07/883,398 QUINOLINE TYPE MEVALONOLACTONES 342163US

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Title of Invention: QUINOLINE TYPE MEVALONOLACTONES

Close Window

07/883,398	QUINOLINE TYPE MEVALONOLACTONES	342163US

Parent Continuity Data

Description	Parent Number	Parent Filing or 371(c) Date	AIA(First Inventor to File)	Parent Status	Patent Number
This application is a Division of	07/631,092	12-19-1990	No	Patented	5,872,130
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Child Continuity Data

07/978,884 filed on 11-19-1992 which is Patented claims the benefit of 07/883,398

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07/883,398	QUINOLINE TYPE MEVALONOLACTONES	342163US

Transaction History

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08-02-2013	PARALEGAL OR ELECTRONIC TERMINAL DISCLAIMER APPROVED
07-31-2013	Terminal Disclaimer Filed
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08-08-2011	FDA Final Eligibility Letter
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SERIAL NUMBER	FILING DATE	CLASS	SUBCLASS	GROUP ART UNIT	EXAMINER
07/883,398	05/15/92 RULE 60	514	311	~~1902~~ 1613	~~Spivack~~ RHOUET

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CONTINUING DATA********

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FOREIGN/PCT APPLICATIONS********

VERIFIED	JAPAN	207224/1987	08/20/87
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Foreign priority claimed 35 USC 119 conditions met	Verified and Acknowledged	Examiner's Initials	AS FILED	STATE OR COUNTRY	SHEETS DRWGS.	TOTAL CLAIMS	INDEP. CLAIMS	FILING FEE RECEIVED	ATTORNEY'S DOCKET NO.
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HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231

IN RE APPLICATION OF: :
YOSHIHIRO FUJIKAWA ET AL :**GROUP ART UNIT: 129**
SERIAL NO.: NEW DIV APPLN :**EXAMINER: RICHTER**
OF 07/631,092
FILED: HEREWITH :
FOR: QUINOLINE TYPE MEVALONOLACTONES

SIR:

Attached hereto for filing are the following papers:

DIVISIONAL APPLICATION, NOTICE OF PRIORITY, EXECUTED DECLARATION OF KELBER, PRELIMINARY AMENDMENT, AND UNEXECUTED DECLARATION OF MASAKI KITAHARA/WITH FEES

Our check in the amount of $690.00 is enclosed covering any required fees. In the event of any variance between the amount enclosed and the Patent Office Charges, please charge or credit the difference to our Deposit Account No. 15-0030. A duplicate copy of this letter is enclosed.

Respectfully submitted,

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Norman F. Oblon
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Steven B. Kelber
Registration No.: 30,073
Attorneys of Record

07/883398

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: :

YOSHIHERO [illegible]IKAWA ET AL : GROUP ART UNIT: 129

SERIAL NUMBER: 07/631,092 : EXAMINER: J. RICHTER

FILED: DECEMBER 19, 1990 :

FOR: QUINOLINE TYPE MEVALONOLACTONES

DECLARATION

HONORABLE COMMISSIONER OF PATENTS & TRADEMARKS
WASHINGTON, D.C. 20231

SIR:

I, **STEVEN B. KELBER**, declare the attached to be a true and accurate copy, as filed, of U.S. Patent Application Serial Number **07/631,092** filed **December 19, 1990 which is a continuation of 07/233,752, filed August 19,1988.**

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

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Our Ref.: NC-115

QUINOLINE TYPE MEVALONOLACTONES

The present invention relates to novel mevalonolactones having a quinoline ring, processes for their production, pharmaceutical compositions containing them and their pharmaceutical uses particularly as anti-hyperlipidemic, hypolipoproteinemic and anti-atherosclerotic agents, and intermediates useful for their production and processes for the production of such intermediates.

Some fermentation metabolic products such as compactine, CS-514, Mevinolin or semi-synthetic derivatives or fully synthetic derivatives thereof are known to be inhibitors against HMG-CoA reductase which is a rate limiting enzyme for cholesterol biosynthesis. (A. Endo J. Med Chem., 28(4) 401 (1985))

CS-514 and Mevinolin have been clinically proved to be potentially useful anti-hyperlipoproteinemic agents, and they are considered to be effective for curing or preventing diseases of coronary artery sclerosis or atherosclerosis. (IXth Int. Symp. Drugs Affect. Lipid

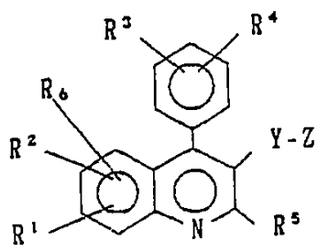
Metab., 1986, p30, p31, p66)

However, with respect to fully synthetic derivatives, particularly hetero aromatic derivatives of inhibitors against HMG-CoA reductase, limited information is disclosed in the following literatures:

WPI ACC NO. 84-158675, 86-028274, 86-098816, 86-332070, 87-124519, 87-220987, 88-07781, 88-008460, 88-091798 and 88-112505.

The present inventors have found that mevalonolactone derivatives having a quinoline ring, the corresponding dihydroxy carboxylic acids and salts and esters thereof have high inhibitory activities against cholesterol biosynthesis wherein HMG-CoA reductase acts as a rate limiting enzyme. The present invention has been accomplished on the basis of this discovery.

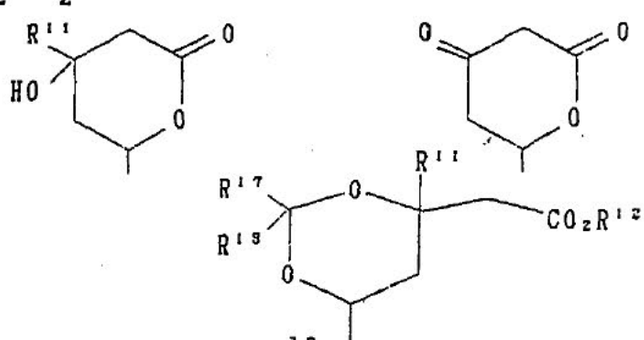
The novel mevalonolactone derivatives of the present invention are represented by the following formula I:



(I)

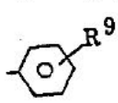
wherein R^1, R^2, R^3, R^4 and R^6 are independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-3} alkoxy, n-butoxy, i-butoxy, sec-butoxy, R^7R^8N- (wherein R^7 and R^8 are independently hydrogen or C_{1-3} alkyl), trifluoromethyl, trifluoromethoxy, difluoromethoxy, fluoro, chloro, bromo,

phenyl, phenoxy, benzyloxy, hydroxy, trimethylsilyloxy, diphenyl-t-butylsilyloxy, hydroxymethyl or $-O(CH_2)_\ell OR^{19}$ (wherein R^{19} is hydrogen or C_{1-3} alkyl, and ℓ is 1, 2 or 3); or when located at the ortho position to each other, R^1 and R^2, or R^3 and R^4 together optionally form $-CH=CH-CH=CH-$; or when located at the ortho position to each other, R^1 and R^2 together optionally form $-OC(R^{15})(R^{16})O-$ (wherein R^{15} and R^{16} are independently hydrogen or C_{1-3} alkyl); Y is $-CH_2-$, $-CH_2CH_2-$, $-CH=CH-$, $-CH_2-CH=CH-$ or $-CH=CH-CH_2-$; and Z is $-Q-CH_2WCH_2-CO_2R^{12}$,



or

(wherein Q is $-C(O)-$, $-C(OR^{13})_2-$ or $-CH(OH)-$; W is $-C(O)-$, $-C(OR^{13})_2-$ or $-C(R^{11})(OH)-$; R^{11} is hydrogen or C_{1-3} alkyl; R^{12} is hydrogen or R^{14} (wherein R^{14} is physiologically hydrolyzable alkyl or M (wherein M is NH_4, sodium, potassium, 1/2 calcium or a hydrate of lower alkylamine, di-lower alkylamine or tri-lower alkylamine)); two R^{13} are independently primary or secondary C_{1-6} alkyl; or two R^{13} together form $-(CH_2)_2-$ or $-(CH_2)_3-$; R^{17} and R^{18} are independently hydrogen or C_{1-3} alkyl; and R^5 is hydrogen, C_{1-6} alkyl, C_{2-3} alkenyl, C_{3-6} cycloalkyl,



(wherein R^9 is hydrogen, C_{1-4} alkyl, C_{1-3}

alkoxy, fluoro, chloro, bromo or trifluoromethyl), phenyl-$(CH_2)_m$- (wherein m is 1, 2 or 3), -$(CH_2)_n$CH(CH_3)-phenyl or phenyl-$(CH_2)_n$CH(CH_3)- (wherein n is 0, 1 or 2).

Various substituents in the formula I will be described in detail with reference to specific examples. However, it should be understood that the present invention is by no means restricted by such specific examples.

C_{1-6} alkyl for R^1, R^2, R^3, R^4, R^6 and R^9 includes, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl and t-butyl. C_{1-3} alkoxy for R^1, R^2, R^3, R^4 and R^6 includes, for example, methoxy, ethoxy, n-propoxy and i-propoxy.

C_{1-3} alkyl for R^{11} includes, for example, methyl, ethyl, n-propyl and i-propyl.

C_{1-3} alkyl for R^{13} includes, for example, methyl, ethyl, n-propyl and i-propyl.

Alkyl for R^{14} includes, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl and i-butyl.

M is a metal capable of forming a pharmaceutically acceptable salt, and it includes, for example, sodium and potassium.

CO_2M includes, for example, -CO_2NH_4 and -CO_2H· (primary to tertiary lower alkylamine such as trimethylamine).

C_{1-6} alkyl for R^5 includes, for example, methyl,

ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, n-pentyl and n-hexyl.

C_{3-6} cycloalkyl for R^5 includes, for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

C_{2-3} alkenyl for R^5 includes, for example, vinyl and i-propenyl.

Phenyl-$(CH_2)_m$- for R^5 includes, for example, benzyl, ß-phenylethyl and γ-phenylpropyl.

Phenyl-$(CH_2)_nCH(CH_3)$- for R^5 includes, for example, α-phenylethyl and α-benzylethyl.

C_{1-3} alkyl for R^7 and R^8 includes, for example, methyl, ethyl, n-propyl and i-propyl.

Further, these compounds may have at least one or two asymmetric carbon atoms and may have at least two to four optical isomers. The compounds of the formula I include all of these optical isomers and all of the mixtures thereof.

Among compounds having carboxylic acid moieties falling outside the definition of $-CO_2R^{12}$ of the carboxylic acid moiety of substituent Z of the compounds of the present invention, those which undergo physiological hydrolysis, after intake, to produce the corresponding carboxylic acids (compounds wherein the $-CO_2R^{12}$ moiety is $-CO_2H$) are equivalent to the compounds of the present invention.

Now, preferred substituents of the compounds of the present invention will be described.

In the following preferred, more preferred still further perferred and most preferred examples, the numerals for the positions of the substituents indicate the positions on the quinoline ring. For example, N' shown by e.g. 1' or 2' indicates the position of the substituent on the phenyl substituted at the 4-position of the quinoline ring (the carbon connected to the quinoline ring is designated as 1'). The meanings of the respective substituents are the same as the above-mentioned meanings.

Preferred substituents for R^1, R^2 and R^6 are hydrogen, fluoro, chloro, bromo, C_{1-3} alkyl, C_{1-3} alkoxy, C_{3-6} cycloalkyl, dimethylamino, hydroxy, hydroxymethyl, hydroxyethyl, trifluoromethyl, trifluoromethoxy, difluoromethoxy, phenoxy and benzyloxy.

Further, when R^6 is hydrogen, it is preferred that R^1 and R^2 together form methylenedioxy.

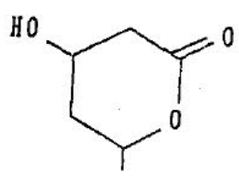
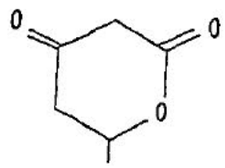
As preferred examples for R^3 and R^4, when R^4 is hydrogen, R^3 is hydrogen, 3'-fluoro, 3'-chloro, 3'-methyl, 4'-methyl, 4'-chloro and 4'-fluoro.

Other preferred combinations of R^3 and R^4 include 3'-methyl-4'-chloro, 3',5'-dichloro, 3',5'-difluoro, 3',5'-dimethyl and 3'-methyl-4'-fluoro.

Preferred examples for R^5 include primary and secondary C_{1-6} alkyl and C_{3-6} cycloalkyl.

Preferred examples for Y include $-CH_2-CH_2-$ and -CH=CH-.

Preferred examples for Z include

$-CH(OH)CH_2CH_2(OH)CH_2CO_2R^{12}$, $-CH(OH)CH_2C(O)CH_2CO_2R^{12}$ and $-CH(OH)CH_2C(OR^{13})_2CH_2CO_2R^{12}$.

Now, more preferred substituents of the compounds of the present invention will be described.

As more preferred examples for R^1, R^2 and R^6, when both R^2 and R^6 are hydrogen, R^1 is hydrogen, 5-fluoro, 6-fluoro, 7-fluoro, 8-fluoro, 5-chloro, 6-chloro, 7-chloro, 8-chloro, 5-bromo, 6-bromo, 7-bromo, 8-bromo, 5-methyl, 6-methyl, 7-methyl, 8-methyl, 5-methoxy, 6-methoxy, 7-methoxy, 8-methoxy, 5-trifluoromethyl, 6-trifluoromethyl, 7-trifluoromethyl, 8-trifluoromethyl, 6-trifluoromethoxy, 6-difluoromethoxy, 8-hydroxyethyl, 5-hydroxy, 6-hydroxy, 7-hydroxy, 8-hydroxy, 6-ethyl, 6-n-butyl and 7-dimethylamino.

When R^6 is hydrogen, R^1 and R^2 together represent 6-chloro-8-methyl, 6-bromo-7-methoxy, 6-methyl-7-chloro, 6-chloro-8-hydroxy, 5-methyl-2-hydroxy, 6-methoxy-7-chloro, 6-chloro-7-methoxy, 6-hydroxy-7-chloro, 6-chloro-7-hydroxy, 6-chloro-8-bromo, 5-chloro-6-hydroxy, 6-bromo-8-chloro, 6-bromo-8-hydroxy, 5-methyl-8-chloro, 7-hydroxy-8-chloro, 6-bromo-8-hydroxy, 6-methoxy-7-methyl, 6-chloro-8-bromo, 6-methyl-8-bromo,

6,7-difluoro, 6,8-difluoro, 6,7-methylenedioxy, 6,8-dichloro, 5,8-dimethyl, 6,8-dimethyl, 6,7-dimethoxy, 6,7-diethoxy, 6,7-dibromo or 6,8-dibromo.

When R^1, R^2 and R^6 are not hydrogen, they together represent 5,7-dimethoxy-8-hydroxy, 5,8-dichloro-6-hydroxy, 6,7,8-trimethoxy, 6,7,8-trimethyl, 6,7,8-trichloro, 5-fluoro-6,8-dibromo or 5-chloro-6,8-dibromo.

As more preferred examples for R^3 and R^4, when R^3 is hydrogen, R^4 is hydrogen, 4'-methyl, 4'-chloro or 4'-fluoro. When both R^3 and R^4 are not hydrogen, they together represent 3',5'-dimethyl or 3'-methyl-4'-fluoro.

As more preferred examples for R^5, the above-mentioned preferred examples of R^5 may be mentioned.

As preferred examples for Y, $-CH_2-CH_2-$ and (E)--CH=CH- may be mentioned. As more preferred examples for Z, the above preferred examples for Z may be mentioned.

Now, still further preferred substituents of the compounds of the present invention will be described. As examples for R^1, R^2 and R^6, when both R^2 and R^6 are hydrogen, R^1 is hydrogen, 6-methyl, 6-ethyl, 6-trifluoromethyl, 6-hydroxy, 6-methoxy, 6-chloro, 6-bromo, 6-n-butyl and 7-dimethylamino.

When only R^6 is hydrogen, R^1 and R^2 represent 6,8-dichloro, 5,8-dimethyl, 6,8-dimethyl, 6,7-dimethoxy, 6,7-diethoxy, 6,7-dibromo, 6,8-dibromo, 6,7-difluoro and 6,8-difluoro.

As still further preferred examples for R^3 and R^4,

when R^3 is hydrogen, R^4 is hydrogen, 4'-chloro or 4'-fluoro, or R^3 and R^4 together represent 3'-methyl-4'-fluoro.

Still further preferred examples for R^5 include ethyl, n-propyl, i-propyl and cyclopropyl.

Still further preferred examples for Y include (E)--CH=CH-.

As still further preferred examples for Z, the above-mentioned preferred example for Z may be mentioned.

Now, the most preferred substituents for the compounds of the present invention will be described.

As the most preferred examples for R^1, R^2 and R^6, when both R^2 and R^6 are hydrogen, R^1 is hydrogen, 6-methyl or 6-chloro.

When only R^6 is hydrogen, R^1 and R^2 together represent, for example, 6,7-dimethoxy.

As the most preferred examples for R^3 and R^4, R^3 is hydrogen and R^4 is hydrogen, 4'-chloro or 4'-fluoro.

The most preferred examples for R^5 include i-propyl and cyclopropyl. The most preferred example for Y may be (E)--CH=CH-.

As the most preferred examples for Z, the above-mentioned preferred examples for Z may be mentioned.

Now, particularly preferred specific compounds of the present invention will be presented. The following compounds (a) to (z) are shown in the form of carboxylic acids. However, the present invention include not only

the compounds in the form of carboxylic acids but also the corresponding lactones formed by the condensation of the carboxylic acids with hydroxy at the 5-position, and sodium salts and lower alkyl esters (such as methyl, ethyl, i-propyl and n-propyl esters) of the carboxylic acids, which can be physiologically hydrolyzed to the carboxylic acids.

(a) (E)-3,5-dihydroxy-7-[4'-(4''-fluorophenyl)-2'-(1''-methylethyl)-quinolin-3'-yl]-hept-6-enoic acid

(b) (E)-3,5-dihydroxy-7-[4'-(4''-fluorophenyl)-2'-(1''-methylethyl)-6'-chloro-quinolin-3'-yl]-hept-6-enoic acid

(c) (E)-3,5-dihydroxy-7-[4'-(4''-fluorophenyl)-2'-(1''-methylethyl)-6'-methyl-quinolin-3'-yl]-hept-6-enoic acid

(d) (E)-3,5-dihydroxy-7-[4'-(4''-fluorophenyl)-2'-(1''-methylethyl)-6',7'-dimethoxy-quinolin-3'-yl]-hept-6-enoic acid

(e) (E)-3,5-dihydroxy-7-[4'-(4''-fluorophenyl)-2'-cyclopropyl-quinolin-3'-yl]-hept-6-enoic acid

(f) (E)-3,5-dihydroxy-7-[4'-(4''-fluorophenyl)-2'-cyclopropyl-6'-chloro-quinolin-3'-yl]-hept-6-enoic acid

(g) (E)-3,5-dihydroxy-7-[4'-(4''-fluorophenyl)-2'-cyclopropyl-6'-methyl-quinolin-3'-yl]-hept-6-enoic acid

(h) (E)-3,5-dihydroxy-7-[4'-(4''-fluorophenyl)-2'-cyclopropyl-6',7'-dimethoxy-quinolin-3'-yl]-hept-6-enoic acid

(i) (E)-3,5-dihydroxy-7-[4'-(4''-chlorophenyl)-2'-(1''-methylethyl)-quinolin-3'-yl]-hept-6-enoic acid

(j) (E)-3,5-dihydroxy-7-[4'-(4''-chlorophenyl)-2'-(1''-methylethyl)-6'-chloro-quinolin-3'-yl]-hept-6-enoic acid

(k) (E)-3,5-dihydroxy-7-[4'-(4''-chlorophenyl)-2'-(1''-methylethyl)-6'-methyl-quinolin-3'-yl]-hept-6-enoic acid

(l) (E)-3,5-dihydroxy-7-[4'-(4''-chlorophenyl)-2'-(1''-methylethyl)-6',7'-dimethoxy-quinolin-3'-yl]-hept-6-enoic acid

(m) (E)-3,5-dihydroxy-7-[4'-(4''-chlorophenyl)-2'-cyclopropyl-quinolin-3'-yl]-hept-6-enoic acid

(n) (E)-3,5-dihydroxy-7-[4'-(4''-chlorophenyl)-2'-cyclopropyl-6'-chloro-quinolin-3'-yl]-hept-6-enoic acid

(o) (E)-3,5-dihydroxy-7-[4'-(4''-chlorophenyl)-2'-cyclopropyl-6'-methyl-quinolin-3'-yl]-hept-6-enoic acid

(p) (E)-3,5-dihydroxy-7-[4'-(4''-chlorophenyl)-2'-cyclopropyl-6'7'-dimethoxy-quinolin-3'-yl]-hept-6-enoic acid

(q) (E)-3,5-dihydroxy-7-[4'-phenyl-2'-(1''-methylethyl)-quinolin-3'-yl]-hept-6-enoic acid

(r) (E)-3,5-dihydroxy-7-[4'-phenyl-2'-(1''-methylethyl)-6'-chloro-quinolin-3'-yl]-hept-6-enoic acid

(s) (E)-3,5-dihydroxy-7-[4'-phenyl-2'-(1''-methylethyl)-6'-methyl-quinolin-3'-yl]-hept-6-enoic acid

(t) (E)-3,5-dihydroxy-7-[4'-phenyl-2'-(1''-

methylethyl)-6',7'-dimethoxy-quinolin-3'-yl]-hept-6-enoic acid

(u) (E)-3,5-dihydroxy-7-[4'-phenyl-2'-cyclopropyl-quinolin-3'-yl]-hept-6-enoic acid

(v) (E)-3,5-dihydroxy-7-[4'-phenyl-2'-cyclopropyl-6'-chloro-quinolin-3'-yl]-hept-6-enoic acid

