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NOTICE OF ENTITLEMENT

I/We OTSUKA PHARMACEUTICAL FACTORY, INC.

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JAPAN

being the applicant(s) and nominated person(s) in respect of an application for a patent for an invention entitled PHOSPHONIC DIESTER DERIVATIVES (Application No. 68558/94), state the following:

1. The nominated person(s) has/have, for the following reasons, gained entitlement from the actual inventor(s):

THE NOMINATED PERSON IS THE ASSIGNEE OF
THE ACTUAL INVENTORS.

2. The nominated person(s) has/have, for the following reasons, gained entitlement from the applicant(s) listed in the declaration under Article 8 of the PCT:

THE APPLICANT AND NOMINATED PERSON IS THE
BASIC APPLICANT.

3. The basic application(s) listed in the declaration under Article 8 of the PCT is/are the first application(s) made in a Convention country in respect of the invention.

DATED: 14 February 1995

OTSUKA PHARMACEUTICAL FACTORY, INC.

GRIFFITH HACK & CO.



Patent Attorney for and
on behalf of the applicant

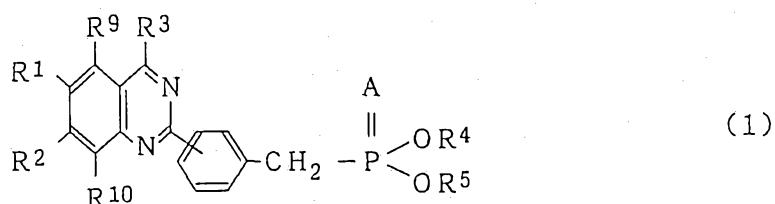


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- (57) Claim

1. A phosphonic diester derivative of the formula:



wherein A represents an oxygen atom or a sulfur atom; R^1 , R^2 , R^9 and R^{10} are the same or different and they each represent a hydrogen atom, a lower alkoxy group, a nitro group, a lower alkyl group, a halogen-substituted lower alkyl group or a halogen atom; R^3 represents a phenyl group or $-B-R^6$ (wherein B represents an oxygen atom or a sulfur atom and R^6 represents a hydrogen atom, a lower alkyl group, a cycloalkyl group, a phenyl group, a phenyl(lower)alkyl group optionally having a halogen atom as a substituent on the phenyl ring, a phenoxy(lower)alkyl group, a lower alkoxycarbonyl(lower)alkyl group, a

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carboxy(lower)alkyl group or a lower alkenyl group) or $-NR^7R^8$ (wherein R^7 and R^8 are the same or different and they each represent a hydrogen atom, a lower alkyl group, an amino group or a cycloalkyl group or combinedly represent a lower alkylene group); and R^4 and R^5 are the same or different and they each represent a hydrogen atom or a lower alkyl group.

7. An antihyperlipidemic composition comprising the phosphonic diester derivative claimed in any one of the claims 1 through 6 as an active ingredient.

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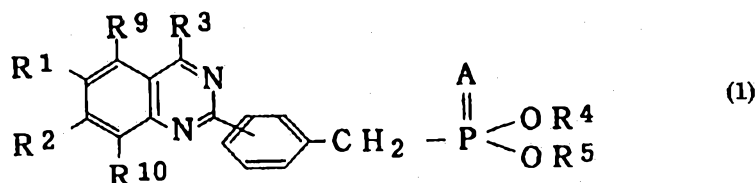


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(21) 国際出願番号 PCT/JP94/00883 (22) 国際出願日 1994年5月31日(31. 05. 94) (30) 優先権データ 特願平5/146528 1993年6月17日(17. 06. 93) JP (71) 出願人(米国を除くすべての指定国について) 株式会社 大塚製薬工場 (OTSUKA PHARMACEUTICAL FACTORY, INC.)(JP/JP) 〒772 徳島県鳴門市撫養町立岩字芥原115 Tokushima, (JP) (72) 発明者; および (75) 発明者/出願人(米国についてのみ) 黒木保久(KUROGI, Yasuhisa)(JP/JP) 〒772 徳島県鳴門市撫養町立岩字五枚189-5 ヴィラセゾン205 Tokushima, (JP) 宮田一義(MIYATA, Kazuyoshi)(JP/JP) 〒772 徳島県鳴門市撫養町齊田字浜端南58-1 ライトビル302 Tokushima, (JP) 中村静夫(NAKAMURA, Shizuo)(JP/JP) 〒772 徳島県鳴門市大津町吉永71-13 Tokushima, (JP) 近藤光由(KONDO, Mitsuyoshi)(JP/JP) 〒772 徳島県鳴門市撫養町南浜字東浜527-1 ダイアパレス鳴門602 Tokushima, (JP) 岩本武史(IWAMOTO, Takeshi)(JP/JP) 〒773 徳島県小松島市田浦町近里83-1 ケントパレス徳島南606 Tokushima, (JP)	奈波智恵子(NABA, Chieko)(JP/JP) 〒772 徳島県鳴門市撫養町南浜字蛸子前東4の4 Tokushima, (JP) 津田可彦(TSUDA, Yoshihiko)(JP/JP) 〒772 徳島県鳴門市撫養町小桑島字前浜127 Tokushima, (JP) 井上泰秀(INOUE, Yasuhide)(JP/JP) 〒772 徳島県鳴門市撫養町弁財天字ハマ11-54 Tokushima, (JP) 金矢 淳(KANAYA, Jun)(JP/JP) 〒771-02 徳島県板野郡北島町中村字東開22-7 Tokushima, (JP) 佐藤圭吾(SATO, Keigo)(JP/JP) 〒771-02 徳島県板野郡松茂町満徳字満徳開拓96-1 Tokushima, (JP) (74) 代理人 弁理士 三枝英二, 外(SAEGUSA, Eiji et al.) 〒541 大阪府大阪市中央区道修町1-7-1 北浜TNKビル Osaka, (JP) (81) 指定国 AU, CA, CN, JP, KR, US, 欧州特許(AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). 添付公開書類 国際調査報告書	

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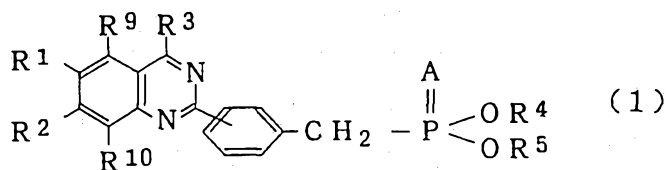
(54) 発明の名称 ホスホン酸ジエステル誘導体



(57) Abstract

A phosphonic diester derivative represented by general formula (1) and useful as remedies for hyperlipidemia, hypertension, diabetes, and so forth. In said formula, A represents oxygen or sulfur; R¹, R², R⁹ and R¹⁰ represent each independently hydrogen, lower alkoxy, nitro, lower alkyl, halogenated lower alkyl or halogen; R³ represents phenyl, -B-R⁶ (wherein B represents oxygen or sulfur; and R⁶ represents hydrogen, lower alkyl, cycloalkyl, phenyl, phenylated lower alkyl wherein the phenyl may be halogenated, phenoxyated lower alkyl, lower-alkoxy carbonyl-substituted lower alkyl, carboxylated lower alkyl or lower alkenyl) or -NR⁷R⁸ (wherein R⁷ and R⁸ represent each independently hydrogen, lower alkyl, amino or cycloalkyl, or R⁷ and R⁸ are combined together to form lower alkylene); and R⁴ and R⁵ represent each independently hydrogen or lower alkyl.

(57) 要約 本発明は、一般式



[式中、Aは酸素原子又は硫黄原子を、 R^1 、 R^2 、 R^9 及び R^{10} は同一又は異なって水素原子、低級アルコキシ基、ニトロ基、低級アルキル基、ハロゲン置換低級アルキル基又はハロゲン原子を、 R^3 はフェニル基、基-B- R^6 （式中、Bは酸素原子又は硫黄原子を、 R^6 は水素原子、低級アルキル基、シクロアルキル基、フェニル基、フェニル環上に置換基としてハロゲン原子を有することのあるフェニル低級アルキル基、フェノキシ低級アルキル基、低級アルコキシカルボニル低級アルキル基、カルボキシ低級アルキル基又は低級アルケニル基を表わす）又は基-N R^7 - R^8 （式中、 R^7 及び R^8 は同一又は異なって水素原子、低級アルキル基、アミノ基又はシクロアルキル基を示すか、或は互いに結合して低級アルキレン基を形成する）を、 R^4 及び R^5 は同一又は異なって水素原子又は低級アルキル基をそれぞれ示す。]

で表わされるホスホン酸ジエステル誘導体を提供する。

本発明誘導体は、高脂質血症治療剤、高血圧治療剤、糖尿病治療剤等として有用である。

情報としての用途のみ

PCTに基づいて公開される国際出願のハンフレッツ第1頁にPCT加盟国を同定するために使用されるコード

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PHOSPHONIC DIESTER DERIVATIVES

TECHNICAL FIELD

The present invention relates to novel phosphonic diester derivatives.

5

PRIOR ART

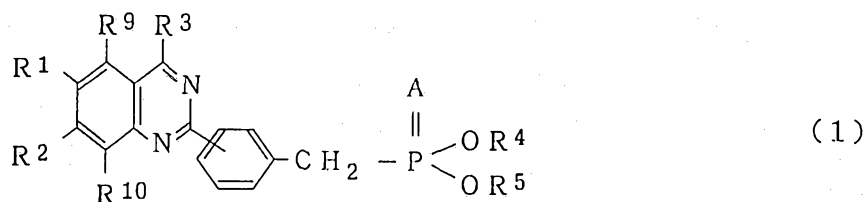
The phosphonic diester derivatives of the invention are novel compounds not heretofore described in the literature.

The object of the invention is to provide compounds of value as medicines as will be described hereinafter.

10

DISCLOSURE OF THE INVENTION

The present invention provides a phosphonic diester derivative of the following general formula (1):



wherein A represents an oxygen atom or a sulfur atom; R^1 , R^2 , R^9 and R^{10} are the same or different and they each represent a hydrogen atom, a lower alkoxy group, a nitro group, a lower alkyl group, a halogen-substituted lower alkyl group or a halogen atom; R^3 represents a phenyl group, $-B-R^6$ (wherein B represents an oxygen atom or a sulfur atom and R^6 represents a hydrogen atom, a lower alkyl group, a cycloalkyl group, a phenyl group, a

15

20



phenyl(lower)alkyl group optionally having a halogen atom as a substituent on the phenyl ring, a phenoxy(lower)alkyl group, a lower alkoxy carbonyl(lower)alkyl group, a carboxy(lower)alkyl group or a lower alkenyl group) or
5 -NR⁷R⁸ (wherein R⁷ and R⁸ are the same or different and they each represent a hydrogen atom, a lower alkyl group, an amino group or a cycloalkyl group or combinedly represent a lower alkylene group); and R⁴ and R⁵ are the same or different and they each represent a hydrogen atom
10 or a lower alkyl group.

Each of the groups relevant to the above general formula (1) includes the following exemplary species.

The lower alkyl group includes straight- or branched-chain lower alkyl groups such as methyl, ethyl, propyl,
15 isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl and so on.

The cycloalkyl group includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and so on.

20 The lower alkoxy group includes methoxy, ethoxy, propoxy, butoxy, pentyloxy, hexyloxy and so on.

The phenyl(lower)alkyl group optionally having a halogen atom as a substituent on the phenyl ring includes benzyl, α -phenethyl, β -phenethyl, 3-phenylpropyl, 4-
25 phenylbutyl, 5-phenylpentyl, 6-phenylhexyl, 2-bromobenzyl,



2-fluorobenzyl, 2-chlorobenzyl, 2-iodobenzyl, 3-
bromobenzyl, 3-fluorobenzyl, 3-chlorobenzyl, 3-iodobenzyl,
4-bromobenzyl, 4-fluorobenzyl, 4-chlorobenzyl, 4-
iodobenzyl, 4-bromo-3-fluorobenzyl, 4-bromo-2-
5 fluorobenzyl, 3-bromo-4-fluorobenzyl, 2-bromo-4-
fluorobenzyl, 4-bromo-3-chlorobenzyl, 4-bromo-2-
chlorobenzyl, 3-bromo-4-chlorobenzyl, 2-bromo-4-
chlorobenzyl, 4-bromo-3-iodobenzyl, 4-bromo-2-iodobenzyl,
3-bromo-4-iodobenzyl, 2-bromo-4-iodobenzyl, 4-bromo-3-
10 fluoro- α -phenetyl, 4-bromo-3-fluoro- β -phenetyl, 3-(4-
bromo-3-fluorophenyl)propyl, 4-(4-bromo-2-
fluorophenyl)butyl, 5-(4-bromo-3-fluorophenyl)pentyl, 6-
(4-bromo-2-fluorophenyl)hexyl and so on.

