P/00/008
Section 29(1)
Regulation 3.1(2)

AUSTRALIA
Patents Act 1990

NOTICE OF ENTITLEMENT

I/We OTSUKA PHARMACEUTICAL FACTORY, INC.

of 115, AZA KUGUHARA, TATEIWA
MUYA-CHO, NARUTO-SHI
TOKUSHIMA 772
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. 40887/93), 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: 12 January 1994

OTSUKA PHARMACEUTICAL FACTORY, INC.

GRIFFITH HACK & CO.

Patent Attorney for and
on behalf of the applicant(s)

AU9340887

(12) PATENT ABRIDGMENT (11) Document No. AU-B-40887/93
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 653681

(54) Title
PHOSPHONIC DIESTER DERIVATIVE

International Patent Classification(s)
(51)[5] C07F 009/6561 A61K 031/675 C07F 009/6506 C07F 009/6541

(21) Application No. : 40887/93 (22) Application Date : 20.05.93

(87) PCT Publication Number : WO93/23409

(30) Priority Data

(31) Number	(32) Date	(33) Country
4-128711	21.05.92	JP JAPAN

(43) Publication Date : 13.12.93

(44) Publication Date of Accepted Application : 06.10.94

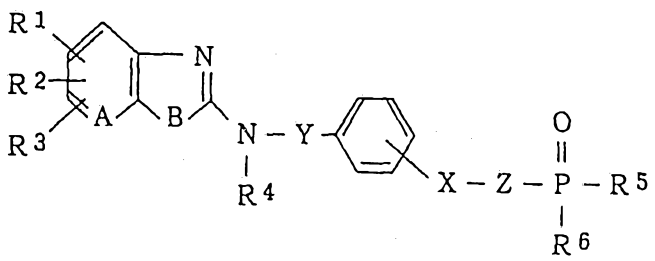
(71) Applicant(s)
OTSUKA PHARMACEUTICAL FACTORY, INC.

(72) Inventor(s)
KAZUYOSHI MIYATA; YASUO SHOJI; YOSHIHIKO TSUDA; KAZUHIKO TSUTSUMI; YASUHIDE INOUE; CHIEKO NABA; YASUHISA KUROGI

(74) Attorney or Agent
GRIFFITH HACK & CO , GPO Box 1285K, MELBOURNE VIC 3001

(57) Claim

1. A phosphonic diester derivative of the general formula



[wherein R^1, R^2 and R^3 are the same or different and each represents a hydrogen atom, a lower alkyl group, a phenyl group, a lower alkoxy group, a halogen-substituted lower alkyl group, a halogen-substituted lower alkoxy group, a lower alkanoyl group, a benzoyl group, a (lower)alkoxy-carbonyl group, a nitro group, a halogen atom, a (lower)alkylthio group, a phenyl(lower)alkoxy group, a carbamoyl group or a (lower)alkoxycarbonyl(lower)alkoxy group; R^4 represents a hydrogen atom, a lower alkyl group or a phenyl(lower)alkyl group; R^5 and R^6 are the same or

.../2

different and each represents a lower alkoxy group, a phenyl group, a phenoxy group, a phenyl(lower)alkoxy group or a hydroxyl group; A represents a carbon atom or a nitrogen atom; B represents a group of the formula $=NR^7$ (where R^7 represents a hydrogen atom, a lower alkyl group or a phenyl(lower)alkyl group), an oxygen atom or a sulfur atom; Y represents a group of the formula C=O or a group of SO_2; X represents an oxygen atom or a bond; Z represents a lower alkylene group optionally having a lower alkyl or phenyl(lower)alkyl group as a substituent or a bond; provided, however, that X and Z do not concurrently represent bonds]

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

8. An antidiabetic composition comprising the phosphonic diester derivative claimed in any of Claims 1 through 6 as an active ingredient.

OPI DATE 13/12/93 APPLN. ID 40887/93
AOJP DATE 24/02/94 PCT NUMBER PCT/JP93/00660
AU9340887

(51) 国際特許分類5
C07F 9/6561, A61K 31/675

A1

(11) 国際公開番号 653681 WO 93/23409

(43) 国際公開日 1993年11月25日 (25.11.1993)

(21) 国際出願番号 PCT/JP93/00660
(22) 国際出願日 1993年5月20日(20. 05. 93)

(30) 優先権データ
特願平4/128711 1992年5月21日(21. 05. 92) JP

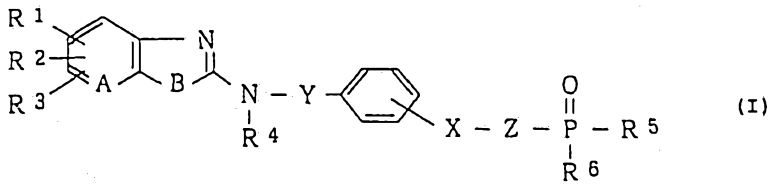
(71) 出願人(米国を除くすべての指定国について)
株式会社 大塚製薬工場
(OTSUKA PHARMACEUTICAL FACTORY, INC.)〔JP/JP〕
〒772 徳島県鳴門市撫養町立岩字芥原115 Tokushima, (JP)
(72) 発明者;および
(75) 発明者/出願人(米国についてのみ)
宮田一義(MIYATA, Kazuyoshi)〔JP/JP〕
〒772 徳島県鳴門市撫養町斉田字浜端南58-1 ライトビル302号 Tokushima, (JP)
小路恭生(SHOJI, Yasuo)〔JP/JP〕
〒772 徳島県鳴門市撫養町南浜字姪子前東20-2 新星ビル302号 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)
堤 一彦(TSUTSUMI, Kazuhiko)〔JP/JP〕
〒770 徳島県徳島市上助任町天神428の7 Tokushima, (JP)
井上泰秀(INOUE, Yasuhide)〔JP/JP〕
〒770 徳島県鳴門市大津町矢倉字参の越35 Tokushima, (JP)
奈波智恵子(NABA, Chieko)〔JP/JP〕
〒772 徳島県鳴門市撫養町南浜字姪子前東4の4 Tokushima, (JP)
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)
(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平野町2-1-2 沢の鶴ビル Osaka, (JP)

(81) 指定国
AT(欧州特許), AU, BE(欧州特許), CA, CH(欧州特許), DE(欧州特許), DK(欧州特許), ES(欧州特許), FR(欧州特許), GB(欧州特許), GR(欧州特許), IE(欧州特許), IT(欧州特許), JP, KR, LU(欧州特許), MC(欧州特許), NL(欧州特許), PT(欧州特許), SE(欧州特許), US.

添付公開書類 国際調査報告書
請求の範囲の補正の期限前であり、補正書受領の際には再公開される。

(54) Title : PHOSPHONIC DIESTER DERIVATIVE

(54) 発明の名称 ホスホン酸ジエステル誘導体



(I)

(57) Abstract

A phosphonic diester derivative represented by general formula (I). It has the effect of reducing blood sugar and lipid levels, and so forth, and is useful for treating diabetes, hyperlipidemia, and the like.

PHOSPHONIC DIESTER DERIVATIVES

TECHNICAL FIELD

The present invention relates to novel phosphonic diester derivatives.