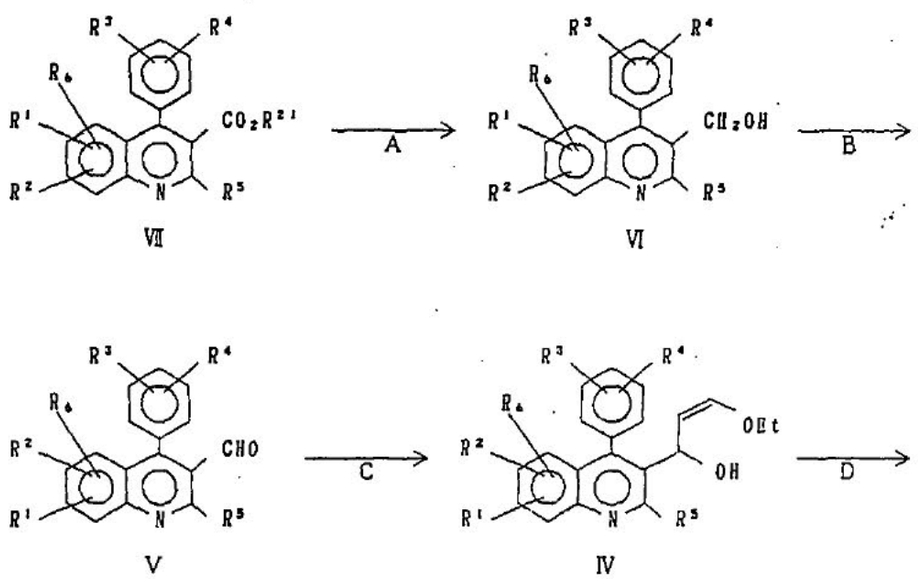
(w) (E)-3,5-dihydroxy-7-[4'-phenyl-2'-cyclopropyl-6'-methyl-quinolin-3'-yl]-hept-6-enoic acid

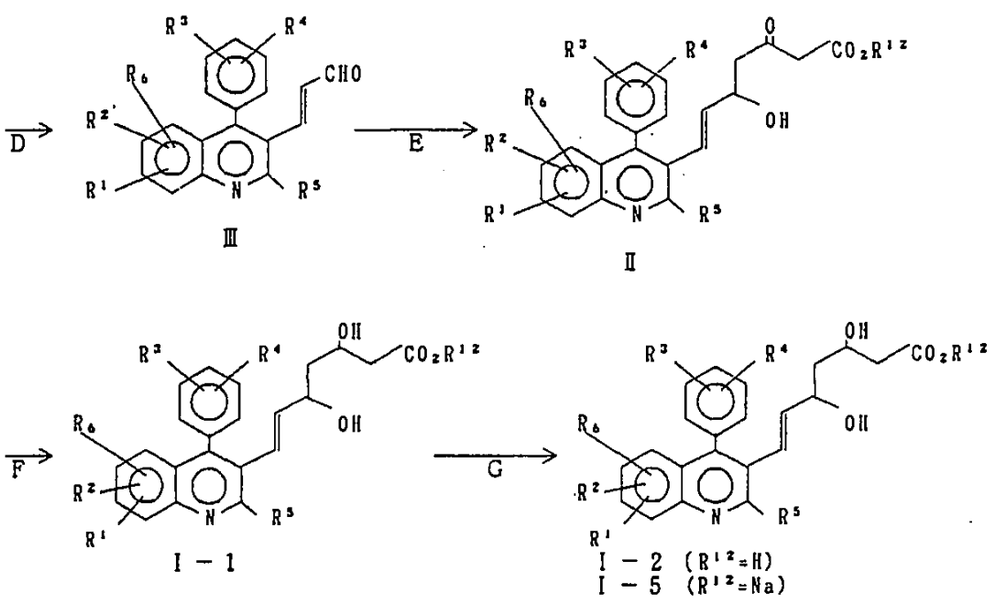
(x) (E)-3,5-dihydroxy-7-[4'-phenyl-2'-cyclopropyl-6',7'-dimethoxy-quinolin-3'-yl]-hept-6-enoic acid

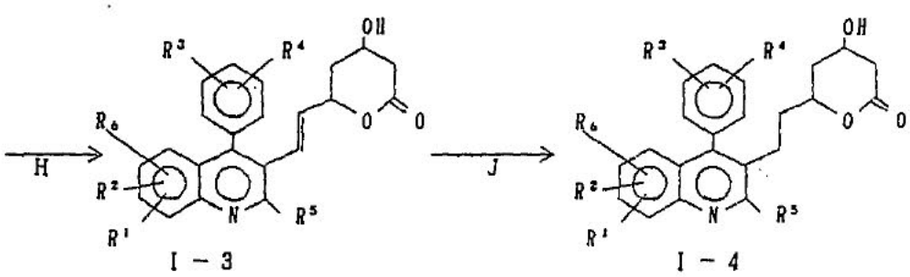
(y) (E)-3,5-dihydroxy-7-[4'-(4''-fluorophenyl)-2'-(1''-methylethyl)-6'-methoxy-quinolin-3'-yl]-hept-6-enoic acid

(z) (E)-3,5-dihydroxy-7-[4'-(4''-fluorophenyl)-2'-cyclopropyl-6'-methoxy-quinolin-3'-yl]-hept-6-enoic acid

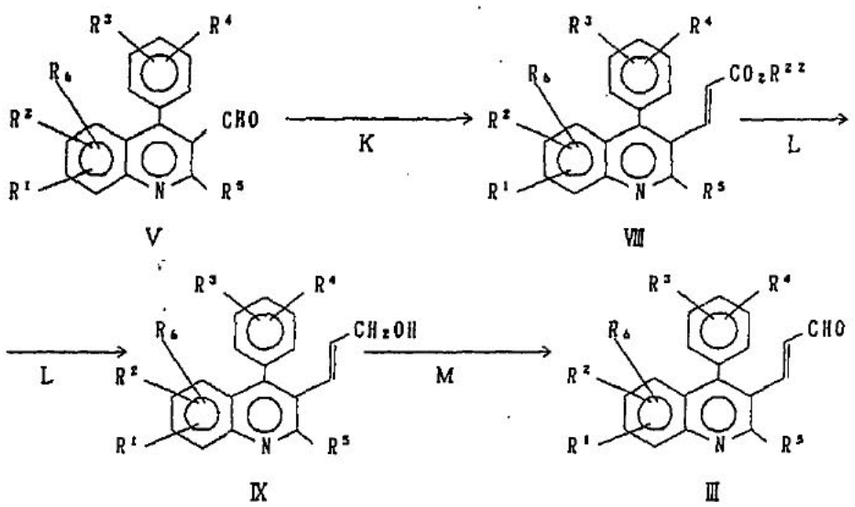
The mevalonolactones of the formula I can be prepared by the following reaction scheme. The enal III can also be prepared by processes K, L and M.

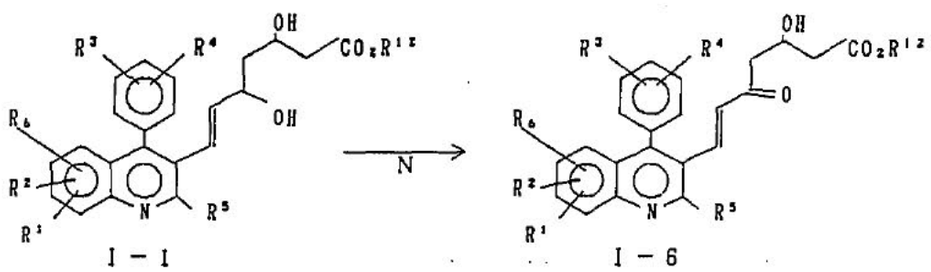

R3
R4
R6
R1
CO2R21
R2
N
R5
A
CH2OH
B
VII
VI
CHO
C
OEt
OH
D
V
IV


D
E
F
G
CHO
OH
CO2R12
III
II
I - 1
I - 2 (R12=H)
I - 5 (R12=Na)



I - 3 I - 4


R3
R4
R6
R2
CHO
R1
N
R5
K
CO2R22
L
V
VII
CH2OH
M
IX
III


R³
R⁴
OH
CO₂R¹²
OH
R⁶
R²
R¹
N
R⁵
I - 1
[N]
R³
R⁴
OH
CO₂R¹²
O
R⁶
R²
R¹
N
R⁵
I - 6

In the above reaction scheme, R^1, R^2, R^3, R^4, R^5, R^6 and R^{12} are as defined above with respect to the formula I, and R^{21} and R^{22} independently represent C_{1-4} lower alkyl such as methyl, ethyl, n-propyl, i-propyl or n-butyl.

Step A represents a reduction reaction of the ester to a primary alcohol. Such reduction reaction can be conducted by using various metal hydrides, preferably diisobutylaluminium hydride, in a solvent such as tetrahydrofuran or toluene at a temperature of from -20 to 20°C, preferably from -10 to 10°C.

Step B represents an oxidation reaction of the primary alcohol to an aldehyde, which can be conducted by using various oxidizing agents. Preferably, the reaction can be conducted by using pyridinium chlorochromate in methylene chloride at a temperature of from 0 to 25°C, or by using oxalyl chloride, dimethyl sulfoxide and a tertiary amine such as triethylamine (Swern oxidation), or by using a sulfur trioxide pyridine complex.

Step C represents a synthesis of a 3-ethoxy-1-hydroxy-2-propene derivative, which can be prepared by reacting a compound V to lithium compound which has been preliminarily formed by treating cis-1-ethoxy-2-(tri-n-butylstannyl)ethylene with butyl lithium in tetrahydrofuran.

As the reaction temperature, it is preferred to employ a low temperature at a level of from -60 to -78°C.

Step D represents a synthesis of an enal by acidic hydrolysis. As the acid catalyst, it is preferred to employ p-toluene sulfonic acid, hydrochloric acid or sulfuric acid, and the reaction may be conducted in a solvent mixture of water and tetrahydrofuran or ethanol at a temperature of from 10 to 25°C. The 3-ethoxy-1-hydroxy-2-propene derivative obtained in Step C can be used in Step D without purification i.e. by simply removing tetra-n-butyl tin formed simultaneously.

Step E represents a double anion condensation reaction between the enal III and an acetoacetate. Such condensation reaction is preferably conducted by using sodium hydride and n-butyl lithium as the base in tetrahydrofuran at a temperature of from -80 to 0°C, preferably from -30 to -10°C.

Step F represents a reduction reaction of the carbonyl group, which can be conudcted by using a metal hydride, preferably sodium borohydride in ethanol at a temperature of from -10 to 25°C, preferably from -10 to 5°C.

Further, the reduction reaction may be conducted by using zinc borohydride in dry ethyl ether or dry tetrahydrofuran at a temperature of -100 to 25°C, preferably from -80 to -50°C.

Step G is a step for hydrolyzing the ester. The hydrolysis can be conducted by using an equimolar amount of a base, preferably potassium hydroxide or sodium hydroxide, in a solvent mixture of water and methanol or

ethanol at a temperature of from 10 to 25°C. The free acid hereby obtained may be converted to a salt with a suitable base.

Step H is a step for forming a mevalonolactone by the dehydration reaction of the free hydroxy acid I-2. The dehydration reaction can be conducted in benzene or toluene under reflux while removing the resulting water or by adding a suitable dehydrating agent such as molecular sieve.

Further, the dehydration reaction may be conducted in dry methylene chloride by using a lactone-forming agent such as carbodiimide, preferably a water soluble carbodiimide such as N-cyclohexyl-N'-[2'-(methylmorpholinium)ethyl]carbodiimide p-toluene sulfonate at a temperature of from 10 to 35°C, preferably from 20 to 25°C.

Step J represents a reaction for hydrogenating the double bond connecting the mevalonolactone moiety and the quinoline ring. This hydrogenation reaction can be conducted by using a catalytic amount of palladium-carbon or rhodium-carbon in a solvent such as methanol, ethanol, tetrahydrofuran or acetonitrile at a temperature of from 0 to 50°C, preferably from 10 to 25°C.

Step K represents a reaction for the synthesis of an α,ß-unsaturated carboxylic acid ester, whereby a trans-form α,ß-unsaturated carboxylic acid ester can be obtained by a so-called Horner-Wittig reaction by using an

alkoxycarbonylmethyl phosphonate. The reaction is conducted by using sodium hydride or potassium t-butoxide as the base in dry tetrahydrofuran at a temperature of from -30 to 0°C, preferably from -20 to -15°C.

Step L represents a reduction reaction of the α,ß-unsaturated carboxylic acid ester to an allyl alcohol. This reduction reaction can be conducted by using various metal hydrides, preferably diisobutylaluminiumhydride, in a solvent such as dry tetrahydrofuran or toluene at a temperature of from -10 to 10°C, preferably from -10 to 0°C.

Step M represents an oxidation reaction of the allyl alcohol to an enal. This oxidation reaction can be conducted by using various oxidizing agents, particularly active manganese dioxide, in a solvent such as tetrahydrofuran, acetone, ethyl ether or ethyl acetate at a temperatrue of from 0 to 100°C, preferably from 15 to 50°C.

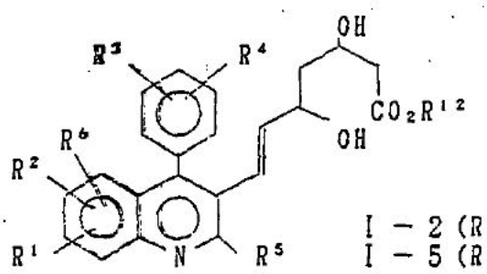
Step N represents a reaction for the synthesis of an α,ß-unsaturated ketone by the selective oxidation of the dihydroxy carboxylic acid ester. This reaction can be conducted by using activated manganese dioxide in a solvent such as ethyl ether, tetrahydrofuran, benzene or toluene at a temperature of from 20 to 80°C, preferably from 40 to 80°C.

In addition to the compounds disclosed in Examples given hereinafter, compounds of the formulas I-2 and I-5

given in Table 1 can be prepared by the process of the present invention. In Table 1, i- means iso, sec- means secondary and c- means cyclo. Likewise, Me means methyl, Et means ethyl, Pr means propyl, Bu means butyl, Pent means pentyl, Hex means hexyl and Ph means phenyl.

Table 1

T-340-X



I − 2 (R^{12}=H)
I − 5 (R^{12}=Na)

R^1	R^2	R^3	R^4	R^5	R^6
6−OMe	H	H	H	i−Pr	H
6−OMe	H	4-F	H	i−Pr	H
6−Br	H	4−F	H	i−Pr	H
6−Me	8−Me	4−F	H	i−Pr	H
7−OMe	8−OMe	4−F	H	i−Pr	H
6−Br	H	2−F	H	i−Pr	H
6,7 		4−F	H	i−Pr	H
H	H	4−F	H		H
H	H	4−Ph	H	i−Pr	H
H	H	4−$PhCH_2$	H	i−Pr	H
6-Cℓ	H	4− F	H	c-Pr	H
6-Cℓ	H	4− F	H	sec-Bu	H
6-OCH_2Ph	H	4− F	H	i-Pr	H
H	H	4− F	H	i-Bu	H
H	H	4− F	H	c-Pent	H
6-Cℓ	H	4− F	H	c-Pent	H
6-Me_2N	H	4− F	H	i-Pr	H

R^1	R^2	R^3	R^4	R^5	R^6
6-Me	H	4 — F	H	c — Pr	H
6-i-Pr	H	4 — F	H	i-Pr	H
7-Me	H	4 — F	H	c — Pr	H
6-OMe	H	4 — F	H	c — Pr	H
6-Br	H	4 — F	H	c — Pr	H
6-i-Pr	H	4 — F	H	c — Pr	H
6-Cℓ	8-Cℓ	4 — F	H	c — Pr	H
5-F	6-Br	4 — F	H	i-Pr	8-Br
6-OMe	7-OMe	4 — F	H	i-Pr	8-OMe
6-Me	7-Me	4 — F	H	i-Pr	8-Me
6-Cℓ	7-Cℓ	4 — F	H	i-Pr	8-Cℓ
H	H	4 — F	H	c-Bu	H
H	H	4 — F	H	c-Hex	H
6-OMe	7-OMe	H	H	i-Pr	H
6-OMe	7-OMe	4-Cℓ	H	i-Pr	H
6-OMe	7-OMe	H	H	c-Pr	H
6-OMe	7-OMe	4-Cℓ	H	c-Pr	H
6-OMe	7-OMe	4-F	H	c-Pr	H

R^1	R^2	R^3	R^4	R^5	R^6
6-Me	H	H	H	i-Pr	H
6-Me	H	4-Cℓ	H	i-Pr	H
6-Me	H	H	H	c-Pr	H
6-Me	H	4-Cℓ	H	c-Pr	H
6-Me	H	4-F	H	c-Pr	H
6-Cℓ	H	H	H	i-Pr	H
6-Cℓ	H	4-Cℓ	H	i-Pr	H
6-Cℓ	H	H	H	c-Pr	H
6-Cℓ	H	4-Cℓ	H	c-Pr	H
6-Cℓ	H	4-F	H	c-Pr	H
H	H	H	H	i-Pr	H
H	H	4-Cℓ	H	i-Pr	H
H	H	H	H	c-Pr	H
H	H	4-Cℓ	H	c-Pr	H
H	H	4-F	H	c-Pr	H

Further, pharmaceutically acceptable salts such as potassium salts or esters such as ethyl esters or methyl esters of these compounds can be prepared in the same manner.

The compounds of the present invention exhibit high inhibitory activities against the cholesterol biosynthesis wherein HMG-CoA reductase acts as a rate limiting enzyme, as shown by the test results given hereinafter, and thus are capable of suppressing or reducing the amount of cholesterol in blood as lipoprotein. Thus, the compounds of the present invention are useful as curing agents against hyperlipidemia, hyperlipoproteinemia and atheroscleosis.

They may be formulated into various suitable formulations depending upon the manner of the administration. The compounds of the present invention may be administered in the form of free acids or in the form of physiologically hydrolyzable and acceptable esters or lactones, or pharmaceutically acceptable salts.

The pharmaceutical composition of the present invention is preferably administered orally in the form of the compound of the present invention per se or in the form of powders, granules, tablets or capsules formulated by mixing the compound of the present invention with a suitable pharmaceutically acceptable carrier including a binder such as hydroxypropyl cellulose, syrup, gum arabic, gelatin, sorbitol, tragacanth gum, polyvinyl pyrrolidone

or CMC-Ca, an excipient such as lactose, sugar, corn starch, calcium phosphate, sorbitol, glycine or crystal cellulose powder, a lubricant such as magnesium stearate, talk, polyethylene glycol or silica, and a disintegrator such as potato starch.

However, the pharmaceutical composition of the present invention is not limited to such oral administration and it is applicable for parenteral administration. For example, it may be administered in the form of e.g. a suppository formulated by using oily base material such as cacao butter, polyethylene glycol, lanolin or fatty acid triglyceride, a transdermal therapeutic base formulated by using liquid paraffin, white vaseline, a higher alcohol, Macrogol ointment, hydrophilic ointment or hydro-gel base material, an injection formulation formulated by using one or more materials selected from the group consisting of polyethylene glycol, hydro-gel base material, distilled water, distilled water for injection and excipient such as lactose or corn starch, or a formulation for administration through mucous membranes such as an ocular mucous membrane, a nasal mucous membrane and an oral mucous membrane.

Further, the compounds of the present invention may be combined with basic ion-exchange resins which are capable of binding bile acids and yet not being absorbed in gastraintestinal tract.

The daily dose of the compound of the formula I is

from 0.05 to 500 mg, preferably from 0.5 to 50 mg for an adult. It is administered from once to three times per day. The dose may of course be varied depending upon the age, the weight or the condition of illness of the patient.

The compounds of the formulas II to VII are novel, and they are important intermediates for the preparation of the compounds of the formula I. Accordingly, the present invention relates also to the compounds of the formulas II to VII and the processes for their production.

Now, the present invention will be described in further detail with reference to Test Examples for the pharmacological activities of the compounds of the present invention, their Preparation Examples and Formulation Examples. However, it should be understood that the present invention is by no means restricted by such specific Examples.

PHARMACOLOGICAL TEST EXAMPLES

Test A: Inhibition of cholesterol biosynthesis from acetate in vitro

Enzyme solution was prepared from liver of male Wistar rat billialy cannulated and discharged bile for over 24 hours. Liver was cut out at mid-dark and microsome and supernatant fraction which was precipitable with 40-80% of saturation of ammonium sulfate (sup fraction) were prepared from liver homogenate according to the modified method of Knauss et. al.; Kuroda, M., et. al., Biochim.

Biophys. Acta, 489, 119 (1977). For assay of cholesterol biosynthesis, microsome (0.1 mg protein) and sup fraction (1.0 mg protein) were incubated for 2 hours at 37°C in 200 µl of the reaction mixture containing ATP; 1 mM, Glutathione; 6 mM, Glucose-1-phosphate; 10 mM, NAD; 0.25 mM, NADP; 0.25 mM, CoA; 0.04 mM and 0.2 mM [2-^{14}C]sodium acetate (0.2 µCi) with 4 µl of test compound solution dissolved in water or dimethyl sulfoxide. To stop reaction and saponify, 1 ml of 15% EtOH-KOH was added to the reactions and heated at 75°C for 1 hour. Nonsaponifiable lipids were extracted with petroleum ether and incorporated ^{14}C radioactivity was counted. Inhibitory activity of compounds was indicated with IC50.

Test B: Inhibition of cholesterol biosynthesis in culture cells

Hep G2 cells at over 5th passage were seeded to 12 well plates and incubated with Dulbecco's modified Eagle (DME) medium containing 10% of fetal bovine serum (FBS) at 37°C, 5% CO_2 until cells were confluent for about 7 days. Cells were exposed to the DME medium containing 5% of lipoprotein deficient serum (LpDS) prepared by ultracentrifugation method for over 24 hours. Medium was changed to 0.5 ml of fresh 5% LpDS containing DME before assay and 10 µl of test compound solution dissolved in water or DMSO were added. 0.2 µCi of [2-^{14}C]sodium acetate (20 µl) was added at 0 hr(B-1) or 4 hrs(B-2) after addition of compounds. After 4 hrs further incubation with [2-^{14}C]sodium acetate, medium was removed and cells

were washed with phosphate buffered saline(PBS) chilled at 4°C. Cells were scraped with rubber policeman and collected to tubes with PBS and digested with 0.2 ml of 0.5 N KOH at 37°C. Aliquot of digestion was used for protein analysis and remaining was saponified with 1 ml of 15% EtOH-KOH at 75°C for 1 hour. Nonsaponifiable lipids were extracted with petroleum ether and ^{14}C radioactivity was counted. Counts were revised by cell protein and indicated with DPM/mg protein. Inhibitory activity of compounds was indicated with IC50.

Test C: Inhibition of cholesterol biosynthesis in vivo

Male Sprague-Dawley rats weighing about 150 g were fed normal Purina chow diet and water ad libitum, and exposed to 12 hours light/12 hours dark lighting pattern (2:00 PM - 2:00 AM dark) prior to use for in vivo inhibition test of cholesterol biosynthesis. Animals were separated groups consisting of five rats as to be average mean body weight in each groups. Test compounds at dosage of 0.02-0.2 mg/kg body weight (0.4 ml/100 g body weight), were dissolved in water or suspended or in 0.5% methyl cellulose and orally administered at 2-3 hours before mid-dark (8:00 PM), while cholesterol biosynthesis reaches to maximum in rats. As control, rats were orally administered only water or vehicle. At 90 minutes after sample administration, rats were injected intraperitoneally with 10 μCi of [2-^{14}C]sodium acetate at volume of 0.2 ml per one. 2 Hours later, blood samples

were obtained and serum were separated immediately. Total lipids were extracted according to the method of Folch et al. and saponified with EtOH-KOH. Nonsaponifiable lipids were extracted with petroleum ether and radio activity incorporated into nonsaponifiable lipids was counted.