The phenoxy(lower)alkyl group includes phenoxymethyl,
15 2-phenoxyethyl, 3-phenoxypropyl, 4-phenoxybutyl, 5-
phenoxypropyl, 6-phenoxyhexyl and so on.

The lower alkylene group includes methylene,
ethylene, trimethylene, tetramethylene, pentamethylene,
hexamethylene and so on.

20 The halogen-substituted lower alkyl group includes
chloromethyl, bromomethyl, fluoromethyl, iodomethyl,
dichloromethyl, dibromomethyl, difluoromethyl,
diiodomethyl, trichloromethyl, tribromomethyl,
trifluoromethyl, triiodomethyl, 2,2-difluoroethyl, 2,2,2-
25 trifluoroethyl, 3-bromopropyl, 4,4-dichlorobutyl, 5,5,5-



trifluoropentyl, 6-iodohexyl and so on.

The lower alkoxy carbonyl(lower)alkyl group includes methoxycarbonylmethyl, ethoxycarbonylmethyl, propoxycarbonylmethyl, butoxycarbonylmethyl,

5 pentyloxycarbonylmethyl, hexyloxycarbonylmethyl, 1-(methoxycarbonyl)ethyl, 2-(methoxycarbonyl)ethyl, 3-(methoxycarbonyl)propyl, 4-(methoxycarbonyl)butyl, 5-(methoxycarbonyl)pentyl, 6-(methoxycarbonyl)hexyl, 1-(ethoxycarbonyl)ethyl, 2-(ethoxycarbonyl)ethyl, 3-
10 (ethoxycarbonyl)propyl, 4-(ethoxycarbonyl)butyl, 5-(ethoxycarbonyl)pentyl, 6-(ethoxycarbonyl)hexyl and so on.

The carboxy(lower)alkyl group includes carboxymethyl, 1-carboxyethyl, 2-carboxyethyl, 1-carboxypropyl, 2-carboxypropyl, 3-carboxypropyl, 1-carboxybutyl, 2-
15 carboxybutyl, 3-carboxybutyl, 4-carboxybutyl, carboxy-t-butyl, 4-carboxypentyl, 5-carboxypentyl, 6-carboxyhexyl and so on.

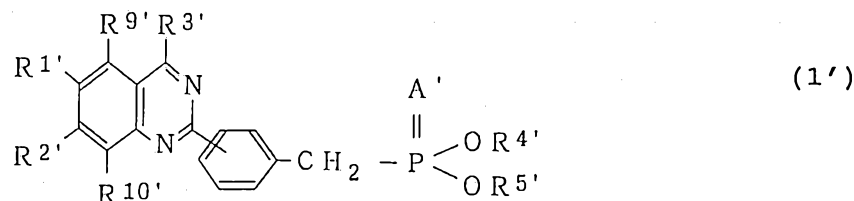
The lower alkenyl group includes ethenyl, 1-propenyl, 2-propenyl, 2-methyl-2-propenyl, 1-butenyl, 2-butenyl, 3-
20 butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl and so on.

The halogen atom includes fluorine, chlorine, bromine and iodine.

25 Among the phosphonic diester derivatives of the



formula (1) according to the present invention, those of the following formula (1') are suitable.



- 5 wherein A' represents an oxygen atom or a sulfur atom; R^{1'} represents a hydrogen atom, a lower alkoxy group, a nitro group or a halogen atom; R^{2'} represents a hydrogen atom, a lower alkoxy group, a lower alkyl group, a halogen-substituted lower alkyl group or a halogen atom; R^{3'}
- 10 represents a phenyl group, -O-R⁶ (wherein R⁶ is as defined in the formula (1)), -S-R^{6'} (wherein R^{6'} represents a hydrogen atom, a lower alkyl group or a phenyl group) or -NR⁷R⁸ (wherein R⁷ and R⁸ are as defined in the formula (1)); R^{4'} represents a lower alkyl group; R^{5'} represents a
- 15 hydrogen atom or a lower alkyl group; R^{9'} represents a hydrogen atom or a halogen atom; and R^{10'} represents a hydrogen atom or a lower alkoxy group.

20 The phosphonic diester derivative of the formula (1) according to the invention has excellent hypolipidemic, vasodepressor and hypoglycemic activities and is useful as therapeutic agents for hyperlipidemic diseases, hypertension, diabetes or the like. More specifically, the derivative can treat or prevent various types of



diseases (hyperlipidemic diseases) such as hypercholesterolemia, hypertriglyceridemia, hyperphospholipidemia and hyper-free fatty acidemia, hypertension and diabetes.

5 Examples of preferable derivatives of the present invention as the active ingredient of therapeutic agents for hyperlipidemic diseases, etc. are those of the formula (1') wherein $R^{1'}$ and $R^{2'}$ each represent a lower alkoxy group; $R^{3'}$ represents $-O-R^6$ (wherein R^6 is as defined
10 above); A' represents an oxygen atom; and $R^{4'}$ and $R^{5'}$ each represent a lower alkyl group.

 Examples of such derivatives also include those of the formula (1') wherein $R^{9'}$ and $R^{10'}$ each represent a hydrogen atom; and $R^{3'}$ represents a hydroxy group, a lower
15 alkoxy group, a phenyl(lower)alkoxy group or a lower alkenyloxy group.

 Specific examples of these preferred derivatives of the invention include the following compounds (1)-(6). Among them the most preferred derivatives of the invention
20 are compounds (3) and (4), which produce excellent pharmacological effects.

- (1) Diethyl 4-(4-hydroxy-6,7-dimethoxyquinazolin-2-yl)benzylphosphonate,
(2) diisopropyl 4-(4-hydroxy-6,7-dimethoxyquinazolin-2-yl)benzylphosphonate,
25



(3) diethyl 4-(4,6,7-trimethoxyquinazolin-2-yl)benzylphosphonate,

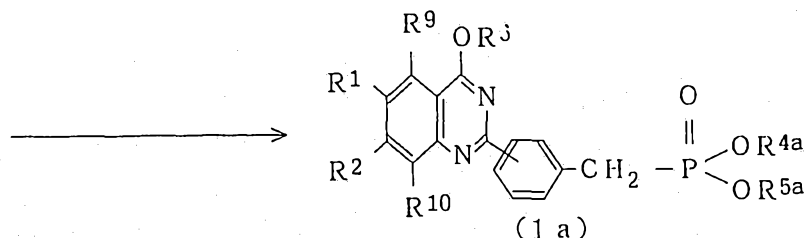
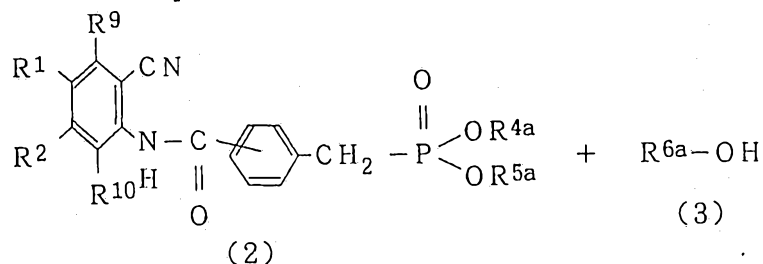
(4) diisopropyl 4-(4,6,7-trimethoxyquinazolin-2-yl)benzylphosphonate,

5 (5) diethyl 4-(4-benzyloxy-6,7-dimethoxyquinazolin-2-yl)benzylphosphonate, and

(6) diethyl 4-(4-allyloxy-6,7-dimethoxyquinazolin-2-yl)benzylphosphonate.

10 The phosphonic diester derivative of the formula (1) according to the invention can be produced by several different processes. Some exemplary processes are schematically shown hereunder.

[Reaction Schema-1]



15 wherein R^1 , R^2 , R^6 , R^9 and R^{10} are as defined above; R^{6a} represents a lower alkyl group, a cycloalkyl group, a phenyl group, a phenyl(lower)alkyl group optionally having



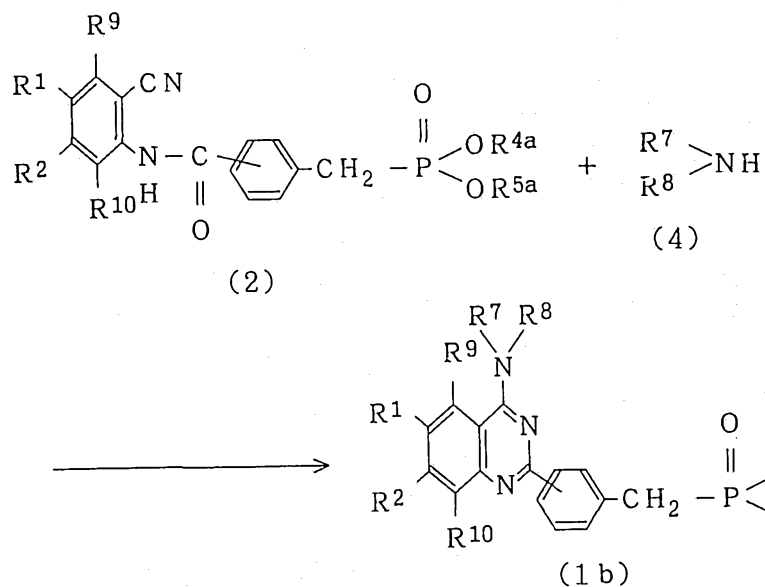
a halogen atom as a substituent on the phenyl ring, a phenoxy(lower)alkyl group or a lower alkenyl group; and R^{4a} and R^{5a} are the same or different and they each represent a lower alkyl group.

5 According to the process shown in Reaction Schema-1, the compound (1a) of the invention can be prepared by reacting the compound (2) with the alcohol (3) in the presence of an acid catalyst such as p-toluenesulfonic acid, benzenesulfonic acid, ammonium chloride and
10 camporsulfonic acid, without using a solvent or in an inert solvent such as benzene, tetrahydrofuran (THF) and toluene. The alcohol (3) is generally used in an equimolar to large excess proportion relative to the compound (2). The amount of the acid catalyst is
15 generally about 0.3 to 1 mole per mole of the compound (2). The reaction can be carried out at room temperature to the reflux temperature of the solvent for about 1-20 hours.

20 The compound (1a) might be obtained as a mixture of the compound of the formula (1a) wherein $R^6 = H$ and the compound of the formula (1a) wherein $R^6 = R^{6a} (\neq H)$. The compounds can be easily isolated by conventional separation and purification procedures as will be described later.



[Reaction Schema-2]

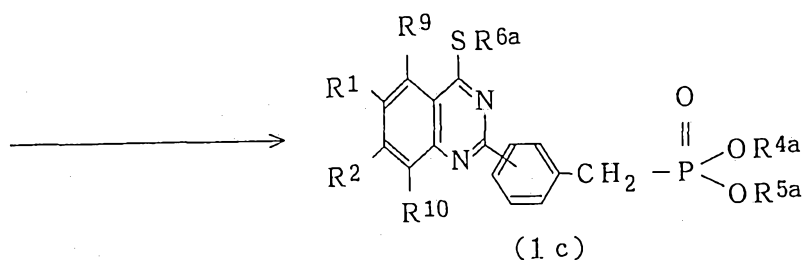
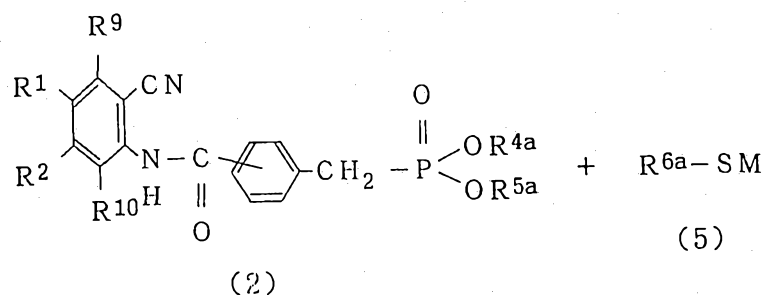


wherein R^1 , R^2 , R^{4a} , R^{5a} , R^7 , R^8 , R^9 and R^{10} are as defined above.