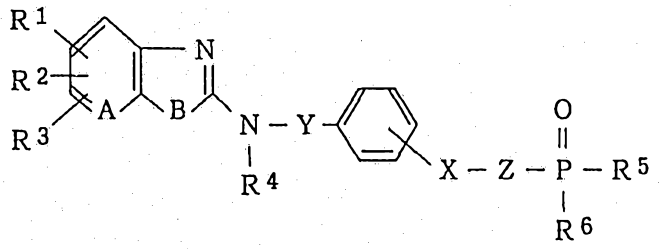
PRIOR ART

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

DISCLOSURE OF THE INVENTION

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

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



[wherein R^1, R^2 and R^3 are the same or different and each represents a hydrogen atom, a lower alkyl group, a phenyl group, a lower alkoxy group, a halogen-substituted lower alkyl group, a halogen-substituted lower alkoxy group, a lower alkanoyl group, a benzoyl group, a (lower)alkoxy-

AUSTRALIA PATENT OFFICE

carbonyl group, a nitro group, a halogen atom, a (lower)alkylthio group, a phenyl(lower)alkoxy group, a carbamoyl group or a (lower)alkoxycarbonyl(lower)alkoxy group; R^4 represents a hydrogen atom, a lower alkyl group or a phenyl(lower) alkyl group; R^5 and R^6 are the same or different and each represents a lower alkoxy group, a phenyl group, a phenoxy group, a phenyl(lower)alkoxy group or a hydroxyl group; A represents a carbon atom or a nitrogen atom; B represents a group of the formula $=NR^7$ (where R^7 represents a hydrogen atom, a lower alkyl group or a phenyl(lower)alkyl group), an oxygen atom or a sulfur atom; Y represents a group of the formula C=O or a group of SO_2; X represents an oxygen atom or a bond; Z represents a lower alkylene group optionally having a lower alkyl or phenyl(lower)alkyl group as a substituent or a bond; provided, however, that X and Z do not concurrently represent bonds]

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, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl and so on.

The lower alkoxy group includes methoxy,

AUSTRALIA PATENT OFFICE

ethoxy, propoxy, isopropoxy, butoxy, pentyloxy, hexyloxy and so on.

The halogen-substituted lower alkyl group includes trifluoromethyl, pentafluoroethyl, heptafluoropropyl, nonafluorobutyl, undecafluoropentyl, tridecafluorohexyl and so on.

The halogen-substituted lower alkoxy group includes trifluoromethoxy, pentafluoroethoxy, heptafluoropropoxy, nonafluorobutoxy, undecafluoropentyloxy, tridecafluorohexyloxy and so on.

The lower alkanoyl group includes acetyl, propionyl, butyryl, valeryl, pivaloyl, hexanoyl, heptanoyl and so on.

The lower alkoxycarbonyl group includes methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl and so on.

The phenyl(lower)alkyl group includes benzyl, 2-phenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl, 6-phenylhexyl and so on.

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

The lower alkylthio group includes methylthio, ethylthio, propylthio, butylthio, pentylthio, hexylthio and so on.

The phenyl(lower)alkoxy group includes

AUSTRALIAN PATENT OFFICE

benzyloxy, 2-phenylethoxy, 3-phenylpropoxy, 4-phenylbutoxy, 5-phenylpentyloxy, 6-phenylhexyloxy and so on.

The lower alkoxycarbonyl(lower)alkoxy group includes methoxycarbonylmethoxy, 2-ethoxycarbonylethoxy, 3-ethoxycarbonylpropoxy, 4-ethoxycarbonylbutoxy, 5-ethoxycarbonylpentyloxy, 6-ethoxycarbonylhexyloxy, 2-butoxycarbonylethoxy, hexyloxycarbonylmethoxy and so on.

The lower alkylene group optionally having a lower alkyl or phenyl(lower)alkyl group as a substituent includes methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, ethylidene, propylidene, butylidene, pentylidene, hexylidene, heptylidene, 2-phenylethylidene, 3-phenylpropylidene, 4-phenylbutylidene, 5-phenylpentylidene, 6-phenylhexylidene, 7-phenylheptylidene and so on.

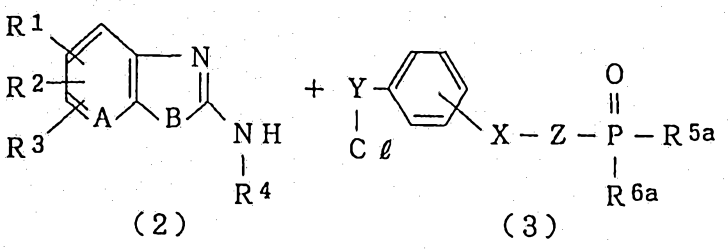
The phosphonic diester derivative of general formula (1) according to the present invention has excellent hypolipidemic and hypoglycemic activities and is, therefore, useful for the treatment and prevention of various types of hyperlipidemic diseases such as hypercholesterolemia, hypertriglyceridemia, hyperphospholipidemia, hyper-free fatty acidemia, etc. and diabetes. Moreover, the phosphonic diester derivative of the invention not only produces therapeutic and prophylactic effects on cataract but has hypotensive

AUSTRALIA 1985 PATENT OFFICE

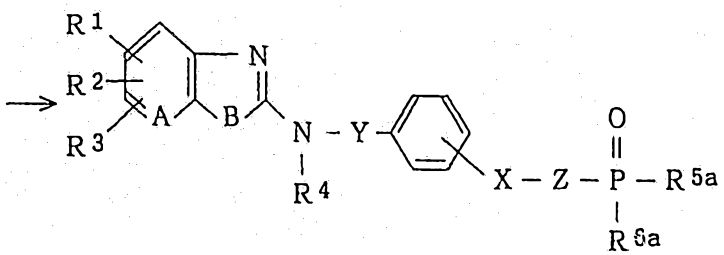
activity as well and is, therefore, of value as a therapeutic and prophylactic agent for cataract and hypertension.

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

(Reaction Schema-1)



(2) (3)



(1a)

[wherein R^1, R^2, R^3, R^4, A, B, X, Y and Z are as defined hereinbefore. R^{5a} and R^{6a} are the same or different and each represents a lower alkoxy group, a phenyl group, a phenyl(lower)alkoxy group or a phenoxy group]

According to the process shown in Reaction Schema-1, the objective compound (1a) of the invention

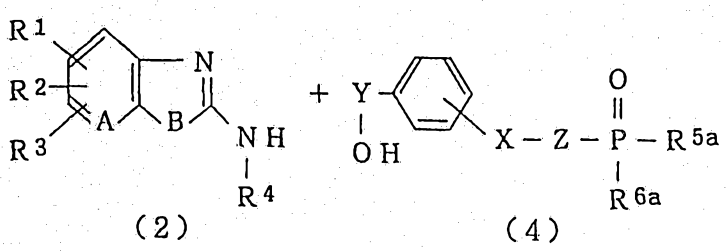
AUSTRALIA PATENT OFFICE

can be obtained by reacting compound (2) with acid chloride derivative (3) in the presence of an acid acceptor in an inert solvent. The inert solvent mentioned above includes, among others, aromatic or aliphatic hydrocarbons such as benzene, toluene, xylene, petroleum ether, etc., acylic or cyclic ethers such as diethyl ether, 1,2-dimethoxyethane, tetrahydrofuran (THF), 1,4-dioxane, etc., ketones such as acetone, methyl ethyl ketone, acetophenone, etc., and halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and so on. The acid acceptor is preferably a tertiary amine such as triethylamine, N,N-diethylaniline, N-methylmorpholine, pyridine, 4-dimethylaminopyridine and so on. The relative amount of said compound (2) and acid chloride derivative (3) is not particularly critical but the latter is preferably used in an equimolar to excess proportion with respect to the former. Usually, the acid acceptor mentioned above is preferably used in an equimolar or excess proportion relative to said acid chloride derivative (3). This reaction proceeds under cooling, at room temperature or under heating but it is usually advantageous to conduct the reaction within the temperature range of 0°C to the reflux temperature of the solvent used. Generally the reaction goes to completion

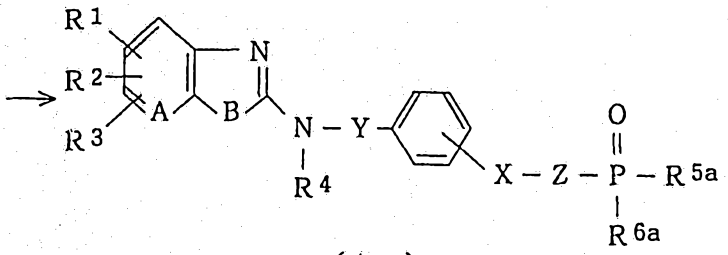
AUSTRALIA PATENT OFFICE

in about 0.5 - 10 hours.