Inhibitory activity was indicated as percent decrease of counts in testing groups (DPM/2 ml serum/2 hours) from that in control group.

With respect to the compounds of the present invention, the inhibitory activities against the cholesterol biosynthesis in which HMG-CoA reductase serves as a rate limiting enzyme, were measured by the above Test A and B. The results are shown in Tables, 2, 2-2, 3 and 3-2. Further, the results of the measurements by Test C are also presented.

Table 2: Inhibitory activities by Test A

Compound	I_{50} (molar concentration)
(Compounds of the present invention)	
I-13	1.25×10^{-7}
I-51	1.0×10^{-8}
I-52	7.1×10^{-8}
I-53	1.9×10^{-7}
(Reference compounds)	
Mevinolin	1.4×10^{-8}
CS-514	9.0×10^{-9}

In Table 2-2, the relative activities are shown based on the activities of CS-514 being evaluated to be 1.

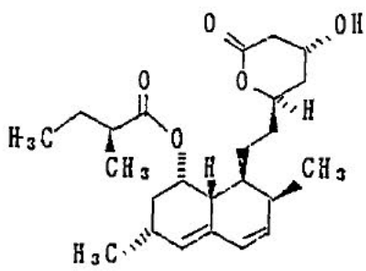
Table 2-2: Relative activities by Test A

Compound	Relative activities
(Comounds of the present invention)	
I-16	1.75
I-116	2.25
I-117	0.37
I-120	3.21
I-522	0.76

Structures of reference compounds:

(1) Mevinolin

T340X



(2) CS-514

T341X

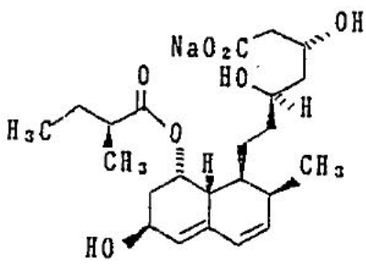


Table 3: Inhibitory activities by Test B-1

Compound	I_{50} (molar concentration)
(Compound of the present invention)	
I-51	1×10^{-7}
(Reference compound)	
CS-514	3.5×10^{-7}

In Table 3-2, the relative activities are shown based on the activities of CS-514 being evaluated to be 1.

Table 3-2: Relative activities by Test B-1

Compound	Relative activities
I-116	19.4
I-520	20.0
II-20	20.8

Results of the measurement of the inhibitory activities by Test C

The percent decrease of counts after the oral administration of 0.05 mg/kg of compound I-520 was 55% relative to the measured value of the control group. The percent decrease of counts after the oral administration of 10 mg/kg of CS-514 was 55% under the same condition. The compounds of the present invention exhibited

activities superior to the reference compound such as CS-514 or Mevinolin in Test A, and exhibited activities superior to CS-514 in Tests B and C.

Test D: Acute toxicity

A 0.5% CMC suspension of a test compound was orally administered to ICR male mice (group of three mice). The acute toxicity was determined based on the mortality after seven days. With compound I-57, I-58, I-59, I-511, I-512, I-513, I-514, I-515, I-517 and I-523 of the present invention, the mortality was 0% even when they were orally administered in an amount of 1000 mg/kg.

EXAMPLE 1

Ethyl (E)-3,5-dihydroxy-7-[4'-(4''-fluorophenyl)-2'-(1''-methylethyl)-quinolin-3'-yl]-hept-6-enoate (compound I-11) (prepared by steps of Example 1-a through Example I-g)

EXAMPLE 1-a: Ethyl 4-(4'-fluorophenyl)-2-(1'-methylethyl)-quinolin-3-yl-carboxylate (compound VII-1)

The synthesis was conducted in accordance with the method disclosed in J. Org. Chem., 2899 (1966).

6.45 g (0.03 mol) of 2-amino-4'-fluorobenzophenone, 5.53 g (0.035 mol) of ethyl isobutyrylacetate and 0.1 ml of conc. sulfuric acid were dissolved in 30 ml of glacial acetic acid, and the mixture was heated at 100°C for about 10 hours. After confirming the substantial disappearance of 2-amino-4'-fluorobenzophenone by thin layer chromatography, the reaction solution was cooled to room

temperature, and a mixture of 45 ml of conc. aqueous ammonia and 120 ml of water cooled with ice, was gradually added thereto. A separated oily substance was solidified when left to stand overnight in a refrigerator. This solid was recrystallized from a small amount of ethanol to obtain 6.47 g (55%) of white powder. Melting point: 68-70.5°C

EXAMPLE 1-b: 4-(4'-fluorophenyl)-3-hydroxymethyl-2-(1'-methylethyl)-quinoline (compound VI-1)

5.4 g (0.016 mol) of compound VII-1 was dissolved in dry toluene under a nitrogen atmosphere and cooled in ice bath to 0°C. To this solution, 40 ml of a 16 wt% diisobutylaluminium hydride-toluene solution was dropwise added, and the mixture was stirred at 0°C for two hours. After confirming the complete disappearance of compound VII-1 by thin layer chromatography, a saturated ammonium chloride solution was added thereto at 0°C to terminate the reaction. Ethyl ether was added to the reaction mixture, and the organic layer was separated. A gelled product was dissolved by an addition of an aqueous sodium hydroxide solution and extracted anew with ethyl ether. The ethyl ether extracts were put together, dried over anhydrous magnesium sulfate and filtered. The solvent was distilled off. The residual oil underwent crystallization when left to stand. It was recrystallized from ethyl acetate-n-hexane to obtain 3.3 g of white crystals. Yield: 70%. Melting point: 136-137°C.

EXAMPLE 1-c: 4-(4'-fluorophenyl)-2-(1'-methylethyl)-quinolin-3-yl-carboxyaldehyde (compound V-1)

2.0 g (9.3 mmol) of pyridinium chlorochromate and 0.4 g of anhydrous sodium acetate was suspended in 10 ml of dry dichloromethane. To this suspension, a solution obtained by dissolving 1 g (3.4 mmol) of compound VI-1 in 10 ml of dry dichloromethane, was immediately added at room temerature. The mixture was stirred for one hour. Then, 100 ml of ethyl ether was added thereto, and the mixture was throughly mixed. The reaction mixture was filtered under suction through a silica gel layer. The filtrate was dried under reduced pressure. The residue was dissolved in the isopropyl ether, and insoluble substances were filtered off. The filtrate was again dried under reduced pressure, and the residue was recrystallized from diisopropyl ether to obtain 0.7 g (Yield: 70%) of slightly yellow prism crystals. Melting point: 124-126°C.

EXAMPLE 1-d: 3-(3'-ethoxy-1'-hydroxy-2'-propenyl)-4-(4'-fluorophenyl)-2-(1'-methylethyl)-quinoline (compound IV-1)

1.13 g (3.13 mmol) of cis-1-ethoxy-2-(tri-n-butylstannyl)ethylene was dissolved in 8 ml of dry tetrahydrofuran, and the solution was cooled to -78°C in a nitrogen stream. To this solution, 2 ml (3.2 mmol) of a 15 wt% n-butyllithium-n-hexane solution was dropwise added. The mixture was stirred for 45 minutes. Then, a solution prepared by dissolving 0.76 g (2.6 mmol) of

compound V-1 in 10 ml of dry tetrahydrofuran was dropwise added thereto. The reaction mixture was stirred at -78°C for two hours. Then, 2 ml of a saturated ammonium chloride solution was added thereto to terminate the reaction. The organic layer was extracted with diethyl ether, and the diethyl ether extract was washed with a saturated sodium chloride aqueous solution and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was separated with n-hexane and acetonitrile. The solvent was distilled off under reduced pressure from the acetonitrile layer, and an oily substance thereby obtained was purified by silica gel column chromatography (eluent: 2.5% methanol-chloroform) to obtain 0.91 g of the desired compound in a purified oily form.

H-MNR ($CDCl_3$) δ ppm:

1.1(t,3H,7Hz) 1.37(d,6H,J=7Hz) 3.7(m,1H)
3.7(q,2H,J=7Hz) 4.75(t,1H,7Hz) 5.7(m,1H)
5.95(m,1H) 7.05-8.2(m,8H)

EXAMPLE 1-e: (E)-3-[4'-(4''-fluorophenyl)-2'-(1''-methylethyl)-quinolin-3'-yl]propenaldehyde (compound III-1)

0.91 g of compound IV-1 was dissolved in 20 ml of tetrahydrofuran, and 5 ml of water and 100 mg of p-toluenesulfonic acid were added thereto. The mixture was stirred at room temperature for 24 hours. The reaction solution was extracted with diethyl ether a few

times. The extracts were washed with a saturated sodium chloride aqueous solution and dried over anhydrous magnesium sulfate. Then, the solvent was distilled off. The residue was purified by silica gel column chromatography (eluent: chloroform) to obtain the desired product as white prism crystals. 0.4 g (50%). Melting point: 127-128°C.

EXAMPLE 1-f: Ethyl (E)-7-[4'-(4''-fluorophenyl)-2'-(1''-methylethyl)-quinolin-3'-yl]-5-hydroxy-3-oxohepto-6-enoate (compound II-1)

50 mg of 60% sodium hydride was washed with dry petroleum ether and dried under a nitrogen stream, and then suspended in 5 ml of dry tetrahydrofuran. The suspension was cooled to -15°C in a nitrogen atmosphere. Then, 120 mg (0.92 mmol) of ethyl acetoacetate was dropwise added thereto, and the mixture was stirred for 15 minutes. Then, 0.6 ml (0.92 mmol) of a 15 wt% n-butyllithium-n-hexane solution was dropwise added thereto, and the mixture was stirred for 30 minutes. Then, a solution prepared by dissolving 160 mg (0.5 mmol) of compound III-1 in dry tetrahydrofuran, was dropwise added thereto, and the mixture was stirred for one hour. To the reaction mixture, 1 ml of a saturated ammonium chloride aqueous solution was added at -15°C. Then, the mixture was extracted three times with diethyl ether. The diethyl ether solution was washed with a saturated sodium chloride aqueous solution and dried over anhydrous

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magnesium sulfate. The solution was evaporated to dryness under reduced pressure. The residue was recrystallized from diisopropyl ether to obtain 130 mg (yield: 59%) of white crystals. Melting point: 99-101°C.

EXAMPLE 1-g: Ethyl (E)-3,5-dihydroxy-7-[4'-(4''-fluorophenyl)-2'-(1''-methylethyl)-quinolin-3'-yl]-hept-6-enoate (compound I-11)

110 mg (0.245 mmol) of compound II-1 was dissolved in 5 ml of ethanol in a nitrogen atmosphere, and the solution was cooled 0°C. Then, 10 mg (0.263 mmol) of sodium borohydride was added, and the mixturer was stirred for one hour. Then, 1 ml of a 10% hydrochloric acid aqueous solution was added thereto, and the mixture was extracted three times with ethyl ether. The ethyl ether solution was washed with a saturated sodium chloride aqueous solution and dried over anhydrous magnesium sulfate. Then, the solution was evaporated to dryness under reduced pressure. The residual oil was purified by silica gel column chromatography (eluent: 5% methanol-chloroform) to obtain the desired product as a pure colorless oily substance. 70 mg (Yield: 64%)

H-NMR ($CDCl_3$) δ ppm:

1.30(t,3H,J=8Hz) 1.39(d,6H,J=8Hz) 1.4-1.8(m,2H)
2.42(d,2H,J=7Hz) 3.0-3.8 (m,2H) 3.50(m,1H)
3.9-4.6(m,2H) 4.20(q,2H,J=8Hz) 5.35(m,1H)
6.59(m,1H) 7.10-8.18(m,8H)

EXAMPLE 2

Sodium salt of (E)-3,5-dihydroxy-7-[4'-(4''-fluorophenyl)-2'-(1''-methylethyl)-quinolin-3'-yl]-hept-6-enoic acid (compound I-51)

60 mg (0.133 mmol) of compound I-11 was dissolved in 3 ml of ethanol. Then, 0.26 ml of a 0.5 N sodium hydroxide aqueous solution was dropwise added thereto. The mixture was stirred at room temperature for further one hour, and ethanol was distilled off under reduced pressure. Then, 5 ml of water was added thereto, and the mixture was extracted with ethyl ether. The aqueous layer was freeze-dried to obtain 40 mg (67%) of hygroscopic white powder. Melting point: 207-209°C (decomposed).

EXAMPLE 3

(E)-3,5-dihydroxy-7-[4'-(4''-fluorophenyl)-2'-(1''-methylethyl)-quinolin-3'-yl]-hept-6-enoic acid (compound I-21)

110 mg (0.244 mmol) of compound I-11 was dissolved in 10 ml of ethanol. Then, 0.79 ml of a 0.5 N sodium hydroxide aqueous solution was dropwise added thereto. The mixture was stirred at room temperature for further one hour, and ethanol was distilled off under reduced pressure. Then, 10 ml of water was added thereto, and the mixture was extracted with ethyl ether. The aqueous layer was weakly acidified (pH 4) with a dilute hydrochloric aqueous solution and extracted three times with ethyl ether. The ethyl ether layers were put together and dried

over anhydrous magnesium sulfate. Then, the solvent was distilled off under reduced pressure to obtain 90 mg of slightly yellow oily substance.

H-NMR ($CDCl_3$) δ ppm:

1.36(d,6H,J=7Hz) 2.4(m,2H) 3.5(m,1H) 3.45(m,1H)
3.8-4.6(m,2H) 5.40(dd,1H,J_1=19Hz,J_2=8Hz)
6.55 (d,1H,J=19Hz) 7.0-8.3(m,8H)

EXAMPLE 4

(E)-6-[4'-(4''-fluorophenyl)-2'-(1''-methylethyl)-quinolin-3'-ylethenyl]-4-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (compound I-31)

90 mg of compound I-21 was dissolved in 10 ml of dry toluene, and the solution was refluxed under heating for 3 hours by means of a Dean Stark apparatus.

Toluene was distilled off under reduced pressure, and the residual solid was recrystallized from diisopropyl ether to obtain 40 mg of colorless prism crystals. Melting point: 182-184°C.

By silica gel thin chromatography, the product gave two absorption spots close to each other attributable to the diastereomers. (Developping solvent: 3% methanol-chloroform)

These diasteromers were separated and isolated by silica gel thin layer chromatography. [Developping solvent: t-BuOMe/hexane/acetone=7/2/1 (v/v), Rf=0.6 and 0.7 (obtained weight ratio: 1/2)]

Rf=0.7: trans lactone

H-NMR ($CDCl_3$) δ ppm:

1.40(d,6H,J=7Hz) 1.6(m,2H) 2.65(m,2H) 3.48(m,1H)
4.20(m,1H) 5.15(m,1H) 5.37(dd,1H,J_1=18Hz,J_2=7Hz)
6.68(d,1H,J=19Hz) 7.1-8.2(m,8H)

Rf=0.6: cis lactone

H-NMR ($CDCl_3$) δ ppm:

1.40(d,6H,J=7Hz) 1.6(m,2H) 2.65(m,2H) 3.48(m,1H)
4.20(m,1H) 4.65(m,1H) 5.40(dd,1H,J_1=18Hz,J_2=7Hz)
6.66(m,1H) 7.0-8.2(m,8H)

EXAMPLE 5

6-[4'-(4''-fluorophenyl)-2'-(1''-methylethyl)-quinolin-3'-ylethynyl]-4-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (compound I-41)

20 mg of a mixture of diastereomers of compound I-31 was dissolved in 5 ml of ethanol, and 10 mg of 5% palladium-carbon was added thereto. The mixture was stirred under a hydrogen atmosphere. After confirming the disappearance of the starting substance and the appearance of a new spot by thin layer chromatography, the palladium-carbon was filtered off, and ethanol was distilled off to obtain colorless oil.

This oil was purified by preparative thin layer chromatography to obtain 16 mg of the desired product as pure colorless oil.

MS(m/e): 408(M^++H), 407(M^+), 366, 292, 278

In the same manner as in Example 1-a, compounds VII-2

to VII-27 were prepared. The physical properties of these compounds are shown in Table 4. (In the Table, R^1, R^2, R^3, R^4, R^5 and R^{21} correspond to the substitients of compound VII.)

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Table 4 (Compounds in this Table are compounds of the formula VII wherein R^6 is hydrogen.)

Compound	R^1	R^2	R^3	R^4	R^5	R^{21}	m. p. (℃)
VII-2	H	H	4-F	H	CH_3	C_2H_5	121-122
VII-3	H	H	H	H	CH_3	C_2H_5	102-102.5
VII-4	H	H	H	H	i-Pr	C_2H_5	85-85.5
VII-5	6-Cℓ	H	H	H	CH_3	C_2H_5	100.5-101.5
VII-6	6-Cℓ	H	H	H	i-Pr	C_2H_5	105.5-106.5
VII-7	H	H	2-F	H	i-Pr	C_2H_5	101.0-102.0
VII-8	7-Me	H	H	H	i-Pr	C_2H_5	oil
VII-9	H	H	4-Cℓ	H	i-Pr	C_2H_5	134.0-136.5
VII-10	H	H	4-OMe	H	i-Pr	C_2H_5	88.0-89.0
VII-11	H	H	4-Me	H	i-Pr	C_2H_5	108.5-109.5
VII-12	6-Cℓ	H	2-Cℓ	H	i-Pr	C_2H_5	101.0-103.0
VII-13	H	H	4-CF_3	H	i-Pr	C_2H_5	117.5-119.0
VII-14	H	H	3-Me	4-F	i-Pr	C_2H_5	oil
VII-15	H	H	3-Me	5-Me	i-Pr	C_2H_5	oil
VII-16	6-OMe	7-OMe	4-F	H	i-Pr	C_2H_5	96.0-98.0
VII-17	H	H	4-F	H	C_2H_5	CH_3	139.0-139.5
VII-18	H	H	4-F	H	n-Pr	C_2H_5	oil
VII-19	6-Cℓ	H	4-F	H	i-Pr	C_2H_5	94.5-95.5
VII-20	H	H	4-F	H	c-Pr	CH_3	113.5-116.5
VII-21	H	H	4-OPh	H	i-Pr	C_2H_5	oil
VII-22	6-Cℓ	8-Cℓ	4-F	H	i-Pr	C_2H_5	96.0-98.0
VII-23	6-Cℓ	H	H	H	Ph	C_2H_5	118.8-119.5

Ⅶ-24	6-Cℓ	H	H	H	c-Pr	CH_3	97.0-98.5
Ⅶ-25	H	H	4-F	H	sec-Bu	CH_3	oil
Ⅶ-26	6-Me	H	4-F	H	i-Pr	C_2H_5	109.0-111.0
Ⅶ-27	6-OMe	7-OMe	4-F	H	c-Pr	CH_3	153.0-153.5

Ⅶ－8

H-NMR (in $CDCℓ_3$) δ ppm :

0.92 (t, 3H, J＝7Hz), 1.41 (d, 6H, J＝6Hz)

2.47 (s, 3H), 3.27 (Heptaplet, 1H, J=6Hz)

3.96 (q, 2H, J＝7Hz), 7.0 －7.8 (m, 8H)

Ⅶ－14

H-NMR (in $CDCℓ_3$) δ ppm :

1.01 (t, 3H, J=7Hz), 1.42 (d, 6H, J=6Hz)

2.38 (s, 3H, J=3Hz), 3.25 (Heptaplet, 1H, J=6Hz)

4.04 (q, 2H, J=7Hz), 6.9－8.1 (m, 7Hz)

Ⅶ－15

H-NMR (in $CDCℓ_3$) δ ppm :

0.97 (t, 3H, J=7Hz), 1.43 (d, 6H, J=6Hz)

2.29 (s, 6H), 3.25 (Heptaplet, 1H, J=6Hz)

4.00 (q, 2H, J=7Hz), 6.8－8.0 (m, 7H)

VII - 18

H-NMR (in $CDC\ell_3$) δ ppm :

0.98 (t, 3H, J=7Hz), 1.02 (t, 3H, J=7Hz)

1.6-2.3(m, 2H), 2.8-3.1(m, 2H)

4.03 (q, 2H, J=7Hz), 6.9-8.1(m, 8H)

VII - 21

H-NMR (in $CDC\ell_3$) δ ppm :

1.03 (t, 3H, J=7Hz), 1.41 (d, 6H, J=6Hz)

3.25(Heptaplet, 1H, J=6Hz) , 4.05(q, 2H, J=7Hz),

6.8-8.1(m, 13H)

VII - 25

H-NMR (in $CDC\ell_3$) δ ppm :

0.97 (d, 6H, J=6Hz), 2.0～2.6(m, 1H)

2.85 (d, 2H, J=7Hz), 3.51(s, 3H),

6.8-8.1(m, 8H)

In the same manner as in Example 1-b, compounds VI-2 to VI-27 were prepared. (In Table 5, R^1, R^2, R^3, R^4 and R^5 correspond to the substituents in compound VI.)

Table 5 (Compounds in this Table are compounds of the formula VI wherein R^6 is hydrogen.)

Compound	R^1	R^2	R^3	R^4	R^5	m. p. (℃)
VI-2	H	H	p-F	H	CH_3	—
VI-3	H	H	H	H	CH_3	149-151
VI-4	H	H	H	H	i-Pr	130-130.5
VI-5	6-Cℓ	H	H	H	CH_3	139-141
VI-6	6-Cℓ	H	H	H	i-Pr	168-169
VI-7	H	H	2-F	H	i-Pr	140.5-142.0
VI-8	7-Me	H	H	H	i-Pr	155.0-157.0
VI-9	H	H	4-Cℓ	H	i-Pr	192.0-195.0
VI-10	H	H	4-OMe	H	i-Pr	186.0-188.5
VI-11	H	H	4-Me	H	i-Pr	161.0-164.0
VI-12	6-Cℓ	H	2-Cℓ	H	i-Pr	122.0 124.0
VI-13	H	H	4-CF_3	H	i-Pr	183.0-186.0
VI-14	H	H	3-Me	4-F	i-Pr	161.0-162.5
VI-15	H	H	3-Me	5-Me	i-Pr	137.0-138.0
VI-16	6-Me	7-OMe	4-F	H	i-Pr	164.0-165.0
VI-17	H	H	4-F	H	C_2H_5	141.5-143.5
VI-18	H	H	4-F	H	n-Pr	146.5-148.5
VI-19	6-Cℓ	H	4-F	H	i-Pr	171.0-172.0

VI-20	H	H	4-F	H	c-Pr	120-126
VI-21	H	H	4-OPh	H	i-Pr	153.0-154.0
VI-22	6-Cℓ	8-Cℓ	4-F	H	i-Pr	98.5-103
VI-23	6-Cℓ	H	H	H	Ph	171.5-172.5
VI-24	6-Cℓ	H	H	H	c-Pr	84.0-86.0
VI-25	H	H	4-F	H	sec-Bu	119.0-121.0
VI-26	6-Me	H	4-F	H	i-Pr	160.0-161.5
VI-27	6-OMe	7-OMe	4-F	H	c-Pr	162.0-163.0

In the same manner as in Example 1-c, compounds V-2 to V-27 were prepared. (In Table 6, R^1, R^2, R^3, R^4 and R^5 correspond to the substituents of compound of V.)

