961.4 g of the granules were mixed with 51.3 g of component (5), 10.26 g of component (6) and 3.08 g of component (7) to yield a powder mixture. This powder mixture was tableted

using a per se known tablet machine to yield a tablet preparation 8.0 mm in diameter and 190 mg in weight containing 12.5 mg of component (1).

Tablets of other dose units were produced in the same manner as above.

The tablets obtained were all found to have excellent tablet properties, including hardness, disintegrability and solubility.

Industrial Applicability

The immunosuppressant containing compound (I) or a pharmaceutically acceptable salt thereof for the present invention is safe and of low toxicity, and can be used to prevent or treat diseases assumed to be associated with immunity, including autoimmune diseases, and to prevent graft rejection following organ transplantation.

And, the pharmaceutical composition comprising a quinoline or quinazoline compound (I) or a pharmaceutically acceptable salt thereof and an immunosuppressant except for the quinoline or quinazoline compound mentioned above, has a remarkable effect beyond the sum effect of both agents in comparison with either agent administered above.

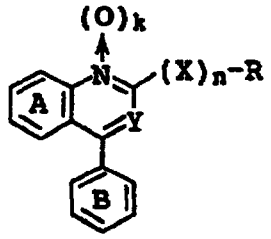
Therefore, the pharmaceutical composition can be used to prevent or treat diseases assumed to be associated with immunity, including autoimmune diseases, and to prevent graft rejection following organ transplantation, with very low prevalence of side effects even in chronic administration, provided that drug combination, administration method, dose etc. are appropriately chosen according to symptoms.

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CLAIMS

1. An immunosuppressant containing as an active ingredient a compound represented by the formula (I):



(I)

wherein Y is a nitrogen atom or C-G (G is an optionally esterified or amidated carboxyl group, an acyl group, an optionally protected hydroxyalkyl group, or a halogen atom); R is an optionally substituted hydrocarbon residue or an optionally substituted heterocyclic group; X is an oxygen atom or an optionally oxidized sulfur atom; n is 0 or 1; k is 0 or 1; G and R may bind together to form a ring; rings A and B may each have a substituent; or a pharmaceutically acceptable salt thereof.

2. The immunosuppressant of claim 1, wherein n is 0, and wherein the optionally substituted hydrocarbon residue represented by R is a group represented by the formula: $-CH_2-X^1-Z^1$
wherein X^1 is an oxygen atom, an optionally oxidized sulfur atom, or $-(CH_2)_m-$ (m is an integer from 0 to 5); Z^1 is a hydrogen atom, an optionally substituted hydrocarbon residue, an optionally substituted heterocyclic group, or an optionally substituted amino group.

3. The immunosuppressant of claim 2, wherein m is 0, provided that X^1 is $-(CH_2)_m-$.

4. The immunosuppressant of claim 1, wherein the optionally substituted heterocyclic group represented by Z^1 is an aromatic 5-membered heterocyclic group containing 2 or 3 hetero atoms.

5. The immunosuppressant of claim 1, wherein Y is C-G.

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6. The immunosuppressant of claim 5, wherein G is a C_{1-6} alkyloxycarbonyl group.

7. The immunosuppressant of claim 1, wherein G is an ethoxycarbonyl group.

8. The immunosuppressant of claim 1, wherein ring A is substituted for by at least 1 alkoxy group.

9. The immunosuppressant of claim 1, wherein ring A is substituted for by 2 methoxy groups.

10. The immunosuppressant of claim 1, wherein ring A is substituted for by 2 methoxy groups respectively at the 6- and 7-positions of the quinoline ring or quinazoline ring.