(Reaction Schema-2)



(2) (4)



(1 a)

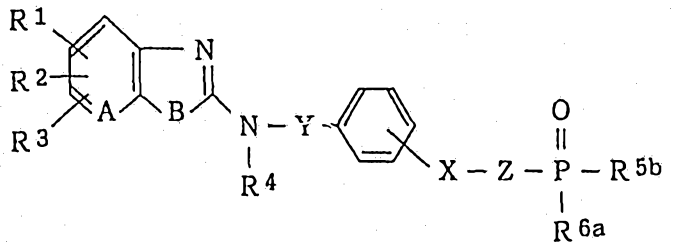
[wherein R^1, R^2, R^3, R^4, R^{5a}, R^{6a}, A, B, X, Y and Z are as defined hereinbefore]

According to the process shown in Reaction Schema-2, the objective compound (1a) of the invention can be obtained by reacting compound (2) with compound (4) in the presence of a condensing agent in an inert solvent. The inert solvent which can be used is any of the known aprotic solvents, although N,N-dimethylformamide (DMF) is particularly useful. The condensing agent includes, among others, N,N'-dicyclohexylcarbodiimide (DCC), 1-hydroxybenzotriazole, N-hydroxysuccinimide, diethyl cyanophosphonate, diphenylphosphoryl azide

AUSTRALIA PATENT OFFICE

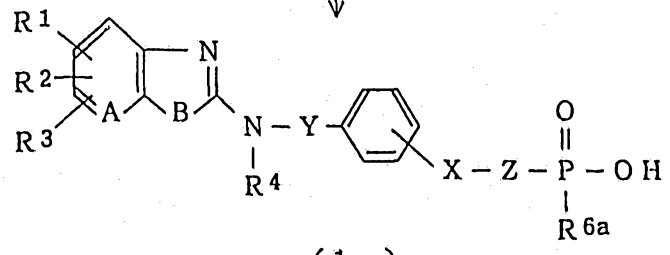
and so on. It is particularly advantageous to employ diethyl cyanophosphonate in combination with triethylamine. The relative amount of compounds (2) and (4) in the above reaction is not critical but can be liberally selected from a broad range. However, it is generally recommendable to use the former compound in an equimolar or excess proportion, preferably an approximately equimolar proportion, relative to the latter compound. The above condensing agent is used in an equimolar to excess proportion, preferably a small excess, relative to compound (4). This reaction is conducted generally under ice-cooling to room temperature for about 0.5 - 2 hours.

(Reaction Schema-3)



(1b)

Partial hydrolysis



(1c)

AUSTRALIA PATENT OFFICE

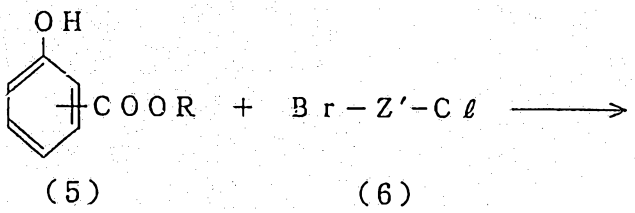
[wherein R^1, R^2, R^3, R^4, R^{6a}, A, B, X, Y and Z are as defined above. R^{5b} represents a lower alkoxy group]

The partial hydrolysis shown in the above Reaction Schema-3 is carried out by reacting compound (1b) with a lithium halide such as lithium bromide, lithium chloride, lithium iodide, etc. and thereafter treating the reaction product with a mineral acid such as hydrochloric acid, sulfuric acid and so on. The above reaction can be carried out in an inert solvent, such as acetonitrile, DMF, etc., using a stoichiometric excess of the lithium halide at room temperature ~ the reflux temperature of the solvent for 5 - 24 hours.

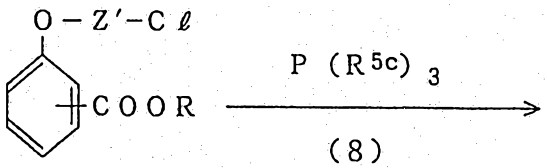
Among the starting compounds for the production of the compound of the invention, compounds of the formulas (3') and (4') can be prepared by the processes shown below in Reaction Schema-4.

PATENT OFFICE

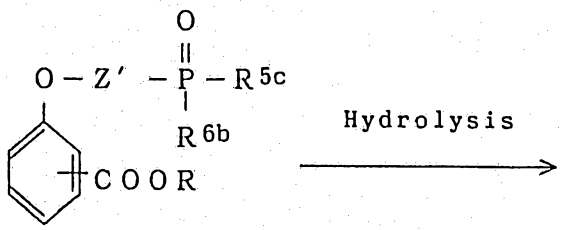
(Reaction Schema-4)



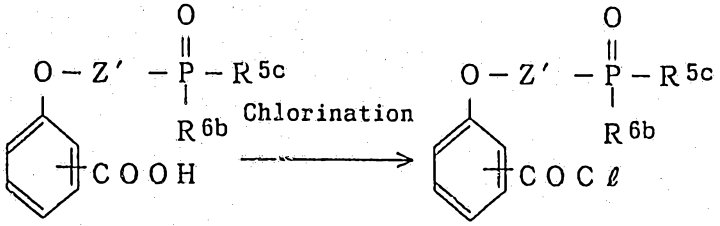
(5) (6)



(7) (8)



(9)



(4′) (3′)

[wherein R^{5c} represents a lower alkoxy group, a phenoxy group or a phenyl(lower)alkoxy group; R^{6b} is identical to R^{5c}; Z′ represents a lower alkylene group; R represents a lower alkyl group]



Referring to the above schema, the reaction between compound (5) and compound (6) is carried out in the presence of an alkali, such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate, sodium hydroxide, etc., in an inert solvent, such as DMF, N,N-dimethylacetamide (DMA), hexamethylphosphoric triamide (HMPA), acetone, methanol, ethanol, methanol-water, ethanol-water and so on. This reaction goes to completion in about 5 - 30 hours at room temperature to the reflux temperature of the solvent.

The resultant compound (7) can be reacted with a phosphorous triester (8) to give compound (9). This reaction can be carried out in a solvent such as lower alcohols, aromatic or aliphatic hydrocarbons, DMF, etc. but is preferably conducted in the absence of a solvent in most cases. If necessary, a salt of iodine such as sodium iodide, potassium iodide, etc. can be added to the reaction system and usually the reaction is preferably conducted using said phosphorous triester (8) in excess at a temperature of about 130 - 170°C for about 1 - 20 hours.

The compound (9) can then be hydrolyzed to compound (4'). This hydrolysis reaction is carried out in the presence of an aqueous alkali solution, such as aqueous sodium hydroxide solution, aqueous potassium

hydroxide solution, etc., in an inert solvent such as methanol, ethanol, 2-propanol, etc. and this reaction goes to completion in about 1 - 15 hours at a temperature somewhere between 0°C and room temperature.

The compound (4') can be chlorinated at the carboxyl function to give compound (5'). This chlorination reaction is carried out using dichloromethane, chloroform, DMF or the like either singly or in combination as the solvent and a small excess of thionyl chloride, phosphorus oxychloride, phosphorus pentachloride or the like as the chlorinating agent at room temperature to about 60 °C for about 1 - 8 hours.

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

Among the species of compound (I) according to the invention, the compound in which Z is a lower alkylene group having a lower alkyl or phenyl(lower)alkyl group as a substituent may exist as optical isomers which, of course, are subsumed in the concept of the compound of the invention. The above optical isomers can be easily fractionated by the conventional resolution

AUSTRALIA PATENT OFFICE

procedures such as optical resolution.