Table 6 (Compounds in this Table are compounds of the formula V wherein R^6 is hydrogen.)

Compound	R^1	R^2	R^3	R^4	R^5	m. p. (°C)
V-2	H	H	p-F	H	CH_3	125-128
V-3	H	H	H	H	CH_3	143-146
V-4	H	H	H	H	i-Pr	92-93
V-5	6-Cℓ	H	H	H	CH_3	220-222

V-6	6-Cℓ	H	H	H	i-Pr	140-140.5
V-7	H	H	2-F	H	i-Pr	121.5-124.0
V-8	7-Me	H	H	H	i-Pr	105.1-109.2
V-9	H	H	4-Cℓ	H	i-Pr	147.0-147.8
V-10	H	H	4-OMe	H	i-Pr	135.6-136.8
V-11	H	H	4-Me	H	i-Pr	119.4-120.4
V-12	6-Cℓ	H	2-Cℓ	H	i-Pr	105.8-106.9
V-13	H	H	4-CF_3	H	i-Pr	163.7-164.2
V-14	H	H	3-Me	4-F	i-Pr	161.1-108.1
V-15	H	H	3-Me	5-Me	i-Pr	120.8-122.3
V-16	6-OMe	7-OMe	4-F	H	i-Pr	164.4-165.2
V-17	H	H	4-F	H	C_2H_5	143.1-144.2
V-18	H	H	4-F	H	n-Pr	150.2-155.3
V-19	6-Cℓ	H	4-F	H	i-Pr	164.5-165.3
V-20	H	H	4-F	H	c-Pr	150.1-151.6
V-21	H	H	4-OPh	H	i-Pr	106.9-107.7
V-22	6-Cℓ	8-Cℓ	4-F	H	i-Pr	135.0-135.7
V-23	6-Cℓ	H	H	H	Ph	174.8-175.3
V-24	6-Cℓ	H	H	H	c-Pr	157.5-158.0
V-25	H	H	4-F	H	sec-Bu	125.0-126.5
V-26	6-Me	H	4-F	H	i-Pr	155.0-157.0
V-27	6-OMe	7-OMe	4-F	H	c-Pr	200.0-200.5

In the same manner as in Example 1-d, compounds IV-2 to IV-6 were prepared. (In Table 7, R^1, R^2, R^3, R^4 and R^5 correspond to the substituents of compound IV.)

Table 7 (Compounds in this Table are compounds of the formula IV wherein R^6 is hydrogen.)

Compound	R^1	R^2	R^3	R^4	R^5	m. p. (°C)
IV − 2	H	H	4-F	H	CH_3	177-179
IV − 3	H	H	H	H	CH_3	—
IV − 4	H	H	H	H	i-Pr	—
IV − 5	6-Cℓ	H	H	H	CH_3	—
IV − 6	6-Cℓ	H	H	H	i-Pr	—

In the same manner as in Example 1-e, compounds III-2 to III-27 were prepared. (In Table 8, R^1, R^2, R^3, R^4 and R^5 correspond to the substituents of compound III.)

Table 8 (Compounds in this Table are compounds of the formula III wherein R^6 is hydrogen.)

Compound	R^1	R^2	R^3	R^4	R^5	m. p. (℃)
III-2	H	H	4-F	H	CH_3	194-196
III-3	H	H	H	H	CH_3	170-171.5
III-4	H	H	H	H	i-Pr	107-108.5
III-5	6-Cℓ	H	H	H	CH_3	192-194
III-6	6-Cℓ	H	H	H	i-Pr	125.5-127
III-7	H	H	2-F	H	i-Pr	80.1-80.2
III-8	7-Me	H	H	H	i-Pr	121.1-122.3
III-9	H	H	4-Cℓ	H	i-Pr	148.0-149.1
III-10	H	H	4-OMe	H	i-Pr	137.4-140.1
III-11	H	H	4-Me	H	i-Pr	111.6-113.1
III-12	6-Cℓ	H	2-Cℓ	H	i-Pr	83.8-84.5
III-13	H	H	4-CF_3	H	i-Pr	126.2-128.8

Ⅲ-14	H	H	3-Me	4-F	i-Pr	124.8-126.4
Ⅲ-15	H	H	3-Me	5-Me	i-Pr	117.6-120.3
Ⅲ-16	6-OMe	7-OMe	4-F	H	i-Pr	147.8-150.9
Ⅲ-17	H	H	4-F	H	C_2H_5	124.3-128.5
Ⅲ-18	H	H	4-F	H	n-Pr	117.8-121.5
Ⅲ-19	6-Cℓ	H	4-F	H	i-Pr	135.2-135.9
Ⅲ-20	H	H	4-F	H	c-Pr	141.3-144.1
Ⅲ-21	H	H	4-OPh	H	i-Pr	oil
Ⅲ-22	6-Cℓ	8-Cℓ	4-F	H	i-Pr	117-122
Ⅲ-23	6-Cℓ	H	H	H	Ph	142.8-144.3
Ⅲ-24	6-Cℓ	H	H	H	c-Pr	161.0-161.5
Ⅲ-25	H	H	4-F	H	sec-Bu	78.0-81.0
Ⅲ-26	6-Me	H	4-F	H	i-Pr	137.0-137.5
Ⅲ-27	6-OMe	7-OMe	4-F	H	c-Pr	189.5-191.0

Ⅲ－22

H-NMR(in $CDCℓ_3$) δ ppm :

1.40(d,6H,J=7Hz), 3.44(Heptaplet,1H,J=7Hz)

5.93(dd,1H,J=8Hz,J=16Hz), 6.8-8.1(m,14H)

9.34(d,1H,J=8Hz)

In the same manner as in Example 1-f, compounds II-2 to II-27 were prepared. (In Table 9, R^1, R^2, R^3, R^4 and R^5 correspond to the substituents of compound II.)

Table 9 (Compounds in this Table are compounds of the formula of II wherein R^6 is hydrogen.)

Compound	R^1	R^2	R^3	R^4	R^5	R^{12}	m. p. (°C)
II-2	H	H	p-F	H	CH_3	C_2H_5	oil
II-3	H	H	H	H	CH_3	C_2H_5	105-106
II-4	H	H	H	H	i-Pr	C_2H_5	88.5-90.5
II-5	6-Cℓ	H	H	H	CH_3	C_2H_5	77-82
II-6	6-Cℓ	H	H	H	i-Pr	C_2H_5	96-98
II-7	H	H	2-F	H	i-Pr	C_2H_5	oil
II-8	7-Me	H	H	H	i-Pr	C_2H_5	68.5-74.0
II-9	H	H	4-Cℓ	H	i-Pr	C_2H_5	91.0-94.0
II-10	H	H	4-OMe	H	i-Pr	C_2H_5	78.0-78.5
II-11	H	H	4-OMe	H	i-Pr	C_2H_5	75.0-78.0
II-12	6-Cℓ	H	2-Cℓ	H	i-Pr	C_2H_5	oil
II-13	H	H	4-CF_3	H	i-Pr	C_2H_5	78.0-83.0
II-14	H	H	3-Me	4-F	i-Pr	C_2H_5	66.0-71.0
II-15	H	H	3-Me	5-Me	i-Pr	C_2H_5	oil

Ⅱ-16	6-OMe	7-OMe	4-F	H	i-Pr	C_2H_5	83.0 -90.0
Ⅱ-17	H	H	4-F	H	C_2H_5	C_2H_5	94.0 -97.0
Ⅱ-18	H	H	4-F	H	n-Pr	C_2H_5	oil
Ⅱ-19	6-Cℓ	H	4-F	H	i-Pr	C_2H_5	111.0-113.5
Ⅱ-20	H	H	4-F	H	c-Pr	C_2H_5	91.0 -93.0
Ⅱ-21	H	H	4-OPh	H	i-Pr	C_2H_5	121.0-125.0
Ⅱ-22	6-Cℓ	8-Cℓ	4-F	H	i-Pr	C_2H_5	oil
Ⅱ-23	6-Cℓ	H	H	H	Ph	C_2H_5	oil
Ⅱ-24	6-Cℓ	H	H	H	c-Pr	C_2H_5	69.0 -71.0
Ⅱ-25	H	H	4-F	H	sec-Bu	C_2H_5	oil
Ⅱ-26	6-Me	H	4-F	H	i-Pr	C_2H_5	oil
Ⅱ-27	6-OMe	7-OMe	4-F	H	c-Pr	C_2H_5	oil

Ⅱ－7

H-NMR(in $CDC\ell_3$) δ ppm :

1.21(t,3H,J=7Hz), 1.32(d,6H,J=6Hz)

2.2-2.4(m,2H), 2.5-2.7(m,1H)

3.28(s,1H), 3.34(Heptaplet,1H,J=6Hz)

4.08(q,2H,J=7Hz), 4.3-4.6(m,1H)

5.28(dd,1H,J=6Hz,J=15Hz),

6.53(dd,1H,J=1.5Hz,J=15Hz), 6.9-8.0(m,8H)

Ⅱ－１２

H-NMR(in $CDC\ell_3$)　　δ ppm :

1.25(t,3H,J=7Hz), 1.33(d,6H,J=6Hz)

2.2-2.4(m,2H), 2.5-2.8(m,1H)

3.32(s,2H), 3.38(Heptaplet, 1H, J=6Hz)

4.13(q,2H,J=7Hz), 4.2-4.6(m,1H)

5.34(dd,1H,J=6Hz,J=15Hz),

6.53(dd,1H,J=1.5Hz,J=15Hz), 7.0-8.0(m,7H)

Ⅱ－１５

H-NMR(in $CDC\ell_3$)　　δ ppm :

1.23(t,3H, J=7Hz), 1.35(d,6H,J=6Hz)

2.2-2.4(m,2H), 2.31(s,6H)

2.6-2.8(m,1H), 3.32(s,2H)

3.35(Heptaplet,1H,J=6Hz), 4.12(q,2H,J=7Hz)

4.3-4.7(m,1H), 5.30(dd,1H,J=6Hz,J=16Hz)

6.51(dd,1H,J=1Hz,J=16Hz), 6.7-8.0(m,7H)

Ⅱ－１８

H-NMR (in $CDC\ell_3$)　　δ ppm :

1.00(t,3H,J=7Hz), 1.26(t,3H,J=7Hz)

1.6-2.3(m,2H), 2.42(d,2H,J=6Hz)

2.6-3.2(m,3H), 3.35(s,2H)

4.11(q,2H,J=7Hz), 4.3-4.7(m,1H)

5.27(dd,1H,J=6Hz,J=16Hz)

6.46(dd,1H,J=1.5Hz,J=16Hz), 6.9-8.0(m,8H)

Ⅱ－2 2

H-NMR(in $CDCl_3$) δ ppm :

1.26(t,3H,J=7Hz), 1.33(d,6H,J=6Hz)

2.43(d,2H,J=6Hz), 2.6-2.9(m,1H)

3.36(s,2H), 3.44 (Heptaplet,1H,J=6Hz)

4.13(q,2H,J=7Hz), 4.3-4.7(m,1H)

5.30(dd,1H,J=6Hz,J=16Hz),

6.53(dd,1H,J=1.5Hz,J=16Hz), 7.0-7.6(m,6H)

Ⅱ－2 3

H-NMR(in $CDCl_3$) δ ppm :

1.23(t,3H,J=7Hz), 2.21(d,2H,J=6Hz)

2.4-2.6(m,1H), 3.25(s,2H)

4.09(q,2H,J=7Hz), 4.1-4.4(m,1H)

5.08(dd,1H,J=6Hz,J=16Hz),

6.26(dd,1H,J=1.5Hz,J=16Hz), 7.0 ～8.0

(m,13H)

Ⅱ－２５

H-NMR(in $CDCl_3$) δ ppm :

0.96(d,6H,J=6Hz), 1.26(t,3H,J=7Hz),
1.8-2.4(m,1H), 2.43(d,2H,J=6Hz),
2.6-2.9(m,1H), 2.88(d,2H,J=7Hz),
3.36(s,2H), 4.14(q,2H,J=7Hz),
4.3-4.7(m,1H), 5.0-5.5(m,1H),
6.3-6.7(m,1H), 6.9-8.1(m,8H)

Ⅱ－２６

H-NMR(in $CDCl_3$) δ ppm :

1.25(t,3H,J=7Hz), 1.32(d,6H,J=6Hz),
2.32(s,3H), 2.39(d,2H,J=7Hz),
2.6-3.1(m,1H), 3.36(s,2H),
3.41(Heptaplet,1H,J=6Hz),
4.11(q,2H,J=7Hz), 4.3-4.7(m,1H),
5.0-5.5(m,1H), 6.3-6.7(m,1H),
6.8-7.9(m,7H)

Ⅱ－２７

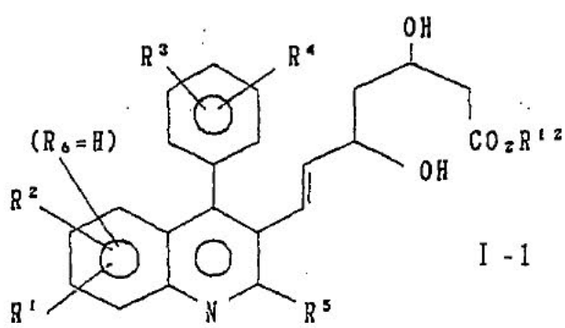
H-NMR(in $CDCl_3$) δ ppm :

0.8-1.5(m,4H), 1.26(t,3H,J=7Hz),

2.0-2.9(m,4H), 3.42(s,2H), 3.71(s,3H),
4.00(s,3H), 4.20(q,2H,J=7Hz),
4.4-4.8(m,1H), 5.3-5.8(m,1H),
6.4-6.9(m,1H), 6.58(s,1H),
7.0-7.5(m,5H)

In the same manner as in Example 1-g, compounds I-12 to I-127 were prepared.

Table 10



I-1

Compound	R1	R2	R3	R4	R5	R12	m.p. (°C) Mass spectrum
I-12	H	H	4-F	H	CH_3	C_2H_5	oil
						M/e	423, 292 264, 249
I-13	H	H	H	H	CH_3	C_2H_5	92-105
I-14	H	H	H	H	i-Pr	C_2H_5	97-100
I-15	6-Cl	H	H	H	CH_3	C_2H_5	oil

I-16	6-Cℓ	H	H	H	i-Pr	C_2H_5	oil
I-17	H	H	2-F	H	i-Pr	C_2H_5	oil
I-18	7-Me	H	H	H	i-Pr	C_2H_5	oil
I-19	H	H	4-Cℓ	H	i-Pr	C_2H_5	98-104
I-110	H	H	4-OMe	H	i-Pr	C_2H_5	94-98
I-111	H	H	4-Me	H	i-Pr	C_2H_5	79-85
I-112	6-Cℓ	H	2-Cℓ	H	i-Pr	C_2H_5	oil
I-113	H	H	4-CF_3	H	i-Pr	C_2H_5	117-128
I-114	H	H	3-Me	4-F	i-Pr	C_2H_5	85-92
I-115	H	H	3-Me	5-Me	i-Pr	C_2H_5	oil
I-116	6-OMe	7-OMe	4-F	H	i-Pr	C_2H_5	gum
I-117	H	H	4-F	H	C_2H_5	C_2H_5	oil
I-118	H	H	4-F	H	n-Pr	C_2H_5	oil
I-119	6-Cℓ	H	4-F	H	i-Pr	C_2H_5	79-82
I-120	H	H	4-F	H	c-Pr	C_2H_5	100-104
I-121	H	H	4-OPh	H	i-Pr	C_2H_5	oil
I-122	6-Cℓ	8-Cℓ	4-F	H	i-Pr	C_2H_5	133-143
I-123	6-Cℓ	H	H	H	Ph	C_2H_5	gum
I-124	6-Cℓ	H	H	H	c-Pr	C_2H_5	oil
I-125	H	H	4-F	H	sec-Bu	C_2H_5	oil

I-126	6-Me	H	4-F	H	i-Pr	C_2H_5	oil
I-127	6-OMe	7-OMe	4-F	H	c-Pr	C_2H_5	gum

I－17

H-NMR (in $CDCl_3$) δ ppm :

1.29(t,3H,J=7Hz), 1.40(d,6H,J=6Hz)
1.4-1.7(m,2H), 2.3-2.5(m,2H)
2.9-3.2(m,1H), 3.49(Heptaplet,1H,J=6Hz)
3.5-3.8(m,1H), 3.9-4.5(m,2H)
4.20(q,2H,J=7Hz), 5.2-5.7(m,1H)
6.5-6.9(m,1H), 7.0-8.2(m,8H)

I－18

H-NMR (in $CDCl_3$) δ ppm :

1.0-1.4(m,2H), 1.31(t,3H,J=7Hz)
1.39(d,6H,J=6Hz), 2.3-2.5(m,2H)
2.52(s,3H), 3.1-3.4(m,1H)
3.48(Heptaplet,1H,J=6Hz),3.5-3.8(m,1H)
3.8-4.1(m,1H), 4.20(q,2H,J=7Hz)
4.2-4.5(m,1H), 5.2-5.6(m,1H)
6.4-6.8(m,1H), 7.0-8.0(m,8H)

I - 19

H-NMR (in $CDC\ell_3$) δ ppm :

1.29(t,3H,J=7Hz), 1.38(d,6H,J=6Hz)

1.4-1.8(m,2H), 2.3-2.5(m,2H)

3.2-3.4(m,1H), 3.49 (Heptaplet,1H,J=6Hz)

3.6-3.8(m,1H), 3.9-4.2(m,1H)

4.20(q,2H,J=7Hz), 4.3-4.5(m,1H)

5.2-5.5(m,1H), 6.5-6.8(m,1H)

7.0-8.2(m,8H)

I - 1 1 0

H-NMR (in $CDC\ell_3$) δ ppm :

1.29(t,3H,J=7Hz), 1.40(d,6H,J=6Hz)

1.5-1.6(m,2H), 2.3-2.5(m,2H)

2.8-3.0(m,1H), 3.4-3.6(m,1H)

3.52(Heptaplet,1H,J=6Hz),3.88(s,3H)

3.9-4.1(m,1H), 4.20(q,2H,J=7Hz)

4.3-4.5(m,1H), 5.3-5.5(m,1H)

6.5-6.7(m,1H), 6.9-8.1(m,8H)

I - 1 1 1

H-NMR (in $CDC\ell_3$) δ ppm :

1.30(t,3H,J=7Hz), 1.3-1.5(m,2H)

1.39(d,6H,J=6Hz), 2.3-2.5(m,2H)
2.43(s,3H), 2.8-3.0(m,1H)
3.50(Heptaplet,1H,J=6Hz), 3.5-3.7(m,1H)
3.9-4.2(m,1H), 4.19(q,2H,J=7Hz)
4.2-4.5(m,1H), 5.2-5.6(m,1H)
6.4-6.8(m,1H), 6.9-8.2(m,8H)

I − 1 1 2

H-NMR (in $CDC\ell_3$) δ ppm :

1.30(t,3H,J=7Hz), 1.3-1.6(m,2H)
1.37(d,6H,J=6Hz), 2.3-2.5(m,2H)
2.9-3.2(m,1H), 3.47(Heptaplet,1H,J=6Hz)
3.5-3.8(m,1H), 3.9-4.1(m,1H)
4.19(q,2H,J=7Hz), 4.2-4.5(m,1H)
5.3-5.7(m,1H), 6.5-6.8(m,1H)
7.1-8.1(m,7H)

I − 1 1 3

H-NMR(in $CDC\ell_3$) δ ppm :

1.0-1.3(m,2H), 1.30(t,3H,J=7Hz)
1.40(d,6H,J=6Hz), 2.3-2.4(m,2H)
3.3-3.5(m,1H), 3.49(Heptaplet,1H,J=6Hz)

3.6-3.7(m,1H), 3.9-4.1(m,1H)
4.18(q,2H,J=7Hz), 4.2-4.5(m,1H)
5.1-5.5(m,1H), 6.5-6.8(m,1H)
7.2-8.2(m,8H)

I－1 1 4

H-NMR (in $CDC\ell_3$) δ ppm :

1.2-1.4(m,2H), 1.30(t,3H,J=7Hz)
1.39(d,6H,J=6Hz), 2.32(bs,3H)
2.3-2.5(m,2H), 3.0-3.3(m,1H)
3.50(Heptaplet,1H,J=6Hz), 3.6-3.8(m,1H)
3.8-4.1(m,1H), 4.20(q,2H,J=7Hz)
4.3-4.6(m,1H), 5.2-5.6(m,1H)
6.5-6.8(m,1H), 7.0-8.2(m,7H)

I－1 1 5

H-NMR (in $CDC\ell_3$) δ ppm :

1.1-1.4(m,2H), 1.30(t,3H,J=7Hz)
1.40(d,6H,J=6Hz), 2.2-2.5(m,2H)
2.35(s,6H), 2.7-3.1(m,1H)
3.51(Heptaplet,1H,J=6Hz), 3.6-3.7(m,1H)
3.8-4.1(m,1H), 4.20(q,2H,J=7Hz)

4.2-4.6(m,1H), 5.2-5.6(m,1H)

6.4-6.8(m,1H), 6.8-8.2(m,7H)

I－116

H-NMR (in $CDCl_3$) δ ppm :

1.30(t,3H,J=7Hz), 1.37(d,6H,J=6Hz)

1.5-1.8(m,2H), 2.3-2.5(m,2H)

2.9-3.2(m,1H), 3.46(Heptaplet,1H,J=6Hz)

3.6-3.8(m,1H), 3.75(s,3H)

3.9-4.1(m,1H), 4.07(s,3H)

4.20(q,2H,J=7Hz), 4.2-4.5(m,1H)

5.1-5.5(m,1H), 6.4-6.8(m,2H)

7.1-7.5(m,5H)