According to the process shown in Reaction Schema-2,
 5 the compound (1b) of the invention can be prepared by reacting the compound (2) with an amine (4) without using a solvent or in an inert solvent such as benzene, xylene, THF, 1,4-dioxane and toluene. The amine (4) is preferably used in an equimolar to small excess proportion relative
 10 to the compound (2). As the amine (4), a 40-70% aqueous amine solution can be also used. The reaction is carried out at room temperature to the reflux temperature of the solvent for about 1-20 hours.



[Reaction Schema-3]



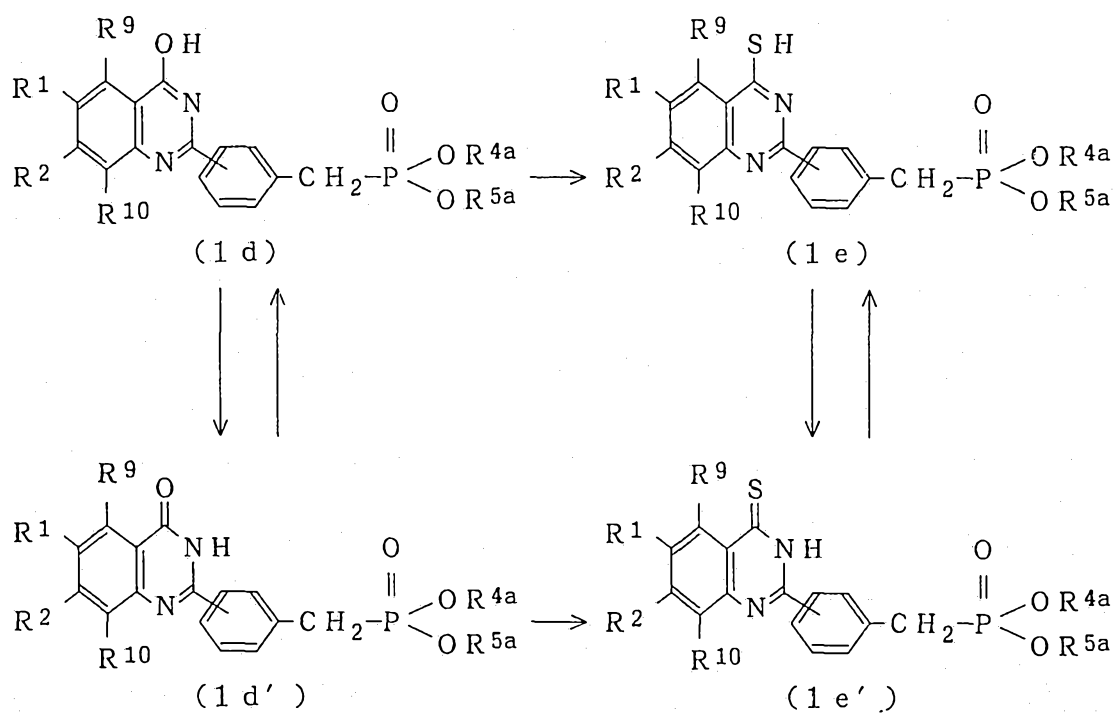
wherein R^1 , R^2 , R^{4a} , R^{5a} , R^{6a} , R^9 and R^{10} are as defined above; and M represents a hydrogen atom or an alkali metal atom.

5 As shown in Reaction Schema-3, the compound (2) can be converted to the compound (1c) of the invention by reacting the compound (2) with a thiol (5) in the presence of an alkali such as sodium hydroxide, potassium hydroxide and sodium hydride in an inert solvent such as benzene,
 10 xylene, THF, 1,4-dioxane and toluene. The thiol (5) is preferably used in an equimolar to excess proportion relative to the compound (2). The alkali is preferably used in an equimolar to small excess proportion relative to the compound (2). In this reaction, as the thiol (5),
 15 a 1-30% aqueous alkali metal salt solution can be also

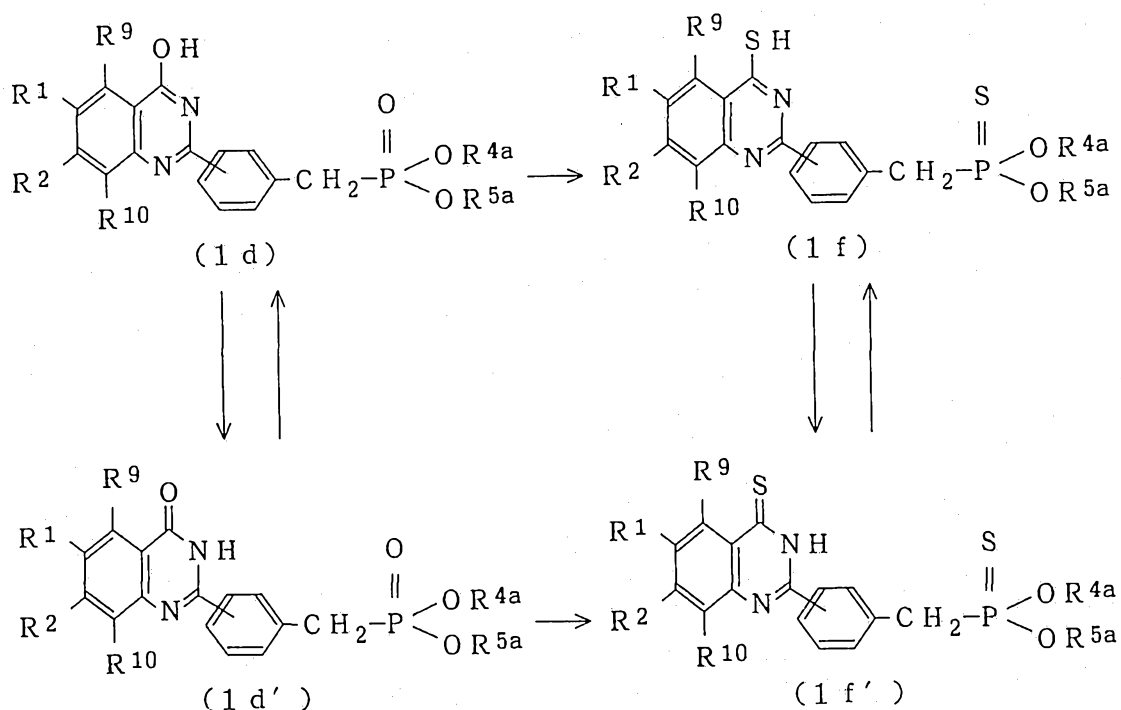


used. The reaction is carried out at room temperature to the reflux temperature of the solvent for about 1-30 hours.

[Reaction Schema-4]



[Reaction Schema-4']



wherein R^1 , R^2 , R^{4a} , R^{5a} , R^9 and R^{10} are as defined above.

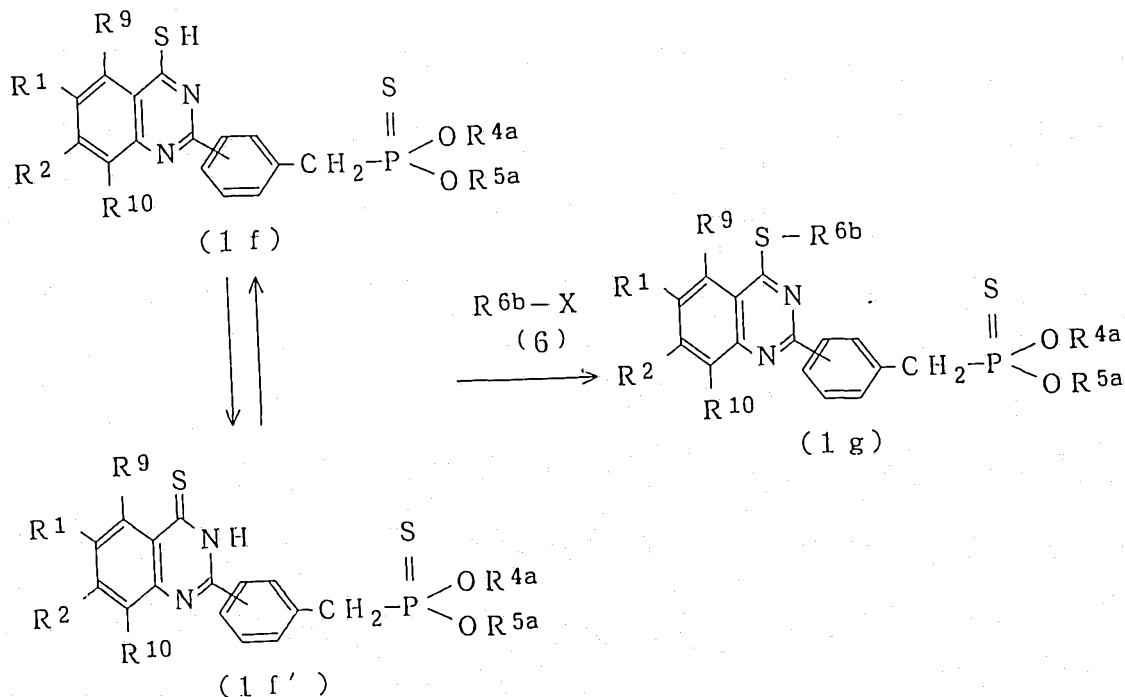
As shown in Reaction Schema-4, the compound (1d) of the invention can be converted to the compound (1e) by treating the compound (1d) with a sulfur-containing reagent such as Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphethane-2,4-disulfide] and diphosphorus pentasulfide. The reaction is carried out using about one equivalent of the sulfur-containing reagent relative to the compound (1d) in an inert solvent such as benzene, toluene, xylene and acetonitrile at the reflux temperature of the solvent for

about 5-30 hours.

As shown in Reaction Schema-4', the compound (1d) of the invention can be converted to the compound (1f) by treating the compound (1d) with at least two equivalents of the sulfur-containing reagent. The reaction solvent and reaction conditions are similar to those used in the reaction of Reaction Schema-4.

The compounds (1d), (1e) and (1f) in the Reaction Schemata-4 and -4' may exist as tautomers (1d'), (1e') and (1f'), which, of course, are subsumed in the concept of the compound of the invention.