The compound of the invention is put to use in a variety of pharmaceutical compositions prepared using suitable pharmaceutically acceptable carriers. Such pharmaceutically acceptable carriers include various diluents or excipients such as fillers, volume builders, binders, humectants, disintegrators, surfactants, lubricants, etc. and are selectively employed according to the desired 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, 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, 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, hydroxypropylcellulose, methylcellulose, polyvinylpyrrolidone, etc., a disintegrator such as carboxymethylcellulose sodium, carboxymethylcellulose

AUSTRALIA MS PATENT OFFICE

calcium, low-substituted hydroxypropylcellulose, dry starch, sodium alginate, agar powder, laminaran powder, sodium hydrogen carbonate, calcium carbonate, etc., a 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, 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 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.

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, gum tragacanth powder, gelatin, ethanol, etc. and disintegrators such as laminaran, starch, etc. can be employed.

The capsules can be manufactured in the conventional manner by blending the compound of the invention

AUSTRALIA MS PATENT OFFICE

with any of the various pharmaceutically acceptable carriers mentioned above and filling the resulting composition into hard gelatin capsule shells, soft gelatin capsule shells or the like.

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

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 alcohol, macrogols, propylene glycol, ethoxylated isostearyl alcohol, polyoxy-isostearyl alcohol, polyoxyethylene sorbitan fatty acid esters, etc. can be employed. In this operation, sodium chloride, glucose or glycerin may be added to the composition in a sufficient amount to provide an isotonic solution and the conventional solubilizer, buffer and local anesthetic can also be added.

The eye-drops can be manufactured in the conventional manner using sterile distilled water as the vehicle, sodium dihydrogen phosphate and/or sodium monohydrogen phosphate, for instance, as the buffer,

AUSTRALIA PATENT OFFICE

sodium chloride or the like as the isotonizing agent, and benzalkonium chloride, chlorobutanol or the like as the antimicrobial agent.

If necessary, various coloring agents, preservatives, perfumes, flavors, sweeteners etc. as well as other pharmacologically active substances can be incorporated in the various dosage forms mentioned above.

There is no particular limitation on the treatment regimen for the pharmaceutical composition of the invention. Thus, the proper regimen 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, pills, solutions, suspensions, emulsions, granules and capsules are administered by the oral route. The injections are administered either as they are or in admixture with the conventional glucose, amino acid or other infusions by the intravenous route or, if necessary, alone by the intramuscular, intradermal, subcutaneous or intraperitoneal route. The suppositories are administered intrarectally and the eye-drops are instilled into the eye.

The proportion of the compound of the invention in the pharmaceutical composition described above is not much critical and can be liberally selected from a broad



range. Generally, however, it is advantageous to insure that the compound accounts for about 1 to 70 weight % of the final composition. The dosing amount of the pharmaceutical composition can be selected according to the selected regimen, patient's age, sex and other characteristics, severity of disease and other conditions. Generally, however, the dosage of the compound of the invention as the active ingredient is preferably about 0.5 - 20 mg per kg body weight and this amount can be administered in 1 ~ 4 divided doses. In the case of an ophthalmic preparation for topical application, the dosage of the active compound is preferably selected from the range of about 0.3 - 2 μg.

BEST MODE FOR PRACTICING THE INVENTION

The following production examples for the compound of the invention, formulation examples for pharmaceutical compositions using the compound of the invention and pharmacological test examples are intended to describe the invention in further detail.

Example 1

Production of diethyl 4-[(2-benzothiazolyl)carbamoyl] benzylphosphonate

In 30 ml of dry dichloromethane were dissolved 3.0 g of 2-aminobenzothiazole and 10 ml of pyridine and while the resulting solution was stirred under ice-

AUSTRALIAN PATENT OFFICE

cooling, a solution of 5.8 g 4-[(diethoxyphosphoryl)-methyl]benzoyl chloride in 10 ml dry dichloromethane was slowly added dropwise. The stirring was continued at room temperature for 10 hours, after which the reaction mixture was diluted with 30 ml of 10% aqueous sodium hydrogen carbonate solution and extracted with chloroform. The chloroform layer was washed serially with 30 ml of 10% hydrochloric acid and 30 ml of water and dried over anhydrous sodium sulfate and the solvent was distilled off under reduced pressure. The residue was subjected to silica gel column chromatography (eluent: chloroform-ethyl acetate = 1:1) and the resulting crude crystals were recrystallized from ethanol to provide 6.8 g of the title compound as colorless crystals. The structure and melting point of the compound thus obtained are shown in Table 1.

Example 2 - 26

Various species of the compound of the invention were obtained in the same manner as Example 1. The structures and melting points of these compounds are also shown in Table 1.

Example 27 - 45

Various species of the compound of the invention were produced in the same manner as Example 1. The structures and melting points of these compounds are

AUSTRALIA PATENT OFFICE

shown in Table 2. As to an oily compound, its ^{1}H-NMR spectrum and mass spectrum (MS) are also shown in the table.

Example 46

Production of ethyl 4-[(4-methoxybenzothiazol-2-yl)-carbamoyl]benzylphosphonate

In 50 ml of dry acetonitrile were suspended 5.2 g (12 mM) of the compound obtained in Example 3 and 5.2 g (60 mM) of lithium bromide and the suspension was refluxed for 20 hours. The reaction mixture was then allowed to cool to room temperature and the resultant precipitate was recovered by filtration and washed with three 60 ml portions of acetonitrile. The crystals thus obtained were dissolved in 400 ml of water and while the solution was stirred at room temperature, 10 ml of concentrated hydrochloric acid was gradually added. The mixture was stirred at room temperature for 30 minutes, at the end of which time the resultant crystals were recovered by filtration and washed with three 300 ml portions of water. The crude crystals thus obtained were suspended in 200 ml of hot methanol and the insolubles were collected by filtration and washed with 50 ml of methanol. The resultant crystals were further suspended in 200 ml of methanol-chloroform (1:1) and the insolubles were recovered by filtration and washed with



50 ml of methanol and 50 ml of chloroform in the order mentioned to provide 1.8 g of the title compound as colorless crystals. The structure and melting point of this compound are shown in Table 2.

Example 47

Production of diethyl 2-[4-{(4-methoxybenzothiazol-2-yl)carbamoyl}phenoxy]ethylphosphonate

To 300 ml of acetonitrile were added 16.6 g (0.1 mole) of ethyl 4-hydroxybenzoate, 31.6 g (0.22 mole) of 1-bromo-2-chloroethane and 60.8 g of anhydrous potassium carbonate and the mixture was refluxed for 20 hours. The reaction mixture was then allowed to cool to room temperature and the solid matter was filtered off. The filtrate was concentrated under reduced pressure. To the resultant oily residue were added 15 g (0.1 mole) of sodium iodide and 50 g (0.3 mole) of triethyl phosphite and the mixture was stirred at 160°C for 18 hours. The reaction mixture was then allowed to cool to room temperature, after which 50 ml of ethanol was added to the reaction mixture. While this mixture was stirred under ice-cooling, 100 ml of 2 N aqueous sodium hydroxide solution was gradually added portionwise. The mixture was stirred at room temperature for 12 hours, at the end of which time 150 ml of water and 150 ml of chloroform were added. After phase separation, the water layer was

AUSTRALIAN PATENT OFFICE

separated. This aqueous solution was acidified with 150 ml of 4 N hydrochloric acid and extracted with chloroform. The chloroform layer was washed with 200 ml of water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: chloroform-ethyl acetate = 1:1) to provide 3.3 g of 4-[2-(diethoxyphosphoryl)ethoxy]benzoic acid as colorless crystals (m.p. 86-88°C).

Then, 3.0 g (10 mM) of the above crystals were suspended in 15 ml of dry dichloromethane and while the suspension was stirred at room temperature, 1.25 g (10.5 mM) of thionyl chloride and 0.22 g (3 mM) of DMF were added. The mixture was further stirred at 40°C for 1 hour. The resulting reaction mixture was then directly subjected to a reaction similar to that described in Example 1 to provide the title compound.

The structure and melting point of this compound are shown in Table 2.