I－117

H-NMR(in $CDCl_3$) δ ppm :

1.30(t,3H,J=7Hz), 1.37(t,3H,J=7Hz)

1.4-1.7(m,2H), 2.2-2.6(m,2H)

2.8-3.2(m,3H), 3.6-3.9(m,1H)

3.9-4.7(m,4H), 5.2-5.7(m,1H)

6.3-6.7(m,1H) 7.0-8.2(m,8H)

I - 118

H-NMR (in $CDC\ell_3$) δ ppm :

1.01(t,3H,J=7Hz), 1.27(t,3H,J=7Hz)
1.4-2.1(m,4H), 2.3-2.6(m,2H)
2.8-3.3(m,3H), 3.6-3.8(m,1H)
3.9-4.1(m,1H), 4.18(q,2H,J=7Hz)
4.2-4.5(m,1H) 5.2-5.6(m,1H)
6.4-6.7(m,1H), 7.0-8.1(m,8H)

I - 119

H-NMR (in $CDC\ell_3$) δ ppm :

1.2-1.5(m,2H), 1.31(t,3H,J=7Hz)
1.37(d,6H,J=7Hz),2.3-2.6(m,2H)
3.0-3.4(m,1H), 3.49(Heptaplet,1H,J=6Hz)
3.6-3.8(m,1H), 3.8-4.2(m,1H)
4.20(q,2H,J=7Hz), 4.3-4.5(m,1H)
5.2-5.6(m,1H), 6.4-6.8(m,1H)
7.0-8.1(m,7H)

I - 120

H-NMR (in $CDC\ell_3$) δ ppm :

0.8-1.8(m,6H), 1.30(t,3H,J=7Hz)
2.1-2.6(m,3H), 2.9-3.3(m,1H)

3.4-3.7(m,1H), 3.8-4.6(m,2H)

4.20(q,2H,J=7Hz), 5.4-5.8(m,1H)

6.4-6.8(m,1H), 6.8-8.0(m,8H)

I − 1 2 1

H-NMR(in $CDCl_3$) δ ppm :

1.29(t,3H,J=7Hz), 1.39(d,6H,J=6Hz)

1.4-1.9(m,2H), 2.3-2.5(m,2H)

2.7-3.2(m,1H), 3.51(Heptaplet,1H,J=6Hz)

3.6-3.8(m,1H), 3.9-4.2(m,1H)

4.19(q,2H,J=7Hz), 4.3-4.6(m,1H)

5.2-5.6(m,1H), 6.4-6.8(m,1H)

6.9-8.2(m,13H)

I − 1 2 2

H-NMR (in $CDCl_3$) δ ppm :

1.1-1.8(m,2H), 1.31(t,3H,J=7Hz)

1.41(d,6H,J=6Hz), 2.3-2.5(m,2H)

2.9-3.4(m,1H), 3.50(Heptaplet,1H,J=6Hz)

3.6-3.8(m,1H), 3.9-4.5(m,2H)

4.20(q,2H,J=7Hz), 5.2-5.6(m,1H)

6.4-6.8(m,1H), 7.1-7.3(m,5H)

7.72(d,1H,J=6Hz)

I－1 2 3

H-NMR (in $CDCl_3$) δ ppm :

0.8-1.5(m,2H), 1.29(t,3H,J=7Hz)

2.2-2.4(m,2H), 2.6-2.9(m,1H)

3.2-3.6(m,1H), 3.7-4.3(m,2H)

4.17(q,2H,J=7Hz), 5.0-5.4(m,1H)

6.1-6.5(m,1H), 7.0-8.2(m,13H)

I－1 2 4

H-NMR (in $CDCl_3$) δ ppm :

0.8-1.8(m,6H), 1.29(t,3H,J=7Hz),

2.2-2.6(m,3H), 2.8-3.2(m,1H),

3.3-3.7(m,1H), 3.9-4.5(m,2H),

4.19(q,2H,J=7Hz), 5.4-5.8(m,1H),

6.5-6.8(m,1H), 7.1-8.0(m,8H),

I－1 2 5

H-NMR (in $CDCl_3$) δ ppm :

0.94(d,6H,J=6Hz), 1.0-1.7(m,3H),

1.27(t,3H,J=7Hz), 1.9-2.5(m,3H),

2.90(d,2H,J=7Hz), 3.3-4.4(m,3H),

4.12(q,2H,J=7Hz), 5.0-5.5(m,1H),
6.2-6.7(m,1H), 6.9-8.0(m,8H),

I − 1 2 6

H-NMR (in $CDCl_3$) δ ppm :

1.0-1.6(m,3H), 1.21(t,3H,J=7Hz),
1.34(d,6H,J=6Hz), 2.34(s,3H),
2.37(d,2H,J=7Hz), 2.9-3.7(m,2H),
3.8-4.5(m,2H), 4.15(q,2H,J=7Hz),
5.0-5.5(m,1H), 6.3-6.7(m,1H),
6.9-8.0(m,7H),

I − 1 2 7

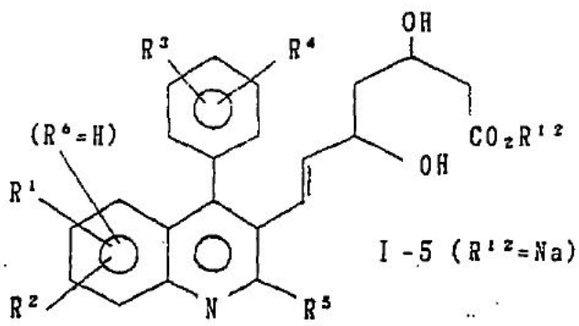
H-NMR (in $CDCl_3$) δ ppm :

0.8-1.9(m,8H), 1.29(t,3H,J=7Hz),
2.1-2.6(m,3H), 2.8-3.2(m,1H),
3.72(s,3H), 4.02(s,3H),
4.19(q,2H,J=7Hz), 4.3-4.6(m,1H),
5.4-5.8(m,1H), 6.4-6.8(m,1H),
6.56(s,1H), 7.0-7.4(m,5H)

In the same manner as in Exmple 2, compounds I-52 to I-527 were prepared.

Table 11

T710X



Compound	R¹	R²	R³	R⁴	R⁵	R¹²	m. p. (°C)
I-52	H	H	4-F	H	CH_3	Na	138-142 (decomposed)
I-53	H	H	H	H	CH_3	Na	130-132 (decomposed)
I-54	H	H	H	H	i-Pr	Na	196-197 (decomposed)
I-55	6-Cℓ	H	H	H	CH_3	Na	211-215 (decomposed)
I-56	6-Cℓ	H	H	H	i-Pr	Na	195-198 (decomposed)
I-57	H	H	2-F	H	i-Pr	Na	193-201 (decomposed)
I-58	7-Me	H	H	H	i-Pr	Na	170-175 (decomposed)
I-59	H	H	4-Cℓ	H	i-Pr	Na	193-202 (decomposed)
I-510	H	H	4-OMe	H	i-Pr	Na	178-193 (decomposed)
I-511	H	H	4-Me	H	i-Pr	Na	187-200 (decomposed)

I-512	6-Cℓ	H	2-Cℓ	H	i-Pr	Na	203-209 (decomposed)
I-513	H	H	4-CF_3	H	i-Pr	Na	200-212 (decomposed)
I-514	H	H	3-Me	4-F	i-Pr	Na	195-200 (decomposed)
I-515	H	H	3-Me	5-Me	i-Pr	Na	192-197 (decomposed)
I-516	6-OMe	7-OMe	4-F	H	i-Pr	Na	239-245 (decomposed)
I-517	H	H	4-F	H	C_2H_5	Na	230-237 (decomposed)
I-518	H	H	4-F	H	n-Pr	Na	193-200 (decomposed)
I-519	6-Cℓ	H	4-F	H	i-Pr	Na	193-198 (decomposed)
I-520	H	H	4-F	H	c-Pr	Na	197-199 (decomposed)
I-521	H	H	4-OPh	H	i-Pr	Na	180-189 (decomposed)
I-522	6-Cℓ	8-Cℓ	4-F	H	i-Pr	Na	183-187 (decomposed)
I-523	6-Cℓ	H	H	H	Ph	Na	190-196 (decomposed)
I-524	6-Cℓ	H	H	H	c-Pr	Na	204-210 (decomposed)
I-525	H	H	4-F	H	sec-Bu	Na	---
I-526	6-Me	H	4-F	H	i-Pr	Na	204-208 (decomposed)
I-527	6-OMe	7-OMe	4-F	H	c-Pr	Na	234-238 (decomposed)

I - 5 7

H-NMR (in DMSO-d^6) δ ppm :

0.9-1.2(m,2H), 1.37(d,6H,J=7Hz)

1.6-2.1(m,2H), 3.48(Heptaplet,1H,J=6Hz)
3.7-4.3(m,4H), 5.3-5.6(m,1H)
6.4-6.7(m,1H), 7.1-8.1(m,8H)

I − 5 8

H-NMR (in DMSO-d^6) δ ppm :

0.9-1.2(m,2H), 1.31(d,6H,J=7Hz)
1.7-2.2(m,2H), 2.50(s,3H)
3.3-4.5(m,5H), 5.2-5.6(m,1H)
6.3-6.6(m,1H), 7.1-7.9(m,8H)

I − 5 9

H-NMR (in DMSO-d^6) δ ppm :

0.9-1.3(m,2H), 1.33(d,6H,J=7Hz)
1.6-2.2(m,2H), 3.48(Heptaplet,1H,J=7Hz)
3.5-4.6(m,4H), 5.2-5.6(m,2H)
6.3-6.6(m,1H), 7.1-8.1(m,8H)

I − 5 1 0

H-NMR (in DMSO-d^6) δ ppm :

1.0-1.3(m,2H), 1.32(d,6H,J=7Hz)
1.6-2.2(m,2H), 3.0-3.8(m,4H)
3.86(s,3H), 4.0-4.3(m,1H)

5.3-5.6(m,1H), 6.3-6.6(m,1H)

6.9-8.1(m,8H)

I－5 1 1

H-NMR (in DMSO-d^6) δ ppm :

0.9-1.3(m,2H), 1.33(d,6H,J=7Hz)

1.7-2.1(m,2H), 2.41(s,3H)

3.2-4.3(m,5H), 5.3-5.6(m,1H)

6.3-6.6(m,1H), 7.0-8.3(m,8H)

I－5 1 2

H-NMR (in DMSO-d^6) δ ppm :

0.9-1.3(m,2H), 1.33(d,6H,J=7Hz)

1.6-2.2(m,2H), 3.1-3.8(m,3H)

3.48(Heptaplet,1H,J=7Hz),3.9-4.2(m,1H)

5.3-5.7(m,1H), 6.3-6.7(m,1H)

7.0-8.1(m,7H)

I－5 1 3

H-NMR (in DMSO-d^6) δ ppm :

0.8-1.3(m,2H), 1.34(d,6H,J=7Hz)

1.6-2.2(m,2H), 2.7-3.9(m,3H)

3.49(Heptaplet,1H,J=7Hz),3.9-4.3(m,1H)

5.2-5.6(m,1H), 6.3-6.7(m,1H)

7.1-8.1(m,8H)

I − 5 1 4

H-NMR (in DMSO-d^6) δ ppm :

0.9-1.3(m,2H), 1.35(d,6H,J=7Hz)

1.7-2.1(m,2H), 2.30(d,3H,J=2Hz)

3.0-3.8(m,3H), 3.51(Heptaplet,1H,J=7Hz)

3.9-4.3(m,1H), 5.3-5.6(m,1H)

6.3-6.6(m,1H), 6.9-8.1(m,7H)

II − 5 1 5

H-NMR (in DMSO-d^6) δ ppm :

1.0-1.2(m,2H), 1.35(d,6H,J=7Hz)

1.6-2.2(m,2H), 2.35(s,6H)

3.0-3.8(m,3H), 3.51(Heptaplet,1H,J=7Hz)

4.0-4.3(m,1H), 5.3-5.6(m,1H)

6.3-6.6(m,1H), 6.8-8.0(m,7H)

I − 5 1 6

H-NMR (in DMSO-d^6) δ ppm :

0.9-1.3(m,2H), 1.31(d,6H,J=7Hz)

1.7-2.0(m,2H), 3.2-3.7(m,4H)

3.62(s,3H), 3.9-4.2(m,1H)
3.94(s,3H), 5.1-5.5(m,1H)
6.2-6.6(m,1H), 7.0-7.5(m,6H)

I－5 1 7

H-NMR (in DMSO-d^6) δ ppm :

0.9-1.5(m,2H), 1.34(t,3H,J=7Hz)
1.6-2.2(m,2H), 2.7-3.4(m,4H)
3.6-4.3(m,2H), 5.2-5.7(m,1H)
6.1-6.6(m,1H), 6.9-8.1(m,8H)

I－5 1 8

H-NMR (in DMSO-d^6) δ ppm :

0.8-1.3(m,2H), 1.01(t,3H,J=7Hz)
1.6-2.1(m,4H), 2.7-3.8(m,5H)
3.9-4.3(m,1H), 5.2-5.7(m,1H)
6.3-6.6(m,1H), 7.1-8.1(m,8H)

I－5 1 9

H-NMR (in DMSO-d^6) δ ppm :

0.9-1.3(m,2H), 1.33(d,6H,J=7Hz)
1.6-2.2(m,2H), 2.9-3.9(m,3H)
3.49(Heptaplet,1H,J=7Hz),4.0-4.3(m,1H)

5.3-5.6(m,1H), 6.3-6.6(m,1H)

7.2-8.1(m,7H)

I－5 2 0

H-NMR (in DMSO-d^6) δ ppm :

0.8-1.5(m,6H), 1.7-2.2(m,2H)

2.3-2.7(m,1H), 3.0-3.9(m,3H)

4.0-4.3(m,1H), 5.5-5.8(m,1H)

6.4-6.7(m,1H), 7.2-8.0(m,8H)

I－5 2 1

H-NMR (in DMSO-d^6) δ ppm :

0.9-1.5(m,2H), 1.36(d,6H,J=7Hz)

1.7-2.3(m,2H), 3.0-3.9(m,3H)

3.50(Heptaplet,1H,J=6Hz),4.0-4.3(m,1H)

5.2-5.6(m,1H) 6.4-6.7(m,1H)

7.0-8.1(m,13H)

I－5 2 2

H-NMR (in DMSO-d^6) δ ppm :

0.8-1.3(m,2H), 1.37(d,6H,J=7Hz)

1.6-2.2(m,2H), 3.1-3.9(m,3H)

3.51(Heptaplet,1H,J=7Hz),4.0-4.3(m,1H)

5.3-5.7(m,1H), 6.3-6.7(m,1H)
7.1-8.0(m,6H)

I − 5 2 3

H-NMR (in DMSO-d^6) δ ppm :

0.8-1.4(m,2H), 1.6-2.1(m,2H)
2.9-3.7(m,3H), 3.7-4.1(m,1H)
5.1-5.4(m,1H), 6.1-6.4(m,1H)
7.1-8.2(m,13H)

I − 5 2 4

H-NMR (in DMSO-d^6) δ ppm :

0.8-1.5(m,5H), 1.6-2.2(m,2H)
2.3-2.7(m,2H), 3.0-3.8(m,3H)
3.9-4.3(m,1H), 5.4-5.8(m,1H)
6.3-6.6(m,1H), 7.0-8.0(m,8H)

I − 5 2 5

H-NMR (in DMSO-d^6) δ ppm :

0.9-1.6(m,2H), 0.96(d,6H,J=6Hz)
1.7-2.6(m,3H), 2.89(d,2H,J=7Hz)
3.0-3.8(m,3H), 3.9-4.2(m,1H)
5.2-5.6(m,1H), 6.2-6.6(m,1H)

7.1-8.1(m,8H)

I－526

H-NMR (in DMSO-d^6) δ ppm :

1.30(d,6H,J=7Hz), 1.7-2.0(m,2H),

2.34(s,3H), 2.4-2.6(m,1H),

3.0-3.3(m,2H), 3.3-3.8(m,3H)

3.9-4.2(m,1H), 5.2-5.6(m,1H)

6.3-6.6(m,1H), 7.0-8.0(m,7H)

I－527

H-NMR (in DMSO-d^6) δ ppm :

0.7-1.5(m,5H), 1.8-2.2(m,2H),

2.2-2.6(m,2H), 3.1-3.3(m,2H),

3.59(s,3H), 3.9-4.2(m,2H),

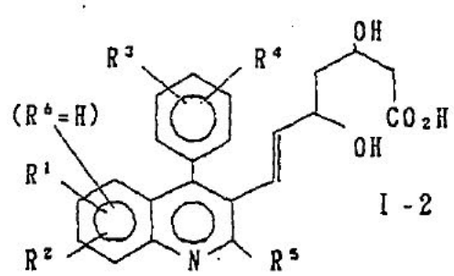
3.91(s,3H), 5.4-5.7(m,1H)

6.3-6.6(m,1H), 6.52(s,1H),

7.0-7.4(m,5H)

In the same manner as in Example 3, compounds I-22 to I-26 can be prepared.

Table 12

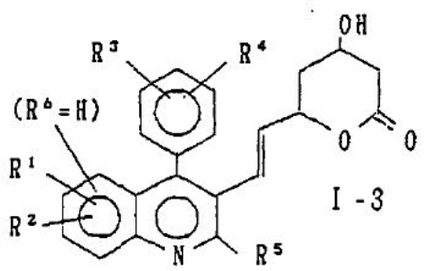


I-2

Compound	R^1	R^2	R^3	R^4	R^5
I-22	H	H	4-F	H	CH_3
I-23	H	H	H	H	CH_3
I-24	H	H	H	H	i-Pr
I-25	6-Cℓ	H	H	H	CH_3
I-26	6-Cℓ	H	H	H	i-Pr

In the same manner as in Example 4, compounds I-32 to I-36 can be prepared.

Table 13



I -3

Compound	R^1	R^2	R^3	R^4	R^5
I −32	H	H	4-F	H	CH_3
I −33	H	H	H	H	CH_3
I −34	H	H	H	H	i-Pr
I −35	6-Cℓ	H	H	H	CH_3
I −36	6-Cℓ	H	H	H	i-Pr

FORMULATION EXAMPLE 1

Tablets

Compound I-51	1.0 g
Lactose	5.0 g
Crystal cellulose powder	8.0 g
Corn starch	3.0 g
Hydroxypropyl cellulose	1.0 g
CMC-Ca	1.5 g
Magnesium stearate	0.5 g
Total	20.0 g

The above components were mixed by a usual method and then tabletted to produce 100 tablets each containing 10 mg of the active ingredient.

FORMULATION EXAMPLE 2

Capsules

Compound I-51	1.0 g
Lactose	3.5 g
Crystal cellulose powder	10.0 g
Magnesium stearate	0.5
Total	15.0 g

The above components were mixed by a usual method and then packed in No. 4 gelatin capsules to obtain 100 capsules each containing 10 mg of the active ingredient.

FORMULATION EXAMPLE 3

Soft capsules

Compound I-51	1.00 g
PEG (polyethylene glycol) 400	3.89 g
Saturated fatty acid triglyceride	15.00 g
Peppermint oil	0.01 g
Polysorbate 80	0.10 g
Total	20.00 g

The above components were mixed and packed in No. 3 soft gelatin capsules by a usual method to obtain 100 soft capsules each containing 10 mg of the active ingredient.

FORMULATION EXAMPLE 4

Ointment

Compound I-51	1.0 g (10.0 g)
Liquid paraffin	10.0 g (10.0 g)
Cetanol	20.0 g (20.0 g)
White vaseline	68.4 g (59.4 g)
Ethylparaben	0.1 g (0.1 g)
L-menthol	0.5 g (0.5 g)
Total	100.0 g

The above components were mixed by a usual method to obtain a 1% (10%) ointment.

FORMULATION EXAMPLE 5

Suppository

Compound I-51	1.0 g
Witepsol H15*	46.9 g
Witepsol W35*	52.0 g
Polysorbate 80	0.1 g
Total	100.0 g

*: Trademark for triglyceride compound

The above components were melt-mixed by a usual method and poured into suppository containers, followed by cooling for solidification to obtain 100 suppositories of 1 g each containing 10 mg of the active component.

FORMULATION EXAMPLE 6

Injection formulation

Compound I-51	1 mg
Distilled water for injection formulation	5 ml

The formulation is prepared by dissolving the compound in the distilled water whenever it is required.

FORMULATION EXAMPLE 7

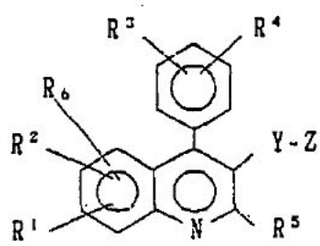
Granules

Compound I-51	1.0 g
Lactose	6.0 g
Crystal cellulose powder	6.5 g
Corn starch	5.0 g
Hydroxypropyl cellulose	1.0 g
Magnesium stearate	0.5 g
Total	20.0 g

The above components were granulated by a usual method and packaged to obtain 100 packages each containing 200 mg of the granules so that each package contains 10 mg of the active ingredient.