11. The immunosuppressant of claim 1, wherein ring B is substituted for by at least 1 alkoxy group.

12. The immunosuppressant of claim 1, wherein ring B is substituted for by 2 identical or different alkoxy groups.

13. The immunosuppressant of claim 1, wherein k is 0.

14. The immunosuppressant of claim 1, wherein the compound represented by the formula (I) is

methyl 4-(3,4-dimethoxyphenyl)-2-ethyl-6,7-dimethoxyquinoline-3-carboxylate;

ethyl 6-chloro-2-methyl-4-(3,4-dimethoxyphenyl)quinoline-3-carboxylate;

6,7-dimethoxy-9-phenylfuro[3,4-b]quinoline-1(3H)-one;

ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-[(1-methylimidazol-2-yl)thiomethyl]quinoline-3-carboxylate;

4-(3,4-dimethoxyphenyl)-2-(2-hydroxyethylthiomethyl)-6,7-dimethoxyquinazoline;

4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-[(4-methyl-1,2,4-triazol-3-yl)thiomethyl]quinazoline;

ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-[(1-methylimidazol-2-yl)ethyl]quinoline-3-carboxylate;

methyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonylquinoline-2-acetate;

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ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate;

ethyl 4-(3-isopropoxy-4-methoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate;

ethyl 4-(3-hydroxy-4-methoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate;

ethyl 4-(4-hydroxy-3-methoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate;

ethyl 7-hydroxy-6-methoxy-4-(3,4-dimethoxyphenyl)-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate;

ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate 1-oxide; or

ethyl 2-(N,N-diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline-3-carboxylate.

15. The immunosuppressant of claim 1 possessing immune cytokine production-suppressing activity.

16. The immunosuppressant of claim 1 for the prophylaxis or therapy of autoimmune diseases.

17. The immunosuppressant of claim 1 for the prophylaxis or therapy of systemic lupus erythematosus, chronic hepatitis, interstitial liver diseases, asthma, psoriasis, ulcerative colitis, Crohn disease, regional ileitis or multiple sclerosis.

18. The immunosuppressant of claim 1 for the prophylaxis of graft rejection following organ transplantation.

19. A method of preventing or treating autoimmune diseases in mammals which comprises administering to the mannals a therapeutically effective amount of a compound represented by the formula (I) of claim 1 or a pharmaceutically acceptable salt thereof.

20. The method of claim 19, wherein autoimmune diseases is systemic lupus erythematosus, chronic hepatitis, interstitial liver diseases, asthma, psoriasis, ulcerative colitis, Crohn disease, regional ileitis or multiple sclerosis.

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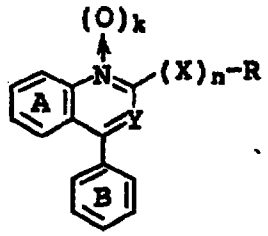
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21. A method of preventing graft rejection following organ transplation in mammals which comprises administering to the mannals a therapeutically effective amount of a compound represented by the formula (I) of claim 1 or a pharmaceutically acceptable salt thereof.

22. Use of a compound represented by the formula (I) of claim 1 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament to be used as an immunosuppressant.

23. A pharmaceutical composition which comprises a quinoline or quinazoline compound represented by the formula (I):



(I)

wherein Y is a nitrogen atom or C-G (G is an optionally esterified or amidated carboxyl group, an acyl group, an optionally protected hydroxyalkyl group, or a halogen atom); R is an optionally substituted hydrocarbon residue or an optionally substituted heterocyclic group; X is an oxygen atom or an optionally oxidized sulfur atom; n is 0 or 1; k is 0 or 1; G and R may bind together to form a ring; rings A and B may each have a substituent; or a pharmaceutically acceptable salt thereof; and an immunosuppressant except for a quinoline or quinazoline compound mentioned above.

24. The pharmaceutical composition of claim 23, wherein n is 0, and wherein the optionally substituted hydrocarbon residue represented by R is a group represented by the formula:

$-CH_2-X^1-Z^1$

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wherein X^1 is an oxygen atom, an optionally oxidized sulfur atom, or $-(CH_2)_m-$ (m is an integer from 0 to 5); Z^1 is a hydrogen atom, an optionally substituted hydrocarbon residue, an optionally substituted heterocyclic group, or an optionally substituted amino group.