Example 48

Production of diethyl 3-[4-{(4-methoxybenzothiazol-2-yl)carbamoyl}phenoxy]propylphosphonate

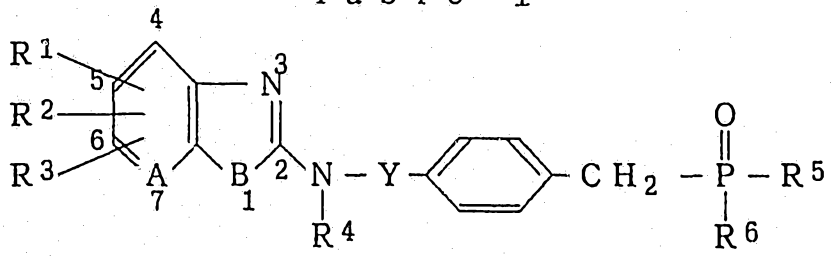
Using 1-bromo-3-chloropropane, the procedure of Exampel 47 was otherwise repeated to provide the title compound via 4-[3-(diethoxyphosphoryl)propoxy]benzoic

AUSTRALIAN PATENT OFFICE

acid (m.p. 107 - 110°C).

The structure and melting point of this compound are shown in Table 2.

Table 1



OEt: ethoxy group, Me: methyl group,
OMe: methoxy group, Ph: phenyl group

Example 1 Structure: $R^1=R^2=R^3=R^4=H$、$R^5=R^6=OEt$、A=CH、B=S、Y=C=O Mp: 189.5-191℃ Recrystallization Solvent: Ethanol
Example 2 Structure: $R^1=4-Me$、$R^2=R^3=R^4=H$、$R^5=R^6=OEt$、A=CH、B=S、Y=C=O Mp: 154-156℃ Recrystallization Solvent: Chloroform-n-hexane
Example 3 Structure: $R^1=4-OMe$、$R^2=R^3=R^4=H$、$R^5=R^6=OEt$、A=CH、B=S、Y=C=O Mp: 166-168℃ Recrystallization Solvent: Ethanol-n-hexane

PATENT OFFICE

Example 4
Structure:
$R^1 = 4-OCF_3$、$R^2 = R^3 = R^4 = H$、$R^5 = R^6 = OEt$、
$A = CH$、$B = S$、$Y = C = O$
Mp: 227-228℃ Recrystallization Solvent: Ethanol

Example 5
Structure:
$R^1 = 4-Cl$、$R^2 = R^3 = R^4 = H$、$R^5 = R^6 = OEt$、
$A = CH$、$B = S$、$Y = C = O$
Mp: 183-184.5℃
Recrystallization Solvent: Chloroform-n-hexane

Example 6
Structure:
$R^1 = 6-Me$、$R^2 = R^3 = R^4 = H$、$R^5 = R^6 = OEt$、
$A = CH$、$B = S$、$Y = C = O$
Mp: 210-212℃
Recrystallization Solvent: Chloroform-n-hexane

Example 7
Structure:
$R^1 = 6-OMe$、$R^2 = R^3 = R^4 = H$、$R^5 = R^6 = OEt$、
$A = CH$、$B = S$、$Y = C = O$
Mp: 175-177℃
Recrystallization Solvent: Chroloform-n-hexane

Example 8
Structure:
$R^1 = 6-OEt$、$R^2 = R^3 = R^4 = H$、$R^5 = R^6 = OEt$、
$A = CH$、$B = S$、$Y = C = O$
Mp: 204.5-206.5℃
Recrystallization Solvent: Chloroform-n-hexane

AUSTRALIA PATENT OFFICE

Example 9
Structure:
R^1 = 6-F, R^2 = R^3 = R^4 = H, R^5 = R^6 = OEt, A = CH, B = S, Y = C = O
Mp: 210.5-212.5℃
Recrystallization Solvent: Chloroform-n-hexane

Example 10
Structure:
R^1 = 6-Cl, R^2 = R^3 = R^4 = H, R^5 = R^6 = OEt, A = CH, B = S, Y = C = O
Mp: 227-229℃
Recrystallization Solvent: Chloroform-n-hexane

Example 11
Structure:
R^1 = 6-Br, R^2 = R^3 = R^4 = H, R^5 = R^6 = OEt, A = CH, B = S, Y = C = O
Mp: 228-229.5℃ Recrystalization Solvent: Ethanol-n-hexane

Example 12
Structure:
R^1 = 6-NO_2, R^2 = R^3 = R^4 = H, R^5 = R^6 = OEt, A = CH, B = S, Y = C = O
Mp: 249-251℃
Recrystallization Solvent: Ethyl acetate-n-hexane

Example 13
Structure:
R^1 = 4-OMe, R^2 = 6-OMe, R^3 = R^4 = H, R^5 = R^6 = OEt, A = CH, B = S, Y = C = O
Mp: 210-211℃
Recrystallization Solvent: Dichloromethane-n-hexane

AUSTRALIAN PATENT OFFICE

Example 14
Structure:
R^1 = 5-Me, R^2 = 6-Me, R^3 = R^4 = H,
R^5 = R^6 = OEt, A = CH, B = S, Y = C=O
Mp: 219-221℃ Recrystallization Solvent: Ethanol-n-hexane

Example 15
Structure:
R^1 = 5-Cl, R^2 = 6-OMe, R^3 = R^4 = H,
R^5 = R^6 = OEt, A = CH, B = S, Y = C=O
Mp: 209-212℃
Recrystallization Solvent: Dichloromethane-n-hexane

Example 16
Structure:
R^1 = 4-COMe, R^2 = 6-OMe, R^3 = 7-OMe, R^4 = H,
R^5 = R^6 = OEt, A = C, B = S, Y = C=O
Mp: 184-187℃
Recrystallization Solvent: Chloroform-n-hexane

Example 17
Structure:
R^1 = 4-OMe, R^2 = R^3 = H, R^4 = Me, R^5 = R^6 = OEt,
A = CH, B = S, Y = C=O
Mp: 168-169℃
Recrystallization Solvent: Dichloromethane-n-hexane

Example 18
Structure:
R^1 = 4-OMe, R^2 = R^3 = H, R^4 = Ph-CH_2-,
R^5 = R^6 = OEt, A = CH, B = S, Y = C=O
Mp: 116-119℃
Recrystallization Solvent: Dichloromethane-n-hexane

Example 19
Structure:
R^1 = 4-OMe、R^2 = R^3 = R^4 = H、R^5 = R^6 = OEt、
A = CH、B = S、Y = SO_2
Mp: 200-204℃
Recrystallization Solvent: Dichloromethane-n-hexane

Example 20
Structure:
R^1 = 4-OMe、R^2 = R^3 = R^4 = H、R^5 = R^6 = OMe、
A = CH、B = S、Y = C = O
Mp: 162.5-164.5℃
Recrystallization Solvent: Ethyl acetate

Example 21
Structure:
R^1 = R^2 = R^3 = R^4 = H、R^5 = R^6 = OEt、
A = N、B = S、Y = C = O
Mp: 206-208℃
Recrystallization Solvent: Methanol-n-hexane

Example 22
Structure:
R^1 = R^2 = R^3 = H、R^4 = Me、
R^5 = R^6 = OEt、A = N、B = S、Y = C = O
Mp: 133-135℃
Recrystallization Solvent: Dichloromethane-n-hexane

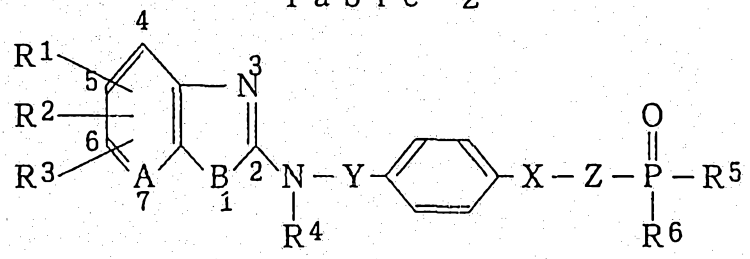
Example 23
Structure:
R^1 = R^2 = R^3 = H、R^4 = Ph-CH_2-、R^5 = R^6 = OEt、
A = N、B = S、Y = C = O
Mp: 137-139℃
Recrystallization Solvent: Dichloromethane-n-hexane