[Reaction Schema-5]



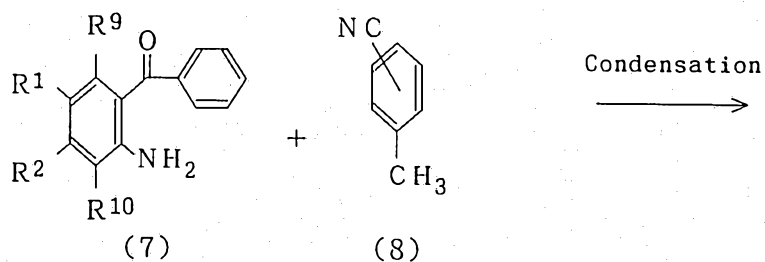
wherein R^1 , R^2 , R^{4a} , R^{5a} , R^9 and R^{10} are as defined above;

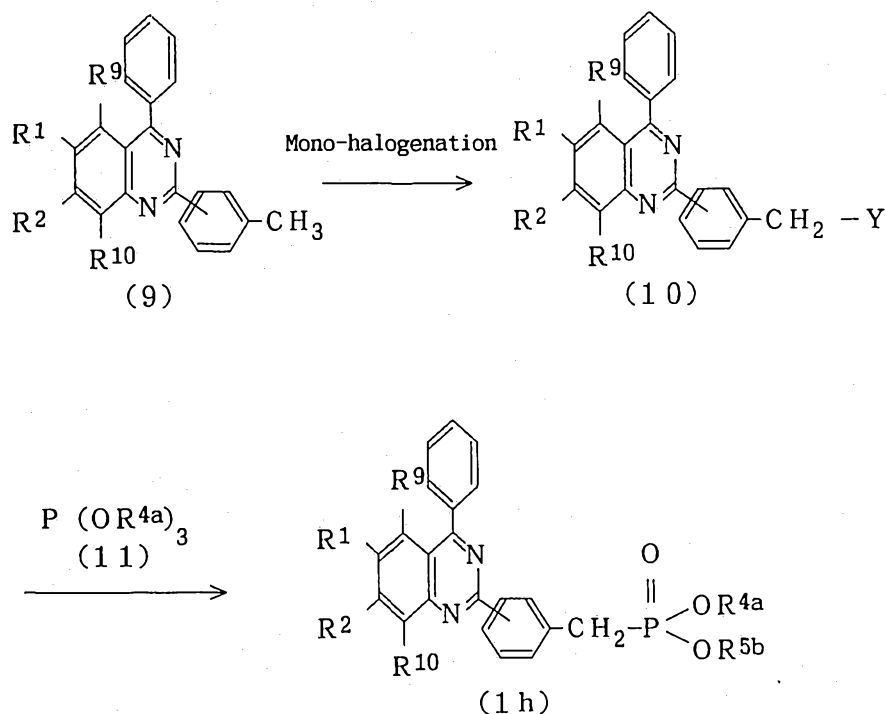


and R^{6b} represents a lower alkyl group, a cycloalkyl group, a phenyl(lower)alkyl group optionally having a halogen atom as a substituent on the phenyl ring, a lower alkoxy carbonyl(lower)alkyl group, a carboxy(lower)alkyl group or a lower alkenyl group; and X represents a halogen atom.

As shown in Reaction Schema-5, the compounds (1f) and (1f') can be converted to the compound (1g) of the invention by reacting the compound (1f) or (1f') with the compound (6) in the presence of a base such as pyridine, collidine, lutidine, triethylamine and N,N-diethylaniline in an inert solvent such as benzene, toluene, xylene, THF and 1,4-dioxane. The compound (6) is preferably used in an equimolar to small excess proportion relative to the compound (1f). The reaction is carried out at room temperature to the reflux temperature of the solvent for about 1-20 hours.

[Reaction Schema-6]





wherein R¹, R², R^{4a}, R⁹ and R¹⁰ are as defined above; R^{5b} is the same as R^{4a}; and Y represents a halogen atom.

In Reaction Schema-6, the condensation reaction of 2-aminobenzophenone derivative (7) and benzonitrile derivative (8) is carried out in the presence of a strong base such as sodium hydride, potassium hydride and sodium amide in an inert solvent such as THF, 1,2-dimethoxyethane, and N,N-dimethylformamide (DMF) at room temperature to the reflux temperature of the solvent for about 0.5-5 hours. The benzonitrile derivative (8) is preferably used in an approximately equimolar proportion relative to the 2-aminobenzophenone derivative (7). The



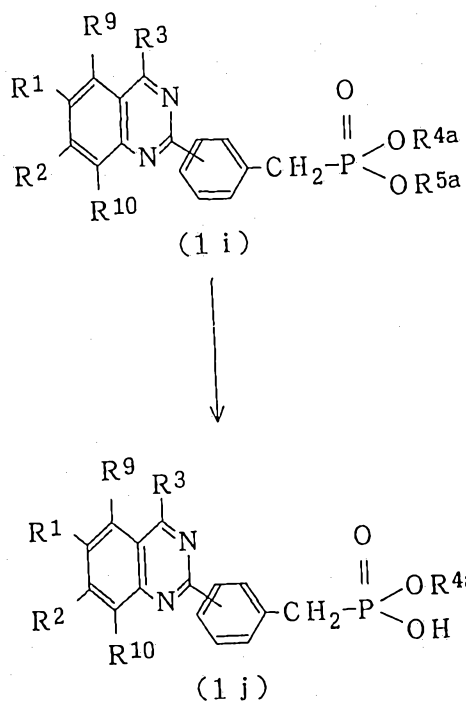
strong base is preferably used in an equimolar to small excess proportion relative to the 2-aminobenzophenone derivative (7).

5 The monohalogenation reaction of the compound (9) can be carried out using a halogenating agent such as N-bromo-succinimide (NBS), N-chloro-succinimide (NCS) and bromine in the presence of a catalyst such as benzoyl peroxide, α,α' -azobisisobutyronitrile (AIBN) in an inert solvent such as benzene and carbon tetrachloride. The amount of
10 the halogenating agent is generally one equivalent to small excess relative to the compound (9). The reaction is carried out at about 50°C to the reflux temperature of the solvent for 2-20 hours.

The objective compound (1h) can be obtained by
15 reacting the resultant monohalide (10) with the trialkyl phosphite (11). The reaction is preferably carried out without using any solvent, though it can be done in an inert solvent, e.g. lower alcohols such as methanol and ethanol, aromatic hydrocarbons such as benzene, toluene
20 and xylene, and DMF. The trialkyl phosphite (11) is used in an approximately equimolar proportion to five moles per mole of the monohalide (10). The reaction is generally carried out at 100-180°C for about 0.5-3 hours, of which condition varies depending on the monohalide (10).



[Reaction Schema-7]



wherein R^1 , R^2 , R^3 , R^{4a} , R^{5a} , R^9 and R^{10} are as defined above.

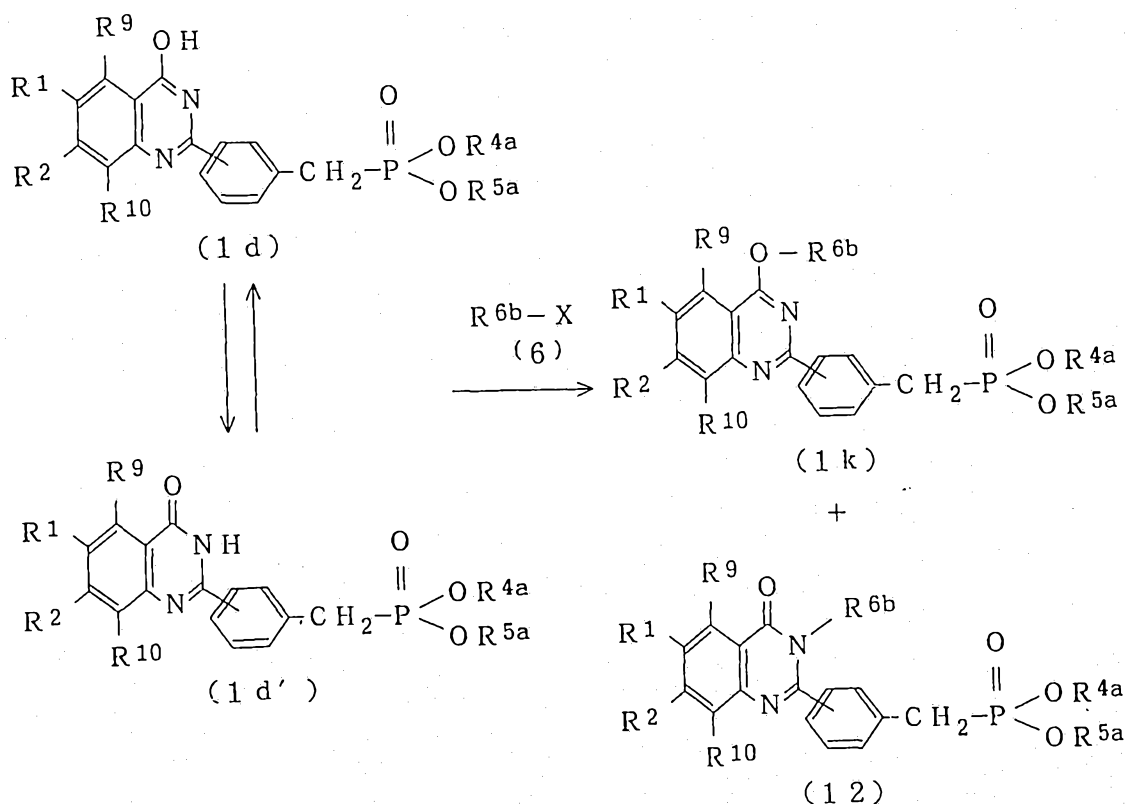
According to the process shown in Reaction Schema-7,
 5 the objective partially hydrolysed compound (1j) can be obtained by reacting the compound (1i) with a lithium halide such as lithium bromide, lithium chloride and lithium iodide and subsequently treating the reaction mixture with an aqueous solution of mineral acid such as
 10 hydrochloric acid and sulfuric acid. The reaction is carried out using a lithium halide in an amount of at



least five moles per mole of the compound (1i) in an inert solvent such as acetonitrile and DMF at room temperature to the reflux temperature of the solvent for 5-24 hours.

5 The starting compound (2) in the reaction schemata-1 to -3 can be prepared, for example, by the process described in Japanese Unexamined Patent Publication No. 151199/1986.

[Reaction Schema-8]



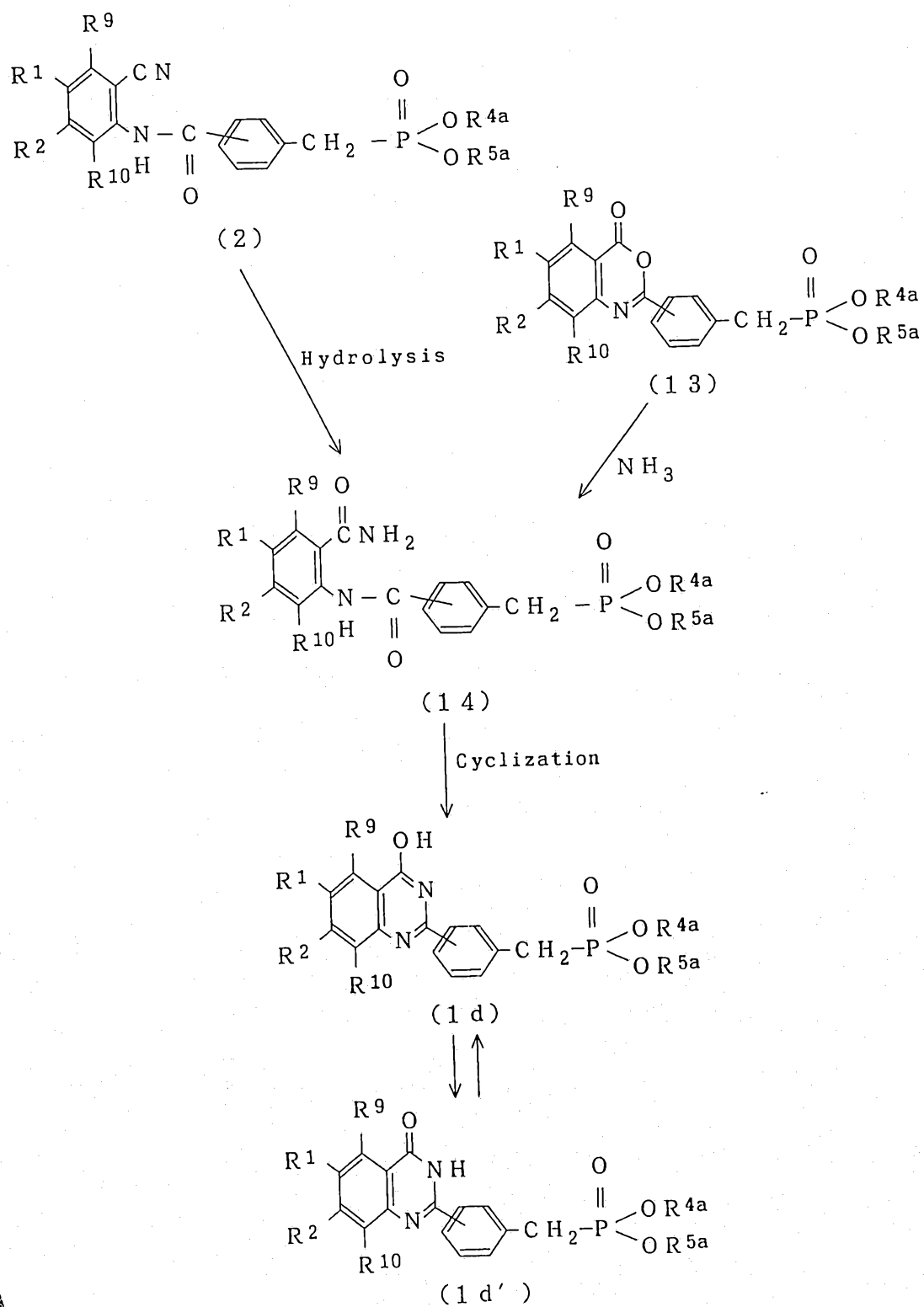
10 wherein R^1 , R^2 , R^{4a} , R^{5a} , R^{6b} , R^9 , R^{10} and X are as defined above.