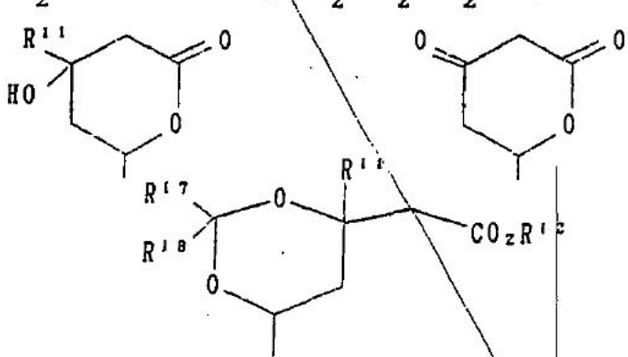
CLAIMS:

1. A compound of the formula:

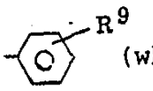


(I)

wherein R^1, R^2, R^3, R^4 and R^6 are independently hydrogen, C_{1-6} alkyl, C_{1-6} cycloalkyl, C_{1-3} alkoxy, n-butoxy, i-butoxy, sec-butoxy, R^7R^8N- (wherein R^7 and R^8 are independently hydrogen or C_{1-3} alkyl), trifluoromethyl, trifluoromethoxy, difluoromethoxy, fluoro, chloro, bromo, phenyl, phenoxy, benzyloxy, hydroxy, trimethylsilyloxy, diphenyl-t-butylsilyloxy, hydroxymethyl or $-O(CH_2)_\ell OR^{19}$ (wherein R^{19} is hydrogen or C_{1-3} alkyl, and ℓ is 1, 2 or 3); or when located at the ortho position to each other, R^1 and R^2, or R^3 and R^4 together form $-CH=CH-CH=CH-$; or when located at the ortho position to each other, R^1 and R^2 together form $-OC(R^{15})(R^{16})O-$ (wherein R^{15} and R^{16} are independently hydrogen or C_{1-3} ~~alkyl~~); Y is $-CH_2-$, $-CH_2CH_2-$, $-CH=CH-$, $-CH_2-CH=CH-$ or $-CH=CH-CH_2-$; and Z is $-Q-CH_2WCH_2-CO_2R^{12}$,

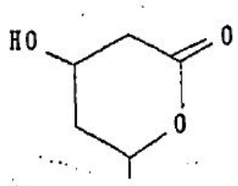
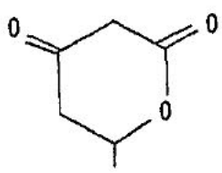


or

(wherein Q is -C(O)-, $-C(OR^{13})_2-$ or -CH(OH)-; W is -C(O)-, $-C(OR^{13})_2-$ or $-C(R^{11})(OH)-$; R^{11} is hydrogen or C_{1-3} alkyl; R^{12} is hydrogen or R^{14} (wherein R^{14} is physiologically hydrolyzable alkyl or M (wherein M is NH_4, sodium, potassium, 1/2 calcium or a hydrate of lower alkylamine, di-lower alkylamine or tri-lower alkylamine)); two R^{13} are independently primary or secondary C_{1-6} alkyl; or two R^{13} together form $-(CH_2)_2-$ or $-(CH_2)_3-$; R^{17} and R^{18} are independently hydrogen or C_{1-3} alkyl; and R^5 is hydrogen, C_{1-6} alkyl, C_{2-3} alkenyl, C_{3-6} cycloalkyl,  (wherein R^9 is hydrogen, C_{1-4} alkyl, C_{1-3} alkoxy, fluoro, chloro, bromo or trifluoromethyl), phenyl-$(CH_2)_m-$ (wherein m is 1, 2 or 3), $-(CH_2)_nCH(CH_3)$-phenyl or phenyl-$(CH_2)_nCH(CH_3)-$ (wherein n is 0, 1 or 2).

2. The compound according to Claim 1, wherein in the formula I, R^1, R^2 and R^6 are independently hydrogen, fluoro, chloro, bromo, C_{1-3} alkyl, C_{1-3} alkoxy, C_{3-6} cycloalkyl, dimethylamino, hydroxy, hydroxymethyl, hydroxyethyl, trifluoromethyl, trifluoromethoxy, difluoromethoxy, phenoxy or benzyloxy; or when R^6 is hydrogen, R^1 and R^2 together form methylenedioxy; when R^4 is hydrogen, R^3 is hydrogen, 3'-fluoro, 3'-chloro, 3'-methyl, 4'-methyl, 4'-chloro or 4'-fluoro; or R^3 and R^4 together represent 3'-methyl-4'-chloro, 3',5'-dichloro, 3',5'-difluoro, 3',5'-dimethyl or 3'-methyl-4'-fluoro; R^5 is primary or

secondary C_{1-6} alkyl or C_{3-6} cycloalkyl; and Y is $-CH_2-CH_2$ or $-CH=CH-$; and Z is

$-CH(OH)CH_2CH(OH)CH_2CO_2R^{12}$, $-CH(OH)CH_2C(O)CH_2CO_2R^{12}$ or $-CH(OH)CH_2C(OR^{13})_2CH_2CO_2R^{12}$.

3. Compound according to Claim 2, wherein when R^2 and R^6 are both hydrogen, R^1 is hydrogen, 5-fluoro, 6-fluoro, 7-fluoro, 8-fluoro, 5-chloro, 6-chloro, 7-chloro, 8-chloro, 5-bromo, 6-bromo, 7-bromo, 8-bromo, 5-methyl, 6-methyl, 7-methyl, 8-methyl, 5-methoxy, 6-methoxy, 7-methoxy, 8-methoxy, 5-trifluoromethyl, 6-trifluoromethyl, 7-trifluoromethyl, 8-trifluoromethyl, 6-trifluoromethoxy, 6-difluoromethoxy, 8-hydroxyethyl, 5-hydroxy, 6-hydroxy, 7-hydroxy, 8-hydroxy, 6-ethyl, 6-n-butyl or 7-dimethylamino; when R^6 is hydrogen, R^1 and R^2 together represent 6-chloro-8-methyl, 6-bromo-7-methoxy, 6-methyl-7-chloro, 6-chloro-8-hydroxy, 5-methyl-2-hydroxy, 6-methoxy-7-chloro, 6-chloro-7-methoxy, 6-hydroxy-7-chloro, 6-chloro-7-hydroxy, 6-chloro-8-bromo, 5-chloro-6-hydroxy, 6-bromo-8-chloro, 6-bromo-8-hydroxy, 5-methyl-8-chloro, 7-hydroxy-8-chloro, 6-bromo-8-hydroxy, 6-methoxy-7-methyl, 6-chloro-8-bromo, 6-methyl-8-bromo, 6,7-difluoro,

6,8-difluoro, 6,7-methylenedioxy, 6,8-dichloro, 5,8-dimethyl, 6,8-dimethyl, 6,7-dimethoxy, 6,7-diethoxy, 6,7-dibromo or 6,8-dibromo; or R^1, R^2 and R^3 together represent 5,7-dimethoxy-8-hydroxy, 5,8-dichloro-6-hydroxy, 6,7,8-trimethoxy, 6,7,8-trimethyl, 6,7,8-trichloro, 5-fluoro-6,8-dibromo or 5-chloro-6,8-dibromo; when R^3 is hydrogen, R^4 is hydrogen, 4'-methyl, 4'-chloro or 4'-fluoro; or when both R^3 and R^4 are not hydrogen, they represent 3',5'-dimethyl or 3'-methyl-4'-fluoro; and Y is $-CH_2-CH_2-$ or (E)--CH=CH-.

4. The compound according to Claim 3, wherein when both R^2 and R^3 are hydrogen, R^1 is hydrogen, 6-methyl, 6-ethyl, 6-n-butyl, 6-trifluoromethyl, 6-chloro, 6-bromo, 6-hydroxy, 6-methoxy or 7-dimethylamino; or when R^6 is hydrogen, R^1 and R^2 together represent 6,8-dichloro, 5,8-dimethyl, 6,8-dimethyl, 6,7-dimethoxy, 6,7-diethoxy, 6,7-dibromo, 6,8-dibromo, 6,7-difluoro or 6,8-difluoro; when R^3 is hydrogen, R^4 is hydrogen, 4'-fluoro or 4'-chloro; or R^3 and R^4 together represent 3'-methyl-4'-fluoro; R^5 is ethyl, n-propyl, i-propyl or cyclopropyl; and Y is (E)--CH=CH-.

5. The compound according to Claim 3, wherein when both R^2 and R^6 are hydrogen, R^1 is hydrogen, 6-methyl or 6-chloro; or when R^6 is hydrogen, R^1 and R^2 together represent 6,7-dimethoxy; when R^3 is hydrogen, R^4 is hydrogen, 4'-chloro or 4'-fluoro; R^5 is i-propyl or cyclopropyl; and Y is (E)--CH=CH-.

6. The compound according to Claim 1, which is (E)-3,5-dihydroxy-7-[4'-(4''-fluorophenyl)-2'-(1''-methylethyl)-quinolin-3'-yl]-hept-6-enoic acid, a lactone formed by the condensation of the carboxylic acid with hydroxy at the 5-position, or a sodium salt or C_{1-3} alkyl ester of the carboxylic acid.

7. The compound according to Claim 1, which is (E)-3,5-dihydroxy-7-[4'-(4''-fluorophenyl)-2'-(1''-methylethyl)-6'-chloro-quinolin-3'-yl]-hept-6-enoic acid, a lactone formed by the condensation of the carboxylic acid with hydroxy at the 5-position, or a sodium salt or C_{1-3} alkyl ester of the carboxylic acid.

8. The compound according to Claim 1, which is (E)-3,5-dihydroxy-7-[4'-(4''-fluorophenyl)-2'-(1''-methylethyl)-6'-methyl-quinolin-3'-yl]-hept-6-enoic acid, a lactone formed by the condensation of the carboxylic acid with hydroxy at the 5-position, or a sodium salt or C_{1-3} alkyl ester of the carboxylic acid.

9. The compound according to Claim 1, which is (E)-3,5-dihydroxy-7-[4'-(4''-fluorophenyl)-2'-(1''-methylethyl)-6',7'-dimethoxy-quinolin-3'-yl]-hept-6-enoic acid, a lactone formed by the condensation of the carboxylic acid with hydroxy at the 5-position, or a sodium salt or C_{1-3} alkyl ester of the carboxylic acid.

10. The compound according to Claim 1, which is (E)-3,5-dihydroxy-7-[4'-(4''-fluorophenyl)-2'-cyclopropyl-quinolin-3'-yl]-hept-6-enoic acid, a lactone formed by the

condensation of the carboxylic acid with hydroxy at the 5-position, or a sodium salt or C_{1-3} alkyl ester of the carboxylic acid.

11. The compound according to Claim 1, which is (E)-3,5-dihydroxy-7-[4'-(4''-fluorophenyl)-2'-cyclopropyl-6'-chloro-quinolin-3'-yl]-hept-6-enoic acid, a lactone formed by the condensation of the carboxylic acid with hydroxy at the 5-position, or a sodium salt or C_{1-3} alkyl ester of the carboxylic acid.

12. The compound according to Claim 1, which is (E)-3,5-dihydroxy-7-[4'-(4''-fluorophenyl)-2'-cyclopropyl-6'-methyl-quinolin-3'-yl]-hept-6-enoic acid, a lactone formed by the condensation of the carboxylic acid with hydroxy at the 5-position, or a sodium salt or C_{1-3} alkyl ester of the carboxylic acid.

13. The compound according to Claim 1, which is (E)-3,5-dihydroxy-7-[4'-(4''-fluorophenyl)-2'-cyclopropyl-6',7'-dimethoxy-quinolin-3'-yl]-hept-6-enoic acid, a lactone formed by the condensation of the carboxylic acid with hydroxy at the 5-position, or a sodium salt or C_{1-3} alkyl ester of the carboxylic acid.

14. The compound according to Claim 1, which is (E)-3,5-dihydroxy-7-[4'-(4''-chlorophenyl)-2'-(1''-methylethyl)-quinolin-3'-yl]-hept-6-enoic acid, a lactone formed by the condensation of the carboxylic acid with hydroxy at the 5-position, or a sodium salt or C_{1-3} alkyl ester of the carboxylic acid.

15. The compound according to Claim 1, which is (E)-3,5-dihydroxy-7-[4'-(4''-chlorophenyl)-2'-(1''-methylethyl)-6'-chloro-quinolin-3'-yl]-hept-6-enoic acid, a lactone formed by the condensation of the carboxylic acid with hydroxy at the 5-position, or a sodium salt or C_{1-3} alkyl ester of the carboxylic acid.

16. The compound according to Claim 1, which is (E)-3,5-dihydroxy-7-[4'-(4''-chlorophenyl)-2'-(1''-methylethyl)-6'-methyl-quinolin-3'-yl]-hept-6-enoic acid, a lactone formed by the condensation of the carboxylic acid with hydroxy at the 5-position, or a sodium salt or C_{1-3} alkyl ester of the carboxylic acid.

17. The compound according to Claim 1, which is (E)-3,5-dihydroxy-7-[4'-(4''-chlorophenyl)-2'-(1''-methylethyl)-6',7'-dimethoxy-quinolin-3'-yl]-hept-6-enoic acid, a lactone formed by the condensation of the carboxylic acid with hydroxy at the 5-position, or a sodium salt or C_{1-3} alkyl ester of the carboxylic acid.

18. The compound according to Claim 1, which is (E)-3,5-dihydroxy-7-[4'-(4''-chlorophenyl)-2'-cyclopropyl-quinolin-3'-yl]-hept-6-enoic acid, a lactone formed by the condensation of the carboxylic acid with hydroxy at the 5-position, or a sodium salt or C_{1-3} alkyl ester of the carboxylic acid.

19. The compound according to Claim 1, which is (E)-3,5-dihydroxy-7-[4'-(4''-chlorophenyl)-2'-cyclopropyl-6'-chloro-quinolin-3'-yl]-hept-6-enoic acid, a lactone

formed by the condensation of the carboxylic acid with hydroxy at the 5-position, or a sodium salt or C_{1-3} alkyl ester of the carboxylic acid.

20. The compound according to Claim 1, which is (E)-3,5-dihydroxy-7-[4'-(4''-chlorophenyl)-2'-cyclopropyl-6'-methyl-quinolin-3'-yl]-hept-6-enoic acid, a lactone formed by the condensation of the carboxylic acid with hydroxy at the 5-position, or a sodium salt or C_{1-3} alkyl ester of the carboxylic acid.

21. The compound according to Claim 1, which is (E)-3,5-dihydroxy-7-[4'-(4''-chlorophenyl)-2'-cyclopropyl-6'7'-dimethoxy-quinolin-3'-yl]-hept-6-enoic acid, a lactone formed by the condensation of the carboxylic acid with hydroxy at the 5-position, or a sodium salt or C_{1-3} alkyl ester of the carboxylic acid.

22. The compound according to Claim 1, which is (E)-3,5-dihydroxy-7-[4'-phenyl-2'-(1''-methylethyl)-quinolin-3'-yl]-hept-6-enoic acid, a lactone formed by the condensation of the carboxylic acid with hydroxy at the 5-position, or a sodium salt or C_{1-3} alkyl ester of the carboxylic acid.

23. The compound according to Claim 1, which is (E)-3,5-dihydroxy-7-[4'-phenyl-2'-(1''-methylethyl)-6'-chloro-quinolin-3'-yl]-hept-6-enoic acid, a lactone formed by the condensation of the carboxylic acid with hydroxy at the 5-position, or a sodium salt or C_{1-3} alkyl ester of the carboxylic acid.

24. The compound according to Claim 1, which is (E)-3,5-dihydroxy-7-[4'-phenyl-2'-(1''-methylethyl)-6'-methyl-quinolin-3'-yl]-hept-6-enoic acid, a lactone formed by the condensation of the carboxylic acid with hydroxy at the 5-position, or a sodium salt or C_{1-3} alkyl ester of the carboxylic acid.

25. The compound according to Claim 1, which is (E)-3,5-dihydroxy-7-[4'-phenyl-2'-(1''-methylethyl)-6',7'-dimethoxy-quinolin-3'-yl]-hept-6-enoic acid, a lactone formed by the condensation of the carboxylic acid with hydroxy at the 5-position, or a sodium salt or C_{1-3} alkyl ester of the carboxylic acid.

26. The compound according to Claim 1, which is (E)-3,5-dihydroxy-7-[4'-phenyl-2'-cyclopropyl-quinolin-3'-yl]-hept-6-enoic acid, a lactone formed by the condensation of the carboxylic acid with hydroxy at the 5-position, or a sodium salt or C_{1-3} alkyl ester of the carboxylic acid.

27. The compound according to Claim 1, which is (E)-3,5-dihydroxy-7-[4'-phenyl-2'-cyclopropyl-6'-chloro-quinolin-3'-yl]-hept-6-enoic acid, a lactone formed by the condensation of the carboxylic acid with hydroxy at the 5-position, or a sodium salt or C_{1-3} alkyl ester of the carboxylic acid.

28. The compound according to Claim 1, which is (E)-3,5-dihydroxy-7-[4'-phenyl-2'-cyclopropyl-6'-methyl-quinolin-3'-yl]-hept-6-enoic acid, a lactone formed by the

condensation of the carboxylic acid with hydroxy at the 5-position, or a sodium salt or C_{1-3} alkyl ester of the carboxylic acid.

29. The compound according to Claim 1, which is (E)-3,5-dihydroxy-7-[4'-phenyl-2'-cyclopropyl-6',7'-dimethoxy-quinolin-3'-yl]-hept-6-enoic acid, a lactone formed by the condensation of the carboxylic acid with hydroxy at the 5-position, or a sodium salt or C_{1-3} alkyl ester of the carboxylic acid.

30. The compound according to Claim 1, which is (E)-3,5-dihydroxy-7-[4'-(4''-fluorophenyl)-2'-(1''-methylethyl)-6'-methoxy-quinolin-3'-yl]-hept-6-enoic acid, a lactone formed by the condensation of the carboxylic acid with hydroxy at the 5-position, or a sodium salt or C_{1-3} alkyl ester of the carboxylic acid.

31. The compound according to Claim 1, which is (E)-3,5-dihydroxy-7-[4'-(4''-fluorophenyl)-2'-cyclopropyl-6'-methoxy-quinolin-3'-yl]-hept-6-enoic acid, a lactone formed by the condensation of the carboxylic acid with hydroxy at the 5-position, or a sodium salt or C_{1-3} alkyl ester of the carboxylic acid.

32. An anti-hyperlipidemia agent containing the compound of the formula I as defined in Claim 1.

33. An anti-hyperlipoproteinemia agent containing the compound of the formula I as defined in Claim 1.

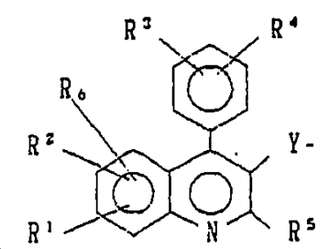
34. An anti-atherosclerosis agent containing the compound of the formula I as defined in Claim 1.

35. A method for reducing hyperlipidemia, hyperlipoproteinemia or atherosclerosis, which comprises administering an effective amount of the compound of the formula I as defined in Claim 1.

Ack'd B'

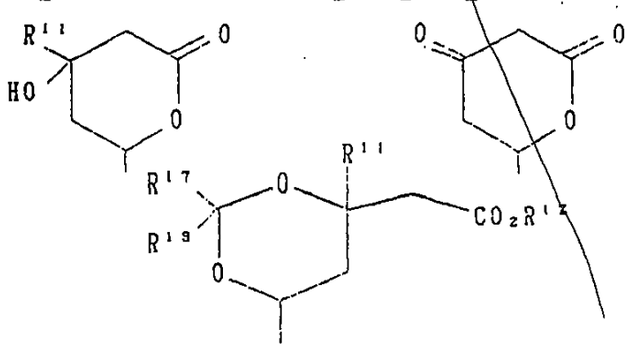
ABSTRACT

A compound of the formula:



(I)

wherein R^1, R^2, R^3, R^4 and R^6 are independently hydrogen, C_{1-6} alkyl, C_{1-6}cycloalkyl, C_{1-3} alkoxy, n-botoxy, i-botoxy, sec-butoxy, R^7R^8N- (wherein R^7 and R^8 are independently hydrogen or C_{1-3} alkyl), trifluoromethyl, trifluoromethoxy, difluoromethoxy, fluoro, chloro, bromo, phenyl, phenoxy, benzyloxy, hydroxy, trimethylsilyloxy, diphenyl-t-butylsilyloxy, hydroxymethyl or $-O(CH_2)_\ell OR^{19}$ (wherein R^{19} is hydrogen or C_{1-3} alkyl, and ℓ is 1,2 or 3); or when located at the ortho position to each other, R^1 and R^2, or R^3 and R^4 together form $-CH=CH-CH=CH-$; or when located at the ortho position to each other, R^1 and R^2 together form $-OC(R^{15})(R^{16})O-$ (wherein R^{15} and R^{16} are independently hydrogen or C_{1-3} alkyl); Y is $-CH_2-$, $-CH_2CH_2-$, $-CH=CH-$, $-CH_2-CH=CH-$ or $-CH=CH-CH_2-$; and Z is $-Q-CH_2WCH_2-CO_2R^{12}$,



or

(wherein Q is -C(O)-, $-C(OR^{13})_2-$ or -CH(OH)-; W is -C(O)-, $-C(OR^{13})_2-$ or $-C(R^{11})(OH)-$; R^{11} is hydrogen atom or C_{1-3} alkyl; R^{12} is hydrogen or R^{14} (wherein R^{14} is physiologically hydrolyzable alkyl or M (wherein M is NH_4, sodium, potassium, 1/2 calcium or a hydrate of lower alkyl amine, di-lower alkyl amine or tri-lower alkyl amine)); two R^{13} are independently primary or secondary C_{1-6} alkyl; or two R^{13} together form $-(CH_2)_2-$ or $-(CH_2)_3$; R^{17} and R^{18} are independently hydrogen or C_{1-3} alkyl; and R^5 is hydrogen, C_{1-6} alkyl, C_{2-3} alkenyl, C_{3-6} cycloalkyl,  (wherein R^9 is a hydrogen atom, C_{1-4} alkyl, C_{1-3} alkoxy, fluoro, chloro, bromo or trifluoromethyl), phenyl-$(CH_2)_m-$ (wherein m is 1,2 or 3), $-(CH_2)_nCH(CH_3)$-phenyl or phenyl-$(CH_2)_nCH(CH_3)-$ (wherein n is 0,1 or 2).

COPY

Declaration, Power Of Attorney and Petition

WE (I) the undersigned inventor(s), hereby declare(s) that:

My residence, post office address and citizenship are as stated below next to my name,

We (I) believe that we are (I am) the original, first, and joint (sole) inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled

QUINOLINE TYPE MEVALONOLACTONES

the specification of which

☐ is attached hereto.

☒ was filed on August 19, 1988 as

Application Serial No. 07/233,752

and amended on _____.

☐ was filed as PCT international application

Number _____

on _____,

and was amended under PCT Article 19

on _____ (if applicable).

We (I) hereby state that we (I) have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We (I) acknowledge the duty to disclose information material to the examination of this application in accordance with Section 1.56(a) of Title 37 Code of Federal Regulations.

We (I) hereby claim foreign priority benefits under Section 119 of Title 35 United States Code, of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Application No.	Country	Day/Month/Year	Priority Claimed
207224/1987	Japan	20/8/87	☒ Yes ☐ No
15585/1988	Japan	26/1/88	☒ Yes ☐ No
Not Yet Allotted	Japan	3/8/88	☒ Yes ☐ No
			☐ Yes ☐ No

We (I) hereby claim the benefit under Section 120 of Title 35 United States Code, of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Section 112 of Title 35 United States Code, We (I) acknowledge the duty to disclose material information as defined in Section 1.56(a) of Title 37 Code of Federal Regulations, which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status (pending, patented, abandoned)

And we (I) hereby appoint Norman F. Oblon, Registration Number 24,618, Stanley P. Fisher, Registration Number 24,344, Marvin J. Spivak, Registration Number 24,913, C. Irvin McClelland, Registration Number 21.124, Gregory J. Maier, Registration Number 25,599, Arthur I. Neustadt, Registration Number 24,854, Robert C. Miller, Registration Number 25,357, Richard D. Kelly, Registration Number 27,757, James D. Hamilton, Registration Number 28,421, Eckhard H. Kuesters, Registration Number 28,870, Robert T. Pous, Registration Number 29,099, Charles L. Gholz, Registration Number 26,395, Vincent J. Sunderdick, Registration Number 29,004, William E. Beaumont, Registration Number 30,996 and Steven B. Kelber, Registration Number 30,073, our (my) attorneys, with full powers of substitution and revocation, to prosecute this application and to transact all business in the Patent Office connected therewith; and we (I) hereby request that all correspondence regarding this application be sent to the firm of OBLON, FISHER, SPIVAK, McCLELLAND & MAIER, P.C., whose Post Office Address is: Crystal Square Five — Suite 400, 1755 South Jefferson Davis Highway, Arlington, Virginia 22202.