AUSTRALIA PATENT OFFICE

Example 24 Structure: $R^1=R^2=R^3=R^4=H$、$R^5=R^6=OEt$、A=CH、 B=NH、Y=C=O Mp: 173.5-175.5℃ Recrystallization Solvent: Ethyl acetate-n-hexane
Example 25 Structure: $R^1=R^2=R^3=R^4=H$、$R^5=R^6=OEt$、A=CH、 B=N-Me、Y=C=O Mp: 188-190℃ Recrystallization Solvent: Ethyl acetate-n-hexane
Example 26 Structure: $R^1=R^2=R^3=R^4=H$、$R^5=R^6=OEt$、A=CH、 B=N-CH_2Ph、Y=C=O Mp: 112-113℃ Recrystallization Solvent: Ethyl acetate-n-hexane

AUSTRALIAN PATENT OFFICE

Table 2



OEt: ethoxy group, Me: methyl group,
OMe: methoxy group, Ph: phenyl group

Example 27 Structure: R^1 = 4-OMe、R^2 = R^3 = R^4 = H、 R^5 = R^6 = $-OCH(CH_3)_2$、A=CH、B=S、 Y= C=O、X=Single bond、Z= $-CH_2-$ Mp: 206.5-207.5℃ Recrystallization Solvent: Ethyl acetate-n-hexane
Example 28 Structure: R^1 = 4-OMe、R^2 = R^3 = R^4 = H、 R^5 = R^6 = $-O-n-C_4H_9$、A=CH、B=S、Y=C=O X=Single bond、Z= $-CH_2-$ Mp: 167-168.5℃ Recrystallization Solvent: Ethanol-n-hexane
Example 29 Structure: R^1 = 4-OMe、R^2 = R^3 = R^4 = H、R^5 = OMe、 R^6 = OEt、A=CH、B=S、Y=C=O、X=Single bond、 Z= $-CH_2-$ Mp: 166-168℃ Recrystallization Solvent: Ethyl acetate-n-hexane



Example 30
Structure:
R^1 = 4-OMe, R^2 = R^3 = R^4 = H, R^5 = OEt,
R^6 = $-OCH(CH_3)_2$, A = CH, B = S, Y = C=O,
X = Single bond, Z = $-CH_2-$
Mp: 155~157℃
Recrystallization Solvent: Ethanol-n-hexane

Example 31
Structure:
R^1 = 4-OMe, R^2 = R^3 = R^4 = H, R^5 = Ph,
R^6 = OEt, A = CH, B = S, Y = C=O
X = Single bond, Z = $-CH_2-$
Mp: 101~104℃
Recrystallization Solvent: Ethyl acetate-n-hexane

Example 32
Structure:
R^1 = 6-CF_3, R^2 = R^3 = R^4 = H, R^5 = R^6 = OEt,
A = CH, B = S, Y = C=O, X = Single bond, Z = $-CH_2-$
Mp: 223-224.5℃
Recrystallization Solvent: Dichloromethane-n-hexane

Example 33
Structure:
R^1 = 4-COPh, R^2 = 6-Cℓ, R^3 = R^4 = H,
R^5 = R^6 = OEt, A = CH, B = S, Y = C=O,
X = Single bond, Z = $-CH_2-$
Mp: 233-234℃ (dec.)
Recrystallization Solvent: Chloroform-n-hexane

PATENT OFFICE

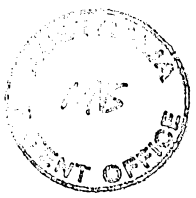
Example 34
Structure:
R^1 = 4-COMe, R^2 = 6-Br, R^3 = R^4 = H,
R^5 = R^6 = OEt, A = CH, B = S, Y = C=O,
X = Single bond, Z = $-CH_2-$
Mp: 219~220℃ (dec.)
Recrystallization Solvent: Dichloromethane-n-hexane

Example 35
Structure:
R^1 = 6-COOEt, R^2 = R^3 = R^4 = H, R^5 = R^6 = OEt,
A = CH, B = S, Y = C=O, X = Single bond, Z = $-CH_2-$
Mp: 225~226.5℃
Recrystallization Solvent: Chloroform-n-hexane

Example 36
Structure:
R^1 = 6-SMe, R^2 = R^3 = R^4 = H, R^5 = R^6 = OEt,
A = CH, B = S, Y = C=O, X = Single bond, Z = $-CH_2-$
Mp: 179-180℃
Recrystallization Solvent: Dichloromethane-n-hexane

Example 37
Structure:
R^1 = 6-OCH_2Ph, R^2 = R^3 = R^4 = H, R^5 = R^6 = OEt,
A = CH, B = S, Y = C=O, X = Single bond, Z = $-CH_2-$
Mp: 182-183℃
Recrystallization Solvent: Chloroform-n-hexane

Example 38
Structure:
R^1 = 6-$CONH_2$, R^2 = R^3 = R^4 = H, R^5 = R^6 = OEt,
A = CH, B = S, Y = C=O, X = Single bond, Z = $-CH_2-$
Mp: 257-258.5℃
Recrystallization Solvent: Chloroform-methanol



Example 39
Structure:
R^1 = 4−OMe、R^2 = R^3 = R^4 = H、R^5 = R^6 = OPh、
A = CH、B = S、Y = C = O、X = O、Z = Single bond
^{1}H−NMR (δ : ppm) [$CDCl_3$] :
3.55 (s, 3H), 6.73 (d, 1H, J = 7.9Hz),
7.1−7.5 (m, 12H), 7.9−8.4 (m, 4H),
12.0 (br. s, 1H)
MS (EI) m/z :
532 (M^+), 353 (M−$C_8H_7N_2OS$, base)

Example 40
Structure:
R^1 = 5−Cl、R^2 = R^3 = R^4 = H、R^5 = R^6 = OEt、
A = CH、B = O、Y = C = O、X = Single bond、Z = $-CH_2-$
Mp: 190.5∼192.0℃
Recrystallization Solvent: Ethyl acetate

Example 41
Structure:
R^1 = 6−$OCH_2-COOEt$、R^2 = R^3 = R^4 = H、
R^5 = R^6 = OEt、
A = CH、B = S、Y = C = O、X = Single bond、Z = $-CH_2-$
Mp: 187.5−188.5℃
Recrystallization Solvent: Chloroform-n-hexane

Example 42
Structure:
R^1 = 4−OMe、R^2 = R^3 = R^4 = H、R^5 = R^6 = OEt、
A = CH、B = S、Y = C = O、X = Single bond、Z = $-\underset{\displaystyle CH_2Ph}{\overset{|}{C}}H-$
Mp: 74−76℃ Recrystallization Solvent: Chloroform-n-hexane

PATENT OFFICE

Example 43
Structure:
R^1 = 4-OMe, R^2 = R^3 = R^4 = H, R^5 = R^6 = OEt,
A = CH, B = S, Y = C = O, X = Single bond, Z = $-\underset{\underset{CH_3}{|}}{CH}-$
Mp: 85-87℃ Recrystallization Solvent: Ethanol-n-hexane

Example 44
Structure:
R^1 = 4-Ph, R^2 = 6-Br, R^3 = R^4 = H,
R^5 = R^6 = OEt, A = CH, B = S, Y = C = O,
X = Single bond, Z = $-CH_2-$
Mp: 208~209℃
Recrystallization Solvent: Chloroform-n-hexane

Example 45
Structure:
R^1 = 4-OMe, R^2 = R^3 = R^4 = H, R^5 = OEt,
R^6 = OCH_2Ph, A = CH, B = S, Y = C = O,
X = Single bond, Z = $-CH_2-$
Mp: 140-143℃
Recrystallization Solvent: Ethyl acetate-n-hexane

Example 46
Structure:
R^1 = 4-OMe, R^2 = R^3 = R^4 = H, R^5 = OH, R^6 = OEt,
A = CH, B = S, Y = C = O, X = Single bond, Z = $-CH_2-$
Mp: 255-256.5℃ (dec.)