As shown in Reaction Schema-8, the compounds (1d) and (1d') can be converted to the compound (1k) of the invention by reacting the compound (1d) or (1d') with the compound (6) in the presence of a base such as metal sodium, metal potassium, potassium t-butoxide, sodium methoxide and sodium ethoxide in an inert solvent such as methanol and propanol. The compound (6) is preferably used in an equimolar to small excess proportion relative to the starting compound. The amount of the base is preferably about one equivalent relative to the starting compound. The reaction is carried out at room temperature to the reflux temperature of the solvent for about 1-24 hours. The compound (12) is obtained as a by-product in some cases.



[Reaction Schema-9]



wherein R^1 , R^2 , R^{4a} , R^{5a} , R^9 and R^{10} are as defined above.

The compounds (1d) and (1d') can be obtained by the process shown in the reaction schema as well. More specifically, the objective compound can be obtained by
5 either hydrolysing the compound (2) or treating the compound (13) with ammonia, and subjecting the resultant compound (14) to cyclization reaction.

The hydrolysis reaction of the compound (2) is carried out in the presence of a base catalyst such as
10 sodium hydroxide and potassium hydroxide using an about 10-30% aqueous hydrogen peroxide solution without using a solvent or in an inert solvent such as THF, methanol and 1,4-dioxane. The hydrogen peroxide is generally used in an equimolar proportion to about ten moles per mole of the
15 compound (2). The base catalyst is generally used in an equimolar to small excess proportion relative to the compound (2). The reaction is carried out at room temperature to the reflux temperature of the solvent for about 2-20 hours.

20 On the other hand, the conversion of the compound (13) to the compound (14) by the treatment with ammonia can be carried out by allowing the compound (13) and an excess amount of aqueous ammonia to stand in an inert solvent such as methanol, ethanol and THF at 0°C to room
25 temperature for about 0.5-10 hours.



The cyclization reaction of the compound (14) obtained by one of the above reactions can be carried out using about 1-6 N aqueous alkali solution such as sodium hydroxide and potassium hydroxide in an inert solvent such as lower alcohols and 1,4-dioxane. The aqueous alkali solution is preferably used in an equimolar to small excess proportion relative to the compound (14). The reaction is carried out at room temperature to the reflux temperature of the solvent for about 1-10 hours.

The compound (13) in the above reaction can be prepared, for example, by the process described in Japanese Unexamined Patent Publication No. 9670/1994.

The objective compound in each of the above processes can be easily isolated and purified by conventional separation procedures. Such procedures include adsorption chromatography, preparative thin-layer chromatography, recrystallization, solvent extraction and so on.

Using suitable pharmaceutically acceptable carriers, the compound of the invention is made into pharmaceutical compositions for use. Useful pharmaceutically acceptable carriers include various conventional diluents or excipients such as fillers, volume builders, binders, humectants, disintegrators, surfactants, lubricants, etc. and are selectively employed according to the desired unit dosage form.



The above pharmaceutical composition can be provided in a variety of unit dosage forms according to the intended medical treatment. Typical examples are tablets, pills, powders, solutions, suspensions, emulsions, 5 granules, capsules, suppositories, injections (solutions, suspensions, etc.) and eye-drops.

The molding of tablets can be made using, as said pharmaceutically acceptable carriers, an excipient such as lactose, sucrose, sodium chloride, glucose, urea, starch, 10 calcium carbonate, kaolin, crystalline cellulose, silicic acid, potassium phosphate, etc., a binder such as water, ethanol, propanol, simple syrup, glucose syrup, starch solution, gelatin solution, carboxymethyl cellulose, hydroxypropyl cellulose, methylcellulose, 15 polyvinylpyrrolidone, etc., a disintegrator such as carboxymethyl cellulose sodium, carboxymethyl cellulose calcium, low-substituted hydroxypropyl cellulose, dry starch, sodium alginate, agar powder, laminaran powder, sodium hydrogen carbonate, calcium carbonate, etc., a 20 surfactant such as polyoxyethylene sorbitan fatty acid ester, sodium lauryl sulfate, stearyl monoglyceride, etc., a disintegration inhibitor such as sucrose, stearin, cacao butter, hydrogenated oil, etc., an absorption promoter such as quaternary ammonium bases, sodium lauryl sulfate, 25 etc., a humectant such as glycerin, starch, etc., an



adsorbent such as starch, lactose, kaolin, bentonite, colloidal silica, etc., and a lubricant such as purified talc, salts of stearic acid, boric acid powder, polyethylene glycol and so on. Furthermore, such tablets
5 can be coated, if necessary, to provide sugar-coated tablets, gelatin-coated tablets, enteric tablets, film-coated tablets, etc. or be processed into double-layer or multiple-layer tablets.

10 In the manufacture of pills, various excipients such as glucose, lactose, starch, cacao butter, hydrogenated vegetable oil, kaolin, talc, etc., binders such as gum arabic powder, tragacanth powder, gelatin, ethanol, etc. and disintegrators such as laminaran, starch, etc. can be employed as the pharmaceutically acceptable carrier.

15 The suppositories can be manufactured using polyethylene glycol, cacao butter, higher alcohols or their esters, gelatin, semisynthetic glycerides, etc. as the carrier.

20 The capsules can be manufactured in the conventional manner by blending the compound of the invention with any of the various pharmaceutically acceptable carriers mentioned above and filling the resulting composition into hard gelatin capsule shells, soft capsule shells or the like.

25 When the compound of the invention is to be provided



in an injectable form such as a solution, emulsion or suspension, the preparation is preferably sterilized and rendered isotonic with respect to the blood. As the diluent for use in such a preparation, water, ethyl
5 alcohol, macrogol, propylene glycol, ethoxylated isostearyl alcohol, polyoxy-isostearyl alcohol, polyoxyethylene sorbitan fatty acid ester, etc. can be employed. In this operation, a sufficient amount of sodium chloride, glucose or glycerin may be added to the
10 composition to provide an isotonic solution. Conventional solubilizers, buffers, local anesthetics, etc. can be also added.

The eye-drops can be manufactured in the conventional manner using sterile distilled water as the vehicle,
15 sodium dihydrogen phosphate and/or sodium monohydrogen phosphate, for instance, as the buffer, sodium chloride or the like as the isotonizing agent, and benzalkonium chloride, chlorobutanol or the like as the antimicrobial agent.

20 Further, coloring agents, preservatives, perfumes, flavors, sweeteners, or other pharmacologically active substances can be optionally incorporated in the compositions in the various dosage forms mentioned above.

There is no particular limitation on the
25 administration method for the pharmaceutical composition



of the invention. Thus, the proper method can be determined according to the particular dosage form, patient's age, sex and other characteristics, severity of disease and other conditions. For example, said tablets,
5 pills, solutions, suspensions, emulsions, granules and capsules are administered by the oral route. The injections are administered singly or in admixture with glucose, amino acid or like conventional infusions by the intravenous route or, if necessary, administered singly by
10 the intramuscular, intradermal subcutaneous or intraperitoneal route. The suppositories are administered intrarectally and the eye-drops are instilled into the eyes.

The proportion of the compound of the formula (1) of
15 the invention in the pharmaceutical composition is not critical but can be liberally selected from a broad range. It is generally preferable that the compound accounts for about 1 to 70 weight % of the final composition. The dosing amount of the pharmaceutical composition can be
20 selected according to the selected administration method, patient's age, sex and other characteristics, severity of disease and other conditions. The dosage of the compound of the invention as the active ingredient is preferably about 0.05-100 mg per kg body weight a day and this amount
25 can be administered in 1 to 4 divided doses. In



preparation of eye-drops, the daily dosage of the active ingredient is preferably selected from the range of about 0.3-2 μ g, and the eye-drops are generally applied once a day.

5

BEST MODE FOR PRACTICING THE INVENTION

Preparation examples and pharmacological test examples for the compound of the invention are given below to clarify the invention in further detail.

Example 1

10

Preparation of diethyl 4-(4-methoxyquinazolin-2-yl)benzylphosphonate

(Process 1)

15

A 15.7 g portion of anthranilonitrile was dissolved in 50 ml of pyridine. While the solution was stirred under ice-cooling, a solution of 40.7 g of 4-[(diethoxyphosphoryl)-methyl]benzoyl chloride in 50 ml of dry dichloromethane was added dropwise. The stirring was continued at room temperature for 12 hours, after which the reaction mixture was diluted with 200 ml of

20

dichloromethane and washed with diluted hydrochloric acid. The organic layer was dried over anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure. The residue was recrystallized from chloroform-n-hexane to provide 25.9 g of diethyl 4-[N-(2-cyanophenyl)carbamoyl]benzyl-

25



phosphonate as colorless crystals.

(Process 2)

5 A 3.7 g quantity of the diethyl 4-[N-(2-cyanophenyl)-
carbamoyl]benzylphosphonate crystals obtained in Process 1
and 0.8 g of p-toluenesulfonic acid monohydrate were
suspended in 100 ml of methanol and heated at 70°C with
stirring for 10 hours. After completion of the reaction,
the solvent was distilled off under reduced pressure. The
residue was subjected to silica gel column chromatography
10 (eluent: chloroform) and the resulting crude crystals were
recrystallized from dichloromethane-n-hexane to provide
1.9 g of the objective compound as colorless crystals.
Table 1 shows the structure and physical property (melting
point) of the compound thus obtained.

15 Examples 2-10

The compounds set forth in Table 1 were prepared in
the same manner as in Example 1. Table 1 also shows the
structures and physical properties (melting points) of
these compounds.

20 Examples 11 and 12

Preparation of diisopropyl 4-(6-bromo-4-methoxyquinazolin-
2-yl)benzylphosphonate and diisopropyl 4-(6-bromo-4-
hydroxyquinazolin-2-yl)benzylphosphonate

25 The reaction was carried out in the same manner as in
Example 1 and the crude product was purified by silica gel



column chromatography (eluent: chloroform : methanol = 40:1) and 4-methoxyquinazoline was obtained from the former fraction, and 4-hydroxyquinazoline from the latter fraction. Table 1 also shows the structures and physical properties (melting points) of these compounds.

Examples 13-20

The compounds set forth in Table 1 were prepared in the same manner as in Examples 11 and 12. Table 1 also shows the structures and physical properties (melting points) of these compounds. Table 2 shows the results of ¹H-NMR analysis of some compounds.

Example 21

Preparation of diethyl 4-(4-methylaminoquinazolin-2-yl)benzylphosphonate

A 3.7 g portion of diethyl 4-[N-(2-cyanophenyl)-carbamoyl]benzylphosphonate and 10 ml of a 40% aqueous methylamine solution were dissolved in 50 ml of THF and refluxed with heating at 70°C for 30 hours. After completion of the reaction, the solvent was distilled off under reduced pressure. The residue was subjected to silica gel column chromatography (eluent: chloroform : methanol = 100:1) and the crude crystals obtained were recrystallized from chloroform-n-hexane to provide 1.0 g of the objective compound as colorless crystals. Table 1 also shows the structure and physical property (melting



point) of the compound thus obtained.

Examples 22-35

The compounds set forth in Table 1 were prepared in the same manner as in Example 21. Table 1 also shows the structures and physical properties (melting points) of these compounds. Table 2 shows the results of ^1H -NMR analysis of some compounds.