We (I) declare that all statements made herein of our (my) own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Yoshihiro Fujikawa 1-00
NAME OF FIRST SOLE INVENTOR

Yoshihiro Fujikawa
Signature of Inventor

October 3, 1988
Date

Residence: Nissan Chemical Industries Ltd.
Chuo Kenkyusho, 722-1, Tsuboi-cho
Funabashi-shi, Chiba-ken, Japan JPX

Citizenship: JAPAN

Post Office Address: same as above

2-00

Mikio Suzuki
NAME OF SECOND JOINT INVENTOR

Mikio Suzuki
Signature of Inventor

October 3, 1988
Date

Residence: Nissan Chemical Industries Ltd.
Chuo Kenkyusho, 722-1, Tsuboi-cho
Funabashi-shi, Chiba-ken, Japan JPX

Citizenship: JAPAN

Post Office Address: same as above

3-00

Hiroshi Iwasaki
NAME OF THIRD JOINT INVENTOR

Hiroshi Iwasaki
Signature of Inventor

October 3, 1988
Date

Residence: Nissan Chemical Industries Ltd.
Chuo Kenkyusho, 722-1, Tsuboi-cho
Funabashi-shi, Chiba-ken, Japan JPX

Citizenship: JAPAN

Post Office Address: same as above

4-00

Mitsuaki Sakashita
NAME OF FOURTH JOINT INVENTOR

Mitsuaki Sakashita
Signature of Inventor

October 3, 1988
Date

Residence: Nissan Chemical Industries Ltd.
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Oaza-shiraoka, Shiraoka-machi
Minamisaitama-gun, Saitama-ken, Japan JPX

Citizenship: JAPAN

Post Office Address: same as above

5-00

Masaki Kitahara
NAME OF FIFTH JOINT INVENTOR

Masaki Kitahara
Signature of Inventor

October 3, 1988
Date

Residence: Nissan Chemical Industries Ltd.
Seibutsukagaku Kenkyusho, 1470
Oaza-shiraoka, Shiraoka-machi
Minamisaitama-gun, Saitama-ken, Japan JPX

Citizenship: JAPAN

Post Office Address: same as above

07/883398

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:	:	
YOSHINARO FUJIKAWA ET AL	:	GROUP ART UNIT: 129
SERIAL NUMBER: NEW DIV. APPLN.	:	EXAMINER: J. RICHTER
FILED: HEREWITH	:	

FOR: QUINOLINE TYPE MEVALONOLACTONES

REQUEST FOR PRIORITY UNDER
35 U.S.C. §119 AND THE INTERNATIONAL CONVENTION

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231

SIR:

In the matter of the above-identified patent application, notice is hereby given that applicants claim as priority dates August 20, 1987, January 26, 1988, and August 03, 1988 , the filing dates of the corresponding convention applications filed in **JAPAN**. The corresponding convention applications bear Serial Numbers **62-207224, 63-15585 and 63-193606,** respectively.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Norman F. Oblon
Registration No.: 24,618

Steven B. Kelber
Registration No.: 30,,073
Attorneys of Record

Fourth Floor
1755 South Jefferson Davis Highway
Arlington, Virginia 22202
703-521-5940
49-169-0 DIV of 49-168-0 CONT

690'20-19

07/883398

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Docket No. 49-168-0 DIV

HONORABLE COMMISSIONER OF PATENTS & TRADEMARKS
WASHINGTON, D.C. 20231

SIR: This is a request for filing a

☐ Continuation

application under 37 C.F.R. 1.60,

☒ Divisional

of copending prior application Serial No. 07/631,092, filed on December 19, 1990 (date)

of YOSHIHIRO FUJIKAWA ET AL (inventor)

for Quinoline Type Mevalonolactones (title of invention)

1. ☒ Enclosed is a copy of the prior application as originally filed and an affidavit or declaration verifying it as a true copy.

2. ☐ Small Entity Status of this application has been established by a Verified Statement submitted in the parent application.

3. ☒ The filing fee is calculated below:

CLAIMS AS FILED, LESS ANY CLAIMS CANCELLED BY AMENDMENT BELOW

For	Number filed		Number extra	Rate	Basic $690	Fee (345)
Total Claims	5	−20	=	x$20(10)	=	−0−
Independent Claims	1	−3	=	x$72(36)	=	−0−
☐ Multiple Claim Fee — $220(110) =						
Total Filing Fee					=	$690

4. ☒ The Commissioner is hereby authorized to charge any fees which may be required for the papers being filed herewith and for which no check is enclosed herewith, or credit any overpayment to Account No. 15-0030. A duplicate copy of this sheet is enclosed.

5. ☒ A check in the amount of $ 690.00 is enclosed.

6. ☒ Cancel Claims 41-45.

7. ☒ Amend the specification by inserting before the first line the sentence:

This is a ___ continuation, X division, of application Serial No. 07/631,092, filed on December 19, 1990, which is a continuation of 07/233,752, filed August 19, 198

8. ☐ New Drawings are enclosed.

9. ☐ The prior application is assigned to: _____

1/92

10. [X] The Power of Attorney in the prior application is to: Norman F. Oblon, Reg. No. 24,618; Marvin J. Spivak, Reg. No. 24,913; C. Irvin McClelland, Reg. No. 21,124; Gregory J. Maier, Reg. No. 25,599; Arthur I. Neustadt, Reg. No. 24,854; Robert C. Miller, Reg. No. 25,357; Richard D. Kelly, Reg. No. 27,757; James D. Hamilton, Reg. No. 28,421; Eckhard H. Kuesters, Reg. No. 28,870; Robert T. Pous, Reg. No. 29,099; Charles L. Gholz, Reg. No. 26,395; Vincent J. Sunderdick, Reg. No. 29,004; William E. Beaumont, Reg. No. 30,996; Steven B. Kelber, Reg. No. 30,073; Stuart D. Dwork, Reg. No. 31,103; Robert F. Gnuse, Reg. No. 27,295; Jean-Paul Lavalleye, Reg. No. 31,451; William B. Walker, Reg. No. 22,498; Timothy R. Schwartz, Reg. No. 32,171; and John H.O. Clarke, Reg. No. 17,373, all of OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C., Fourth Floor, 1755 Jefferson Davis Highway, Arlington, Virginia 22202.

a. [X] The power appears in the original papers of the prior application. (Copy Attached)

b. [ ] Since the power does not appear in the original papers, a copy of the power in the prior application is enclosed.

c. [ ] Recognize as associate attorney and address all future communications to:

_____

_____

_____

name, registration number and address

11. [X] A Preliminary Amendment is enclosed.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Norman F. Oblon
Attorney of Record
Registration No. 35,618

Steven B. Kelber
Registration No. 30,073

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07/883398

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Docket No. 49-168-0 DIV

HONORABLE COMMISSIONER OF PATENTS & TRADEMARKS
WASHINGTON, D.C. 20231

SIR: This is a request for filing a

☐ Continuation

application under 37 C.F.R. 1.60,

☒ Divisional

of copending prior application Serial No. 07/631,092, filed on December 19, 1990 (date)

of YOSHIHIRO FUJIKAWA ET AL (inventor)

for Quinoline Type Mevalonolactones (title of invention)

1. ☒ Enclosed is a copy of the prior application as originally filed and an affidavit or declaration verifying it as a true copy.

2. ☐ Small Entity Status of this application has been established by a Verified Statement submitted in the parent application.

3. ☒ The filing fee is calculated below:

CLAIMS AS FILED, LESS ANY CLAIMS CANCELLED BY AMENDMENT BELOW

For	Number filed		Number extra		Rate		Basic $690	Fee (345)
Total Claims	5	−20	=		x$20(10)	=		−0−
Independent Claims	1	−3	=		x$72(36)	=		−0−
☐ Multiple Claim Fee − $220(110) =								
Total Filing Fee							=	$690

4. ☒ The Commissioner is hereby authorized to charge any fees which may be required for the papers being filed herewith and for which no check is enclosed herewith, or credit any overpayment to Account No. 15-0030. A duplicate copy of this sheet is enclosed.

5. ☒ A check in the amount of $ 690.00 is enclosed.

6. ☒ Cancel Claims 41-48.

7. ☒ Amend the specification by inserting before the first line the sentence:

This is a ___ continuation, X division, of application Serial No. 07/631,092, filed on December 19, 1990, which is a continuation of 07/233,752, filed August 19, 1988.

8. ☐ New Drawings are enclosed.

9. ☐ The prior application is assigned to: _____

1/92

10. [X] The Power of Attorney in the prior application is to: Norman F. Oblon, Reg. No. 24,618; Marvin J. Spivak, Reg. No. 24,913; C. Irvin McClelland, Reg. No. 21,124; Gregory J. Maier, Reg. No. 25,599; Arthur I. Neustadt, Reg. No. 24,854; Robert C. Miller, Reg. No. 25,357; Richard D. Kelly, Reg. No. 27,757; James D. Hamilton, Reg. No. 28,421; Eckhard H. Kuesters, Reg. No. 28,870; Robert T. Pous, Reg. No. 29,099; Charles L. Gholz, Reg. No. 26,395; Vincent J. Sunderdick, Reg. No. 29,004; William E. Beaumont, Reg. No. 30,996; Steven B. Kelber, Reg. No. 30,073; Stuart D. Dwork, Reg. No. 31,103; Robert F. Gnuse, Reg. No. 27,295; Jean-Paul Lavalleye, Reg. No. 31,451; William B. Walker, Reg. No. 22,498; Timothy R. Schwartz, Reg. No. 32,171; and John H.O. Clarke, Reg. No. 17,373, all of OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C., Fourth Floor, 1755 Jefferson Davis Highway, Arlington, Virginia 22202.

a. [X] The power appears in the original papers of the prior application. (Copy Attached)

b. [ ] Since the power does not appear in the original papers, a copy of the power in the prior application is enclosed.

c. [ ] Recognize as associate attorney and address all future communications to:

_____

_____

_____

name, registration number and address

11. [X] A Preliminary Amendment is enclosed.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Norman F. Oblon
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07883398

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:	:	
YOSHIHIRO FUJIKAWA ET AL	:	GROUP ART UNIT: 129
SERIAL NUMBER: NEW DIVISIONAL	:	EXAMINER: RICHTER
FILED: HEREWITH	:	

FOR: QUINOLINE TYPE MEVALONOLACTONES

PRELIMINARY AMENDMENT

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231

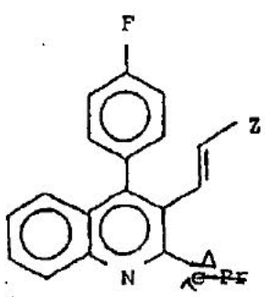
SIR:

In advance of prosecution of the above-captioned patent application, entry of the following amendments is respectfully requested.

IN THE CLAIMS:

Please cancel Claims 41-45 and insert new Claims 46-50.

~~--36.~~ A compound of the formula,



[A]

Z=-CH(OH)-CH_2-CH(OH)-CH_2-COO · 1/2Ca

~~37.~~ An anti-hyperlipidemia agent containing ~~the compound of~~ the formula A as defined in Claim ~~36~~.

~~38.~~ An anti-hyperlipoproteinemia agent containing the compound of the formula A as defined in Claim ~~36~~.

~~39.~~ An anti-atherosclerosis agent containing the compound ~~of the formula A as defined in Claim 36.~~

~~40.~~ A method for reducing hyperlipidemia, hyperlipoproteinemia or atherosclerosis, which comprises administering an effective amount of the compound of formula A as defined in Claim ~~36~~. --

REMARKS:

Claims 41-45 have been cancelled in favor of new Claims 46-50 in order to more clearly define the invention.

Upon entry, the claims are believed to be in conformance with the requirements of Title 35, and in condition for examination on the merits. The same is respectfully requested, in light of the Rule 132 Declaration of Masaki Kitahara submitted herewith. Applicants are submitting at this time an unexecuted Declaration, an executed Declaration will be submitted when available.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Norman F. Oblon
Registration No.: 24,618

Steven B. Kelber
Registration No.: 30,073
Attorneys of Record

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1755 South Jefferson Davis Highway
Arlington, Virginia 22202
703-521-5940

07/883398

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF: :

YOSHIHIRO FUJIKAWA ET AL : GROUP ART UNIT: 129

DIVISIONAL APPLICATION : EXAMINER: J. RICHTER
DIVIDED FROM
SERIAL NO.: 07/631,092 :

FOR: QUINOLINE TYPE MEVALONOLACTONES

DECLARATION UNDER 37 CFR 1.132

HONORABLE COMMISSIONER OF PATENTS & TRADEMARKS

WASHINGTON, D.C. 20231

SIR:

I, Masaki Kitahara, do hereby declare and state that:

1. I am a named co-inventor in the above-captioned patent application, an employee of Nissan Chemical Industries, Limited, and a citizen and resident of Japan.

2. I am familiar with the above-captioned patent application, and Claims presented by Divisional Application.

3. To demonstrate the unobvious superiority of the subject matter claimed therein, comparative tests were conducted, demonstrating the importance and unobvious superiority conferred on these compounds by the selection of the cyclopropyl (c-Pr) substituent. These are described as follows:

MISSING PAGE(S)

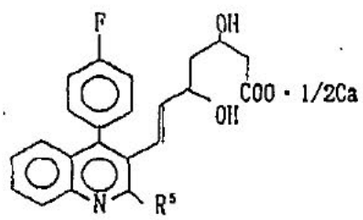
FROM THE U.S. PATENT OFFICE

OFFICIAL FILE WRAPPER

pg. 2 of Declaration

(see executed copy of Decl. w/paper # 4)

Data was obtained with regard to the following compound having the formula:



		TEST METHOD	
Compound	R^5	Test A Evaluation	Test B Evaluation
Compound of this Invention	cyclopropyl (c-Pr)	4.4×10^{-9}	35.0×10^{-9}
Reference Compound	isopropyl (i-Pr)	23.0×10^{-9}	105×10^{-9}

Test A. Inhibition of cholesterol biosynthesis from acetate in vitro

This test was carried out as described on pages 28-29 of the specification. The above numerical values indicate IC_{50} (molar concentration).

Test B: Inhibition of cholesterol biosynthesis in culture cells

This test was carried out as described on pages 29 to 30 of the specification. The above numerical values indicate IC_{50} (molar concentration).

4. Based on the data reported above, it can be determined that the compound of this invention exhibits unobvious superiority, and in particular, sharply enhanced inhibition of cholesterol biosynthesis, in vitro, and culture cell, when compared with the referenced compound of the prior art, and compounds having an identical structure save for the selection of cyclopropyl, as opposed to isopropyl substituent, for R^5. This enhanced activity could not be predicted on the basis of structure, or information available to those of ordinary skill in the art as of the effective filing date of this application.

All statements made herein of my own knowledge are true, and all statements made on information and belief are believed true. I am aware that willful false statements and the like are punishable by fine, imprisonment or both, 18 U.S.C. §1001, and that such willful false statements may jeopardize the validity of the above-captioned patent application and any patent issuing thereon.

FURTHER, I SAYETH NOT.

_____ _____

Date Masaki Kitahara

12 G ... 2/9...

OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C.
ATTORNEYS AT LAW
FOURTH FLOOR
1755 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202 U.S.A.

TELEPHONE
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FACSIMILE
(703) 486-2347
TELEX
248855 OPAT UR

Docket No.: 49-168-0 DIV

92 JUN 22 AM 11:25
GROUP 120

HON. COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231

IN RE APPLICATION OF: :
YOSHIHIRA FUJIKAWA ET AL :
SERIAL NUMBER: 07/883,398 :
FILED: MAY 15, 1992 :
FOR: QUINOLINE TYPE MEVALONOLACTONES

GROUP ART UNIT: ~~129~~
EXAMINER: RICHTER

SIR:

Attached hereto for filing are the following papers:

PRELIMINARY AMENDMENT, EXECUTED DECLARATION OF KITAHARA

Our check in the amount of $ -0- is attached covering any required fees. In the event any variance exists between the amount enclosed and the Patent Office charges for filing the above-noted documents, including any fees required under 37 CFR 1.136 for any necessary Extension of Time to make the filing of the attached documents timely, please charge or credit the difference to our Deposit Account No. 15-0030. Further, if these papers are not considered timely filed, then a petition is hereby made under 37 C.F.R. 1.136 for the necessary extension of time. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Norman F. Oblon
Registration No.: 24,618

Steven B. Kelber
Registration No.: 30,073
Attorneys of Record

49-168-0 DIV

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:	:	
YOSHIHIRA FUJIKAWA ET AL	:	GROUP ART UNIT: 129
SERIAL NUMBER: 07/883,398	:	EXAMINER: RICHTER
FILED: MAY 15, 1992	:	
FOR: QUINOLINE TYPE MEVALONOLACTONES		

PRELIMINARY AMENDMENT

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231

SIR:

Prior to examination on the merits in the above-captioned patent application, entry of the following amendments is respectfully requested.

IN THE CLAIMS:

Please cancel Claims 1-35.

Please renumber Claims 46-50 submitted in the Preliminary Amendment of May 15, 1992 as Claims 36-40.

REMARKS:

Entry and consideration of the above amendments, together with the executed Declaration of Kitahara, submitted herewith, is respectfully requested prior to the examination on the merits.

This application is a divisional application, the immediate parent application being U.S. Application Serial No. 631,092, a continuation of U.S. Application Serial No. 233,752. In filing the application, a Preliminary Amendment was filed which inadvertently sought to cancel Claims 41-45 (never presented in this application) and insert new Claims 46-50. In fact, of course, applicants intended, and undersigned Counsel respectfully requests, that Claims 1-35 be cancelled. Further, the claims identified as 46-50 in the Preliminary Amendment of May 15, 1992 should be correctly renumbered as Claims 36-40. The claims cancelled and added by the May 15, 1992 Preliminary Amendment were inadvertently misnumbered, based on the status of claims in the parent application. Any inconvenience is regretted.

Submitted herewith is the executed Declaration of Kitahara,

identical to the unexecuted Declaration submitted with the divisional application filing on May 15, 1992. The Declaration clearly demonstrates that the subject matter of the Count of Interference exhibits unobviously superior bioactivity, when compared with the closest isomeric form. Indeed, the IC_{50} values obtained for both evaluation methods reported in the Declaration are 4-5 fold superior to the isomeric form, something that could not have been predicted on the basis of the structure alone, given the information available to those of ordinary skill in the art as of the effective filing date of the application. See the Declaration, paragraph 4.

Accordingly, examination and allowance of the claims originally presented in the Preliminary Amendment and numbered 46-50, properly numbered 36-40, is respectfully requested.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Norman F. Oblon
Registration No.: 24,618

Steven B. Kelber
Registration No.: 30,073
Attorneys of Record

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF: :

YOSHIHIRO FUJIKAWA ET AL : GROUP ART UNIT:

DIVISIONAL APPLICATION DIVIDED FROM
SERIAL NO.: 07/631,092 :

: EXAMINER:

FOR: QUINOLINE TYPE MEVALONOLACTONES :

DECLARATION UNDER 37 CFR 1.132

HONORABLE COMMISSIONER OF PATENTS & TRADEMARKS

WASHINGTON, D.C. 20231

SIR:

I, Masaki Kitahara, do hereby declare and state that:

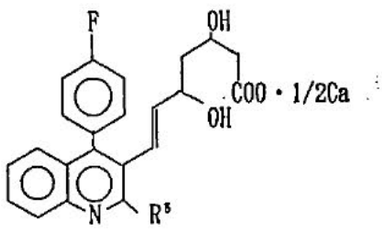
1. I am a named co-inventor in the above-captioned patent application, an employee of Nissan Chemical Industries, Limited, and a citizen and resident of Japan.

2. I am familiar with the above-captioned patent application, and Claims presented by Divisional Application.

3. To demonstrate the unobvious superiority of the subject matter claimed therein, comparative tests were conducted, demonstrating the importance and unobvious superiority conferred on these compounds by the selection

of the cyclopropyl (c-Pr) substituent. These are described as follows:

Data was obtained with regard to the following compound having the formula:



TEST METHOD

Compound	R^5	Test A Evaluation	Test B Evaluation
Compound of this Invention	cyclopropyl (c-Pr)	4.4×10^{-9}	35.0×10^{-9}
Reference Compound	isopropyl (i-Pr)	23.0×10^{-9}	105×10^{-9}

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Test B: Inhibition of cholesterol biosynthesis in culture cells

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4. Based on the data reported above, it can be determined that the compound of this invention exhibits unobvious superiority, and in particular, sharply enhanced inhibition of cholesterol biosynthesis, in vitro, and culture cell, when compared with the referenced compound of the prior art, and compounds having an identical structure save for the selection of cyclopropyl, as opposed to isopropyl substituent, for R^5. This enhanced activity could not be predicted on the basis of structure, or information available to those of ordinary skill in the art as of the effective filing date of this application.

All statements made herein of my own knowledge are true, and all statements made on information and belief are believed true. I am aware that willful false statements and the like are punishable by fine, imprisonment or both, 18 U.S.C. §1001, and that such willful false statements may jeopardize the validity of the above-captioned patent application and any patent issuing thereon.

FURTHER, I SAYETH NOT.

May 25, 1992
Date

Masaki Kitahara
Masaki Kitahara

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address : COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO
07/883,398	05/15/92	FUJIKAWA	49-10[illegible]

RICHTER, J

OBLON, SPIVAK, MC CLELLAND,
MAIER & NEUSTADT
4TH FLR., 1755 JEFFERSON DAVIS HWY.
ARLINGTON, VA 22202

EXAMINER

ART UNIT	PAPER NUMBER
1201	5

DATE MAILED: 09/24/92

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ___ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 36-40 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☑ Claims 36, 40 are allowed.
4. ☑ Claims 37-39 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☑ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☑ not been received
    ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 9-89)

The Abstract of the Disclosure is objected to because of undue length. Correction is required. See M.P.E.P. § 608.01(b).