Example 47
Structure:
R^1 = 4-OMe、R^2 = R^3 = R^4 = H、R^5 = R^6 = OEt、
A = CH、B = S、Y = C = O、X = O、Z = $-CH_2\ CH_2-$
Mp: 150-153℃
Recrystallization Solvent: Dichloromethane-n-hexane

Example 48
Structure:
R^1 = 4-OMe、R^2 = R^3 = R^4 = H、R^5 = R^6 = OEt、
A = CH、B = S、Y = C = O、X = O、Z = $-CH_2\ CH_2\ CH_2-$
Mp: 168～170.5℃
Recrystallization Solvent: Ethanol-n-hexane



Formulation Example 1

Manufacture of tablets using the compound obtained in Example 3 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)
Compound of Example 3	250
Lactose (JP)	33.5
Corn starch (JP)	16.5
Carboxymethylcellulose calcium (JP)	12.5
Methylcellulose (JP)	6.0
Magnesium stearate (JP)	1.5
Total	320.0

According to the above formula, the compound of Example 3, lactose, corn starch and carboxymethyl cellulose calcium were well blended and granulated using an aqueous solution of methyl cellulose. The granulation was passed through a 24-mesh sieve and the granules under the sieve were mixed with magnesium stearate and compression-molded.

Formulation Example 2 Manufacture of capsules

Using the compound obtained in Example 5 as an active ingredient, hard gelatin capsules (1000 units)

PATENT OFFICE

each containing 250 mg of the active ingredient were manufactured according to the following formula.

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

Thus, according to the above formula, the respective ingredients were finely divided and the powders obtained were 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

Using the compound obtained in Example 13 as an active ingredient, granules (1000 g) containing 500 mg of the active ingredient in each gram were manufactured according to the following formula.

Ingrdient	Amount (g)
Compound of Example 13	500
Crystalline cellulose (JP)	100
Corn starch (JP)	250

PATENT OFFICE

Lactose (JP)	100
Carboxymethylcellulose calcium (JP)	40
Hydroxypropylmethylcellulose (JP)	10
Total	1000

Thus, according to the above formula, the compound of Example 13, lactose, corn starch, crystalline cellulose and carboxymethylcellulose calcium were thoroughly blended and kneaded with an aqueous solution of hydroxypropylcellulose. 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

Hypolipidemic effect in rats with Triton WR1339-induced hyperlipidemia

An experiment for assaying hypolipidemic activity in rats with Triton WR1339-induced hyperlipidemia was performed according to the method of Kuroda et al. [Biochem. Biophys. Acta., 489, 119 (1977)], as follows.

Thus, using 6 - 7-week-old male Wistar rats in groups of 6 (test groups), a solution of 300 mg/kg Triton in physiological saline was administered into the tail vein and, at the same time, 100 mg/kg of the test compound suspended in 5% gum arabic solution was



administered orally.

As a control group, a group of 6 rats given Triton were orally dosed with 5% gum arabic solution.

Twenty-four hours after administration of Triton, blood was withdrawn from the abdominal aorta and the plasma total cholesterol and triglyceride were determined using Cholesterol C-Test Wako and Triglyceride G-Test Wako (both available from Wako Pure Chemical Industries, Ltd.), respectively.

Using the measured values in the control group as references, the rates of decrease (%) in plasma total cholesterol and triglyceride in the test group were calculated by means of the following equation.

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

The test rats were deprived of food before Triton administration through completion of blood sampling but allowed free access to drinking water. The rates of decrease in total cholesterol are shown in Table 3 and those in triglyceride are shown in Table 4.

AUSTRALIA PATENT OFFICE

Table 3

Test compound (Example No.)	Rate of decrease in total cholesterol (%)
1	40
3	56
13	70
26	43
27	42
29	47
30	79
31	69
34	71
42	45
43	45
45	62

Table 4

Test compound (Example No.)	Rate of decrease in triglyceride (%)
1	62
2	44
3	83
4	47
10	40
11	44
13	94
20	48
25	54
26	63
27	81
29	87
30	95
31	92
32	47
34	97
42	81
43	80
45	91

REGISTERED PATENT OFFICE

It is apparent from Tables 3 and 4 that all species of the compound of the invention have excellent hypolipidemic activity.

Pharmacological Test Example 2

Hypoglycemic effect in rats with streptozotocin-induced diabetes

The rat model of streptozotocin-induced diabetes was constructed according to Doi's method [Folia Endocrinologica Japonica, 51 (3), 129 (1975)] as below and the hypoglycemic activity of the compound of the invention was assayed in the model by the following procedure.

Thus, using 5-week-old male Wistar rats in groups of 7 (test groups), 100 mg/kg of streptozotocin dissolved in 0.01 M citrate buffer (pH 4.5) was administered into the tail vein and on day 6 after this administration, a suspension of 30 mg/kg of the compound obtained in Example 3 in 5% gum arabic solution was orally administered.

As a control group, a group of 6 rats given streptozotocin were orally dosed with 5% gum arabic solution.

Four hours after administration of the test compound or 5% gum arabic solution, blood was withdrawn from the abdominal aorta and the plasma glucose was

determined using Glucose C II-Test Wako (Wako Pure Chemical Industries, Ltd.).

The results in terms of mean ± SD are shown below in Table 5.

Table 5

	Plasma glucose level (mg/dl)
Control group	588 ± 69
Test group	495 ± 53**

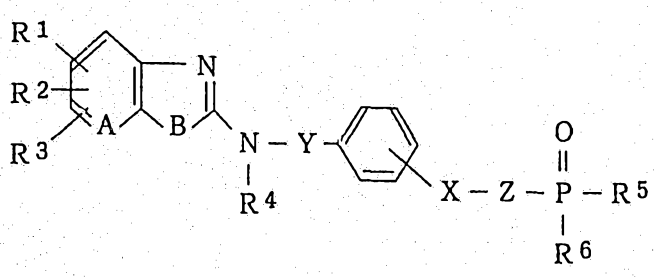
**: P<0.01 [Dunnet's test]

It is apparent from the above table that the plasma glucose level in the test group was significantly depressed as compared with the control group, indicating that the compound of the invention has excellent hypoglycemic activity.

AUSTRALIAN PATENT OFFICE

Claims

1. A phosphonic diester derivative of the general formula

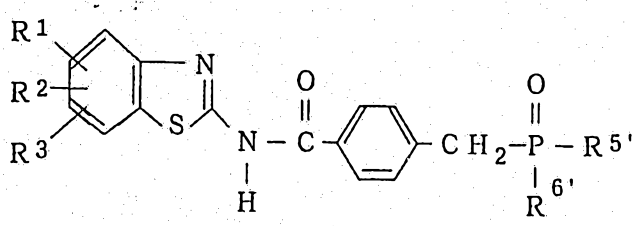


[wherein R^1, R^2 and R^3 are the same or different and each represents a hydrogen atom, a lower alkyl group, a phenyl group, a lower alkoxy group, a halogen-substituted lower alkyl group, a halogen-substituted lower alkoxy group, a lower alkanoyl group, a benzoyl group, a (lower)alkoxy-carbonyl group, a nitro group, a halogen atom, a (lower)alkylthio group, a phenyl(lower)alkoxy group, a carbamoyl group or a (lower)alkoxycarbonyl(lower)alkoxy group; R^4 represents a hydrogen atom, a lower alkyl group or a phenyl(lower)alkyl group; R^5 and R^6 are the same or different and each represents a lower alkoxy group, a phenyl group, a phenoxy group, a phenyl(lower)alkoxy group or a hydroxyl group; A represents a carbon atom or a nitrogen atom; B represents a group of the formula $=NR^7$ (where R^7 represents a hydrogen atom, a lower alkyl group or a phenyl(lower)alkyl group), an oxygen atom or a sulfur atom; Y represents a group of the formula C=O or a



group of SO_2; X represents an oxygen atom or a bond; Z represents a lower alkylene group optionally having a lower alkyl or phenyl(lower)alkyl group as a substituent or a bond; provided, however, that X and Z do not concurrently represent bonds]