Example 36

Preparation of diethyl 4-(6-bromo-4-ethylthioquinazolin-2-yl)benzylphosphonate

A 4.5 g portion of diethyl 4-[N-(4-bromo-2-cyanophenyl)carbamoyl]benzylphosphonate (obtained in the same manner as in Process 1 of Example 1), 50 ml of ethanethiol and 0.4 g of sodium hydroxide were added to 50 ml of THF and heated with stirring in nitrogen atmosphere at 60°C for 30 hours. After adding 100 ml of 1N aqueous sodium hydroxide solution, the reaction mixture was extracted with chloroform. The chloroform layer was washed with water, dried over sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (eluent: chloroform) and the crude crystals obtained were recrystallized from chloroform-n-hexane to provide 0.8 g of the objective compound as colorless crystals. Table 1 shows the structure and physical property (melting point)



of the compound.

Examples 37-38

The compounds set forth in Table 1 were prepared in the same manner as in Example 36. Table 1 also shows the structures and physical properties (melting points) of these compounds.

Example 39

Preparation of diethyl 4-(4-phenylquinazolin-2-yl)benzylphosphonate

A 7.9 g portion of 2-aminobenzophenone, 4.7 g of 4-methylbenzonitrile and 2.0 g of 60% sodium hydride were suspended in 40 ml of THF and heated at 60°C with stirring for 2 hours. After completion of the reaction, the reaction mixture was allowed to cool and the precipitate was collected by filtration, thus giving 5.7 g of 2-(4-methylphenyl)-4-phenylquinazoline as a crude product. Then 4.4 g of the compound thus obtained, 2.7 g of NBS and 0.2 g of benzoyl peroxide were suspended in 50 ml of carbon tetrachloride and refluxed with heating for 2 hours. The reaction mixture was allowed to cool and 20 ml of diethyl ether was added thereto. The crystals precipitated were separated by filtration. The filtrate was concentrated under reduced pressure. The residue was recrystallized from chloroform-n-hexane to provide 1.9 g of 2-(4-bromomethylphenyl)-4-phenylquinazoline as



colorless needles. Then 1.9 g of the crystals thus
obtained were suspended in 10 ml of triethyl phosphite and
heated with stirring at 130°C for 2 hours. After
completion of the reaction, an excess of triethyl
5 phosphite was distilled off under reduced pressure and the
residue was purified by silica gel column chromatography
(eluent: chloroform : n-hexane = 1:1) and recrystallized
from diethyl ether-n-hexane to provide 0.2 g of the
objective compound as colorless needles. Table 1 shows
10 the structure and physical property (melting point) of the
compound.

Examples 40-42

The compounds set forth in Table 1 were prepared in
the same manner as in Example 39. Table 1 also shows the
15 structures and physical properties (melting points) of
these compounds.

Example 43

Preparation of ethyl 4-(6-bromo-4-methoxyquinazolin-2-
yl)benzylphosphonate

20 A 0.9 g quantity of the compound obtained in Example
13 and 0.9 g of lithium bromide were suspended in 30 ml of
dry acetonitrile and refluxed with heating for 20 hours.
After completion of the reaction, the reaction mixture was
allowed to cool and the precipitate was collected by
25 filtration, washed with acetonitrile twice, added to 10 ml



of 3N hydrochloric acid and stirred at room temperature for 10 minutes. A 10 ml portion of distilled water was added thereto and the crystals precipitated was collected by filtration and washed with water, thus giving 0.1 g of the objective compound as colorless crystals. Table 1 shows the structure and physical property (melting point) of the compound.

Examples 44-50

The compounds set forth in Table 1 were prepared in the same manner as in Example 43. Table 1 also shows the structures and physical properties (melting points) of these compounds. Table 2 shows the results of ^1H -NMR analysis of some compounds.

Example 51

Preparation of diethyl 4-(6-bromo-4-mercaptoquinazolin-2-yl)benzylphosphonate

A 10 g quantity of the compound obtained in Example 14 and 4.5 g of Lawesson's reagent were suspended in 80 ml of toluene and refluxed with heating for 1 hour. After completion of the reaction, the solvent was distilled off under reduced pressure and the residue was purified by silica gel column chromatography (eluent: chloroform: methanol = 30:1) and recrystallized from chloroform-n-hexane to provide 7.6 g of the objective compound as light yellow crystals. Table 1 shows the structure and physical



property (melting point) of the compound thus obtained.

Example 52

Preparation of diethyl 4-(6-bromo-4-mercaptoquinazolin-2-yl)benzyl(thio)phosphonate

- 5 A 3.0 g quantity of the compound obtained in Example 14 and 3.0 g of Lawesson's reagent were suspended in 20 ml of toluene and refluxed with heating for 2 hours. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column
- 10 chromatography (eluent: chloroform) and recrystallized from chloroform-n-hexane to provide 2.2 g of the objective compound as yellow crystals (melting point: 196-199°C).

Example 53

- Preparation of diethyl 4-(6-bromo-4-methylthioquinazolin-
- 15 2-yl)benzyl(thio)phosphonate

- A 0.60 g quantity of the compound obtained in Example 52 was dissolved in 10 ml of THF, and 0.2 ml of triethylamine and 0.1 ml of methyl iodide were serially added thereto with stirring at room temperature. The
- 20 stirring was continued at room temperature for 30 minutes. After adding 30 ml of water, the reaction mixture was extracted with chloroform. The chloroform layer was washed with water, dried over sodium sulfate and concentrated under reduced pressure. The residue was
- 25 purified by silica gel column chromatography (eluent:



chloroform : n-hexane = 2:1) and recrystallized from diethyl ether-n-hexane to provide 0.43 g of the objective compound as yellow crystals (melting point: 126-127°C).

Examples 54-61

5 The compounds set forth in Table 3 were prepared in the same manner as in Examples 11 and 12. Table 3 also shows the structures and physical properties (melting points) of these compounds.

10 Table 2 shows the results of ¹H-NMR analysis of the compound obtained in Example 57.

Example 62

Preparation of diethyl 4-(7-fluoro-4-hydroxyquinazolin-2-yl)benzylphosphonate

15 A 10 g portion of 2-amino-5-fluorobenzoic acid was dissolved in 100 ml of dichloromethane and 100 ml of pyridine. A solution of 36 g of 4-[(diethoxyphosphoryl)-methyl]benzoyl chloride in 50 ml of dichloromethane and 20 ml of DMF was dropwise added with stirring under ice cooling and the stirring was continued at room temperature
20 for 20 hours. After completion of the reaction, the reaction mixture was diluted with 300 ml of dichloromethane and washed serially with diluted
25 hydrochloric acid and saturated sodium bicarbonate. The organic layer was dried over anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure.



The residue was recrystallized from dichloromethane-diethylether-n-hexane to provide 17.6 g of diethyl 4-(7-fluoro-4H-3,1-benzoxazin-4-on-2-yl)benzylphosphonate as colorless crystals.

5 Then 14.3 g of the crystals thus obtained were dissolved in 100 ml of ethanol, and 50 ml of 25% aqueous ammonia was added thereto and stirred at room temperature for 2 hours. After completion of the reaction, the solvent was distilled off to provide the residue
10 containing diethyl 4-[N-(2-carbamoyl-5-fluorophenyl)-carbamoyl]benzylphosphonate as colorless powders.

 The residue was dissolved in 100 ml of ethanol, and 50 ml of 2N aqueous sodium hydroxide solution was added thereto and stirred at room temperature for 15 hours. The
15 reaction mixture was diluted with 300 ml of dichloromethane. The organic layer was washed with diluted hydrochloric acid and dried over anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure. The residue was recrystallized from
20 dichloromethane-diethyl ether to provide 9.8 g of the objective compound as colorless crystals. Table 3 shows the structure and physical property (melting point) of the compound thus obtained.

Examples 63-69

25 The compounds set forth in Table 3 were prepared in



the same manner as in Example 62. Table 3 also shows the structures and physical properties (melting points) of these compounds.

Example 70

- 5 Preparation of diethyl 4-(4-benzyloxy-6,7-dimethoxy-quinazolin-2-yl)benzylphosphonate

A 4.32 g quantity of the compound obtained in Example 20 was dissolved in 50 ml of anhydrous methanol. A 0.25 g quantity of metal sodium and 1.71 g of benzyl bromide were serially added thereto at room temperature and stirred at 40°C for 17 hours. The reaction mixture was diluted with 200 ml of dichloromethane and then washed with diluted hydrochloric acid. The organic layer was dried over magnesium sulfate and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography and the former fraction was recrystallized from dichloromethane-diethyl ether to provide 0.2 g of the objective compound as colorless crystals.

- 20 As a by-product, diethyl 4-(3-benzyl-6,7-dimethoxy-4(3H)-quinazolinon-2-yl)benzylphosphonate was obtained from the latter fraction. Table 3 shows the structure and physical property (melting point) of the compound obtained.

- 25 Examples 71-81

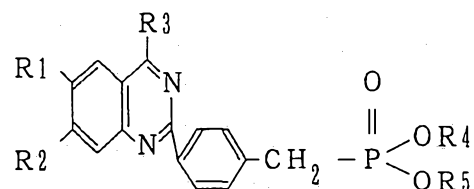


The compounds set forth in Table 3 were prepared in the same manner as in Example 70. Table 3 also shows the structures and physical properties (melting points) of these compounds.





Table 1



Ph : Phenyl group

No	R ¹	R ²	R ³	R ⁴	R ⁵	Mp (°C)
1	H	H	-OCH ₃	C ₂ H ₅	C ₂ H ₅	85.0~86.0
2	H	H	-OC ₂ H ₅	C ₂ H ₅	C ₂ H ₅	115.0~116.0
3	Br	H	-OCH ₃	CH ₃	CH ₃	93.0~94.0
4	Br	H	-OC ₂ H ₅	C ₂ H ₅	C ₂ H ₅	99.5~100 (dec.)
5	Br	H	-OCH(CH ₃) ₂	C ₂ H ₅	C ₂ H ₅	102~105
6	Br	H	-OC ₆ H ₁₃	C ₂ H ₅	C ₂ H ₅	114~116
7	Br	H	-O- 	C ₂ H ₅	C ₂ H ₅	96~99
8	Br	H	-OPh	C ₂ H ₅	C ₂ H ₅	141~143 (dec.)
9	Br	H	-OCH ₂ Ph	C ₂ H ₅	C ₂ H ₅	168~171
10	Br	H	-O-(CH ₂) ₂ OPh	C ₂ H ₅	C ₂ H ₅	134~136



Table 1 (cont.)

No	R ¹	R ²	R ³	R ⁴	R ⁵	Mp (°C)
11	Br	H	-OCH ₃	-CH(CH ₃) ₂	-CH(CH ₃) ₂	124.0~125.0
12	Br	H	OH	-CH(CH ₃) ₂	-CH(CH ₃) ₂	193.0~194.0
13	Br	H	-OCH ₃	C ₂ H ₅	C ₂ H ₅	148.0~149.0
14	Br	H	OH	C ₂ H ₅	C ₂ H ₅	211.0~212.0
15	Cl	H	-OCH ₃	C ₂ H ₅	C ₂ H ₅	130.0~130.5
16	Cl	H	OH	C ₂ H ₅	C ₂ H ₅	188.5~189.5
17	NO ₂	H	-OCH ₃	C ₂ H ₅	C ₂ H ₅	166~170(dec.)
18	NO ₂	H	OH	C ₂ H ₅	C ₂ H ₅	>250
19	CH ₃ O-	CH ₃ O-	-OCH ₃	C ₂ H ₅	C ₂ H ₅	138~139(dec.)
20	CH ₃ O-	CH ₃ O-	OH	C ₂ H ₅	C ₂ H ₅	185.0~186.0
21	H	H	-NHCH ₃	C ₂ H ₅	C ₂ H ₅	165.0~165.5
22	H	H	-NHC ₂ H ₅	C ₂ H ₅	C ₂ H ₅	123.0~124.0
23	Br	H	-NHCH ₃	CH ₃	CH ₃	>250
24	Br	H	-NHC ₂ H ₅	CH ₃	CH ₃	>250
25	Br	H	-NHCH ₃	C ₂ H ₅	C ₂ H ₅	194.0~195.0
26	Br	H	-NHC ₂ H ₅	C ₂ H ₅	C ₂ H ₅	202.0~203.0
27	Br	H	-NHC ₄ H ₉	C ₂ H ₅	C ₂ H ₅	191~193
28	Br	H	-NH- 	C ₂ H ₅	C ₂ H ₅	247~249



Table 1 (cont.)