25. The pharmaceutical composition of claim 24, wherein m is 0, provided that X^1 is $-(CH_2)_m-$.

26. The pharmaceutical composition of claim 23, wherein the optionally substituted heterocyclic group represented by Z^1 is an aromatic 5-membered heterocyclic group containing 2 or 3 hetero atoms.

27. The pharmaceutical composition of claim 23, wherein Y is C-G.

28. The pharmaceutical composition of claim 23, wherein G is a C_{1-6} alkyloxycarbonyl group.

29. The pharmaceutical composition of claim 23, wherein G is an ethoxycarbonyl group.

30. The pharmaceutical composition of claim 23, wherein ring A is substituted for by at least 1 alkoxy group.

31. The pharmaceutical composition of claim 23, wherein ring A is substituted for by 2 methoxy groups.

32. The pharmaceutical composition of claim 23, wherein ring A is substituted for by 2 methoxy groups respectively at the 6- and 7-positions of the quinoline ring or quinazoline ring.

33. The pharmaceutical composition of claim 23, wherein ring B is substituted for by at least 1 alkoxy group.

34. The pharmaceutical composition of claim 23, wherein ring B is substituted for by 2 identical or different alkoxy groups.

35. The pharmaceutical composition of claim 23, wherein k is 0.

36. The pharmaceutical composition of claim 23, wherein the compound represented by the formula (I) is



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methyl 4-(3,4-dimethoxyphenyl)-2-ethyl-6,7-dimethoxyquinoline-3-carboxylate;

ethyl 6-chloro-2-methyl-4-(3,4-dimethoxyphenyl)quinoline-3-carboxylate;

6,7-dimethoxy-9-phenylfuro[3,4-b]quinoline-1(3H)-one;

ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-[(1-methylimidazol-2-yl)thiomethyl]quinoline-3-carboxylate;

4-(3,4-dimethoxyphenyl)-2-(2-hydroxyethylthiomethyl)-6,7-dimethoxyquinazoline;

4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-[(4-methyl-1,2,4-triazol-3-yl)thiomethyl]quinazoline;

ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-[(1-methylimidazol-2-yl)ethyl]quinoline-3-carboxylate;

methyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonylquinoline-2-acetate;

ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate;

ethyl 4-(3-isopropoxy-4-methoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate;

ethyl 4-(3-hydroxy-4-methoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate;

ethyl 4-(4-hydroxy-3-methoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate;

ethyl 7-hydroxy-6-methoxy-4-(3,4-dimethoxyphenyl)-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate;

ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate 1-oxide; or

ethyl 2-(N,N-diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline-3-carboxylate.

37. The pharmaceutical composition of claim 23 possessing immune cytokine production-suppressing activity.

38. The pharmaceutical composition of claim 23 for the prophylaxis or therapy of autoimmune diseases.

39. The pharmaceutical composition of claim 23 for the prophylaxis or therapy of systemic lupus erythematosus, chronic hepatitis, interstitial liver diseases, asthma,



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psoriasis, ulcerative colitis, Crohn disease, regional ileitis or multiple sclerosis.

40. The pharmaceutical composition of claim 23 for the prophylaxis of graft rejection following organ transplantation.

41. The pharmaceutical composition of claim 23 wherein the immunosuppressant is Tacrolimus, cyclosporin or methotrexate.

42. A method of preventing or treating autoimmune diseases in mammals which comprises administering to the mammals a therapeutically effective amount of a pharmaceutical composition of claim 23.

43. The method of claim 42, wherein autoimmune diseases is systemic lupus erythematosus, chronic hepatitis, interstitial liver diseases, asthma, psoriasis, ulcerative colitis, Crohn disease, regional ileitis or multiple sclerosis.

44. A method of preventing graft rejection following organ transplantation in mammals which comprises administering to the mammals a therapeutically effective amount of a pharmaceutical composition of claim 23.

45. Use of a pharmaceutical composition of claim 23 for the manufacture of a medicament to be used as an immunosuppressant.

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