2. The phosphonic diester derivative of Claim 1 which is represented by the general formula



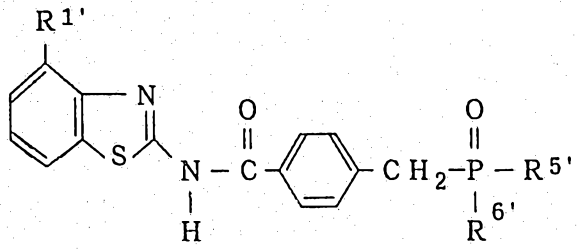
[wherein R^1, R^2 and R^3 are the same or different and each represents a hydrogen atom, a lower alkyl group, a phenyl group, a lower alkoxy group, a halogen-substituted lower alkyl group, a halogen-substituted lower alkoxy group, a lower alkanoyl group, a benzoyl group, a (lower)alkoxycarbonyl group, a nitro group, a halogen atom, a (lower)alkylthio group, a phenyl(lower)alkoxy group, a carbamoyl group or a (lower)alkoxycarbonyl(lower)alkoxy group; $R^{5'}$ and $R^{6'}$ are the same or different and each represents a lower alkoxy group, a phenyl group or a phenyl(lower)alkoxy group]

3. The phosphonic diester derivative of Claim 2 wherein R^1, R^2 and R^3 are groups selected from the class consisting of a hydrogen atom, a lower alkoxy group, a

AUSTRALIAN PATENT OFFICE

lower alkanoyl group and a halogen atom.

4. The phosphonic diester derivative of Claim 3 which may be represented by the general formula



[wherein $R^{1'}$ represents a lower alkoxy group, $R^{5'}$ and $R^{6'}$ are the same or different and each represents a lower alkoxy group, a phenyl group or a phenyl(lower)alkoxy group].

5. The phosphonic diester derivative of Claim 3 which is a compound selected from the class consisting of

(1) Diethyl 4-[(4-methoxybenzothiazol-2-yl)carbamoyl]-benzylphosphonate,

(2) Diethyl 4-[(4,6-dimethoxybenzothiazol-2-yl)-carbamoyl]benzylphosphonate,

(3) Diethyl 4-[(4-acetyl-6-bromobenzothiazol-2-yl)carbamoyl]benzylphosphonate, and

(4) Diethyl 4-[(4-chlorobenzothiazol-2-yl)carbamoyl]benzylphosphonate.

6. The phosphonic diester derivative of Claim 5 which is diethyl 4-[(4-methoxybenzothiazol-2-yl)-carbamoyl]benzylphosphonate.

7. An antihyperlipidemic composition comprising

AUSTRALIAN PATENT OFFICE

the phosphonic diester derivative claimed in any of Claims 1 through 6 as an active ingredient.

8. An antidiabetic composition comprising the phosphonic diester derivative claimed in any of Claims 1 through 6 as an active ingredient.

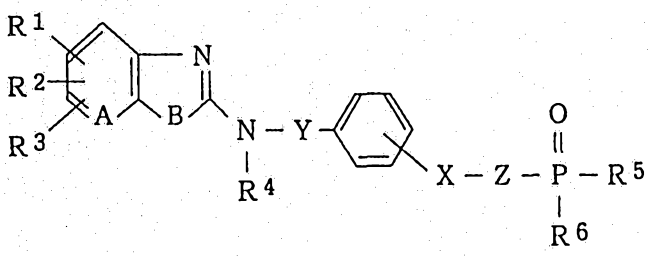
9. A method of treating hyperlipidemia characterized by administering to a patient a pharmacologically effective amount of the antihyperlipidemic composition claimed in Claim 7.

10. A method of treating diabetes characterized by administering a pharmacologically effective amount of the antidiabetic composition claimed in Claim 8.

AUSTRALIA PATENT OFFICE

ABSTRACT

The invention provides a phosphonic diester derivative of the general formula



The phosphonic diester derivative of the invention has hypoglycemic and hypolipidemic activities, for instance, and is of value as an antidiabetic or anti-hyperlipidemic agent.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP93/00660

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl^5 C07F9/6561, 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. Cl^5 C07F9/6561, A61K31/675

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.
A	JP, A, 2-500744 (Aktiebolaget Haessle), March 15, 1990 (15. 03. 90), & WO, A, 8803921 & EP, A, 279149 & US, A, 5215974	1-8

☐ 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	Date of mailing of the international search report
September 21, 1993 (21. 09. 93)	October 12, 1993 (12. 10. 93)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP93/00660

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. [X] Claims Nos.: 9, 10
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 9 and 10 pertain to methods for treatment of the human body by therapy.

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.

国際調査報告

国際出願番号 PCT/JP 93/00660

A. 発明の属する分野の分類（国際特許分類（IPC））

Int. Cl[5] C07F9/6561, 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[5] C07F9/6561, A61K31/675

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

国際調査で使用した電子データベース（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
A	JP, A, 2-500744（アクチエボラゲット・ヘッスレ） 15. 3月. 1990（15. 03. 90） &WO, A, 8803921&EP, A, 279149 &US, A, 5215974	1-8

☐ C欄の続きにも文献が列挙されている。

☐ 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
21. 09. 93

国際調査報告の発送日
12.10.93

名称及びあて先
日本国特許庁（ISA/JP）
郵便番号100
東京都千代田区霞が関三丁目4番3号

特許庁審査官（権限のある職員）
佐藤 修 印
4H 7106

電話番号 03-3581-1101 内線 3445

様式PCT/ISA/210（第2ページ）（1992年7月）

国際調査報告

国際出願番号 PCT/JP 93/00660

第Ⅰ欄 請求の範囲の一部の調査ができないときの意見（第1ページの1の続き）

法第8条第3項（PCT17条(2)(a)）の規定により、この国際調査報告は次の理由により請求の範囲の一部について作成しなかった。

1. ☑ 請求の範囲 9，10 は、この国際調査機関が調査をすることを要しない対象に係るものである。
つまり、

人の身体の治療による処置方法の発明である。

2. ☐ 請求の範囲＿＿＿＿＿＿＿＿は、有意義な国際調査をすることができる程度まで所定の要件を満たしていない国際出願の部分に係るものである。つまり、

3. ☐ 請求の範囲＿＿＿＿＿＿＿＿は、従属請求の範囲であってPCT規則6.4（a）の第2文及び第3文の規定に従って記載されていない。

第Ⅱ欄 発明の単一性が欠如しているときの意見（第1ページの2の続き）

次に述べるようにこの国際出願に二以上の発明があるとこの国際調査機関は認めた。

1. ☐ 出願人が必要な追加調査手数料をすべて期間内に納付したので、この国際調査報告は、すべての調査可能な請求の範囲について作成した。

2. ☐ 追加調査手数料を要求するまでもなく、すべての調査可能な請求の範囲について調査することができたので、追加調査手数料の納付を求めなかった。

3. ☐ 出願人が必要な追加調査手数料を一部のみしか期間内に納付しなかったので、この国際調査報告は、手数料の納付のあった次の請求の範囲のみについて作成した。

4. ☐ 出願人が必要な追加調査手数料を期間内に納付しなかったので、この国際調査報告は、請求の範囲の最初に記載されている発明に係る次の請求の範囲について作成した。

追加調査手数料の異議の申立てに関する注意
☐ 追加調査手数料の納付と共に出願人から異議申立てがあった。
☐ 追加調査手数料の納付と共に出願人から異議申立てがなかった。