No	R ¹	R ²	R ³	R ⁴	R ⁵	Mp (°C)
29	Br	H		C ₂ H ₅	C ₂ H ₅	200~202
30	Br	H		C ₂ H ₅	C ₂ H ₅	146~148
31	Br	H	-NHNH ₂	C ₂ H ₅	C ₂ H ₅	194~198
32	Br	H	-NHCH ₃	-CH(CH ₃) ₂	-CH(CH ₃) ₂	222~223 (dec.)
33	Br	H	-NHC ₂ H ₅	-CH(CH ₃) ₂	-CH(CH ₃) ₂	212~213 (dec.)
34	Cl	H	-NHCH ₃	C ₂ H ₅	C ₂ H ₅	188.0~189.0
35	CH ₃ O-	CH ₃ O-	-NHCH ₃	C ₂ H ₅	C ₂ H ₅	>250
36	Br	H	-SC ₂ H ₅	C ₂ H ₅	C ₂ H ₅	95.0~96.0
37	Br	H	-SCH ₃	C ₂ H ₅	C ₂ H ₅	120~122
38	Br	H	-SPh	C ₂ H ₅	C ₂ H ₅	135~138
39	H	H	Ph	C ₂ H ₅	C ₂ H ₅	139.5~140.5
40	Br	H	Ph	CH ₃	CH ₃	171.0~172.0
41	Cl	H	Ph	CH ₃	CH ₃	158~159 (dec.)
42	Cl	H	Ph	C ₂ H ₅	C ₂ H ₅	151.5~152.5
43	Br	H	-OCH ₃	C ₂ H ₅	H	198~200 (dec.)
44	Br	H	-OC ₂ H ₅	C ₂ H ₅	H	>250
45	Br	H	-Ph	C ₂ H ₅	H	250 (dec.)



Table 1 (cont.)

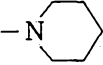
No	R ¹	R ²	R ³	R ⁴	R ⁵	Mp (°C)
46	Br	H	-NHCH ₃	C ₂ H ₅	H	240 (dec.)
47	Br	H	-NHC ₂ H ₅	C ₂ H ₅	H	>250
48	Br	H	-N 	C ₂ H ₅	H	127~129
49	Br	H	-N(CH ₃) ₂	C ₂ H ₅	H	92~94 (dec.)
50	Br	H	-SC ₂ H ₅	C ₂ H ₅	H	205~207 (dec.)
51	Br	H	SH	C ₂ H ₅	C ₂ H ₅	155~156 (dec.)

Table 2

No.	¹ H-NMR (δ : ppm, Internal standard: TMS)
18	1. 29 (t, J=6. 9, 6H)、3. 28 (d, J=21. 8, 2H)、 4. 0-4. 1 (m, 2H)、7. 4-7. 5 (m, 2H)、 7. 91 (d, J=8. 9, 1H)、8. 09 (d, J=7. 4, 2H)、 8. 5-8. 6 (m, 1H)、9. 14 (d, J=2. 5, 1H) [CDCl ₃ - CD ₃ OD]
23	3. 13 (d, J=4. 5, 3H)、3. 15 (d, J=21. 8, 2H)、 3. 51 (s, 3H)、3. 55 (s, 3H)、 7. 39 (dABq, J=2. 0, 7. 4, 2H)、 7. 69 (ABq, J=8. 9, 1H)、 7. 87 (dABq, J=2. 0, 8. 9, 1H)、 8. 40 (ABq, J=7. 4, 2H)、 8. 48 (d, J=2. 0, 1H) [DMSO-d ₆]
24	1. 33 (t, J=7. 2, 3H)、3. 24 (d, J=22. 0, 2H)、 3. 54 (s, 3H)、3. 58 (s, 3H)、 3. 7-3. 9 (m, 2H)、7. 49 (ABq, J=8. 2, 2H)、 7. 92 (ABq, J=8. 5, 1H)、 8. 04 (ABq, J=8. 5, 1H)、 8. 36 (ABq, J=8. 2, 2H)、 8. 71 (s, 1H)、9. 5 (br. s, 1H) [DMSO-d ₆]
35	1. 26 (t, J=6. 9, 6H)、3. 24 (d, J=21. 8, 2H)、 3. 25 (d, J=5. 0, 3H)、3. 9-4. 1 (m, 4H)、 3. 99 (s, 3H)、4. 03 (s, 3H)、 5. 6-5. 7 (br. q, 1H)、6. 96 (s, 1H)、 7. 29 (s, 1H)、7. 40 (dABq, J=2. 5, 8. 4, 2H)、 8. 49 (ABq, J=8. 4, 2H) [CDCl ₃]



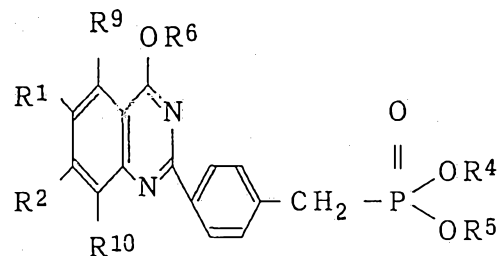
Table 2 (cont.)

No.	$^1\text{H-NMR}$ (δ : ppm, Internal standard: TMS)
44	1. 17 (t, J=6. 9, 3H)、1. 52 (t, J=7. 2, 3H)、 3. 18 (d, J=21. 8, 2H)、3. 8-4. 0 (m, 2H)、 4. 76 (q, J=7. 2, 2H)、 7. 45 (dABq, J=2. 0, 7. 9, 2H)、 7. 90 (ABq, J=8. 9, 1H) 8. 07 (dABq, J=2. 5, 8. 9, 1H)、 8. 26 (d, J=2. 5, 1H)、8. 43 (ABq, J=7. 9, 2H) (DMSO-d_6)
47	1. 3 (br. t, 3H)、1. 4 (br. t, 3H)、 3. 26 (d, J=22. 0, 2H)、3. 9-4. 0 (m, 2H)、 4. 0-4. 1 (m, 2H)、7. 5-7. 6 (m, 2H)、 7. 9-8. 1 (m, 1H)、8. 18 (d, J=8. 9, 1H)、 8. 36 (d, J=7. 4, 2H)、8. 63 (s, 1H) (CDCCl_3-CD$_3$ OD)
57	3. 27 (d, J=22. 3, 2H)、 3. 71 (d, J=10. 9, 6H)、 4. 04 (s, 6H)、7. 24 (s, 1H)、 7. 50 (dd, J=2. 5, 8. 4, 2H)、 7. 64 (s, 1H)、8. 14 (d, J=7. 9, 2H)、 11. 0 (br, 1H) (CDCCl_3)





Table 3



Et : Ethyl group

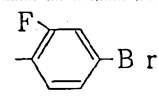
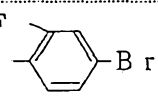
iPr : Isopropyl group

Ph : Phenyl group

No.	R ¹	R ²	R ⁴	R ⁵	R ⁶	R ⁹	R ¹⁰	Mp (°C)
54	H	H	Et	Et	CH ₃	F	H	80~81
55	H	H	Et	Et	H	F	H	172~173
56	-OCH ₃	-OCH ₃	CH ₃	CH ₃	CH ₃	H	H	138~139
57	-OCH ₃	-OCH ₃	CH ₃	CH ₃	H	H	H	230以上
58	-OCH ₃	-OCH ₃	iPr	iPr	CH ₃	H	H	133~134
59	-OCH ₃	-OCH ₃	iPr	iPr	H	H	H	190~191
60	H	Cl	Et	Et	CH ₃	H	H	106~107
61	H	Cl	Et	Et	H	H	H	209~211
62	H	F	Et	Et	H	H	H	184~186
63	H	H	Et	Et	H	H	H	187~189
64	H	H	CH ₃	CH ₃	H	H	H	199~200
65	H	H	Et	Et	H	Cl	H	192~193



Table 3 (cont.)

No	R ¹	R ²	R ⁴	R ⁵	R ⁶	R ⁹	R ¹⁰	Mp (°C)
66	H	CF ₃	Et	Et	H	H	H	210 (dec.)
67	CH ₃	H	Et	Et	H	H	H	198.5~200
68	H	NO ₂	Et	Et	H	H	H	252~254
69	H	Cl	Et	Et	H	Cl	H	263.5~264.5
70	-OCH ₃	-OCH ₃	Et	Et	-CH ₂ Ph	H	H	141~142
71	Br	H	Et	Et	-CH ₂ 	H	H	101~102
72	Br	H	Et	Et	-CH ₂ COOH	H	H	170 (dec.)
73	-OCH ₃	-OCH ₃	Et	Et	-CH ₂ CH=CH ₂	H	H	109~110
74	-OCH ₃	-OCH ₃	iPr	iPr	-CH ₂ Ph	H	H	123 (dec.)
75	-OCH ₃	-OCH ₃	iPr	iPr	-CH ₂ CH ₂ Ph	H	H	150 (dec.)
76	-OCH ₃	-OCH ₃	Et	Et	-CH ₂ COOCH ₃	H	H	86~87
77	-OCH ₃	-OCH ₃	Et	Et	-CH ₂ 	H	H	145~146
78	H	H	Et	Et	-CH ₂ Ph	F	H	109~110
79	H	Cl	Et	Et	-CH ₂ Ph	H	H	105 (dec.)
80	H	Cl	Et	Et	-CH ₂ COOCH ₃	H	H	80 (dec.)
81	-OCH ₃	-OCH ₃	Et	Et	H	H	-OCH ₃	169~170

Formulation examples of the compound of the invention are described below.

Formulation Example 1 Manufacture of tablets

5 Using the compound obtained in Example 58 as an active ingredient, tablets (1000 tablets) each containing 250 mg of the active ingredient were manufactured according to the following formula.

	Ingredient	Amount (g)
10	Compound of Example 58	250
	Lactose (product of Japanese pharmacopeia: JP)	33.5
	Corn starch (JP)	16.5
	Carboxymethyl cellulose calcium (JP)	12.5
	Methylcellulose (JP)	6.0
15	Magnesium stearate (JP)	1.5
	Total	320.0

20 According to the above formula, the compound of Example 58, lactose, corn starch and carboxymethyl cellulose calcium were well blended and granulated using an aqueous solution of methyl cellulose. The granulated mixture was passed through a 24-mesh sieve and the granules under the sieve were mixed with magnesium stearate and compression-molded into tablets.

25 Formulation Example 2 Manufacture of capsules

Using the compound obtained in Example 19 as an



active ingredient, hard gelatin capsules (1000 units) each containing 250 mg of the active ingredient were manufactured according to the following formula.

5	Ingredient	Amount (g)
	Compound of Example 19	250
	Crystalline cellulose (JP)	30
	Corn starch (JP)	17
	Talc (JP)	2
10	Magnesium stearate (JP)	1
	Total	300

Thus, according to the above formula, the ingredients were finely pulverized and the powders obtained were
15 blended to give a homogeneous composition. This composition was filled into proper-sized gelatin capsule shells for oral administration to provide the objective capsules.

Formulation Example 3 Manufacture of granules

20 Using the compound obtained in Example 73 as an active ingredient, granules (1000 g) containing 500 mg of the active ingredient in each gram were manufactured according to the following formula.



	Ingredient	Amount (g)
	Compound of Example 73	500
5	Crystalline cellulose (JP)	100
	Corn starch (JP)	250
	Lactose (JP)	100
	Carboxymethyl cellulose calcium (JP)	40
10	Hydroxypropylmethyl cellulose (JP)	10
	Total	1000

Thus, according to the above formula, the compound of Example 73, lactose, corn starch, crystalline cellulose and carboxymethyl cellulose calcium were thoroughly
15 blended and kneaded with an aqueous solution of hydroxypropylmethyl cellulose. The resultant composition was granulated using an extrusion granulator and dried at 50°C for 2 hours to provide the objective granules.

Pharmacological Test Example 1

20 Preventive and therapeutic effects of the compound of the invention on hyperlipidemia were determined using rats with Triton-induced hyperlipidemia according to the method of Kuroda et al. [Biochem. Biophys. Acta., 489, 119 (1977)] as follows.

25 Using 6 to 7-week-old male Wistar rats in groups of 5 (test groups), a solution of 300 mg/kg Triton (Triton WR 1339) in physiological saline was administered into the



tail vein and, at the same time, 100 mg/kg of the test compound suspended in a 0.5% CMC-Na solution was administered orally. As a control group, a group of 5 rats given Triton were orally dosed with a 0.5% aqueous CMC-Na solution.

Twenty four hours after administration of Triton, blood was taken from the rats and the plasma total triglyceride was determined using Triglyceride G-Test Wako (product of Wako Pure Chemical Industries, Ltd.). Using the measured values in the control group as references, the rate of decrease (%) in plasma total triglyceride in the test group was calculated by the equation given below. The test rats were deprived of food before Triton administration through completion of blood sampling but allowed free access to drinking water.

$$\text{Rate of decrease (\%)} = \left[1 - \frac{(\text{Test group value})}{(\text{Control group value})} \right] \times 100$$

Table 5 shows the results.



Table 5

Test compound (Example No.)	Rate of decrease of triglyceride (%)
19	86
20	37
58	81
59	31
70	40
73	71

Industrial Applicability

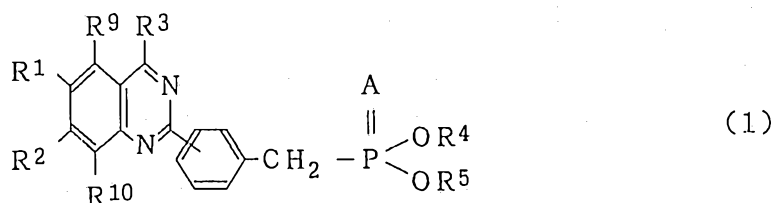
The present invention provides a novel phosphonic diester derivative, which is useful as therapeutic agents for hyperlipidemic diseases, hypertension, diabetes and the like.

5



CLAIMS

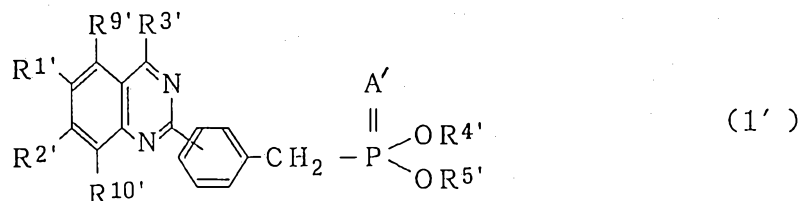
1. A phosphonic diester derivative of the formula:



wherein A represents an oxygen atom or a sulfur atom; R^1 , R^2 , R^9 and R^{10} are the same or different and they each represent a hydrogen atom, a lower alkoxy group, a nitro group, a lower alkyl group, a halogen-substituted lower alkyl group or a halogen atom; R^3 represents a phenyl group or $-\text{B}-\text{R}^6$ (wherein B represents an oxygen atom or a sulfur atom and R^6 represents a hydrogen atom, a lower alkyl group, a cycloalkyl group, a phenyl group, a phenyl(lower)alkyl group optionally having a halogen atom as a substituent on the phenyl ring, a phenoxy(lower)alkyl group, a lower alkoxycarbonyl(lower)alkyl group, a carboxy(lower)alkyl group or a lower alkenyl group) or $-\text{NR}^7\text{R}^8$ (wherein R^7 and R^8 are the same or different and they each represent a hydrogen atom, a lower alkyl group, an amino group or a cycloalkyl group or combinedly represent a lower alkylene group); and R^4 and R^5 are the same or different and they each represent a hydrogen atom or a lower alkyl group.



2. A phosphonic diester derivative of the formula:



wherein A' represents an oxygen atom or a sulfur atom; R^{1'} represents a hydrogen atom, a lower alkoxy group, a nitro group or a halogen atom; R^{2'} represents a hydrogen atom, a lower alkoxy group, a lower alkyl group, a halogen-substituted lower alkyl group or a halogen atom; R^{3'} represents a phenyl group, -O-R⁶ (wherein R⁶ represents a hydrogen atom, a lower alkyl group, a cycloalkyl group, a phenyl group, a phenyl(lower)alkyl group optionally having a halogen atom as a substituent on the phenyl ring, a phenoxy(lower)alkyl group, a lower alkoxycarbonyl(lower)-alkyl group, a carboxy(lower)alkyl group or a lower alkenyl group), -S-R^{6'} (wherein R^{6'} represents a hydrogen atom, a lower alkyl group or a phenyl group) or -NR⁷R⁸ (wherein R⁷ and R⁸ are the same or different and they each represent a hydrogen atom, a lower alkyl group, an amino group or a cycloalkyl group or combinedly represent a lower alkylene group); R^{4'} represents a lower alkyl group; R^{5'} represents a hydrogen atom or a lower alkyl group; R^{9'} represents a hydrogen atom or a halogen atom; and R^{10'} represents a hydrogen atom or a lower alkoxy group.



3. The phosphonic diester derivative of Claim 2 which is represented by the formula 1' wherein $R^{1'}$ and $R^{2'}$ each represent a lower alkoxy group; $R^{3'}$ represents $-O-R^6$ wherein R^6 represents a hydrogen atom, a lower alkyl group, a cycloalkyl group, a phenyl group, a phenyl(lower)alkyl group optionally having a halogen atom as a substituent on the phenyl ring, a phenoxy(lower)alkyl group, a lower alkoxycarbonyl(lower)alkyl group, a carboxy(lower)alkyl group or a lower alkenyl group; A' represents an oxygen group; and $R^{4'}$ and $R^{5'}$ each represent a lower alkyl group.

4. The phosphonic diester derivative of Claim 2 which is represented by the formula 1' wherein $R^{9'}$ and $R^{10'}$ each represent a hydrogen atom and $R^{3'}$ represents a hydroxy group, a lower alkoxy group, a phenyl(lower)alkoxy group or a lower alkenyloxy group.

5. The phosphonic diester derivative of Claim 4 which is a compound selected from the class consisting of (1) diethyl 4-(4-hydroxy-6,7-dimethoxyquinazolin-2-yl)benzylphosphonate, (2) diisopropyl 4-(4-hydroxy-6,7-dimethoxyquinazolin-2-yl)benzylphosphonate, (3) diethyl 4-(4,6,7-trimethoxyquinazolin-2-yl)benzylphosphonate, (4) diisopropyl 4-(4,6,7-trimethoxyquinazolin-2-yl)benzylphosphonate, (5) diethyl 4-(4-benzyloxy-6,7-dimethoxyquinazolin-2-yl)benzylphosphonate and (6) diethyl



4-(4-allyloxy-6,7-dimethoxyquinazolin-2-yl)benzylphosphonate.

6. The phosphonic diester derivative of Claim 5 which is diethyl 4-(4,6,7-trimethoxyquinazolin-2-yl)benzylphosphonate or diisopropyl 4-(4,6,7-trimethoxyquinazolin-2-yl)benzylphosphonate.

7. An antihyperlipidemic composition comprising the phosphonic diester derivative claimed in any one of the claims 1 through 6 as an active ingredient.

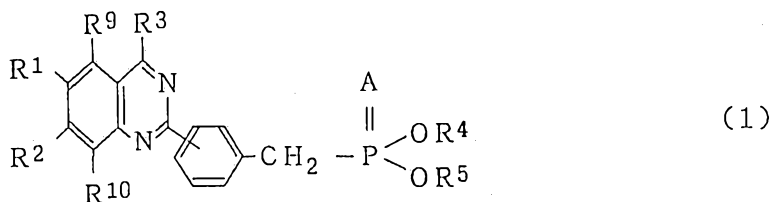
8. A method of treating hyperlipidemia which comprises administering to a patient a pharmacologically effective amount of the antihyperlipidemic composition claimed in Claim 7.

9. Use of the phosphonic diester derivative claimed in any one of the claims 1 through 6 for preparation of an antihyperlipidemic composition.



ABSTRACT

The present invention provides a phosphonic diester derivative of the following general formula (1):



wherein A represents an oxygen atom or a sulfur atom; R^1 , R^2 , R^9 and R^{10} are the same or different and they each represent a hydrogen atom, a lower alkoxy group, a nitro group, a lower alkyl group, a halogen-substituted lower alkyl group or a halogen atom; R^3 represents a phenyl group, $-\text{B}-\text{R}^6$ (wherein B represents an oxygen atom or a sulfur atom and R^6 represents a hydrogen atom, a lower alkyl group, a cycloalkyl group, a phenyl group, a phenyl(lower)alkyl group optionally having a halogen atom as a substituent on the phenyl ring, a phenoxy(lower)alkyl group, a lower alkoxycarbonyl(lower)alkyl group, a carboxy(lower)alkyl group or a lower alkenyl group) or $-\text{NR}^7\text{R}^8$ (wherein R^7 and R^8 are the same or different and they each represent a hydrogen atom, a lower alkyl group, an amino group or a cycloalkyl group or combinedly represent a lower alkylene group); and R^4 and R^5 are the same or different and they each represent a hydrogen atom or a lower alkyl group.



-57-

The derivative of the present invention is useful as therapeutic agents for hyperlipidemic diseases, hypertension, diabetes and the like.



INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP94/00883

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl⁵ C07F9/6512, A61K31/675

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int. Cl⁵ C07F9/547, A61K31/66

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JP, A, 5-43589 (Otsuka Pharmaceutical Factory, Inc.), February 23, 1993 (23. 02. 93), (Family: none)	1-7, 9
Y	JP, A, 4-243888 (Otsuka Pharmaceutical Factory, Inc.), August 31, 1992 (31. 08. 92), (Family: none)	1-7, 9

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

August 3, 1994 (03. 08. 94)

Date of mailing of the international search report

September 6, 1994 (06. 09. 94)

Name and mailing address of the ISA/

Japanese Patent Office

Facsimile No.

Authorized officer

Telephone No.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP94/00883

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

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

1. ☒ Claims Nos.: 8
because they relate to subject matter not required to be searched by this Authority, namely:
Claim 8 pertains to methods for treatment of the human or animal body by therapy, and thus relates to a subject matter which this International Searching Authority is not required, under the provisions of Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

A. 発明の属する分野の分類 (国際特許分類 (IPC))

Int. Cl.⁸ C07F9/6512 . A61K31/675

B. 調査を行った分野

調査を行った最小限資料 (国際特許分類 (IPC))

Int. Cl.⁸ C07F9/547 . A61K31/66

最小限資料以外の資料で調査を行った分野に含まれるもの

国際調査で使用了電子データベース (データベースの名称、調査に使用した用語)

CAS ONLINE

C. 関連すると認められる文献

引用文献の カテゴリー*	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する 請求の範囲の番号
Y	JP, A, 5-43589 (株式会社 大塚製薬工場), 23. 2月. 1993 (23. 02. 93) (ファミリーなし)	1-7, 9
Y	JP, A, 4-243888 (株式会社 大塚製薬工場), 31. 8月. 1992 (31. 08. 92) (ファミリーなし)	1-7, 9

☐ C欄の続きにも文献が列举されている。

☐ パテントファミリーに関する別紙を参照。

* 引用文献のカテゴリー

「A」 特に関連のある文献ではなく、一般的技術水準を示すもの
「E」 先行文献ではあるが、国際出願日以後に公表されたもの
「L」 優先権主張に疑義を提起する文献又は他の文献の発行日
若しくは他の特別な理由を確立するために引用する文献
(理由を付す)
「O」 口頭による開示、使用、展示等に言及する文献
「P」 国際出願日前で、かつ優先権の主張の基礎となる出願の日
の後に公表された文献

「T」 国際出願日又は優先日後に公表された文献であって出願と
矛盾するものではなく、発明の原理又は理論の理解のため
に引用するもの
「X」 特に関連のある文献であって、当該文献のみで発明の新規
性又は進歩性がないと考えられるもの
「Y」 特に関連のある文献であって、当該文献と他の1以上の文
献との、当業者にとって自明である組合せによって進歩性
がないと考えられるもの
「&」 同一パテントファミリー文献

国際調査を完了した日

03. 08. 94

国際調査報告の発送日

06.09.94

名称及びあて先

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