Applicant is reminded of the proper language and format of an Abstract of the Disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 250 words. It is important that the abstract not exceed 250 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said", should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," *etc.*

Pages 27, 32 and 41 of the specification are missing. Replacement copies are required. They must be accompanied by a statement that they contain no new matter.

Claims 37-39 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term, "agent", renders the claims indefinite. Likewise, the term "containing" is open ended, leaving the claim open to the inclusion of unrecited ingredients, even in major amounts.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Richter whose telephone number is (703) 308-4532.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

Richter: ach
September 22, 1992

JOHANN RICHTER
PRIMARY EXAMINER
GROUP 120

OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C.
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PATENT, TRADEMARK AND COPYRIGHT LAW
AND RELATED FEDERAL AND ITC LITIGATION

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*REGISTERED PATENT AGENT

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ARTHUR I. NEUSTADT
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DENNIS R. DALEY
STEVEN P. WEINROUCH
P. JAY HINES*
JOSEPH T. LEONE*
FREDERICK D. VASTINE, PH.D.
MURRAY TILLMAN*
STEPHEN G. BAXTER, PH.D.
ROBERT W. HAHL, PH.D.
RICHARD L. CHINN, PH.D.
SURINDER SACHAR*
JAMES A. LISEHORA*
ANDREW D. FORTNEY, PH.D.
MARC R. LABGOLD, PH.D.*
RICHARD A. NEIFELD, PH.D.*
RICHARD T. PETERSON, PH.D.*
J. DEREK MASON, PH.D.*
KENNETH B. WELLS*
KAREN I. KRUPEN, PH.D.*
JAMES J. KULBASKI*
ANDREW B. GRIFFIS*

OF COUNSEL
MILTON STERMAN*
SAMUEL H. BLECH*
JOHN O. TRESANSKY*
ALTON D. ROLLINS
JOHN H.O. CLARKE*

Docket Number: 49-168-0 DIV

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231

IN RE APPLICATION OF:	:	
YOSHIRA FUJIKAWA ET AL	:	**GROUP ART UNIT : 1201**
SERIAL NUMBER: 07/883,398	:	
FILING DATE: MAY 15, 1992	:	**EXAMINER: RICHTER**
FOR: QUINOLINE TYPE MEVALONOLACTONES	:	

Sir:

Attached hereto for filing are the following papers:

Amendment (with copies of pages 27, 32 and 41 of the specification as originally filed and a new Abstract of the Disclosure)

A check in the amount of $ .00 is attached covering any required fees. In the event any variance exists between the amount enclosed and the Patent Office charges for filing the above-noted documents, including any fees required under 37 CFR 1.136 for any necessary extension of time to make the filing of the attached documents timely, please charge or credit the difference to our Deposit Account Number 15-0030. Further, if these papers are not considered timely filed, then a petition is hereby made under 37 CFR 1.136 for the necessary extension of time. A duplicate copy of this paper is enclosed.

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Norman F. Oblon
Registration Number 24,618

Steven B. Kelber
Registration Number 30,073

Attorneys of Record

Fourth Floor
1755 Jefferson Davis Highway
Arlington, Virginia 22202
(703) 521-5940

DOCKET NUMBER: 49-168-0 DIV

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:

YOSHIRA FUJIKAWA ET AL

SERIAL NUMBER: 07/883,398

FILED: MAY 15, 1992

FOR: QUINOLINE TYPE MEVALONOLACTONES

GROUP ART UNIT: 1201

EXAMINER: RICHTER

AMENDMENT

HONORABLE COMMISSIONER OF PATENTS & TRADEMARKS
WASHINGTON, D. C. 20231

Sir:

Responsive to the outstanding Office Action of September 24, 1992, entry of the following amendments is respectfully requested.

IN THE CLAIMS:

Please cancel Claims 37-39.

R E M A R K S

Claims 36 and 40 remaining pending upon entry of the above amendments. These claims have been allowed,and the Examiner's indication of the same is deeply appreciated.

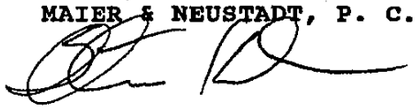
Submitted herewith please find copies of pages 27, 32 and 41 of the specification as originally filed. As these pages are

identical to the pages of the application as originally filed, no new matter is contained therein. Substitution of the Abstract set forth on the attached page, for the Abstract of the disclosure as originally filed, is respectfully requested. This is believed to meet the Examiner's objection to the Abstract.

As the sole claims pending, 36 and 40, have been previously allowed, and the Examiner's objections to the specification and disclosure have been met, allowance of this case is respectfully requested.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P. C.



Norman F. Oblon
Registration Number 24,618

Steven B. Kelber
Registration Number 30,073

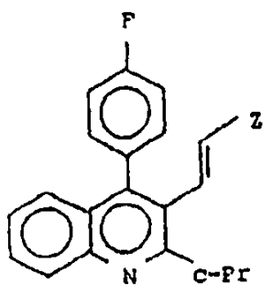
Attorneys of Record

Fourth Floor
1755 Jefferson Davis Highway
Arlington, Virginia 22202
(703) 521-5940

883398

ABSTRACT OF THE DISCLOSURE

A compound of the formula



[A]

Z = $-CH(OH)-CH_2-CH(OH)-CH_2-COO \cdot \frac{1}{2}Ca$ have HMG - CoA inhibiting effects, making them useful as inhibitors of cholesterol biosynthesis. The compound may be prepared as a pharmaceutical for reducing hyperlipidemia, hyperlipoproteinemia or atherosclerosis.

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address : COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
07/883,398	05/15/92	FUJIKAWA Y	49-168-0-DIV

OBLON, SPIVAK, MC CLELLAND,
MAIER & NEUSTADT
4TH FLR., 1755 JEFFERSON DAVIS HWY.
ARLINGTON, VA 22202

EXAMINER	
RICHTER, J	
ART UNIT	PAPER NUMBER
1201	7

DATE MAILED: 02/24/93

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents.

All claims are allowable. However, due to a potential interference, *ex parte* prosecution is SUSPENDED FOR A PERIOD OF SIX MONTHS FROM THE DATE OF THIS LETTER.

Upon expiration of the period of suspension, applicant should make an inquiry as to the status of the application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Richter whose telephone number is (703) 308-4532.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

JOHANN RICHTER
PRIMARY EXAMINER
GROUP 120

Richter:lb
February 22, 1993

UNITED STATES DE. .RTMENT OF COMMERCE
Patent and Trademark Office

Address : COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
07/883,936	05/15/92	FUJIKAWA	Y [illegible]

12MC/9419

OBLON,SPIVAK, MC CLELLAND,
MAIER & NEUSTADT
4TH FLR., 1755 JEFFERSON DAVIS HWY.
ARLINGTON, VA 22202

EXAMINER	
SPRINGER D	
ART UNIT	PAPER NUMBER
1201	8

DATE MAILED: 04/19/94

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents.

Action in this application is further suspended for six months from the date of this letter due to a possible interference.

Upon expiration of the period of suspension, applicants should again make an inquiry as to the status of the application. Manual of Patent Examining Procedure Section 709; 37 C.F.R. 1.103.

John F. Terapane
Director, Group 1200
Organic Chemistry

1-Patent Application File Copy

883,398

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT		ATTORNEY DOCKET NO.
~~07/883,398~~	~~05/15/92~~	FUJIKAWA	Y	49-168-0-DIV

12M1/0313

OBLON, SPIVAK, MC CLELLAND,
MAIER & NEUSTADT
4TH FLR., 1755 JEFFERSON DAVIS HWY.
ARLINGTON, VA 22202

EXAMINER	
SPRINGER, D.	
ART UNIT	PAPER NUMBER
1201	9

DATE MAILED: 03/13/95

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents

Action in this application is further suspended for six months from the date of this letter due to a possible interference.

Upon expiration of the period of suspension, applicants should again make an inquiry as to the status of the application. Manual of Patent Examining Procedure Section 709; 37 CFR 1.103.

Richard V. Fisher, Director
Patent Examining Group 1200
Organic Chemistry

PTOL-90 (Rev. 6/84)

1 - PATIENT APPLICATION FILE COPY

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
[illegible]	05/15/92	[illegible]	[illegible]

[illegible]
[illegible]
[illegible]
[illegible]

EXAMINER	
ART UNIT	PAPER NUMBER
1201	10

DATE MAILED: [illegible]

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents

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Upon expiration of the period of suspension, applicants should again make an inquiry as to the status of the application. Manual of Patent Examining Procedure Section 709; 37 CFR 1.103.

Richard V. Fisher

Richard V. Fisher, Director
Patent Examining Group 1200
Organic Chemistry

PTOL-90 (Rev. 6/84)

1 - PATENT APPLICATION FILE COPY

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT		ATTORNEY DOCKET NO.
07/863,398	05/15/92	FUJIKAWA	Y	49-168-0-DIV

12M2/0918

OBLON, SPIVAK, MC CLELLAND,
MAIER & NEUSTADT
4TH FLR., 1755 JEFFERSON DAVIS HWY.
ARLINGTON, VA 22202

EXAMINER	
SPRINGER, D	
ART UNIT	PAPER NUMBER
1201	

DATE MAILED: 09/18/96

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents

PTOL-90 (Rev. 6/84)

1 - PATENT APPLICATION FILE COPY

UNITED STATES D. ARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	10

DATE MAILED:

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents.

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Richard V. Fisher, Director
Patent Examining Group 1200
Organic Chemistry

SUBSTITUTE PTOL-90

DOCKET NO. 0049-0168-0 DIV

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:	:	
Yoshihiro FUJIKAWA, et al.	:	GROUP: 1201
SERIAL NUMBER: 07/883,398	:	EXAMINER: Springer
FILED: May 15, 1992	:	

FOR: QUINOLINE TYPE MEVALONOLACTONES

STATUS REQUEST

Honorable Commissioner of Patents & Trademarks
Washington, D.C. 20231

SIR:

The undersigned respectfully requests the status of the above-captioned application.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Norman F. Oblon
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UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
07/883,398	5/15/92	Fujikawa et al.	49168-0-DIV

EXAMINER	
STOCKTON, L.	
ART UNIT	**PAPER NUMBER**
1613	13

DATE MAILED:

INTERVIEW SUMMARY

All participants (applicant, applicant's representative, PTO personnel):

(1) Mr. Steven Kelber (3) Mr. Tsuchiya

(2) Mr. Masuda (4) Mr. Johann Richter

Date of Interview Sept. 24, 1998 (5) Laura L. Stockton

Type: ☐ Telephonic ☒ Personal (copy is given to ☐ applicant ☐ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☐ No If yes, brief description: _____

Agreement ☒ was reached. ☐ was not reached.

Claim(s) discussed: ALL

Identification of prior art discussed: _____

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: Claims are now in condition for allowance

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

1. ☐ It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph above has been checked to indicate to the contrary. A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a response to the last Office action has are ready been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW.

2. ☐ Since the Examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the interview unless box 1 above is also checked.

Examiner Note: You must sign this form unless it is an attachment to another form.

Laura L. Stockton

FORM PTOL-413 (REV.1-96)

Interview Summary

Application No.	Applicant(s)
07/883,398	Yoshihiro Fujikawa et al.
Examiner	**Group Art Unit**
Laura L. Stockton	1613

All participants (applicant, applicant's representative, PTO personnel):

(1) *Laura L. Stockton* (3) _____

(2) *Mr. Steven B. Kelber* (4) _____

Date of Interview *Sep 28, 1998*

Type: ☒ Telephonic ☐ Personal (copy is given to ☐ applicant ☐ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☒ No. If yes, brief description:

Agreement ☒ was reached. ☐ was not reached.

Claim(s) discussed: *36*

Identification of prior art discussed:

Description of the general nature of what was agreed to if an agreement was reached, or any other comments:
The Examiner called Applicants' representative for permission to change the "c-Pr" group to a cyclopropyl group.

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendents which would render the claims allowable is available, a summary thereof must be attached.)

1. ☒ It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paregraph above has been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a response to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW.

2. ☐ Since the Examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the interview unless box 1 above is also checked.

Examiner Note: You must sign and stamp this form unless it is an attachment to a signed Office action.

LAURA L. STOCKTON
PATENT EXAMINER
ART UNIT 1613

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
07/883,398	05/15/92	FUJIKAWA	Y 49-168-0-DIV

HM42/0930

OBLON, SPIVAK, MC CLELLAND,
MAIER & NEUSTADT
4TH FLR., 1755 JEFFERSON DAVIS HWY.
ARLINGTON VA 22202

EXAMINER	
STOCKTON, L	
ART UNIT	PAPER NUMBER
1613	15 E

DATE MAILED: 09/30/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

NOTICE OF ALLOWABILITY

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance and Issue Fee Due or other appropriate communication will be mailed in due course.

☐ This communication is responsive to _____

☒ The allowed claim(s) ☛are 36 and 40 now renumbered claims 1 and 2, respectively.

☐ The drawings filed on _____ are acceptable.

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☒ received in Application No. (Series Code/Serial Number) 07/233,752.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE **THREE MONTHS** FROM THE "DATE MAILED" of this Office action. Failure to timely comply will result in ABANDONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses that the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.

☐ Applicant MUST submit NEW FORMAL DRAWINGS

☐ because the originally filed drawings were declared by applicant to be informal.

☐ including changes required by the Notice of Draftperson's Patent Drawing Review, PTO-948, attached hereto or to Paper No. _____.

☐ including changes required by the proposed drawing correction filed on _____, which has been approved by the examiner.

☐ including changes required by the attached Examiner's Amendment/Comment.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the reverse side of the drawings. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftperson.

☐ Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Any response to this letter should include, in the upper right hand corner, the APPLICATION NUMBER (SERIES CODE/SERIAL NUMBER). If applicant has received a Notice of Allowance and Issue Fee Due, the ISSUE BATCH NUMBER and DATE of the NOTICE OF ALLOWANCE should also be included.

Attachment(s)

☒ Notice of References Cited, PTO-892 {References cited to show the state of the art.}

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☒ Interview Summary, PTO-413

☒ Examiner's Amendment/Comment

☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material

☐ Examiner's Statement of Reasons for Allowance

Laura L. Stockton
Laura L. Stockton
Patent Examiner
Art Unit 1613

07/883,398

PTOL-37 (Rev. 10/95) ★ U.S. GPO: 1998-404-496/40509

EXAMINER'S AMENDMENT

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Mr. Steven B. Kelber on September 28, 1998.

2. The application has been amended as follows:

Claim 36:

in the formula on line 2: replace "c-Pr" with -- Δ --.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura L. Stockton whose telephone number is (703) 308-1875.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

A facsimile center has been established. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703) 308-4556 or 305-3592.

Laura L. Stockton
Patent Examiner
Art Unit 1613, Group 1610
Technology Center 1

September 28, 1998

Notice of References Cited

Application No.	Applicant(s)		
07/883,398	Yoshihiro Fujikawa et al.		
Examiner		Group Art Unit	Page 1 of 1
Laura L. Stockton		1613	

U.S. PATENT DOCUMENTS

		DOCUMENT NO.	DATE	NAME	CLASS	SUBCLASS
	A	5,753,675	05-1998	Wattanasin	514	311
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUBCLASS
	N						
	O						
	P						
	Q						
	R						
	S						
	T						

NON-PATENT DOCUMENTS

		DOCUMENT (Including Author, Title, Source, and Pertinent Pages)	DATE
	U		
	V		
	W		
	X		

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

NOTICE OF ALLOWANCE AND ISSUE FEE DUE

HM42/0930

OBLON,SPIVAK, MC CLELLAND,
MAIER & NEUSTADT
4TH FLR., 1755 JEFFERSON DAVIS HWY,
ARLINGTON VA 22202

APPLICATION NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
07/883,398	05/15/92	002	STOCKTON, L	1613 09/30/98

First Named Applicant: FUJIKAWA, YOSHIHIRO

TITLE OF INVENTION: QUINOLINE TYPE MEVALONOLACTONES

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
1 49-168-0-DIV	514-311.000	J91	UTILITY	NO	$1320.00	12/30/98

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED.

THE ISSUE FEE MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED.

HOW TO RESPOND TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.
If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is changed, pay twice the amount of the FEE DUE shown above and notify the Patent and Trademark Office of the change in status, or
B. If the status is the same, pay the FEE DUE shown above.

If the SMALL ENTITY is shown as NO:

A. Pay FEE DUE shown above, or

B. File verified statement of Small Entity Status before, or with, payment of 1/2 the FEE DUE shown above.

II. Part B-Issue Fee Transmittal should be completed and returned to the Patent and Trademark Office (PTO) with your ISSUE FEE. Even if the ISSUE FEE has already been paid by charge to deposit account, Part B Issue Fee Transmittal should be completed and returned. If you are charging the ISSUE FEE to your deposit account, section "4b" of Part B-Issue Fee Transmittal should be completed and an extra copy of the form should be submitted.

III. All communications regarding this application must give application number and batch number.
Please direct all communications prior to issuance to Box ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PATENT AND TRADEMARK OFFICE COPY

PTOL-85 (REV. 10-96) Approved for use through 06/30/99. (0651-0033)

ISSUE FEE TRANSMITTAL

149-1320

Complete and mail this form, together with applicable fees, to: Box ISSUE FEE
Assistant Commissioner for Patents
Washington, D.C. 20231

can't find

OCT - 7 1998

2952

MAILING INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE. Blocks 1 through 4 should be completed where appropriate. All further correspondence including the Issue Fee Receipt, the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Legibly mark-up with any corrections or use Block 1)

HM42/0930
OBLON, SPIVAK, MC CLELLAND,
MAIER & NEUSTADT
4TH FLR., 1755 JEFFERSON DAVIS HWY
ARLINGTON VA 22202

Note: The certificate of mailing below can only be used for domestic mailings of the Issue Fee Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing.

Certificate of Mailing

I hereby certify that this Issue Fee Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Box Issue Fee address above on the date indicated below.

(Depositor's name)

(Signature)

(Date)

APPLICATION NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
07/883,398	05/15/92	002	STOCKTON, L. 1613	09/30/98

First Named Applicant: FUJIKAWA, YOSHIHIRO

TITLE OF INVENTION: QUINOLINE TYPE MEVALONOLACTONES

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
1 49-168-0-DIV	514-311.000	J91	UTILITY	NO	$1320.00	12/30/98

1. Change of correspondence address or indication of " Fee Address" (37 CFR 1.363). Use of PTO form(s) and Customer Number are recommended, but not required.
   - ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
   - ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47) attached.

2. For printing on the patent front page, list (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
   1 OBLON, SPIVAK,
   2 McCLELLAND, MAIER
   3 & NEUSTADT, P.C.

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)
   PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the PTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.
   (A) NAME OF ASSIGNEE
   Nissan Chemical Industries Ltd.
   (B) RESIDENCE: (CITY & STATE OR COUNTRY)
   Tokyo, JAPAN
   Please check the appropriate assignee category indicated below (will not be printed on the patent)
   ☐ Individual ☒ corporation or other private group entity ☐ government

4a. The following fees are enclosed (make check payable to Commissioner of Patents and Trademarks):
   - ☒ Issue Fee
   - ☐ Advance Order - # of Copies -0-

4b. The following fees or deficiency in these fees should be charged to:
   DEPOSIT ACCOUNT NUMBER 15-0030
   (ENCLOSE AN EXTRA COPY OF THIS FORM)
   - ☒ Issue Fee
   - ☐ Advance Order - # of Copies -0-

The COMMISSIONER OF PATENTS AND TRADEMARKS IS requested to apply the Issue Fee to the application identified above.

(Authorized Signature) [signature] 27395 (Date) 10/5/98

NOTE: The Issue Fee will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the Patent and Trademark Office.

10/15/1998 HCORTES 00000067 07883398
01 FC:142 1320.00 OP

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending on the needs of the individual case. Any comments on the amount of time required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, D.C. 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND FEES AND THIS FORM TO: Box Issue Fee, Assistant Commissioner for Patents, Washington D.C. 20231

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMIT THIS FORM WITH FEE

PTO UTILITY GRANT
Paper Number 16

The United States of America

The Commissioner of Patents and Trademarks

Has received an application for a patent for a new and useful invention. The title and description of the invention are enclosed. The requirements of law have been complied with, and it has been determined that a patent on the invention shall be granted under the law.

Therefore, this

United States Patent

Grants to the person(s) having title to this patent the right to exclude others from making, using, offering for sale, or selling the invention throughout the United States of America or importing the invention into the United States of America for the term set forth below, subject to the payment of maintenance fees as provided by law.

If this application was filed prior to June 8, 1995, the term of this patent is the longer of seventeen years from the date of grant of this patent or twenty years from the earliest effective U.S. filing date of the application, subject to any statutory extension.

If this application was filed on or after June 8, 1995, the term of this patent is twenty years from the U.S. filing date, subject to an statutory extension. If the application contains a specific reference to an earlier filed application or applications under 35 U.S.C. 120, 121 or 365(c), the term of the patent is twenty years from the date on which the earliest application was filed, subject to any statutory extension.

Bruce Lehman
Commissioner of Patents and Trademarks

Attest

Form PTO-1584 (Rev. 2/97)

PATENT APPLICATION FEE DETERMINATION RECORD

Effective December 16, 1991

Application or Docket Number: 883398

CLAIMS AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE	SMALL ENTITY FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY FEE
BASIC FEE				$ 345.00	OR		$ 690.00
TOTAL CLAIMS	35 minus 20 =	* 15	x $10 =		OR	x $20 =	300
INDEPENDENT CLAIMS	1 minus 3 =	*	x 36 =		OR	x 72 =	
MULTIPLE DEPENDENT CLAIM PRESENT			+ 110 =		OR	+ 220 =	
			TOTAL		OR	TOTAL	990

* If the difference in column 1 is less then zero, enter "0" in column 2

CLAIMS AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE	SMALL ENTITY ADDITIONAL FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY ADDITIONAL FEE
AMENDMENT A	Total	*	Minus	**	=	x $10 =		OR	x $20 =	
	Independent	*	Minus	***	=	x 36 =		OR	x 72 =	
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM					+ 110 =		OR	+ 220 =	
						TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	
AMENDMENT B	Total	*	Minus	**	=	x $10 =		OR	x $20 =	
	Independent	*	Minus	***	=	x 36 =		OR	x 72 =	
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM					+ 110 =		OR	+ 220 =	
						TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	
AMENDMENT C	Total	*	Minus	**	=	x $10 =		OR	x $20 =	
	Independent	*	Minus	***	=	x 36 =		OR	x 72 =	
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM					+ 110 =		OR	+ 220 =	
						TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Form PTO-875 (Rev. 12-91)
*U.S. Government Printing Office: 1992 — 308-890
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE