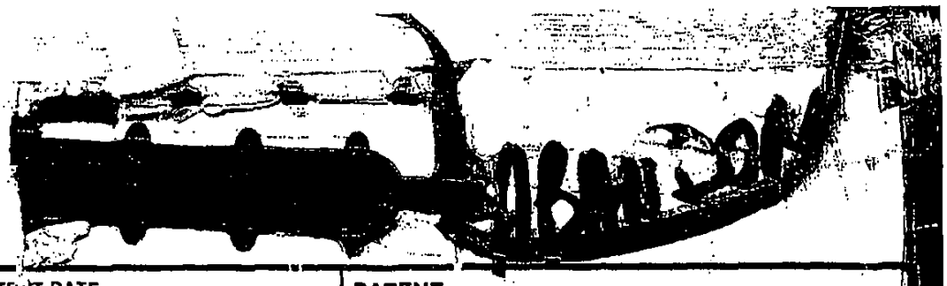

233752	PATENT DATE	PATENT NUMBER

IAL NUMBER	FILING DATE	CLASS	SUBCLASS	GROUP ART UNIT	EXAMINER
07/233,752	08/19/88	544	114	123	Richter

YOSHIHIRO FUJIKAWA, FUNABASHI, JAPAN; MIKIO SUZUKI, FUNABASHI, JAPAN; HIROSHI IWASAKI, FUNABASHI, JAPAN; MITSUAKI SAKASHITA, MINAMISAITAMA-G, JAPAN; MASAKI KITAHARA, MINAMISAITAMA-G, JAPAN.

CONTINUING DATA******** NONE
VERIFIED

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

VERIFIED			
	JAPAN	207224/1987	08/20/87
	JAPAN	15585/1988	01/26/88

n priority claimed ☐yes ☐no C 119 conditions met ☐yes ☐no d and Acknowledged Examiner's Initials	AS FILED	STATE OR COUNTRY	SHEETS DRWGS.	TOTAL CLAIMS	INDEP. CLAIMS	FILING FEE RECEIVED	ATTORNEY'S DOCKET NO.
	→	JPX	0	35	1	$ 630.00	49-111-0

OBLON, FISHER, SPIVAK,
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ARLINGTON, VA 22202

QUINOLINE-TYPE MEVALONOLACTONES

OF APPLICATION
SEPARATELY

E OF ALLOWANCE MAILED	PREPARED FOR ISSUE		CLAIMS ALLOWED	
	Assistant Examiner	Docket Clerk	Total Claims	Print Claim
ISSUE FEE			**DRAWING**	
Due / Date Paid		Primary Examiner	Sheets Drwg. / Figs. Drwg. / Print Fig.	
Label Area	**ISSUE CLASSIFICATION**		**ISSUE BATCH NUMBER**	
	Class	Subclass		

233752

PATENT APPLICATION SERIAL NO.

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

080 08/22/88 233752 1 101 630.00 CK

PTO-1556
(5/87)

DOCK NO. 49-111-0

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

233752

SIR:

TRANSMITTED HEREWITH FOR FILING IS THE PATENT APPLICATION OF

INVENTOR(S) YOSHIHIRO FUJIKAWA ET AL

FOR QUINOLINE TYPE MEVALONOLACTONES

ENCLOSED ARE

☐ _____ SHEETS OF DRAWINGS.

☐ A CERTIFIED COPY OF A _____ APPLICATION.

☐ AN ASSIGNMENT OF THE INVENTION TO _____

_____

☐ A VERIFIED STATEMENT TO ESTABLISH SMALL ENTITY STATUS UNDER 37 CFR 1.27.

☒ LIST OF INVENTORS' NAMES AND ADDRESSES, NOTICE OF PRIORITY WHITE ADVANCE SERIAL NUMBER POSTCARD

THE FILING FEE IS CALCULATED BELOW

	(COL. 1)	(COL. 2)	SMALL ENTITY		OTHER THAN A SMALL ENTITY	
FOR	NO. FILED	NO. EXTRA	RATE	FEE	RATE	FEE
BASIC FEE				$ 170		$ 340
TOTAL CLAIMS	35-20	15	x 6		x 12	180
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☐ MULTIPLE DEPENDENT CLAIM PRESENTATION			+55		+110	0
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OBLON, FISHER, SPIVAK,
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: YOSHIHIRO FUJIKAWA ET AL

FOR : QUINOLINE TYPE MEVALONOLACTONES

LETTER

HONORABLE COMMISSIONER OF PATENTS
WASHINGTON, D. C. 20231

SIR:

Attached hereto is a list of the inventors' names and addresses.

A Declaration containing all the necessary information will be submitted at a later date.

Respectfully submitted,

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Our Ref.: NC-115

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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

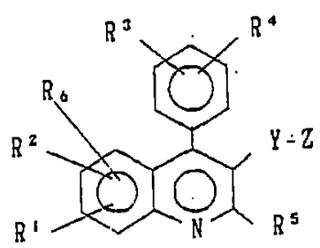
Metab., 1986, p30, p31, p66)

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.

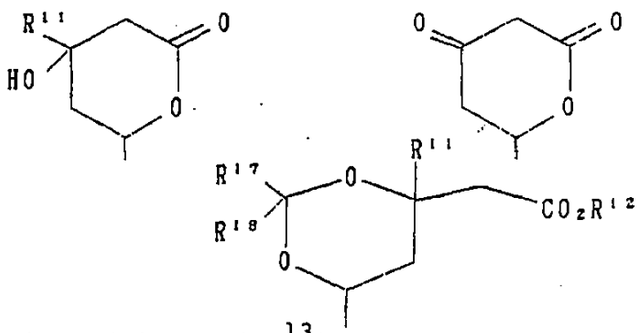
The novel mevalonolactone derivatives of the present invention are represented by the following formula I:



(I)

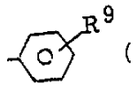
wherein R^1, R^2, R^3, R^4 and R^6 are independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-3} alkoxy, n-butoxy, i-butoxy, sec-butoxy, R^7R^8N- (wherein R^7 and R^8 are independently hydrogen or C_{1-3} alkyl), trifluoromethyl, trifluoromethoxy, difluoromethoxy, fluoro, chloro, bromo,

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}

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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 physiclogical 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

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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.

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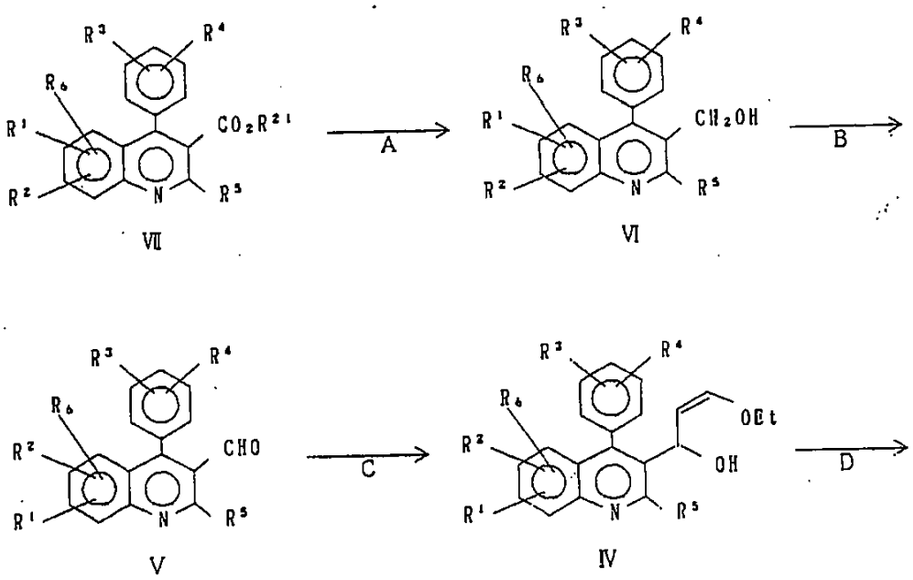
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R4
R6
R1
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R2
N
R5
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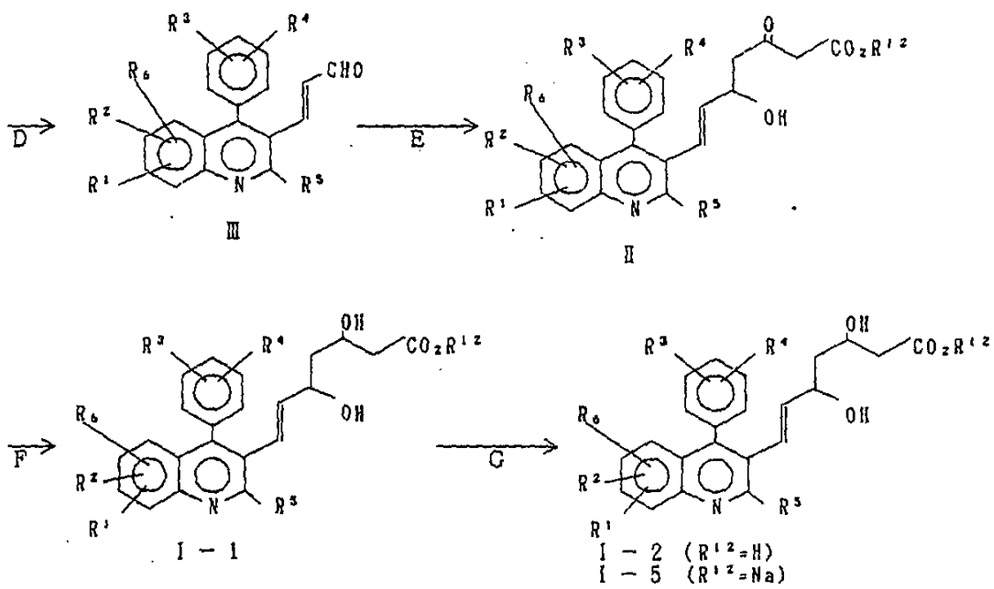
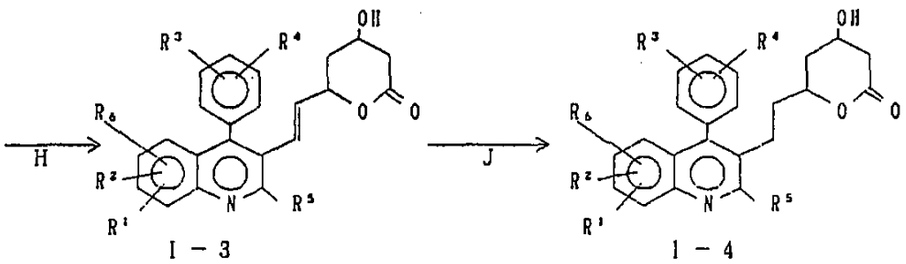
CH2OH
VI
B
CHO
V
C
OEt
OH
IV
D


D
E
F
G
CHO
OH
CO2R'2
III
II
I - 1
I - 2 (R'2=H)
I - 5 (R'2=Na)



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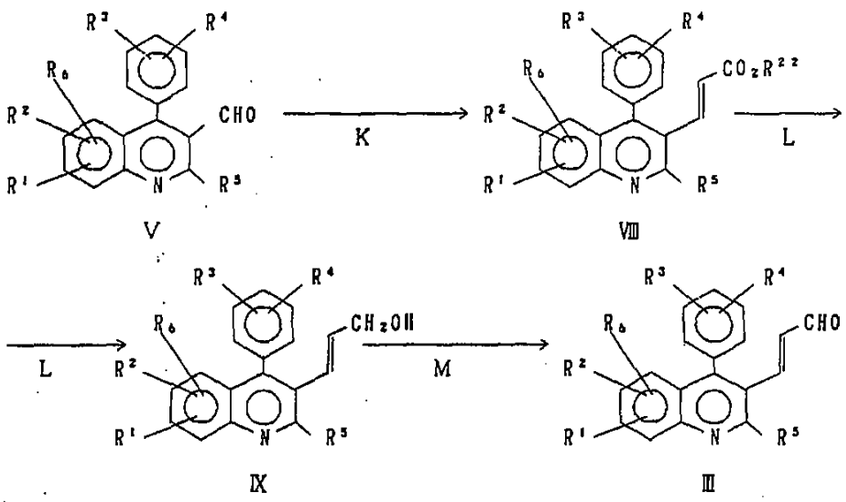
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R4
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R1
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K
CO2R22
VIII
L
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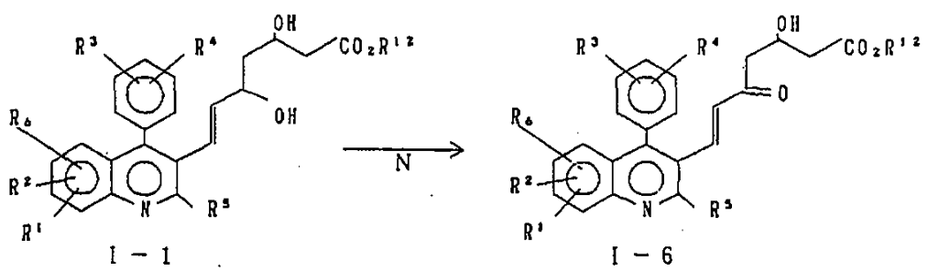
IX
M
III


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

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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.

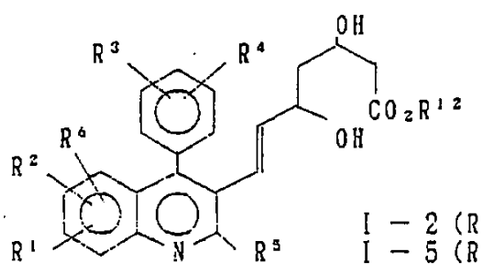
Step M represents an oxidation reaction of the allyl alcohol to an enal. This oxidation reaction can be conducted by using various oxidizing agents, particularly active manganese dioxide, in a solvent such as tetrahydrofuran, acetone, ethyl ether or ethyl acetate at a temperatrue of from 0 to 100°C,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



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

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 O 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	IC_{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}

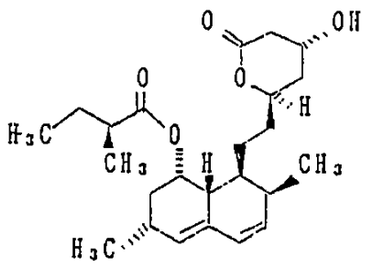
In Table 2-2, the relative activities are shown based on the activities of CS-514 being evaluated to be 1.

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



(2) CS-514

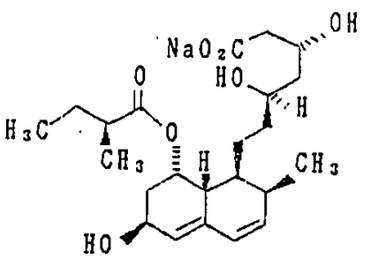


Table 3: Inhibitory activities by Test B-1

Compound	IC_{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-q)

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

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: <u>(E)-3-[4'-(4''-fluorophenyl)-2'-(1''-methylethyl)-quinolin-3'-yl]propenaldehyde (compound III-1)</u>

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

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)

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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)-

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.)

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. (°C)
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 $CDCl_3$) 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 $CDCl_3$) 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 $CDCl_3$) 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.)

Tale 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. (°C)
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. (℃)
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 $CDCl_3$)　　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 $CDCl_3$)　　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 $CDCl_3$)　　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－２２

H-NMR(in $CDC\ell_3$) 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－２３

H-NMR(in $CDC\ell_3$) 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 $CDC\ell_3$)　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 $CDC\ell_3$)　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

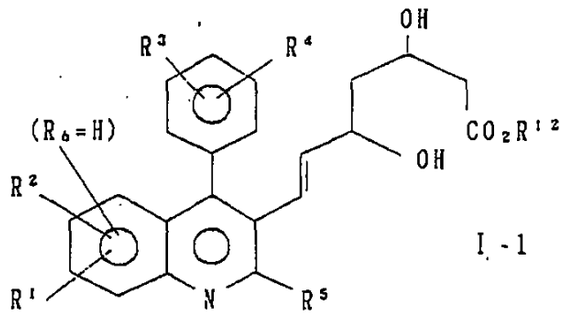
H-NMR(in $CDC\ell_3$)　δ ppm :

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	R^1	R^2	R^3	R^4	R^5	R^{12}	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 $CDCl_3$) 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 $CDCl_3$) 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)

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－123

H-NMR (in $CDC\ell_3$) 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－124

H-NMR (in $CDC\ell_3$) 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－125

H-NMR (in $CDC\ell_3$) 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),

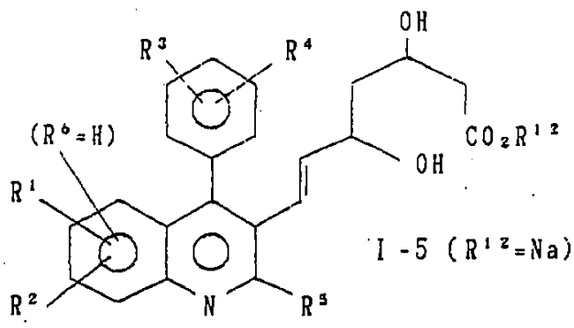
I − 1 2 7

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



I-5 (R^{12}=Na)

Compound	R^1	R^2	R^3	R^4	R^5	R^{12}	m. p. (℃)
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－57

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－58

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－59

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－510

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－517

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－518

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－519

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)

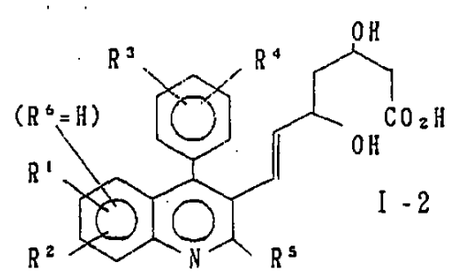
I－527

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

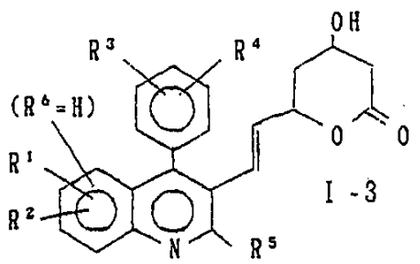


I-2

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 g
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

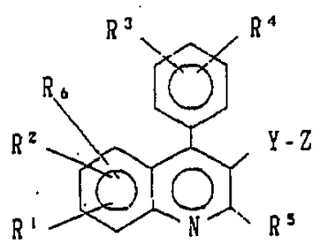
Granules

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.

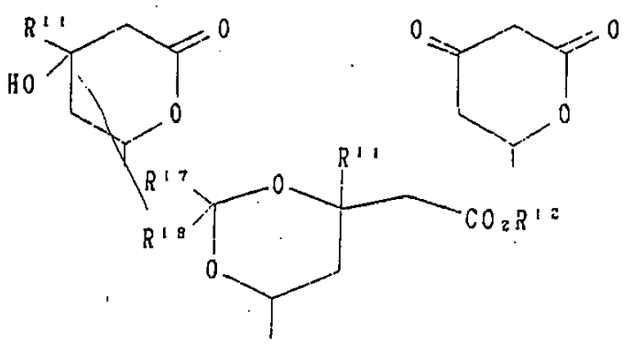
CLAIMS:

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 optionally 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~~ 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

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

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.

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

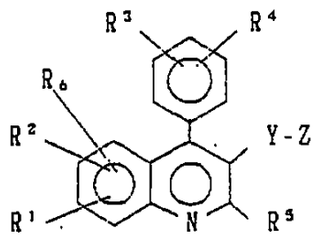
add E'

add D'

add G'

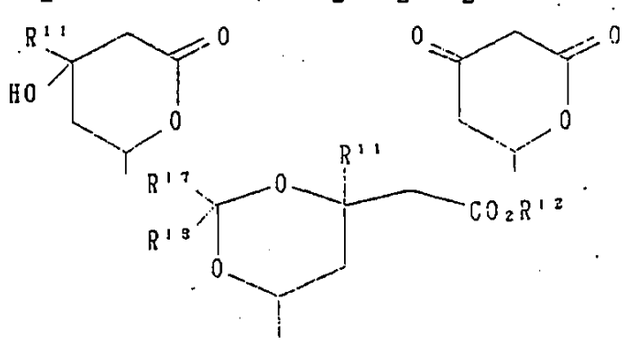
ABSTRACT

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).

UNITED STATES DEPARTMENT OF COMMERCE
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Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
07/233,752	08/19/88	FUJIKAWA Y	49-111-0

OBLON, FISHER, SPIVAK,
MC CLELLAND & MAIER
1755 S. JEFF. DAVIS HWY.
CRYSTAL SQ. FIVE-STE. 400
ARLINGTON, VA 22202

000

DATE MAILED: 09/12/88

NOTICE TO FILE MISSING PARTS OF APPLICATION— FILING DATE GRANTED

A filing date has been granted to this application. However, the following parts are missing.

If all missing parts are filed within the period set below, the total amount owed by applicant as a ☒ large entity, ☐ small entity (verified statement filed), is $ _____.

1. ☐ The statutory basic filing fee is: ☐ missing. ☐ insufficient. Applicant as a ☐ large entity, ☐ small entity, must submit $ _____ to complete the basic filing fee and MUST ALSO SUBMIT THE SURCHARGE AS INDICATED BELOW.
2. ☐ Additional claim fees of $ _____ as a ☐ large entity, ☐ small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due. NO SURCHARGE IS REQUIRED FOR THIS ITEM.
3. ☒ The oath or declaration:
   ☒ is missing.
   ☐ does not cover items omitted at the time of execution.

   An oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Serial Number and Filing Date is required. A SURCHARGE MUST ALSO BE SUBMITTED AS INDICATED BELOW.
4. ☐ The oath or declaration does not identify the application to which it applies. An oath or declaration in compliance with 37 CFR 1.63 identifying the application by the above Serial Number and Filing Date is required. A SURCHARGE MUST ALSO BE SUBMITTED AS INDICATED BELOW.
5. ☐ The signature to the oath or declaration is: ☐ missing; ☐ a reproduction; ☐ by a person other than the inventor or a person qualified under 37 CFR 1.42, 1.43, or 1.47. A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Serial Number and Filing Date is required. A SURCHARGE MUST ALSO BE SUBMITTED AS INDICATED BELOW.
6. ☐ The signature of the following joint inventor(s) is missing from the oath or declaration: _____. Applicant(s) should provide, if possible an oath or declaration signed by the omitted inventor(s), identifying this application by the above Serial Number and Filing Date. A SURCHARGE MUST ALSO BE SUBMITTED AS INDICATED BELOW.
7. ☐ The application was filed in a language other than English. Applicant must file a verified English translation of the application and a fee of $26.00 under 37 CFR 1.17(k), unless this fee has already been paid NO SURCHARGE UNDER 37 CFR 1.16(e) IS REQUIRED FOR THIS ITEM.
8. ☐ A $20.00 processing fee is required for returned checks. (37 CFR 1.21(m)).
9. ☐ Your filing receipt was mailed in error because check was returned.
10. ☐ Other:

A Serial Number and Filing Date have been assigned to this application. However, to avoid abandonment under 37 CFR 1.53(d), the missing parts and fees identified above in items 1 and 3-6 must be timely provided ALONG WITH THE PAYMENT OF A SURCHARGE OF $110.00 for large entities or $55.00 for small entities who have filed a verified statement claiming such status. The surcharge is set forth in 37 CFR 1.16(e). Applicant is given ONE MONTH FROM THE DATE OF THIS LETTER, OR TWO MONTHS FROM THE FILING DATE of this application, WHICHEVER IS LATER, within which to file all missing parts and pay any fees. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

Direct the response to, and any questions about, this notice to the undersigned, Attention: Application Branch.

A copy of this notice MUST be returned with response.

For: Manager, Application Branch
(703) 557-3254

For Office Use Only	
☐ 102	☐ 202
☐ 103	☐ 203
☐ 104	☐ 204
☐ 105	☐ 205

FORM PTO-1533 (REV. 7-87) OFFICE COPY

DOCKET NO. 49-111-0

IN RE APPLICATION OF YOSHIHIRO FUJIKAWA ET AL

SERIAL NO. 07/233,752

FILED AUGUST 19, 1988

FOR QUINOLINE TYPE MEVALONOLACTONES

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

Sir

Transmitted herewith is an amendment in the above-identified application.

☒ No additional fee is required.

☐ Small entity status of this application under 37 CFR 1.9 and 1.27 has been established by a verified statement previously submitted.

☐ Small entity status of this application under 37 CFR 1.9 and 1.27 is established by a verified statement submitted herewith.

☒ Additional documents filed herewith:

RULE 63 DECLARATION - executed, SUBMISSION OF DECLARATION
RETURN COPY OF NOTICE TO FILE MISSING PARTS
ASSIGNMENT

The fee has been calculated as shown below.

	(Col. 1) Claims Remaining After		(Col. 2) Highest No. Previously Paid For	(Col. 3) Present Extra
Total	* 35	Minus	** 35	= 0
Indep	* 1	Minus	*** 3	= 0
☐ First presentation of multiple dep. claim				

Small Entity		OR	Other Than a Small Entity	
Rate	Addit. Fee		Rate	Addit. Fee
x6 =	$		x12 =	$ 0
x17=	$		x34 =	$ 0
+55=	$		+110=	$ 0
Total	$	OR	Total	$ 0

☒ A check in the amount of $ 7.00 is attached.

☐ Charge $_____ to deposit account no. _____. A duplicate copy of this sheet is enclosed.

☒ Please charge any additional fees or credit any overpayment to deposit account no. 15-0030. A duplicate copy of this sheet is enclosed.

☒ Please charge any additional fees or credit any overpayment of fees required under 37 CFR 1.136 for any necessary extension of time to make the filing of the attached response timely to deposit account no. 15-0030. A duplicate copy of this sheet is enclosed.

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

Norman F. Oblon
ATTORNEY OF RECORD
REGISTRATION NO. 24,618

Samuel H. Blech
Registration No: 32,082

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1755 S. JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA
(703) 521-5940

* If the entry in Column 2 is less than the entry in Column 1 write "0" in Column 3
** If the "Highest Number Previously paid for " IN THIS SPACE is less than 20 write "20" in this space.
*** If the "Highest Number Previously paid for " IN THIS SPACE is less than 3 write "3" in this space.

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

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
07/233,752	08/19/88	FUJIKAWA	Y . 49-111-0

OBLON, FISHER, SPIVAK,
MC CLELLAND & MAIER
1755 S. JEFF. DAVIS HWY.
CRYSTAL SQ. FIVE-STE. 400
ARLINGTON, VA 22202

000

DATE MAILED: 09/12/88

NOTICE TO FILE MISSING PARTS OF APPLICATION— FILING DATE GRANTED

A filing date has been granted to this application. However, the following parts are missing.

If all missing parts are filed within the period set below, the total amount owed by applicant as a ☐ large entity, ☐ small entity (verified statement filed), is $ _____.

1. ☐ The statutory basic filing fee is: ☐ missing. ☐ insufficient. Applicant as a ☐ large entity, ☐ small entity, must submit $ _____ to complete the basic filing fee and MUST ALSO SUBMIT THE SURCHARGE AS INDICATED BELOW.
2. ☐ Additional claim fees of $ _____ as a ☐ large entity, ☐ small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due. NO SURCHARGE IS REQUIRED FOR THIS ITEM.
3. ☑ The oath or declaration:
   ☑ is missing.
   ☐ does not cover items omitted at the time of execution.

   An oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Serial Number and Filing Date is required. A SURCHARGE MUST ALSO BE SUBMITTED AS INDICATED BELOW.
4. ☐ The oath or declaration does not identify the application to which it applies. An oath or declaration in compliance with 37 CFR 1.63 identifying the application by the above Serial Number and Filing Date is required. A SURCHARGE MUST ALSO BE SUBMITTED AS INDICATED BELOW.
5. ☐ The signature to the oath or declaration is: ☐ missing; ☐ a reproduction; ☐ by a person other than the inventor or a person qualified under 37 CFR 1.42, 1.43, or 1.47. A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Serial Number and Filing Date is required. A SURCHARGE MUST ALSO BE SUBMITTED AS INDICATED BELOW.
6. ☐ The signature of the following joint inventor(s) is missing from the oath or declaration: _____. Applicant(s) should provide, if possible an oath or declaration signed by the omitted inventor(s), identifying this application by the above Serial Number and Filing Date. A SURCHARGE MUST ALSO BE SUBMITTED AS INDICATED BELOW.
7. ☐ The application was filed in a language other than English. Applicant must file a verified English translation of the application and a fee of $26.00 under 37 CFR 1.17(k), unless this fee has already been paid NO SURCHARGE UNDER 37 CFR 1.16(e) IS REQUIRED FOR THIS ITEM.
8. ☐ A $20.00 processing fee is required for returned checks. (37 CFR 1.21(m)).
9. ☐ Your filing receipt was mailed in error because check was returned.
10. ☐ Other:

A Serial Number and Filing Date have been assigned to this application. However, to avoid abandonment under 37 CFR 1.53(d), the missing parts and fees identified above in items 1 and 3-6 must be timely provided ALONG WITH THE PAYMENT OF A SURCHARGE OF $110.00 for large entities or $55.00 for small entities who have filed a verified statement claiming such status. The surcharge is set forth in 37 CFR 1.16(e). Applicant is given ONE MONTH FROM THE DATE OF THIS LETTER, OR TWO MONTHS FROM THE FILING DATE of this application, WHICHEVER IS LATER, within which to file all missing parts and pay any fees. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

Direct the response to, and any questions about, this notice to the undersigned, Attention: Application Branch.

A copy of this notice MUST be returned with response.

For: Manager, Application Branch
(703) 557-3254

For Office Use Only	
☐ 102	☐ 202
☐ 103	☐ 203
☐ 104	☑ 204
☐ 105	☐ 205

49-1111-0

#3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:

YOSHIHIRO FUJIKAWA ET AL

SERIAL NUMBER: 07/233,752

FILED: AUGUST 19, 1988

FOR: QUINOLINE TYPE MEVALONOLACTONES

ATTN: HEAD, APPLICATION DIVISION

SUBMISSION OF DECLARATION IN COMPLIANCE WITH 37 CFR 1.53(d)

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

Sir:

In accordance with the provisions of 37 CFR 1.53(d), Applicants submit herewith a Rule 63 Declaration. The required fee was paid at the time of filing of the application.

The Declaration enclosed herewith contains the following information:

List of Inventors' Names and Addresses
Title of Invention
Filing Date

thereby adequately identifying the above-identified application in accordance with 37 CFR 1.63, as set forth in 1035 O.G. 3, of October 4, 1983.

In light of the foregoing, the application is deemed to be complete and in condition for examination, and such favorable action is earnestly solicited.

Respectfully submitted,

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

Norman F. Oblon
Attorney of Record
Registration No. 24,618

Samuel H. Blech
Registration No: 32,082

Crystal Square Five - Suite 400
1755 S. Jefferson Davis Highway
Arlington, Virginia 22202
(703) 521-5940

NC-115-US
(1573)

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

Mikio Suzuki 40200
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
Citizenship: JAPAN JPX
Post Office Address: same as above

Hiroshi Iwasaki 40300
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
Citizenship: JAPAN JPX
Post Office Address: same as above

Mitsuaki Sakashita 40400
NAME OF FOURTH JOINT INVENTOR

Residence: Nissan Chemical Industries Ltd.
Seibutsukagaku Kenkyusho, 1470
Oaza-shiraoka, Shiraoka-machi

[redacted]

49-111-0

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION: :

YOSHIHIRO FUJIKAWA ET AL : GROUP ART UNIT:

SERIAL NO: 07/233,752 :

FILED: AUGUST 19, 1988 : EXAMINER:

FOR: QUINOLINE TYPE MEVALONOLACTONES :

PRELIMINARY AMENDMENT

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

SIR:

Preliminary to an action on the merits of the case, please amend the above-identified application as follows:

IN THE SPECIFICATION

Page 32, line 5, correct "I_{50}" to read --IC_{50}--.

Page 34, line 5, correct "I_{50}" to read --IC_{50}--.

Page 81, line 21, correct "0.5" to read --0.5 g--.

REMARKS

The Amendment corrects obvious inadvertent errors.

An action on the merits of the claims is requested.

Respectfully submitted,

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

Norman F. Oblon
Attorney of Record
Registration No: 24,618

Samuel H. Blech
Registration No: 32,082

Crystal Square Five - Suite 400
1755 Jefferson Davis Hwy.
Arlington, Virginia 22202
(703) 521-5940
ds

Docket No. 49-111-0

#5 JMB 1-6-89

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:	:	
YOSHIHIRO FUJIKAWA ET AL	:	GROUP ART UNIT:
SERIAL NUMBER: NEW APPLICATION	:	
FILED: HEREWITH	:	EXAMINER:
FOR: QUINOLINE TYPE MEVALONOLACTONES	:	

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

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

SIR:

In the matter of the above-identified application for patent, notice is hereby given that Applicants claim as priority dates 8/20/87, 1/26/88, 8/3/88, the filing dates of the corresponding applications filed in Japan. The corresponding convention applications bear Serial Numbers 207224, 15585, Not yet allotted respectively.

Certified copies of the corresponding convention applications will be submitted prior to the payment of the Base Issue Fee.

Respectfully submitted,

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

Norman F. Oblon
Registration No. 24,618
Attorney for Applicants

Samuel H. Blech
Registration No: 32,082

Crystal Square Five - Suite 400
1755 S. Jefferson Davis Highway
Arlington, Virginia 22202
(703) 521-5940
/jmc

49-111-0

6/B
4/1/89

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION:	:	
YOSHIHIRO FUJIKAWA ET AL	:	GROUP ART UNIT:
SERIAL NO: 07/233,752	:	
FILED: AUGUST 19, 1988	:	EXAMINER:
FOR: QUINOLINE TYPE MEVALONOLACTONES	:	

PRELIMINARY AMENDMENT

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

SIR:

Preliminary to an action on the merits of the case, please amend the above-identified application as follows.

IN THE SPECIFICATION

Page 3, lines 5 and 7, after "together" insert --optionally--, each instance.

IN THE CLAIMS

Claim 1, lines 17 and 19, after "together" insert --optionally--, each instance.

REMARKS

The specification and Claim 1 have been amended to more clearly define the invention. It has now been made

clear that the definitions of the radicals refered to in the amended sections are alternative optional variants.

An action on the merits of the claims is solicited.

Respectfully submitted,

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

Norman F. Oblon
Attorney of Record
Registration No: 24,618

Samuel H. Blech
Registration No: 32,082

Crystal Square Five - Suite 400
1755 Jefferson Davis Hwy.
Arlington, Virginia 22202
(703) 521-5940
ds

DOCKET NO. 49-111-0

#7
4/1/89

IN RE APPLICATION OF YOSHIHIRO FUJIKAWA ET AL

SERIAL NO. 07/233,752

FILED AUGUST 19, 1988

FOR QUINOLINE TYPE MEVALONOLACTONES

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

RECEIVED
89 MAR 23 PM 3:08
GROUP 100

Sir

Transmitted herewith is an amendment in the above-identified application.

XX No additional fee is required.

☐ Small entity status of this application under 37 CFR 1.9 and 1.27 has been established by a verified statement previously submitted.

☐ Small entity status of this application under 37 CFR 1.9 and 1.27 is established by a verified statement submitted herewith.

XX Additional documents filed herewith:

NOTICE OF PRIORITY
PRIORITY DOCUMENTS (3)

The fee has been calculated as shown below.

	(Col. 1) Claims Remaining After		(Col. 2) Highest No. Previously Paid For	(Col. 3) Present Extra
Total	* 35	Minus	** 35	= 0
Indep	* 1	Minus	*** 3	= 0
☐ First presentation of multiple dep. claim				

Small Entity		OR	Other Than a Small Entity	
Rate	Addit. Fee		Rate	Addit. Fee
x6 =	S		x12 =	$ 0
x17=	S		x34 =	$ 0
+55=	S		+110=	$ 0
Total	S	OR	Total	$ 0

☐ A check in the amount of S _____ is attached.

☐ Charge S_____ to deposit account no. _____. A duplicate copy of this sheet is enclosed.

XX Please charge any additional fees or credit any overpayment to deposit account no. 15-0030. A duplicate copy of this sheet is enclosed.

XX Please charge any additional fees or credit any overpayment of fees required under 37 CFR 1.136 for any necessary extension of time to make the filing of the attached response timely to deposit account no. 15-0030. A duplicate copy of this sheet is enclosed.

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

Norman F. Oblon
ATTORNEY OF RECORD
REGISTRATION NO. 24,618

Samuel H. Blech
Registration No: 32,082

CRYSTAL SQUARE FIVE – SUITE 400
1755 S. JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA
(703) 521-5940

* If the entry in Column 2 is less than the entry in Column 1 write "0" in Column 3.
** If the "Highest Number Previously paid for " IN THIS SPACE is less than 20 write "20" in this space.
*** If the "Highest Number Previously paid for " IN THIS SPACE is less than 3 write "3" in this space.

DOCKET NO. 49-111-0

IN RE APPLICATION OF YOSHIHIRO FUJIKAWA ET AL

SERIAL NO. 07/233,752

FILED AUGUST 19, 1988

FOR QUINOLINE TYPE MEVALONOLACTONES

ChgLoc 12X 1-6-89

Sprunger

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

Sir

Transmitted herewith is an amendment in the above-identified application.

XX No additional fee is required.

☐ Small entity status of this application under 37 CFR 1.9 and 1.27 has been established by a verified statement previously submitted.

☐ Small entity status of this application under 37 CFR 1.9 and 1.27 is established by a verified statement submitted herewith.

XX Additional documents filed herewith:

NOTICE OF PRIORITY
PRIORITY DOCUMENTS (3)

The fee has been calculated as shown below.

	(Col. 1) Claims Remaining After		(Col. 2) Highest No. Previously Paid For	(Col. 3) Present Extra
Total	* 35	Minus	** 35	= 0
Indep	* 1	Minus	*** 3	= 0
☐ First presentation of multiple dep. claim				

Small Entity		OR	Other Than a Small Entity	
Rate	Addit. Fee		Rate	Addit. Fee
x6 =	S		x12 =	S 0
x17=	S		x34 =	S 0
+55=	S		+110=	S 0
Total	S	OR	Total	S 0

☐ A check in the amount of S _____ is attached.

☐ Charge S_____ to deposit account no. _____. A duplicate copy of this sheet is enclosed.

XX Please charge any additional fees or credit any overpayment to deposit account no. 15-0030. A duplicate copy of this sheet is enclosed.

XX Please charge any additional fees or credit any overpayment of fees required under 37 CFR 1.136 for any necessary extension of time to make the filing of the attached response timely to deposit account no. 15-0030. A duplicate copy of this sheet is enclosed.

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

Norman F. Oblon
ATTORNEY OF RECORD
REGISTRATION NO. 24,618

Samuel H. Blech
Registration No: 32,082

CRYSTAL SQUARE FIVE – SUITE 400
1755 S. JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA
(703) 521-5940

* If the entry in Column 2 is less than the entry in Column 1 write "0" in Column 3.
** If the "Highest Number Previously paid for" IN THIS SPACE is less than 20 write "20" in this space.
*** If the "Highest Number Previously paid for" IN THIS SPACE is less than 3 write "3" in this space.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:	:	
YOSHIHIRO FUJIKAWA ET AL	:	
SERIAL NUMBER: 07/233,752	:	GROUP:
FILED: AUGUST 19, 1988	:	EXAMINER:
FOR: QUINOLINE TYPE MEVALONOLACTONES	:	

REQUEST FOR PRIORITY UNDER 35 USC 119
AND THE INTERNATIONAL CONVENTION

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

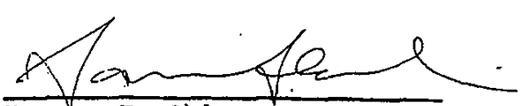
Sir:

In the matter of the above-identified application for patent, notice is hereby given that Applicant claims as priority dates August 20, 1987, January 26, 1988 and August 3, 1988, the filing dates of the corresponding Convention Applications filed in Japan. The corresponding Convention Applications bear Serial Numbers 207224, 15585 and 193606, respectively.

Certified copies of the corresponding Convention Applications are being submitted herewith.

Respectfully submitted,

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



Norman F. Oblon
Attorney of Record
Registration No. 24,618

Samuel H. Blech
Registration No: 32,082

Crystal Square Five - Suite 400
1755 S. Jefferson Davis Highway
Arlington, Virginia 22202
(703) 521-5940

MISSING PAGE(S)

FROM THE U.S. PATENT OFFICE

OFFICIAL FILE WRAPPER

Priority Documents
(3)

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.
07/233,752	08/19/88	FUJIKAWA Y	49-111-0

OBLON, FISHER, SPIVAK,
MC CLELLAND & MAIER
1755 S. JEFF. DAVIS HWY.
CRYSTAL SQ. FIVE-STE. 400
ARLINGTON, VA 22202

EXAMINER	
SPRINGER, D	
ART UNIT	PAPER NUMBER
129	8

DATE MAILED: 06/06/89

This is a communication from the examiner in charge of your application.

COMMISSIONER OF PATENTS AND TRADEMARKS

for restriction only.

[X] 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~~ months), 30 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. [X] Claims 1-35 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. [ ] Claims _____ have been cancelled.

3. [ ] Claims _____ are allowed.

4. [ ] Claims _____ are rejected.

5. [ ] Claims _____ are objected to.

6. [X] Claims 1-35 are subject to restriction or election requirement.

7. [ ] This application has been filed with informal drawings which are acceptable for examination purposes until such time as allowable subject matter is indicated.

8. [ ] Allowable subject matter having been indicated, formal drawings are required in response to this Office action.

9. [ ] The corrected or substitute drawings have been received on _____. These drawings are [ ] acceptable; [ ] not acceptable (see explanation).

10. [ ] The [ ] proposed drawing correction and/or 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 _____, has been [ ] approved. [ ] disapproved (see explanation). However, the Patent and Trademark Office no longer makes drawing changes. It is now applicant's responsibility to ensure that the drawings are corrected. Corrections MUST be effected in accordance with the instructions set forth on the attached letter "INFORMATION ON HOW TO EFFECT DRAWING CHANGES", PTO-1474.

12. [ ] Acknowledgment is made of the claim for priority under 35 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

FILE

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-31 are, drawn to quinolinoyl substituted hepteneoic acids, classified in Class 546, subclass 175 and claims 32-35 directed to compositions and a medical use thereof classified in 514/.

II. Claim 1 (part), drawn to silyloxy containing quinoline compounds, classified in Class 546. subclass 14 and claims 32-35 (part of each) directed to compositions and a medical use thereof, classified in 514/184.

III. Claim 1 (part), drawn to quinoline compounds containing a hetero oxygen containing ring fused thereto as in the definition "R^1 and R^2 ... from -OC (R^{15}) (R^{16})-O-", classified in Class 546, subclass 90 and claims 32-35 (part of each) directed to compositions and a method of use thereof classified in 514/291.

IV. Claim 1 (part), drawn to quinoline compounds containing a carbocyclic ring fused there to as in the definitions of "R^1 and R^2 ... form -C=CH-CH=CH-", classified in Class 546. subclass 101 and claims 33-35 directed to compositions of and a method of use thereas classified in 514/290.

The inventions are distinct, each from the other, because of the following reasons:

Inventions I and each of Inventions II-IV are related as subcombinations disclosed as useable together in a single combination. The subcombinations are distinct from each other if they are shown to be separately useable. In the instant case, invention of each of groups I-IV expectedly have has separate utility such as reduction of hyperlipidemia hyperlipoproteinemia or atherosclerosis as set forth in claim 15. See MPEP 806.05(d).

It is noted the compounds of each of groups I-IV have not been restricted from the three materially different methods of use in claim 35 under the provisions of MPEP 806.05(h) since one and only one of these three methods will be examined with the inventive compounds group elected.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and recognized divergent subject matter restriction for examination purposes as indicated is proper.

A telephone call was made to Mr. Samuel H. Blech, applicants attorney, on May 19, 1989 to request an oral election to the above restriction requirement, but did not result in an election being made, due to the complexity and the fact applicants are foreign.

Applicants are further required to elect a single disclosed species from the group elected and requested to submit as claim thereto if one is not already present.

Based upon this election of a single species it may be required to limit the case to an inventive generic concept embraced thereby due to the complexity and variety of substituents an the basic structure,

David B. Springer
DAVID B. SPRINGER
EXAMINER
ART UNIT 129

SPRINGER:cwh
A/C 703
557-3920
06-05-89

DOCKET NO. 49-111-0

IN RE APPLICATION OF YOSHIHIRO TOMIKAWA ET AL

SERIAL NO. 07/233,752

FILED AUGUST 19, 1988

FOR QUINOLINE TYPE MEVALONOLACTONES

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

Sir:

Transmitted herewith is an amendment in the above-identified application.

☐ No additional fee is required.

☐ Small entity status of this application under 37 CFR 1.9 and 1.27 has been established by a verified statement previously submitted.

☐ Small entity status of this application under 37 CFR 1.9 and 1.27 is established by a verified statement submitted herewith.

XX☐ Additional documents filed herewith:

CITED DECISION

The fee has been calculated as shown below.

	(Col. 1) Claims Remaining After		(Col. 2) Highest No. Previously Paid For	(Col. 3) Present Extra
Total	* 36	Minus	** 35	= 1
Indep	* 1	Minus	*** 3	= 0
☐ First presentation of multiple dep. claim				

Small Entity		OR	Other Than a Small Entity	
Rate	Addit. Fee		Rate	Addit. Fee
x6 =	$		x12 =	$ 12
x18=	$		x36 =	$ 0
+60=	$		+120=	$ 0
Total	$	OR	Total	$ 12

XX☐ A check in the amount of $ 12.00 is attached.

☐ Charge $_____ to deposit account no. _____. A duplicate copy of this sheet is enclosed.

XX☐ Please charge any additional fees for the papers being filed herewith and for which no check is enclosed herewith, or credit any overpayment to deposit account no. 15-0030. A duplicate copy of this sheet is enclosed.

XX☐ Please charge any additional fees or credit any overpayment of fees required under 37 CFR 1.136 for any necessary extension of time to make the filing of the attached response timely to deposit account no. 15-0030. A duplicate copy of this sheet is enclosed.

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

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* If the entry in Column 2 is less then the entry in Column 1 write "0" in Column 3.
** If the "Highest Number Previously paid for " IN THIS SPACE is less than 20 write "20" in this space.
*** If the "Highest Number Previously paid for " IN THIS SPACE is less than 3 write "3" in this space.

12,100 - 103 -

49-111-0
65/

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF: :

YOSHIHIRO FUJIKAWA ET AL : GROUP ART UNIT: 129

SERIAL NO: 07/233,752 :

FILED: AUGUST 19, 1988 : EXAMINER: SPRINGER

FOR: QUINOLINE TYPE MEVA- :
LONOLACTONES

RESTRICTION RESPONSE

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

SIR:

Responsive to the restriction requirement of June 6, 1989.

ELECTION

Applicants herewith elect, with traverse, the invention as defined by the claims of Group I.

As a single disclosed species, Applicants herewith elect compound I-31, the compound of Example 4 at page 42 to 43 of the specification.

IN THE CLAIMS

Please amend the above-identified application by adding the following claim:

--36. The compound according to Claim 1, which is (E)-6-[4'-(4"-fluorophenyl)-2'-(1"-methylethyl)-

C1

quinolin-3'-ylethenyl)-4-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one.--

REMARKS

The Examiner has required restriction between:

I. Claims 1-31 drawn to quinolinoyl substituted hepteneoic acids, and a medical use thereof,

II. Claim 1 (part), drawn to silyloxy containing quinoline compounds, compositions and a medical use thereof,

III. Claim 1 (part) drawn to quinoline compounds containing a heterooxygen containing ring fused thereto, compositions and a method of use thereof, and

IV. Claim 1 (part), drawn to quinoline compounds containing a carbocyclic ring fused thereto, compositions and a method of use thereof.

Applicants have elected the compounds of the claims of Group I, compositions and medical use thereof, and specifically the compound of newly added Claim 36.

Claims 1-6 and 32-36 read on the elected invention.

The restriction requirement is traversed.

It is submitted that "unity of invention", as defined in In re Harnisch, 206 USPQ 300, is present herein.

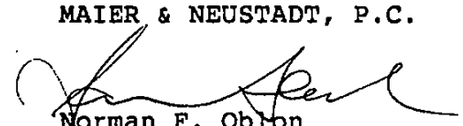
All of the claimed compounds are of the same general structure and possess a community of properties. They are all useful for the claimed purpose.

Under such circumstances, it is submitted that restriction is improper and its withdrawal is requested.

An action on the merits of all of the claims, i.e., Claims 1-36, is requested.

Respectfully submitted,

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



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JOHN H. WEBER*

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COUNSEL TO THE FIRM

IRVING MARCUS
1919-1988

PATENT, TRADEMARK AND COPYRIGHT LAW
AND RELATED FEDERAL AND ITC LITIGATION

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*BAR MEMBERSHIP OTHER THAN VIRGINIA
*REGISTERED PATENT AGENT

DOCKET NO.: 49-111-0

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231

RE: U.S. APPLICATION SERIAL NO.: 07/233,752
APPLICANT(S): FUJIKAWA ET AL
FILING DATE: AUGUST 19, 1988
FOR: QUINOLINE TYPE MEVALONOLACTONES

SIR:

Attached hereto for filing are the following papers:

AMENDMENT AND REQUEST FOR DECLARATION OF INTERFERENCE

Our check in the amount of $ -0- 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,

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

Norman F. Oblon
Registration No.: 24,618

Steven B. Kelber
Registration No.: 30,073

12c

Gp 129

49-111-0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:	:	
YOSHIHIRO FUJIKAWA ET AL	:	GROUP ART UNIT: 129
SERIAL NO.: 07/233,752	:	EXAMINER: SPRINGER
FILED: AUGUST 19, 1988	:	
FOR: QUINOLINE TYPE MEVALONOLACTONES	:	

AMENDMENT

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231

SIR:

Supplementing Applicants' Restriction Response of July 6, 1989, entry of the following amendments is respectfully requested.

IN THE CLAIMS:

Claim 1, line 13, please delete "trimethylsilyloxy,",

line 14, please delete "diphenyl-t-butylsilyloxy",

line 17, please delete "R^1 and R^2,",

please delete lines 18, 19 and 20 in their entirety and insert therefor -- -CH=CH-CH=CH-; --,

line 21, please delete "alkyl".

Claim 2, line 6, please delete "or when R^6 is", please delete line 7 and insert therefor --when R^4--.

Claim 35, line 1, please change "reducing" to --treating--, please delete line 2, and insert therefor --which comprises--.

Please add the following new Claims 37 and 38.

--37. A method for treating hyperlipoproteinemia, which comprises administering an effective amount of the compound of the formula I as defined in Claim 1.

38. A method for treating atherosclerosis, which comprises administering an effective amount of the compound of the formula

to the remaining groups identified, will be pursued in divisional applications.

Support for new Claims 37 and 38 may be found at page 26 of the specification, lines 5-12, as well as Claim 35 as originally presented.

As the amendments presented serve only to more clearly define the invention, and conform the claims to outstanding restriction requirement, entry is respectfully requested. Upon entry, Claims 1-38 remain pending in the case.

Respectfully submitted,

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

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Registration No.: 30,073
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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YOSHIHIRO FUJIKAWA ET AL	:	GROUP ART UNIT: 129
SERIAL NO.: 07/233,752	:	EXAMINER: SPRINGER
FILED: AUGUST 19, 1988	:	
FOR: QUINOLINE TYPE MEVALONOLACTONES	:	

REQUEST FOR DECLARATION OF INTERFERENCE, 37 CFR §1.607

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231

SIR:

Applicants, Fujikawa et al, hereby request a Declaration of Interference, pursuant to Rule 607, between the above-captioned patent application and U.S. Patent 4,761,419.

As the claims of this application and the '419 patent overlap to a significant extent, but are not identical, applicants submit the following proposed Counts.

COUNT 1

A compound of the structural formula I as recited in Claim 1 of U.S. Patent 4,761,419 or Claim 1 of U.S. Patent Application Serial No. 07/233,752.

COUNT 2

A method for inhibiting cholesterol biosynthesis and thereby treating hyperlipidemia, hyperlipoproteinemia or atherosclerosis, comprising administering a cholesterol synthesis inhibiting amount of the compound of Count 1.

Such phantom Count practice is widely accepted for Interference purposes.

As claims corresponding to proposed Count 1, applicants identify Claims 1-14 of U.S. Patent 4,761,419, and Claims 1-31 and 36 of the above-captioned application. Claims 1-13 of the '419 patent, and Claims 1-34 and 36 of the above-captioned patent application are each directed to a compound within the scope of proposed Count 1. Claim 14 of the '419 patent is directed to a pharmaceutical composition relying on the subcombination of Claim

1 for its patentability and limiting feature. Claim 14 is not patentably distinct from the compound of Count 1.

As claims corresponding to proposed Count 2, applicants identify Claim 15 of the '419 patent, and Claims 35, 37 and 38 of the above-captioned patent application, each directed to the method of Count 2.

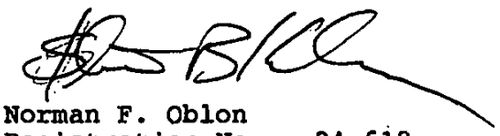
As grounds for the request for Interference, applicants note that the compound claims of the '419 patent closely correspond to, and quite clearly overlap with applicants' claims. For example, when R^1 - R^6 and R^{11} of Claim 1 of the above-captioned patent application are all hydrogen, Y is CH_2CH_2 or CH=CH, and Z of formula I is the hydroxy gamma-valerolactone substituent set forth at line 25 of Claim 1, the compound embraced is identical to the compound of Claim 1 of the '419 patent, wherein R_1 or R_2 are phenyl, and the remaining R_1 or R_2 as well as R_3 - R_6 are hydrogen. Thus, a clear overlap between the claims of the application and U.S. Patent 4,761,419 is made out. Moreover, there is absolutely no evidence of record that the varying species embraced by both claims are patentably distinct from the unsubstituted compound discussed above.

The current application, with claims as broad or broader than those presented and on the basis of which an Interference is requested, was originally filed August 19, 1988, well within the one-year date of issuance of U.S. Patent 4,761,419. Applicants claim priority of Japanese Patent Applications 207,224/1987 and

15585/1988, filed August 20, 1987 and January 26, 1988, respectively. Accordingly, Declaration of the Interference is believed appropriate.

Respectfully submitted,

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



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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.
07/233,752	08/19/88	FUJIKAWA Y	46-111-0

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ARLINGTON, VA 22202

EXAMINER	
SPRINGER, D	
ART UNIT	**PAPER NUMBER**
129	11

DATE MAILED: 11/27/89

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 1-38 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-38 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

FILE

Claims 1-38 are pending.

Applicants request for an interference is noted but was not accompanied by any specific indication as to compounds herein claimed rendering compounds claimed in U.S. Patent 4,761,419 unpatentable and vice versa. The only basis for the interference presented is that a claim could be drawn which would cover subject matter in both patents and infact applicants "phantom counts" purportedly do so. However, as there has been no claimed compound actually proposed to render a specific compound in the patent in question unpatentable, no action will be taken by the examiner to set up an interference, especially as none of the claims in the case have been examined on the merits, the request for an interference is premature.

One further comment is that it is strange indeed that an interference be proposed when no art has been cited, discussed and provided under 37 CFR 1.97-99 as is applicants declared duty of disclosure under 37 CFR 1.56(a). An information disclosure statement is requested.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention

is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-38 were rejected under 35 USC 103 as unpatentable over picardet al U.S. 4[illegible]
Claims 1-38 are rejected under 35 U.S.C. 103 as being unpatentable over Merck Frost Canada and European Patent which teach quinoline compounds of the type claimed. No patentable distinction thereover is apparent absent applicants election of and presentation of a single disclosed species claim (hereby required under 35 USC 121) (if not already presented) to which the case will be limited in the event no generic claim is found to be allowable.

The other U.S. Patents are made of record.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner David Springer whose telephone

number is (703) 557-0177.

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) 557-3920.

11/09/89;rbb

David B. Springer
DAVID B. SPRINGER
EXAMINER
ART UNIT 129

Gr 129

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DOCKET NO.: 49-111-0

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
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IN RE APPLICATION OF:
YOSHIHIRO FUJIKAWA ET AL GROUP ART UNIT: 129
SERIAL NO.: 07/233,752 EXAMINER: SPRINGER
FILED: AUGUST 19, 1988
FOR: QUINOLINE TYPE MEVALONOLACTONES

SIR:

Attached hereto for filing are the following papers:

Response, copies of two certified translations of Japanese Patent Applications, Decision in In re Dillon, and Copy of U.S. Patent 4,761,419

Our check in the amount of $ -0- 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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Registration No.: 30,073

49-111-0

#12
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:	:	
YOSHIHIRO FUJIKAWA ET AL	:	GROUP ART UNIT: 129
SERIAL NO.: 07/233,752	:	EXAMINER: SPRINGER
FILED: AUGUST 19, 1988	:	
FOR: QUINOLINE TYPE MEVALONOLACTONES	:	

RESPONSE, 37 CFR §1.115

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231

SIR:

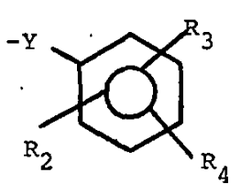
Responsive to the outstanding Office Action in the above-captioned patent issued November 27, 1989, withdrawal of the rejections therein for obviousness, 35 U.S.C. §103, and grant of applicants' request for a declaration of an Interference, originally made August 21, 1989, is respectfully requested, in light of the comments set forth below, and the certified translations submitted herewith.

All claims pending, Claims 1-38, are directed to mevalonolactone derivatives, within the general formula of Claim

1, as amended, and particularly and critically characterized by the presence of a mevalonic acid chain, designed by substituents Y-Z at the 3-position of the quinoline ring of the claimed compounds. The presence of this mevalonic acid chain is essential in exhibiting utilities as anti-hyperlipidemic hypolipoproteinemic and anti-atherosclerotic utilities, through the inhibition of HMG-CoA reductase.

These claims stand rejected as obvious, 35 U.S.C. §103 over European Patent Publication 0 219 307, published April 22, 1987. The rejection is respectfully traversed.

As reflected on page 2 of the application, the subject matter of the European Patent Publication is <u>not</u> mevalonic acid derivatives or mevalonolactones. Of particular importance is the fact that the 2-position of the quinoline ring of the compounds of the reference are substituted by the structural moiety



which clearly precludes insertion of a mevalonic acid chain at the 3-position of the quinoline ring. Note, in particular, that R^1 of the reference cannot be a mevalonic acid chain in any event.

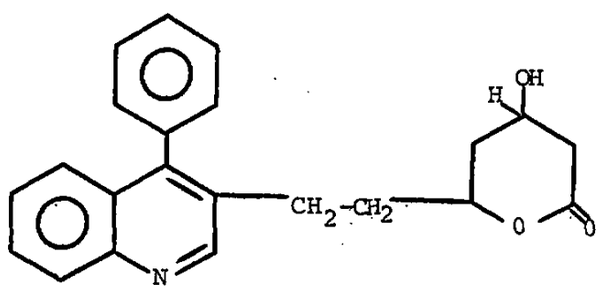
There is absolutely no disclosure in the reference as to the insertion of a mevalonic acid at the 3-position of the quinoline ring of the compound, and on that basis alone, withdrawal of the rejection over prior art is respectfully requested. In this respect, applicants cite the recent decision In re Dillon, Docket 88-1245 of the U.S. Court of Appeals for the Federal Circuit, dated December 29, 1989, a copy of which is submitted herewith. As noted in Dillon, a first inquiry is whether the compounds claimed are structurally obvious over the prior art. In the current situation, it is clear there is no structural obviousness, for the reasons discussed above with regard to the absence of a mevalonic acid chain in the prior art compounds. Moreover, it should be noted that in the prior art, the aromatic ring is connected to the quinoline ring via an ethylene or ethylyne group whereas in the claimed invention, it is linked by a single bond. There is no motivation in the prior art of record to delete this highly active doubly or triply bonded ethyl moiety. Beyond that inspection, as confirmed in Dillon, unless there is some reason, in the prior art, to suspect the claimed compounds would exhibit the recited HMG-CoA reductase inhibitory activity, no obviousness is shown, even if the

structures are related. In the current application, it is quite clear that the activities are entirely distinct, and one of ordinary skill in the art is left without direction as to how to modify the European Patent Publication compound so as to achieve reductase inhibitors. Accordingly, withdrawal of the rejection for obviousness is believed appropriate.

The claims also stand rejected as obvious over U.S. Patent 4,761,419, Picard et al, a copy of which is submitted herewith. The reference bears an effective date of December 7, 1987. Applicants submit herewith copies of certified translations of the priority documents involved herein, including Japanese Patent Application 207224/1987, filed August 20, 1987, as well as Japanese Patent Application 15585/1988, filed January 26, 1988 and Japanese Patent Application 193606/1988, filed on August 3, 1988. It is immediately clear that applicants are entitled to the original filing date of August 20, 1987, under 35 U.S.C. §119, in view of

NEW REQUEST FOR DECLARATION OF INTERFERENCE

A request for declaration of Interference, 37 CFR §1.607 was filed together with the Preliminary Amendment of August 21, 1989. Initially, this request was rejected. In the outstanding Office Action, the Examiner indicated that the request could not be granted because no compound claimed in both patents had been presented. Notwithstanding the lack of requirement for such a showing in the rules, applicants submit the following compound to be clearly embraced by the claims of U.S. Patent 4,761,419 and the claims pending in the above-captioned patent application.



Clearly, this is not the only compound embraced by both sets of claims, but it is a representative compound wherein all substitutents in the claimed invention are hydrogen, save for Y and Z, which are presented as indicated, and in the claims of the Picard et al, X is an ethyl moiety, R_1 is phenyl, and R_2-R_6 are hydrogen, and A is as indicated, column 18, line 15 of Picard et al. Accordingly, it is respectfully submitted that declaration of an Interference is now required. Applicants further note that under the current Interference rules, 37 CFR §1.601, it is not necessary that there be any actual overlap between the claims, but rather, a question of obviousness presented. The utility of the compounds of Picard et al is identical to that claimed herein, inhibition of HMG-CoA reductase, and its applications are identical as well. Certainly, at a minimum, the compounds claimed are more closely related than the compounds of the European Patent Publication, over which the claims were rejected. Accordingly, given the Examiner's rejection over the claims presented as obvious over Picard et al, a declaration of Interference is now required, and the same is respectfully requested.

Applicants note the Examiner's requirement for an Information Disclosure Statement. None is provided, for the simple reason that the Picard et al reference is the only reference of record of which applicants are aware, a copy is submitted herewith, and the reference is not properly prior art. No further discussion of the

#12

1-05-90

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF:	:	
YOSHIHIRO FUJIKAWA ET AL	:	GROUP ART UNIT: 129
SERIAL NO.: 07/07/233,752	:	
FILED: AUGUST 19, 1988	:	EXAMINER: SPRINGER
FOR: QUINOKINE TYPE MEVALONOLACTONES	:	

DECLARATION

HONORABLE COMMISSIONER OF PATENTS & TRADEMARKS

WASHINGTON, D.C. 20231

SIR:

Now comes MIDORIKO MATSUDA who deposes and says:

That my name is MIDORIKO MATSUDA;

That my address is 11-3, Kamiosaki 2-chome, Shinagawa-ku, Tokyo, Japan;

That I know well both the English and Japanese languages;

That the attached English language translation is true and correct translation of Japanese Patent Application No. 15585/1988 filed on January 26, 1988 to the best of my knowledge and belief;

I hereby declare further that all statements made herein of 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 this application or any patent issuing thereon.

FURTHER DEPONENT SAITH NOT.

January 19, 1990 Midoriko Matsuda

Date Midoriko Matsuda

PATENT OFFICE
JAPANESE GOVERNMENT

This is to certify that the annexed is a true copy of the following application as filed with this Office.

Date of Application:	January 26, 1988
Application Number:	Patent Application No. 15585/1988
Applicant:	Nissan Chemical Industries Ltd.

October 7, 1988

Fumitake Yoshida
Director-General, Patent Office

(Internal priority claimed under Patent Law Article 42-2-1)
(Filing Date of the earlier application August 20, 1987)
(Application Number of the earlier application 207224/1987)

International Patent Classification
C07D 215/00

PETITION FOR PATENT APPLICATION

January 26, 1988

To: Director-General, Patent Office: Kunio Ogawa

1. Title of the Invention:

QUINOLINE TYPE MEVALONOLACTONES

2. Number of Inventions stated in Claims:

1

3. Inventor(s):

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Funabashi-shi, Chiba-ken

4. Patent Applicant:

Name: (398) Nissan Chemical Industries Ltd.

Representative: Takeo Nakai

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Chiyoda-ku, Tokyo 101

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5. List of Attached Documents:

(1) Specification 1 copy
(2) Duplicate of Petition 1 copy

6. Inventors except above-mentioned:

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Name:	Hiroshi Iwasaki
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Address:	same as above

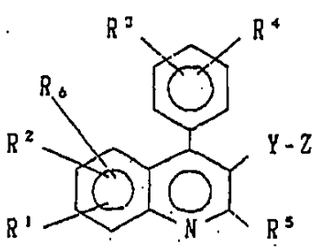
SPECIFICATION

1.TITLE OF THE INVENTION:

QUINOLINE TYPE MEVALONOLACTONES

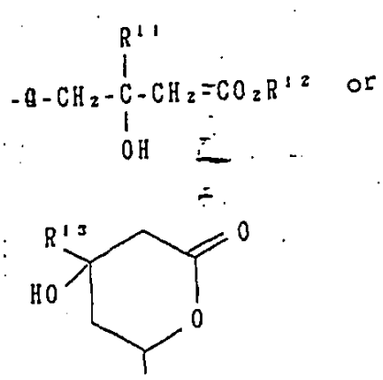
2.SCOPE OF THE CLAIM:

1. A compound of the formula:

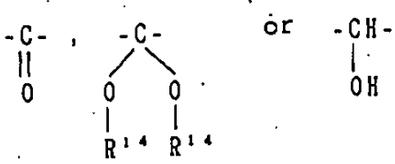


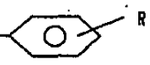
(I)

wherein R^1, R^2, R^3, R^4 and R^6 are independently hydrogen, C_{1-4} alkyl, C_{1-3} alkoxy, n-butoxy, i-butoxy, sec-butoxy, R^7R^8N- (wherein R^7 and R^8 are independently hydrogen or a lower alkyl), trifluoromethyl, fluoro, chloro, bromo, phenyl, phenoxy or benzyloxy; 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-; Y is $-CH_2-$, $-CH_2CH_2-$, -CH=CH-, $-CH_2$-CH=CH- or -CH=CH-CH_2-; and Z is



or

(wherein Q is );

R^{11} is hydrogen or C_{1-3} alkyl; R^{12} is hydrogen, R^{15} (wherein R^{15} is physiologically hydrolyzable alkyl) or M (wherein M is NH_4, a metal capable of forming a salt which is pharmaceutically acceptable, or an amine·H); R^{13} is hydrogen or C_{1-3} alkyl, two R^{14} are the same primary or secondary C_{1-6} alkyl; or two R^{14} together form $-(CH_2)_2-$, or $-(CH_2)_3-$) and R^5 is hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl,  (wherein R^7 is C_{1-3} alkyl, C_{1-3} alkoxy, fluoro, chloro, bromo or trifluoromethyl), phenyl-(CH_2)m- (wherein m is 1, 2 or 3), or phenyl-$(CH_2)_n CH(CH_3)$ (wherein m is 1 or 2).

3. DETAILED DESCRIPTION OF THE INVENTION:

[Industrial Field of Utilization]

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 hypolipoproteinemic and anti-atherosclerotic agents, and intermediates useful for their production and processes for the production of such intermediates.

[Prior Art and its Problem]

Some fermentation metabolic products such as compactine, CS-514, Mevinolin or semi-synthetic

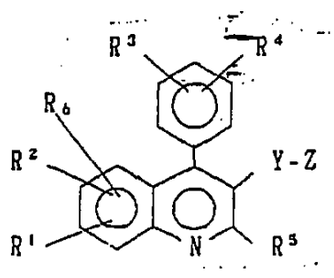
derivatives or fully synthetic derivatives thereof are known to be inhibitors against HMG-CoA reductase which is a rate limiting enzyme for cholesterol biosynthesis. (A. Endo J. Med. Chem., 28(4) 401 (1985))

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 heterocyclic derivatives of inhibitors against HMG-CoA reductase, there has been disclosed limited information.

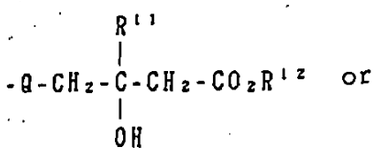
The present inventors have found that mevalonolactone derivatives having a quinoline ring, the corresponding dihydroxy carboxylic acids and salts and esters thereof have high inhibitory activities against cholesterol biosynthesis wherein HMG-CoA reductase acts as a rate limiting enzyme. The present invention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

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

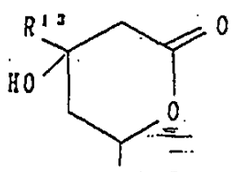


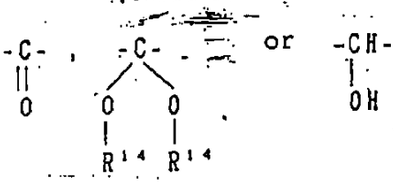
(I)

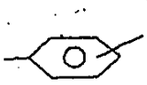
wherein R^1, R^2, R^3, R^4 and R^6 are independently hydrogen, C_{1-4} alkyl, C_{1-3} alkoxy, n-butoxy, i-butoxy, sec-butoxy, trifluoromethyl, fluoro, chloro, bromo, phenyl, phenoxy or benzyloxy; or when located at the ortho position to each other, R^1 and R^2, or R^3 and R^4 together form $-CH=CH-CH=CH-$; Y is $-CH_2-$, $-CH_2CH_2-$, $-CH=CH-$, $-CH_2-CH=CH-$ or $-CH=CH-CH_2-$; and Z is



or



(wherein Q is );

R^{11} is hydrogen or C_{1-3} alkyl; R^{12} is hydrogen, R^{15} (wherein R^{15} is physiologically hydrolyzable alkyl) or M (wherein M is NH_4, a metal capable of forming a salt which is pharmaceutically acceptable, or an amine·H); R^{13} is hydrogen or C_{1-3} alkyl, two R^{14} are the same primary or secondary C_{1-6} alkyl; or two R^{14} together form $-(CH_2)_2-$, or $-(CH_2)_3-$) and R^5 is hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl,  (wherein R^7 is C_{1-3} alkyl, C_{1-3}

alkoxy, fluoro, chloro, bromo or trifluoromethyl), phenyl-(CH_2)m- (wherein m is 1, 2 or 3), or phenyl-$(CH_2)_2CH(CH_3)$ (wherein n is 1 or 2).

The compound of the formula I will be described in detail with reference to the examples of the substituents.

C_{1-4} alkyl for R^1, R^2, R^3, R^4, R^6 and R^7 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).

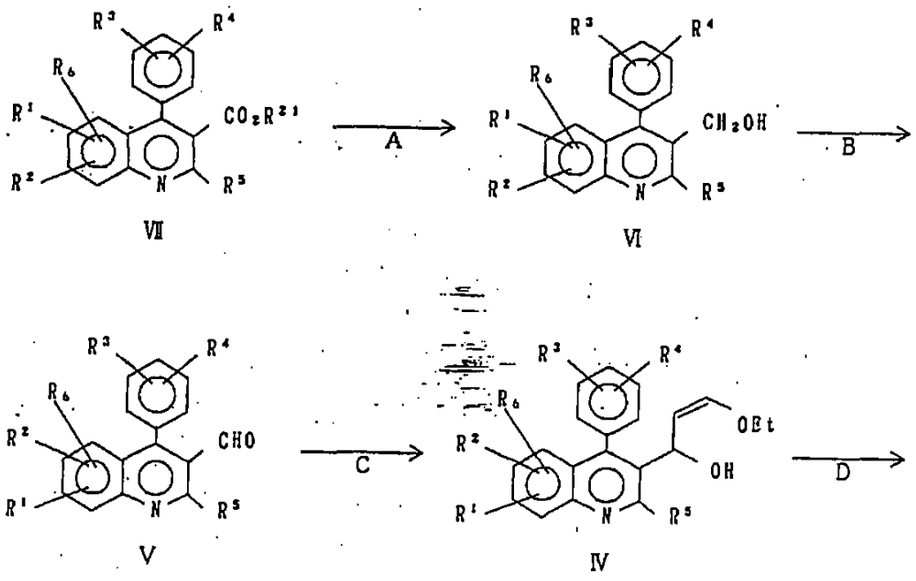
C_{1-6} alkyl for R^5 includes, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, n-pentyl and n-hexyl.

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

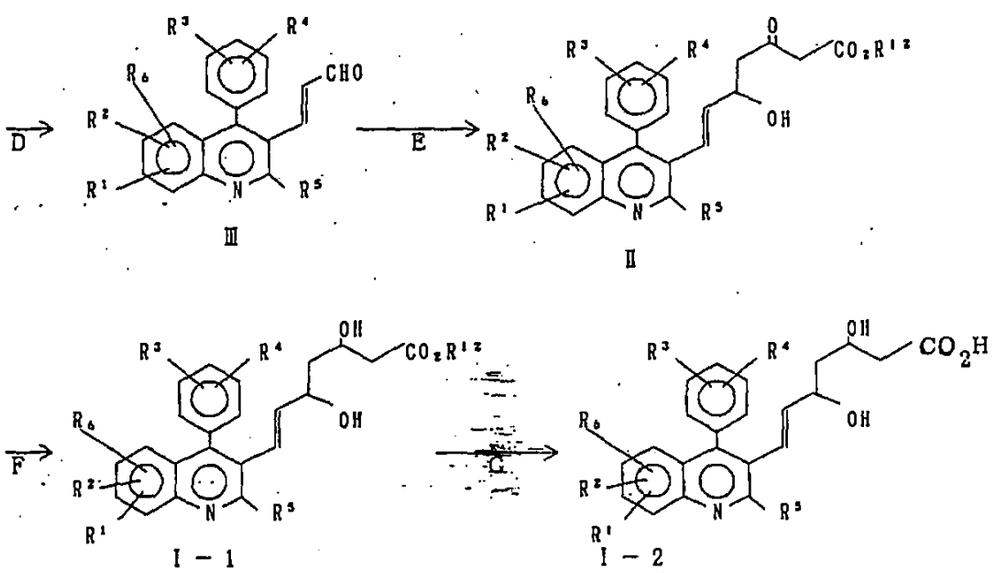
Phenyl-(CH_2)m- for R^5 includes, for example, benzyl,

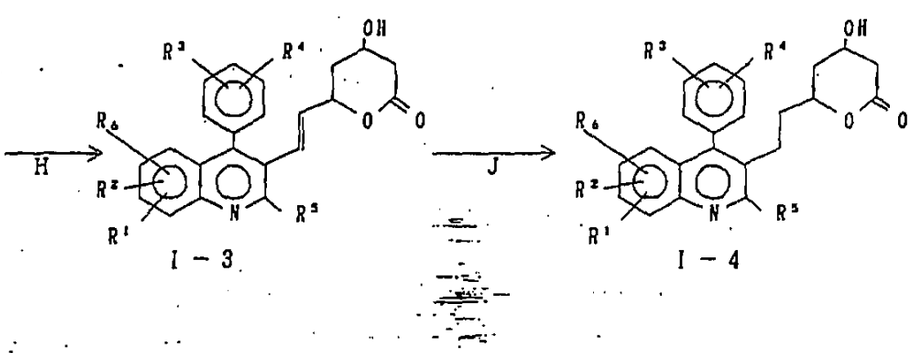
ß-phenylethyl and γ-phenylpropyl. Phenyl-$(CH_2)_nCH(CH_3)$- for R^5 includes, for example, α-phenylethyl and α-benzylethyl.

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.

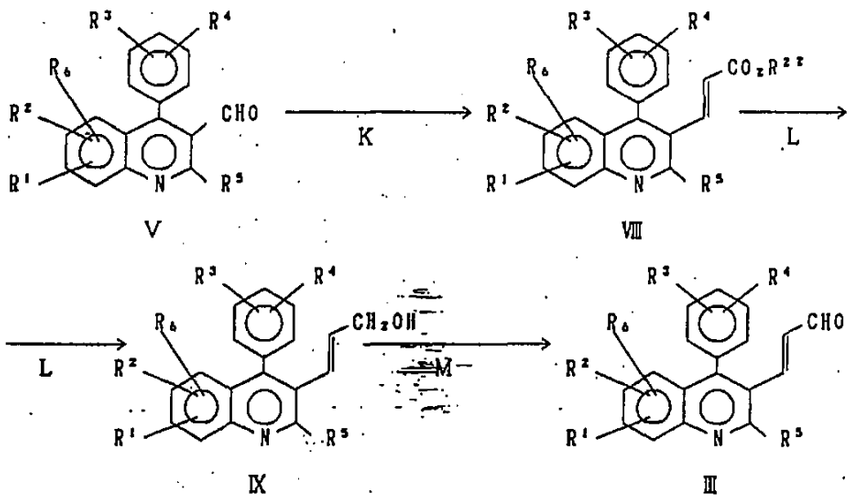


VII VI V IV


D
E
F
G
CHO
OH
CO_2R^{12}
CO_2H
Ⅲ
Ⅱ
I − 1
I − 2



I − 3　　I − 4


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

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-triethyl amine-dimethyl sulfoxide (Swern oxidation).

Step C represents a synthesis of a hydroxyvinyl ether,

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 hydroxyvinyl ether in Step C can be used in Step D without purification i.e. by simply removing tetra-n-butyl tin formed simultaneously.

The step E represents a double anion condensation reaction between the enal (IV) and an acetoacetate. Such condensation reaction is preferably conducted by using sodium hydride and n-butyl lithium as the base in tetrahydrofuran at -78°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

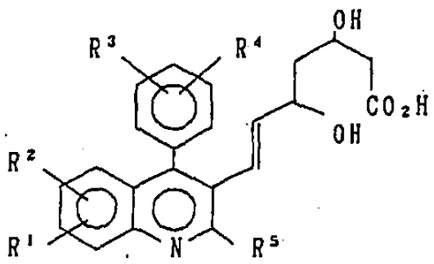
from -30 to 0°C, preferably from -20 to -15°C.

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.

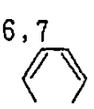
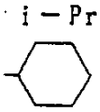
Step M represents an oxidation reaction of the allyl alcohol to an enal. This oxidation reaction can be conducted by using various oxidizing agents, particularly active manganese dioxide, in a solvent such as tetrahydrofuran, ethyl ether or ethyl acetate at a temperatrue of from 0 to 100°C, preferably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

In addition to the compounds disclosed in Examples given hereinafter, compounds of the formula I-2 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



(I－2)

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

R^1	R^2	R^3	R^4	R^5	R^6
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	H	H	c−Pr	H
6-OMe	7-OMe	4− F	H	c−Pr	H
H	H	4− F	H	sec-Bu	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
6-i-Pr	H	4− F	H	i-Pr	H
6-Me	H	4− F	H	c−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

R^1	R^2	R^3	R^4	R^5	R^6
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-C ℓ	7-C ℓ	4 — F	H	i-Pr	8-C ℓ
H	H	4 — F	H	c-Bu	H
H	H	4 — F	H	c-Hex	H

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 binder such as syrup, gum arabic, gelatin, sorbitol, tragacanth gum, polyvinyl pyrrolidone, an excipient such as lactose, sugar, corn starch, calcium phosphate, sorbitol, glycine or 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

from 0.05 to 500 mg, preferably from 0.5 to 30 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 VI 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 VI and the processes for their production.

[Examples]

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

prepared from liver homogenate according to the modified method of Knauss et al.; Kuroda, M., et. al., Biochim. Biophys. Acta, 489, 119 (1977). By the cannulation to the bile-duct of rats, it has been confirmed that the ability for cholesterol biosynthesis is increased from a few to 10 timtes. The measurement of the ability for cholesterol biosynthesis was conducted in accordance with a method of Endo, The Metabolism, 16, 1757 (1979). Namely, microsome (0.1 mg protein) and sup fraction (1.0 mg protein) were incubated for 2 hours at 37°C in 200 µl of reaction mixture containing ATP; 1 mM, Glutathione; 6 mM and 0.2 mM [2-^{14}C] sodium acetate (0.1 µCi) with 4 µl of test compound solution in water or dimethyl sulfoxide (DMSO). 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, which is the concentration for inhibiting radioactivity incorporated in the nonsaponifiable lipids at the level of 50%.

Test B: Inhibition of cholesterol biosynthesis in culture cells

Human liver cancer cells, (Hep G2 cells) at from several to several tenspassage were seed to 6 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 and the incubation was continued. By changing the FBS containing medium to the LpDS containing medium, it has been confirmed that the ability for cholesterol biosynthesis in vivo increases about 1.4 times. After 24 hrs incubation the medium was removed, 1.5 ml of DME medium containing 5% LpDS was added fresh and 15 µl of test compound solution dissolved in water or DMSO was added. 0.5 µCi of [2-^{14}C]sodium acetate 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 three times. Cells were scraped with rubber policeman and collected to tubes. To the resulting cell pellet, 200 µl of 0.5 NKOH was added and the cells were digested by heating them overnight. Aliquot of the digestion was saponified with 15% EtOH-KOH. 3ß-Hydroxysterol was separated from the resulting nonsaponifiable lipids by precipitatiton method with digitonin in accordance with the method of Sperry et al., J.Biol Chem., 187, 97 (1950).

On the other hand, the amount of the protein was measured by using the remaining of the cell digestion. The ability of cholesterol biosynthesis was indicated with DPM/mg cell protein. Inhibitory activity of compounds was

indicated with IC_{50}, which is the concentration for inhibiting radioactivity incorporated in the digitonide at the level of 50%.

With respect to the compounds of the present invention, the inhibitory activities against the cholesterol biosynthesis in which HMG-CoA reductase acts as a rate limiting enzyme, were measured by above Test A and B. The results are as shown in Table 2.

Table 2: Inhibitory activities by Test A

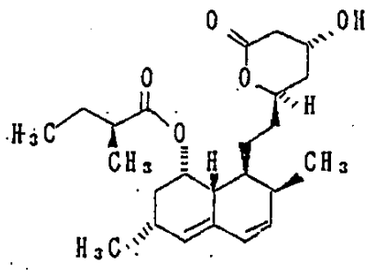
Compound	IC_{50} (molar concentration)
(Compounds of the present invention)	
I-51	1.0×10^{-8}
I-52	7.1×10^{-8}
I-53	1.9×10^{-7}
I-13	1.25×10^{-7}
(Reference compounds)	
Mevinolin	1.4×10^{-8}
CS-514	9.0×10^{-9}

With respect to the following compounds, the relative activities are shown based on the activities of CS-514 being evaluated to be 1.

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

Structures of reference compounds:

(1) Mevinolin



(2) CS-514

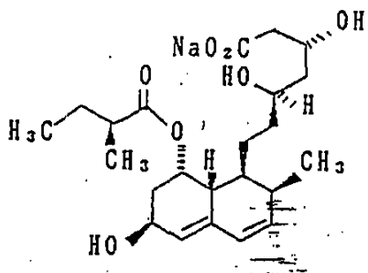


Table 3: Inhibitory activities by Test B-1

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

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.

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-q)

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 gradually added into a mixture solution of 45 ml of conc. aqueous ammonia and 120 ml of water cooled with ice. 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 thoroughly 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.

NMR (in $CDCl_3$) δppm:

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

3.7 (m, 1H) 3.7 (q, J=7Hz, 2H)

4.75(t, J=7Hz, 1H) 5.7(m, 1H) 5.95(m, 1H)

7.05～8.2 (m, 8H)

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

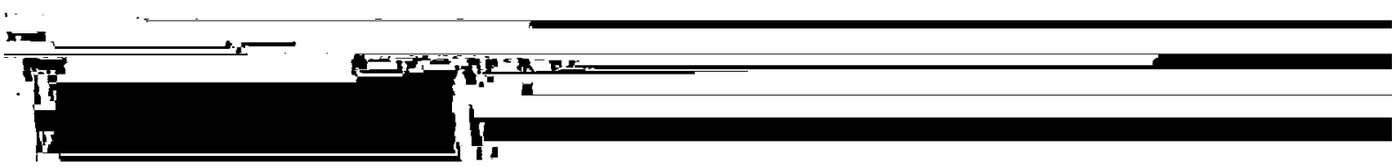
1.13 g (3.13 mmol) of cis-1-ethoxy-2-(tri-n-butylstannyl)ethylene was dissolved in 8 ml of dry tetrahydrofuran, and the solution was cooled to -78°C in a nitrogen stream. To this solution, 2 ml (3.2 mmol) of a 15 wt% n-butyllithium-n-hexane solution was dropwise added. The mixture was stirred for 45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

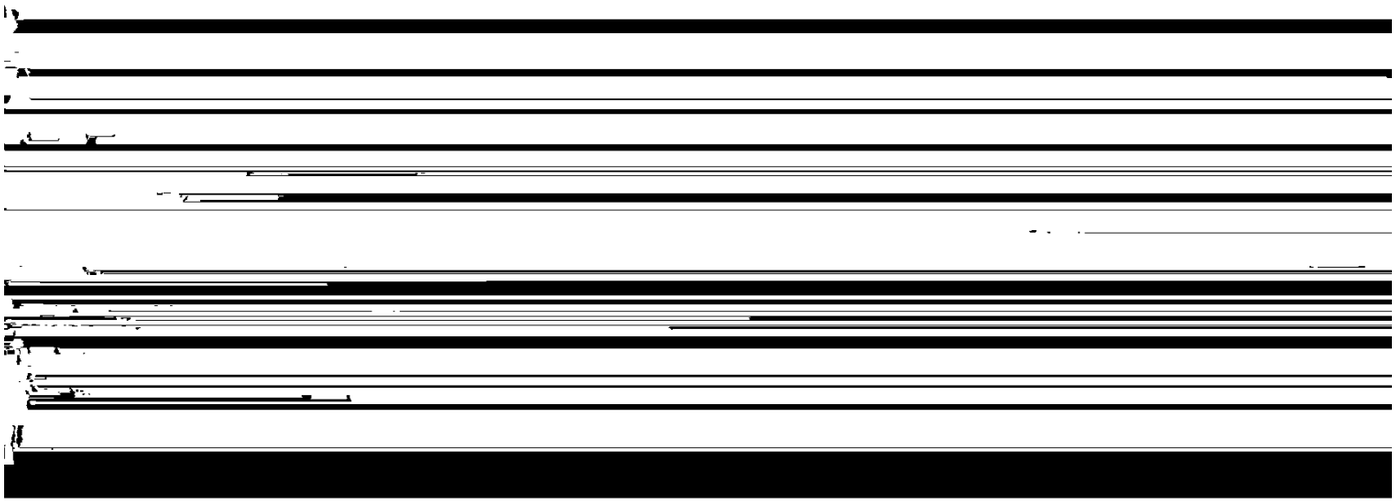
EXAMPLE 1-e: (E)-3-[4'-(4''-fluorophenyl)-2'-(1''-methylethyl)-quinolin-3'-yl]propenaldehyde (compound III-1)

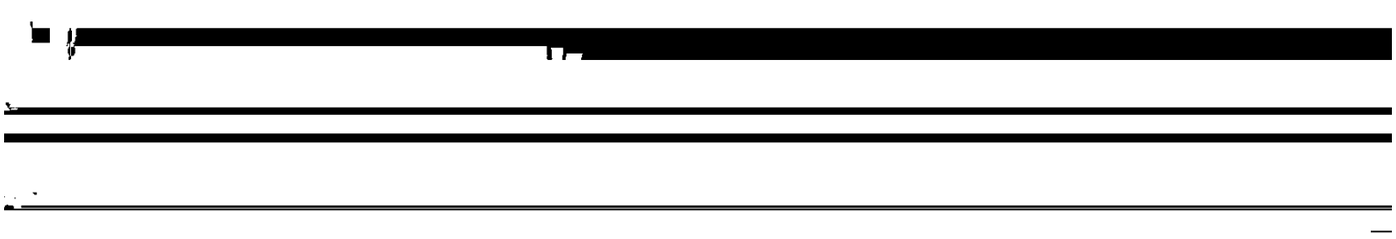
0.91 g of compound IV-1 was dissolved in 20 ml of tetrahydrofuran, and 5 ml of water and 100 mg of p-toluenesulfonic acid were added thereto. The mixture was stirred at room temperature for 24 hours. The reaction solution was extracted with diethyl ether a few times. The extracts were washed with a saturated sodium chloride aqueous solution and dried over anhydrous magnesium sulfate. Then, the solvent was distilled off under reduced pressure. 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.

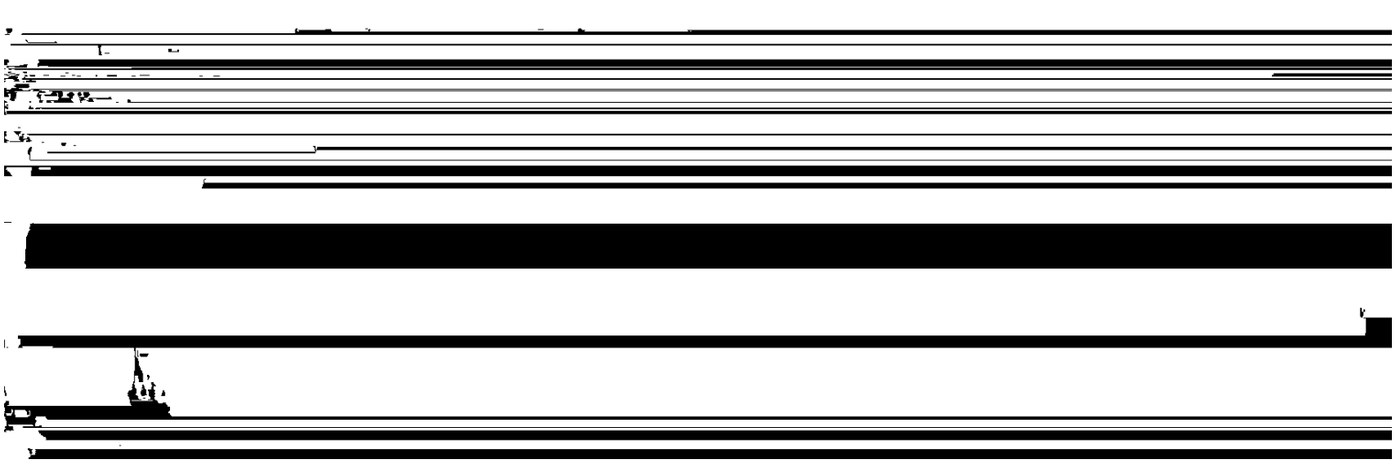
EXAMPLE 1-f: Ethyl (E)-7-[4'-(4''-fluorophenyl)-2'-(1''-methylethyl)-quinolin-3'-yl]-5-hydroxy-3-oxohepto-6-enoate (compound II-1)

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.









obtain the desired product as a pure colorless oily substance. 70 mg (Yield: 64%)

NMR (in $CDCl_3$) δppm:

1.30 (t, J=8Hz, 3H) 1.39 (d, J=8Hz, 6H)
1.4 ~1.8 (m, 2H) 2.42 (d, J=7Hz, 2H)
3.0 ~3.8 (m, 2H) 3.50 (m, 1H) 3.9~ 4.6
(m, 2H) 4.20 (q, J=8Hz, 2H) 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 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. (Developing solvent: 3% methanol-chloroform)

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

In the same manner as in Example 1-a, compounds VII-2 to VII-23 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.)

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. (°C)
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－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 $CDCl_3$) 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 $CDCl_3$) 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)

In the same manner as in Example 1-b, compounds VI-2 to VI-23 were prepared. (In Table 5, R^1, R^2, R^3, R^4 and R^5 correspond to the substituents in compound VI.)

Tale 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	4-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

In the same manner as in Example 1-c, compounds V-2 to V-23 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. (℃)
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

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. (℃)
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-23 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－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-23 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 - 7

H-NMR(in $CDCℓ_3$) 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($CDCl_3$) 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($CDCl_3$) 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($CDCl_3$) 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－２２

H-NMR($CDCl_3$) 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－２３

H-NMR($CDCl_3$) 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)

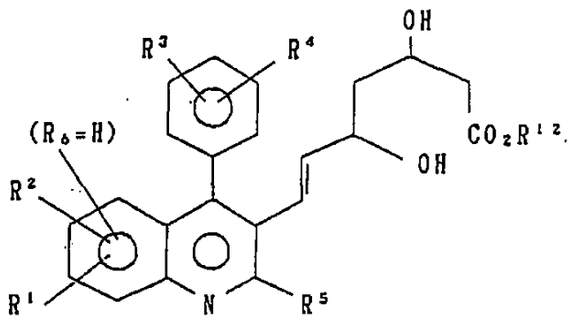
5.08(dd,1H,J=6Hz,J=16Hz),

6.26(dd,1H,J=1.5Hz,J=16Hz), 7.0 ～8.0

(m,13H)

In the same manner as in Example 1-g, compounds I-12 to I-123 were prepared.

Table 10



Compound No.	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－17

H-NMR($CDCℓ_3$) 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($CDCl_3$) 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($CDCl_3$) 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－110

H-NMR($CDCl_3$) 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($CDCl_3$) 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($CDCl_3$) 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－113

H-NMR($CDCl_3$) 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－114

H-NMR($CDCl_3$) 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－115

H-NMR($CDCl_3$) 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($CDCl_3$) 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($CDCl_3$) 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($CDCl_3$) 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($CDCl_3$) 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($CDCl_3$) 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－121

H-NMR($CDCl_3$) 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－122

H-NMR($CDCl_3$) 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)

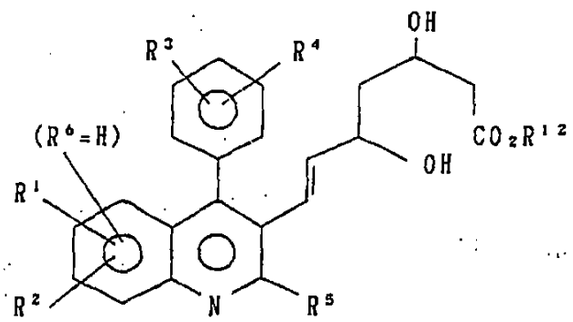
I－123

H-NMR($CDCl_3$) 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)

In the same manner as in Exmple 2, compounds I-52 to I-523 were prepared.

Table 11



Compound No.	R^1	R^2	R^3	R^4	R^5	R^{12}	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-5.7

^{1}H-NMR(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(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(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(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(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(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(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(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－５１５

H-NMR(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－５１６

H-NMR(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－５１７

H-NMR(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－５１８

H-NMR(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－５１９

H-NMR(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－５２０

H-NMR(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(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(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(DMSO-d^6) δ ppm :

0.8-1.4(m,2H), 1.6-2.1(m,2H)

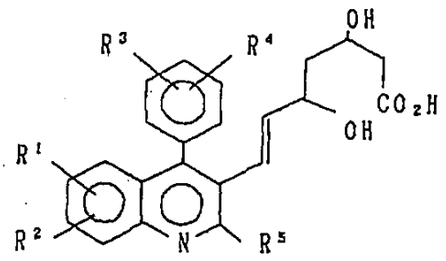
2.9-3.7(m,3H), 3.7-4.1(m,1H)

5.1-5.4(m,1H), 6.1-6.4(m,1H)

7.1-8.2(m,13H)

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

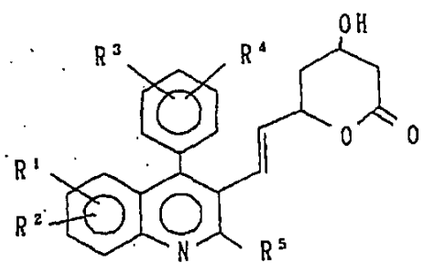
Table 12



Compound No.	R^1	R^2	R^3	R^4	R^5	m.p. (^oC) mass spectrum
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



Compound No.	R^1	R^2	R^3	R^4	R^5	m.p. (°C)
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	

Examples of formulations containing the compound of the present invention will be described.

FORMULATION EXAMPLE 1: Tablets

Components (for 100 tablets)

Composition	weight
Compound I-51	1 (g)
Potato starch	20
Carboxymethyl cellulose	2
Polyvinyl alcohol	1.5
Magnesium stearate	0.5
Total	25

The above components were weighed, put into a V-type mixer and mixed uniformly. The mixture powders were formed in tablets by a direct tableting method. The weight per one tablet was 250 mg.

FORMULATION EXAMPLE 2: Soft capsules

Components (for 100 capsules)

Composition	weight
Compound I-51	1 (g)
Olive oil	19
Total	20

The above components were weighed, mixed uniformly, packed in soft capsules each containing 200 mg of the

components, and dried.

FORMULATION EXAMPLE 3: Granules

Components (for 100 packages)

Composition	weight
Compound I-51	1 (g)
Silicic acid anhydride	3
Crystal cellulose powder	9
Lactose	6
Magnesium stearate	1
Total	20

The above components were uniformly mixed, granulated and packaged so that each package contains 200 mg of the components.

FORMULATION EXAMPLE: Suppository

Components (for 100 suppositories)

Composition	weight
Compound I-51	1 (g)
Cacao butter	79
Total	80

The above components were weighed, melt-mixed uniformly at 38°C and poured into suppository containers, which were cooled preliminarily to a slight degree. The weight per one suppository was 0.8 g.

Applicant for Patent: Nissan Chemical Industries Ltd.

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF:	:	
YOSHIHIRO FUJIKAWA ET AL	:	GROUP ART UNIT: 129
SERIAL NO.: 07/07/233,752	:	
FILED: AUGUST 19, 1988	:	EXAMINER: SPRINGER
FOR: QUINOKINE TYPE MEVALONOLACTONES	:	

DECLARATION

HONORABLE COMMISSIONER OF PATENTS & TRADEMARKS

WASHINGTON, D.C. 20231

SIR:

Now comes MIDORIKO MATSUDA who deposes and says:

That my name is MIDORIKO MATSUDA;

That my address is 11-3, Kamiosaki 2-chome, Shinagawa-ku, Tokyo, Japan;

That I know well both the English and Japanese languages;

That the attached English language translation is true and correct translation of Japanese Patent Application No. 193606/1988 filed on August 3, 1988 to the best of my knowledge and belief;

I hereby declare further that all statements made herein of 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 this application or any patent issuing thereon.

FURTHER DEPONENT SAITH NOT.

January 19, 1990 — Date

Midoriko Matsuda — Midoriko Matsuda

PATENT OFFICE
JAPANESE GOVERNMENT

This is to certify that the annexed is a true copy of the following application as filed with this Office.

Date of Application:	August 3, 1988
Application Number:	Patent Application No. 193606/1988
Applicant:	Nissan Chemical Industries Ltd.

November 14, 1988

Fumitake Yoshida
Director-General, Patent Office

(Internal priority claimed under Patent Law Article 42-2-1)
(Filing Date of the earlier application August 20, 1987)
(Application Number of the earlier application 207224/1987)
(Filing Date of the earlier application January 26, 1988)
(Application Number of the earlier application 015585/1988)

International Patent Classification
C07D 215/00

PETITION FOR PATENT APPLICATION

August 3, 1988

To: Director-General, Patent Office: Fumitake Yoshida

1. Title of the Invention:

QUINOLINE TYPE MEVALONOLACTONES

2. Number of Inventions stated in Claims:

34

3. Inventor(s):

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4. Patent Applicant:

Name: (398) Nissan Chemical Industries Ltd.

Representative: Takeo Nakai

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Please contact: TEL. 0474-65-1111

5. List of Attached Documents:

(1) Specification 1 copy
(2) Duplicate of Petition 1 copy

6. Inventors except above-mentioned:

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Name:	Masaki Kitahara
Address:	same as above

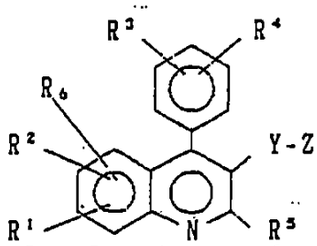
SPECIFICATION

1.TITLE OF THE INVENTION:

QUINOLINE TYPE MEVALONOLACTONES

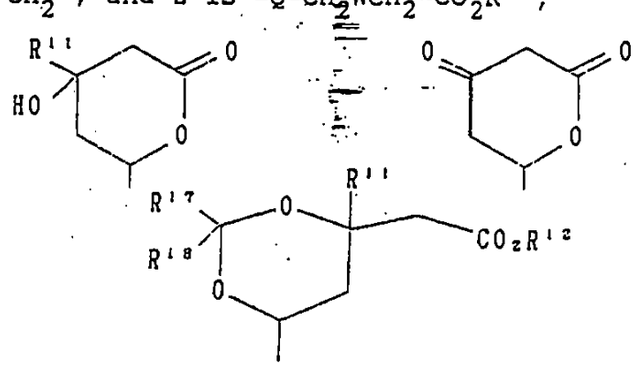
2.SCOPE OF THE CLAIMS:

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 $-Q-CH_2WCH_2-CO_2R^{12}$,

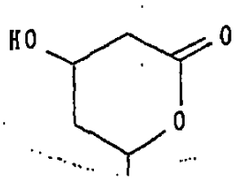


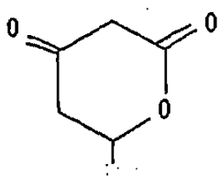
or

(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^6 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^6 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'-

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.

3. DETAILED DESCRIPTION OF THE INVENTION:

[Industrial Field of Utilization]

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 hypolipoproteinemic and anti-atherosclerotic agents, and intermediates useful for their production and processes for the production of such intermediates.

[Prior Art and its Problem]

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))

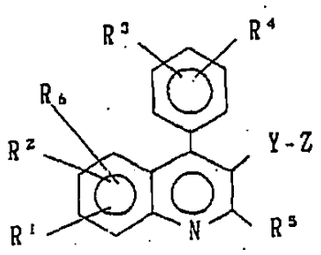
CS-514 and Mevinolin have been clinically proved to be potentially useful anti-hyperlipoproteinemic agents, and they are considered to be effective for curing or preventing diseases of coronary artery sclerosis or atherosclerosis. (IXth Int. Symp. Drugs Affect. Lipid Metab., 1986, p30, p31, p66)

However, with respect to fully synthetic derivatives, particularly heterocyclic 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, 88-007781, 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.

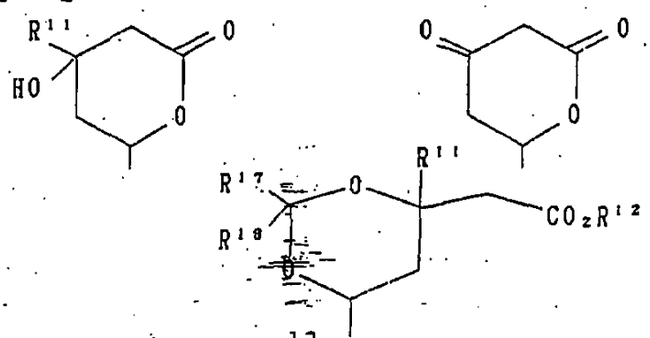
The novel mevalonolactone derivatives of the present invention are represented by the following formula I:



(I)

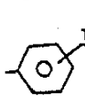
wherein R^1, R^2, R^3, R^4 and R^6 are independently hydrogen, C_{1-6} alkyl, C_{1-6} cycloalkyl, C_{1-3} alkoxy, n-butoxy, i-butoxy, sec-butoxy, R^7R^8N- (wherein R^7 and R^8 are independently hydrogen or C_{1-3} alkyl), trifluoromethyl, trifluoromethoxy, difluoromethoxy, fluoro, chloro, bromo,

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), -$(CH_2)_n$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_{1-4} 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 $-CO_2H\cdot$ (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-$(CH_2)_n CH(CH_3)$- 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 have at least one or two asymmetric carbon atoms and 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 and most 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, trifluoromethoxy, difluoromethoxy, phenoxy and benzyloxy.

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

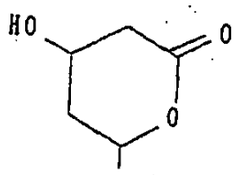
As preferred examples for R^3 and R^4, when R^4 is hydrogen, R^3 is hydrogen, 3'-fluoro, 3'-chloro, 3'-methyl, 4'-methyl, 4'-chloro and 4'-fluoro.

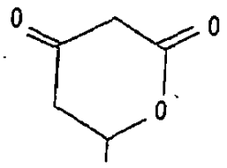
Other preferred combinations of R^3 and R^4 include 3'-methyl-4'-chloro, 3',5'-dichloro, 3',5'-difluoro, 3',5'-dimethyl and 3'-methyl-4'-fluoro.

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





$-CH(OH)CH_2CH(OH)CH_2CO_2R^{12}$, $-CH(OH)CH_2C(O)CH_2CO_2R^{12}$ 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 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

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

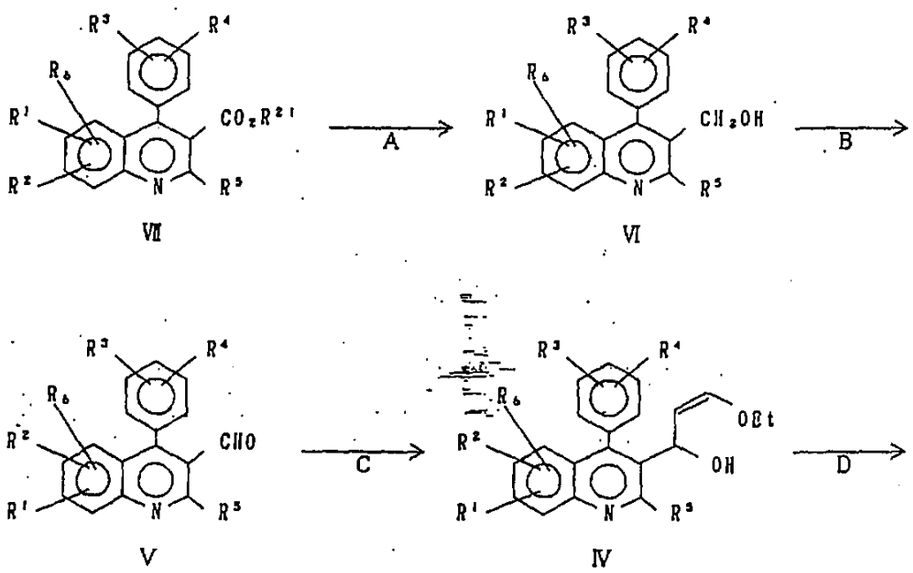
(w) (E)-3,5-dihydroxy-7-[4'-phenyl-2'-cyclopropyl-6'-methyl-quinolin-3'-yl]-hept-6-enoic acid

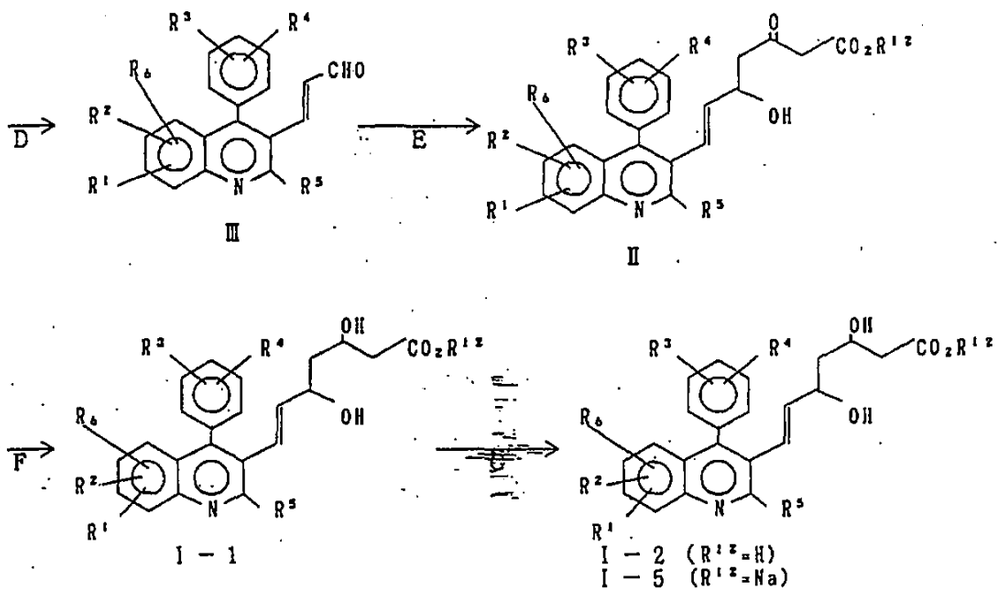
(x) (E)-3,5-dihydroxy-7-[4'-phenyl-2'-cyclopropyl-6',7'-dimethoxy-quinolin-3'-yl]-hept-6-enoic acid

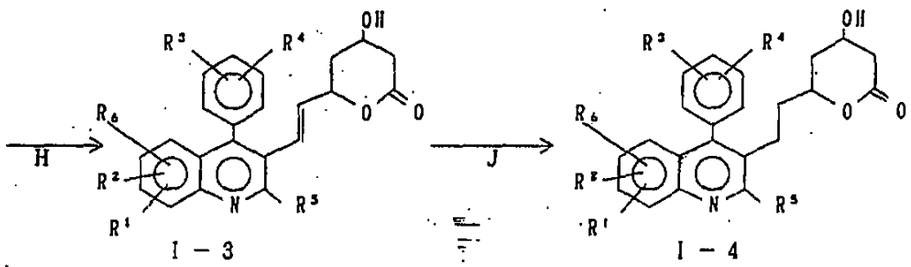
(y) (E)-3,5-dihydroxy-7-[4'-(4''-fluorophenyl)-2'-(1''-methylethyl)-6'-methoxy-quinolin-3'-yl]-hept-6-enoic acid

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

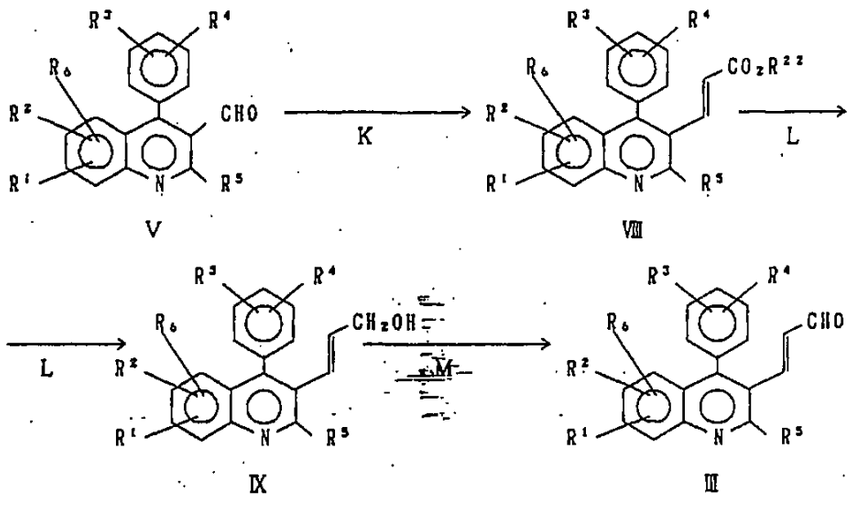
The mevalonolactones of the formula I can be prepared by the following reaction scheme. The enal III can also be prepared by processes K, L and M.

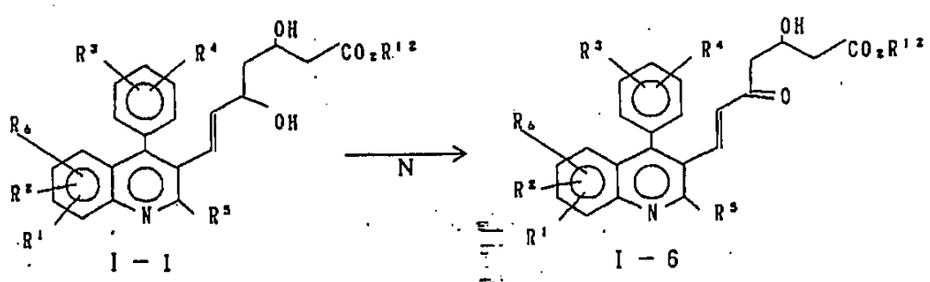

R3
R4
R5
R1
R2
N
CO2R21
A
CH2OH
B
VII
VI
CHO
C
OEt
OH
D
V
IV


D
E
F
CHO
OH
CO_2R^{12}
Ⅲ
Ⅱ
I − 1
I − 2 (R^{12}=H)
I − 5 (R^{12}=Na)



I - 3　　I - 4


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


OH
CO₂R¹²
R³
R⁴
OH
R⁶
R²
N
R⁵
R¹
I - 1
N
OH
CO₂R¹²
R³
R⁴
O
R⁶
R²
N
R⁵
R¹
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.

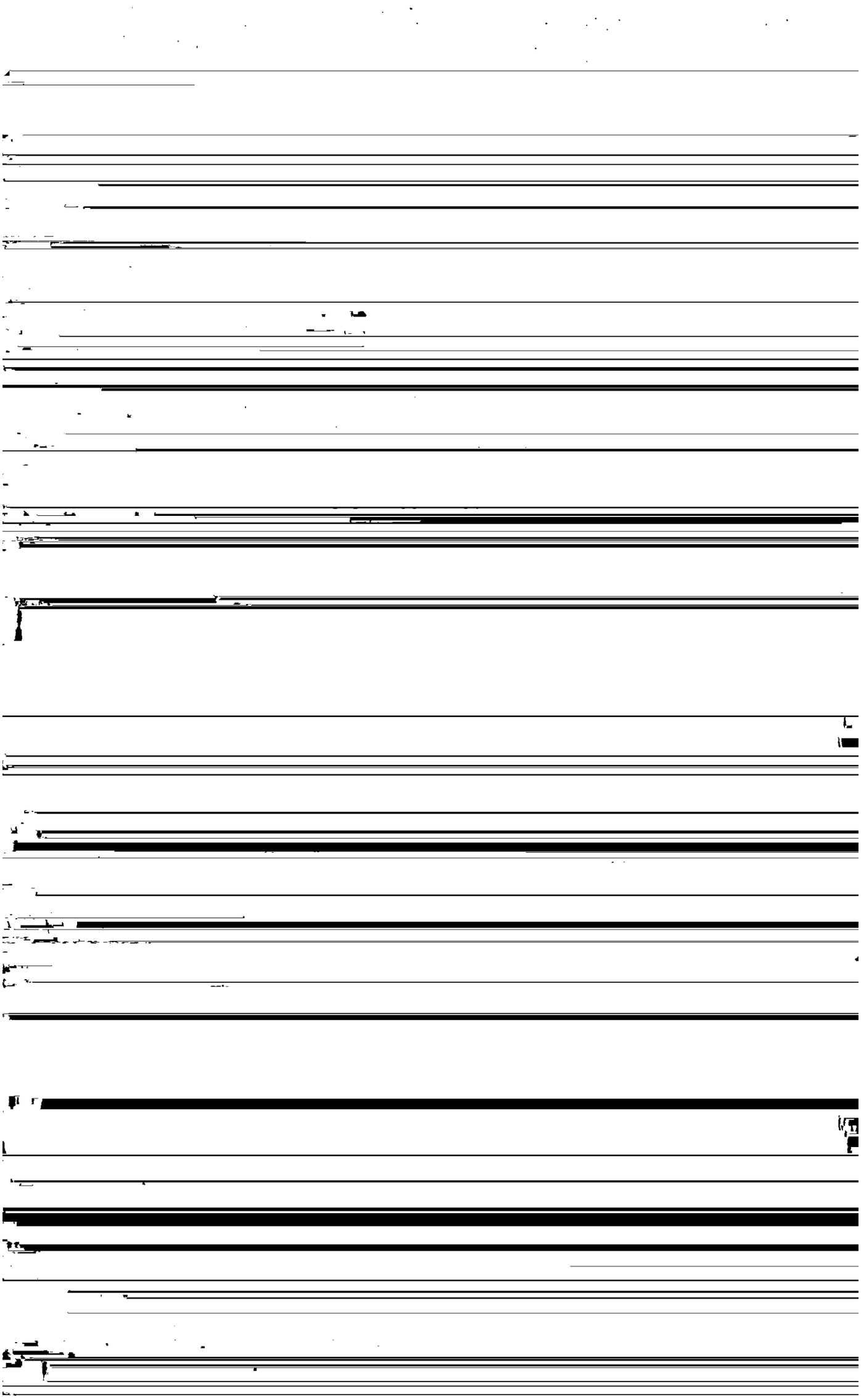
Step D represents a synthesis of an enal by acidic hydrolysis. As the acid catalyst, it is preferred to employ p-toluene sulfonic acid, hydrochloric acid or sulfuric acid, and the reaction may be conducted in a solvent mixture of water and tetrahydrofuran or ethanol at a temperature of from 10 to 25°C. 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



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.

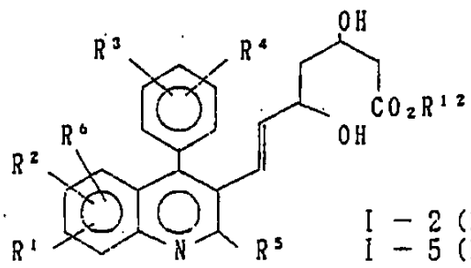
Step M represents an oxidation reaction of the allyl alcohol to an enal. This oxidation reaction can be conducted by using various oxidizing agents, particularly active manganese dioxide, in a solvent such as tetrahydrofuran, ethyl ether or ethyl acetate at a temperatrue of from 0 to 100°C, preferably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



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 atherosclerosis.

They may be formulated into various suitable

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 anion-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.

[Examples]

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 (weighing from 200 to 250 g) cannulated to the bile-duct and discharged bile for over 24 hours. Liver was cut out at mid-dark and microsome and 105000 xg 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).

By the cannulation to the bile-duct of rats, it has been confirmed that the ability for cholesterol biosynthesis is increased from a few to 10 times. The measurement of the ability for cholesterol biosynthesis was conducted in accordance with a method of Endo, The Metabolism, 16, 1757 (1979). Namely, microsome (0.1 mg protein) and sup fraction (1.0 mg protein) were incubated for 2 hours at 37°C in 200 µl of reaction mixture containing ATP; 1 mM, Glutathione; 6 mM and 0.2 mM [2-^{14}C] sodium acetate (0.2 µCi) with 4 µl of test compound solution in water or dimethyl sulfoxide (DMSO). 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

was continued. By changing the FBS containing medium to the LpDS containing medium, it has been confirmed that the ability for cholesterol biosynthesis in vivo increases about 1.4 times. After 24 hrs incubation the medium was removed, 0.5 ml of DME medium containing 5% LpDS was added fresh and 10 µl of test compound solution dissolved in water or DMSO was added. 0.2 µCi of [2-^{14}C]sodium acetate 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 three times. Cells were scraped with rubber policeman and collected to tubes. To the resulting cell pellet, 200 µl of 0.5 NKOH was added and the cells were digested by heating them overnight. Aliquot of the digestion was saponified with 15% EtOH-KOH. Nonsaponifiable lipids obtained were extracted with petroleum ether and ^{14}C radioactivity was counted. On the other hand, the amount of the protein was measured by using the remaining of the cell digestion. The ability of cholesterol biosynthesis was indicated with DPM/mg cell protein. Inhibitory activity of compounds was indicated with IC_{50}, which is the concentration for inhibiting radioactivity incorporated in the nonsaponifiable lipids at the level of 50%.

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	IC_{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}

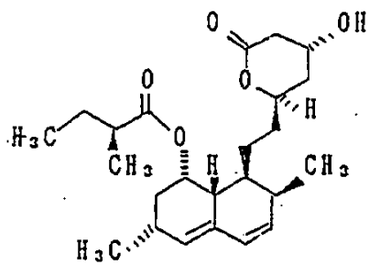
In Table 2-2, the relative activities are shown based on the activities of CS-514 being evaluated to be 1.

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



(2) CS-514

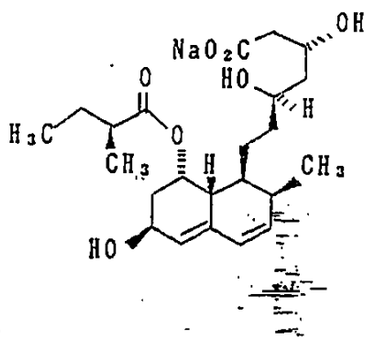


Table 3: Inhibitory activities by Test B-1

Compound	IC_{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.

Acute toxicity test examples

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-q)

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 gradually added into a mixture solution of 45 ml of conc. aqueous ammonia and 120 ml of water cooled with ice. 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 thoroughly 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, J=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 under reduced pressure. 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

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 to 0°C. Then, 10 mg (0.263 mmol) of sodium borohydride was added, and the mixture 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 (in $CDCl_3$) 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 (in $CDCl_3$) 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. (Developing solvent: 3% methanol-chloroform)

These diasteromers were separated and isolated by silica gel thin layer chromatography. [Developing 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 (in $CDCl_3$) 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 (in $CDCl_3$) 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.)

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 $CDCl_3$) 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 $CDCl_3$) 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 $CDCl_3$) 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.)

Tale 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. (°C)
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 $CDCl_3$)　　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 $CDCl_3$)　　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 $CDCl_3$)　　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 $CDC\ell_3$)　　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 $CDC\ell_3$)　　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

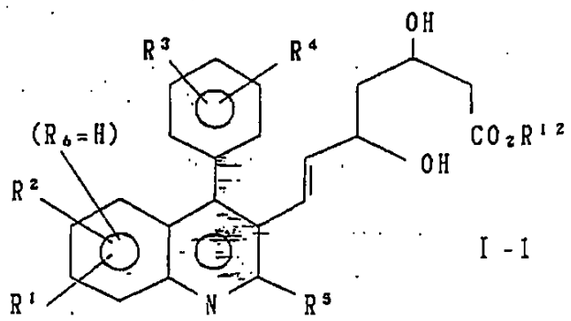
H-NMR(in $CDC\ell_3$)　　δ ppm :

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 $CDCl_3$) 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 $CDCl_3$) 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)

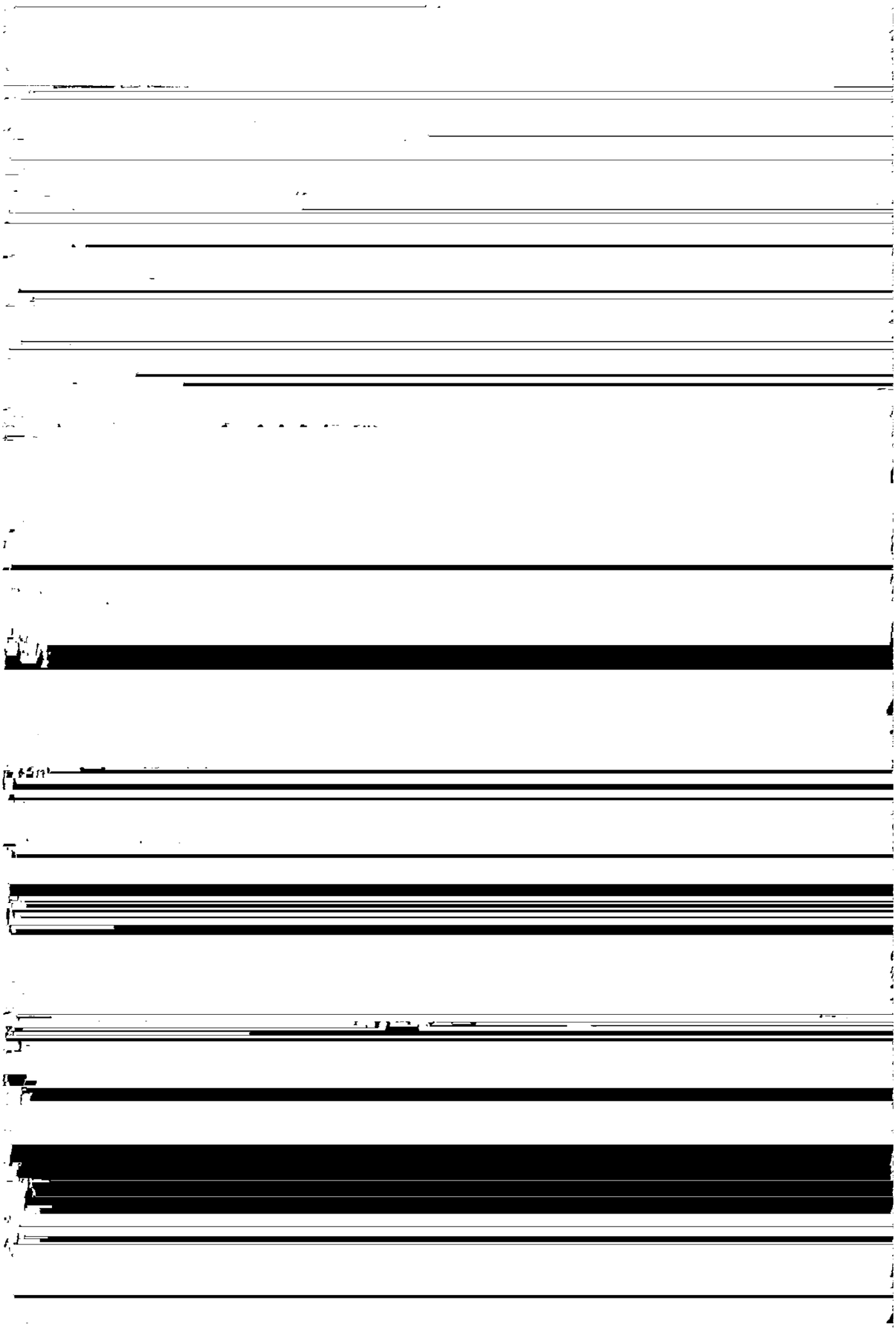
4.3-4.5(m,1H), 5.3-5.5(m,1H)

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

I - 1 1 1

H-NMR (in $CDCl_3$) δ ppm :

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



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 $CDCl_3$) 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 $CDCl_3$) 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 $CDCl_3$) 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 $CDCl_3$) 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 $CDCl_3$) 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=5Hz), 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

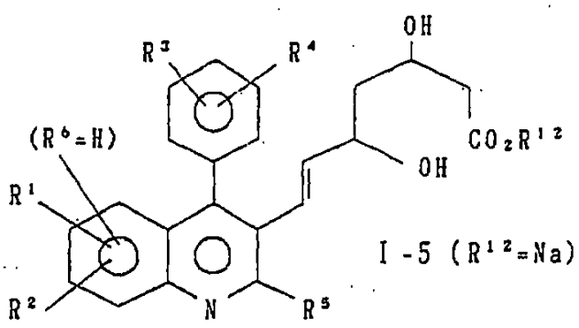
H-NMR (in $CDCl_3$) δ ppm :
1.0-1.6(m,3H), 1.21(t,3H,J=7Hz),
1.34(d,6H,J=6Hz), 2.34(s,3H),
2.37(d,2H,J=7Hz), 2.9-3.7(m,2H),
3.8-4.5(m,2H), 4.15(q,2H,J=7Hz),
5.0-5.5(m,1H), 6.3-6.7(m,1H),
6.9-8.0(m,7H),

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



I-5 (R^{12}=Na)

Compound	R^1	R^2	R^3	R^4	R^5	R^{12}	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-57

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)

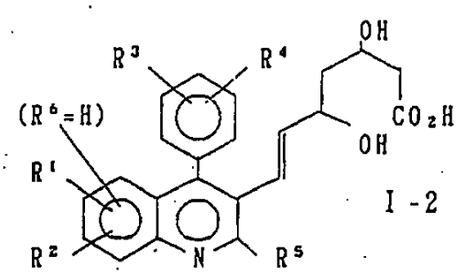
I－527

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

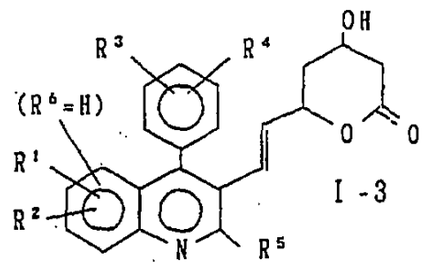


I-2

Compound	R^1	R^2	R^3	R^4	R^5	m.p. (°C) Mass spectrum
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	m.p. (°C)
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.

Applicant for Patent: Nissan Chemical Industries Ltd.

MISSING PAGE(S)

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Declaration For
Translation of JP-207224/1987

PATENT OFFICE
JAPANESE GOVERNMENT

This is to certify that the annexed is a true copy of the following application as filed with this Office.

Date of Application:	August 20, 1987
Application Number:	Patent Application No. 207224/1987
Applicant:	Nissan Chemical Industries Ltd.

October 7, 1988

Fumitake Yoshida
Director-General, Patent Office

International Patent Classification
C07D 215/00

PETITION FOR PATENT APPLICATION

August 20, 1987

To: Director-General, Patent Office: Kunio Ogawa

1. Title of the Invention:

QUINOLINE TYPE MEVALONOLACTONES

2. Inventor(s):

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4. List of Attached Documents:

(1) Specification 1 copy
(2) Duplicate of Petition 1 copy

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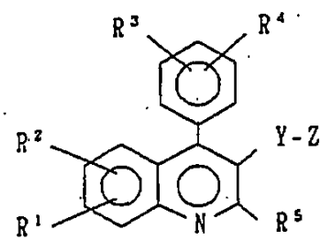
SPECIFICATION

1.TITLE OF THE INVENTION:

QUINOLINE TYPE MEVALONOLACTONES

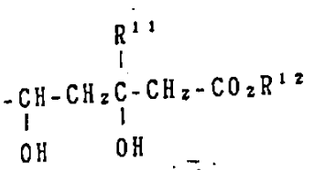
2.SCOPE OF THE CLAIM:

1. A compound of the formula:

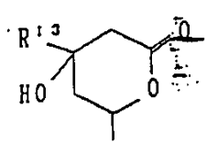


(I)

wherein R^1, R^2, R^3 and R^4 are independently hydrogen, C_{1-4} alkyl, C_{1-3} alkoxy, n-butoxy, i-butoxy, sec-butoxy, trifluoromethyl, fluoro, chloro, bromo, phenyl, phenoxy or benzyloxy; or when located at the ortho position to each other, R^1 and R^2, or R^3 and R^4 together form $-CH=CH-CH=CH-$; Y is $-CH_2-$, $-CH_2CH_2-$, $-CH=CH-$, $-CH_2-CH=CH-$ or $-CH=CH-CH_2-$; and Z is



or



wherein R^{11} is hydrogen or C_{1-3} alkyl, R^{12} is hydrogen, R^{14} (wherein R^{14} is physiologically hydrolyzable alkyl or

M (wherein M is NH_4, a metal capable of forming a salt which is pharmaceutically acceptable, or an amine·H) and R^{13} is hydrogen or C_{1-3} alkyl) and R^5 is hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl-$(CH_2)_m$- (wherein m is 1, 2 or 3).

3. DETAILED DESCRIPTION OF THE INVENTION:

[Industrial Field of Utilization]

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 hypolipoproteinemic and anti-atherosclerotic agents, and intermediates useful for their production and processes for the production of such intermediates.

[Prior Art and its Problem]

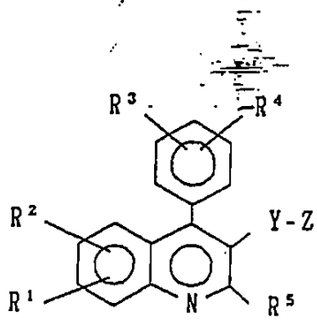
Some fermentation metabolic products such as compactine, CS-514, Mevinolin or semi-synthetic derivatives or fully synthetic derivatives thereof are known to be inhibitors against HMG-CoA reductase which is a rate limiting enzyme for cholesterol biosynthesis. (A. Endo J. Med. Chem., 28(4) 401 (1985))

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 heterocyclic derivatives of inhibitors against HMG-CoA reductase, there has been disclosed limited information.

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 HMG-CoA reductase. The present invention has been accomplished on the basis of this discovery.

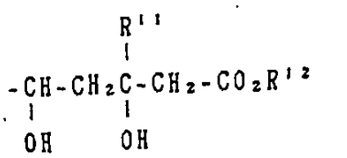
The novel mevalonolactone derivatives of the present invention having high inhibitory activities against HMG-CoA reductase are represented by the following formula I:



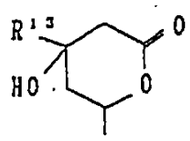
(I)

wherein R^1, R^2, R^3 and R^4 are independently hydrogen, C_{1-4} alkyl, C_{1-3} alkoxy, n-butoxy, i-butoxy, sec-butoxy, trifluoromethyl, fluoro, chloro, bromo, phenyl, phenoxy or benzyloxy, 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-; Y is $-CH_2-$

$-CH_2CH_2-$, $-CH=CH-$, $-CH_2-CH=CH-$ or $-CH=CH-CH_2-$; and Z is



or



wherein R^{11} is hydrogen or C_{1-3} alkyl, R^{12} is hydrogen, R^{14} (wherein R^{14} is physiologically hydrolyzable alkyl) or M (wherein M is NH_4, a metal capable of forming a salt which is pharmaceutically acceptable or an amine.H) and R^{13} is hydrogen or C_{1-3} alkyl; and R^5 is hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl or phenyl-$(CH_2)_m$- (wherein m is 1, 2 or 3).

Various substituents in the formula I will be described in detail with reference to specific examples.

C_{1-4} alkyl for R^1, R^2, R^3 and R^4 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 and R^4 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.

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

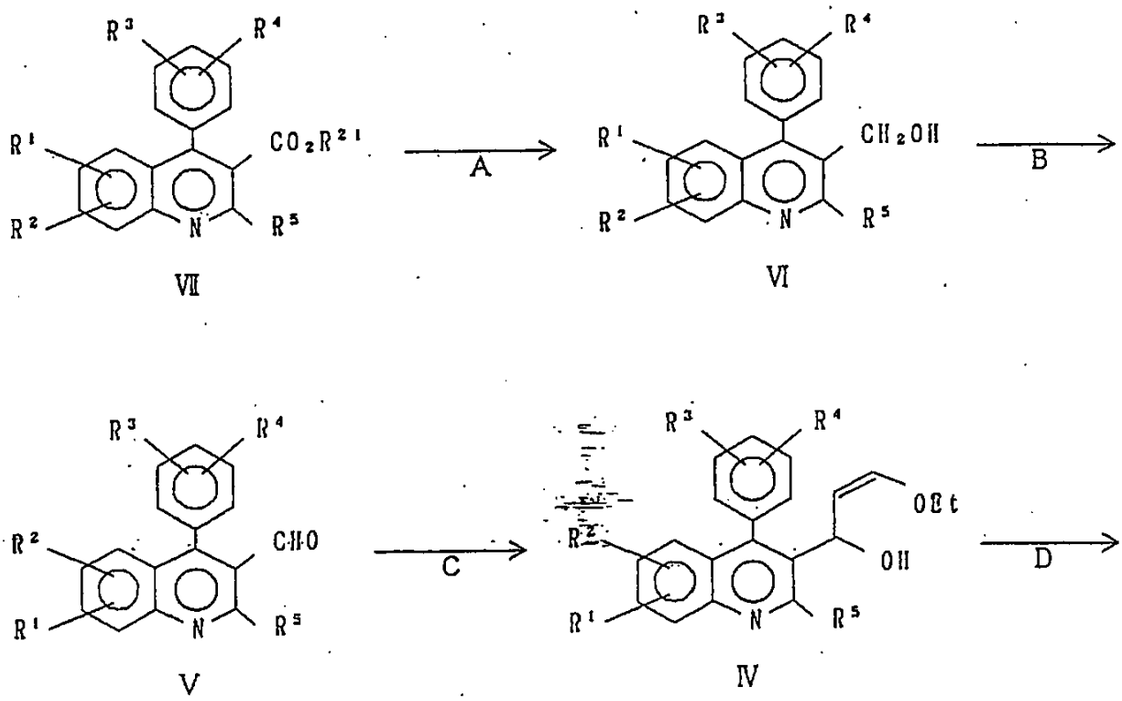
CO_2M includes, for example, $-CO_2NH_4$ and $-CO_2H \cdot$ (primary to tertiary lower alkylamine such as trimethylamine).

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.

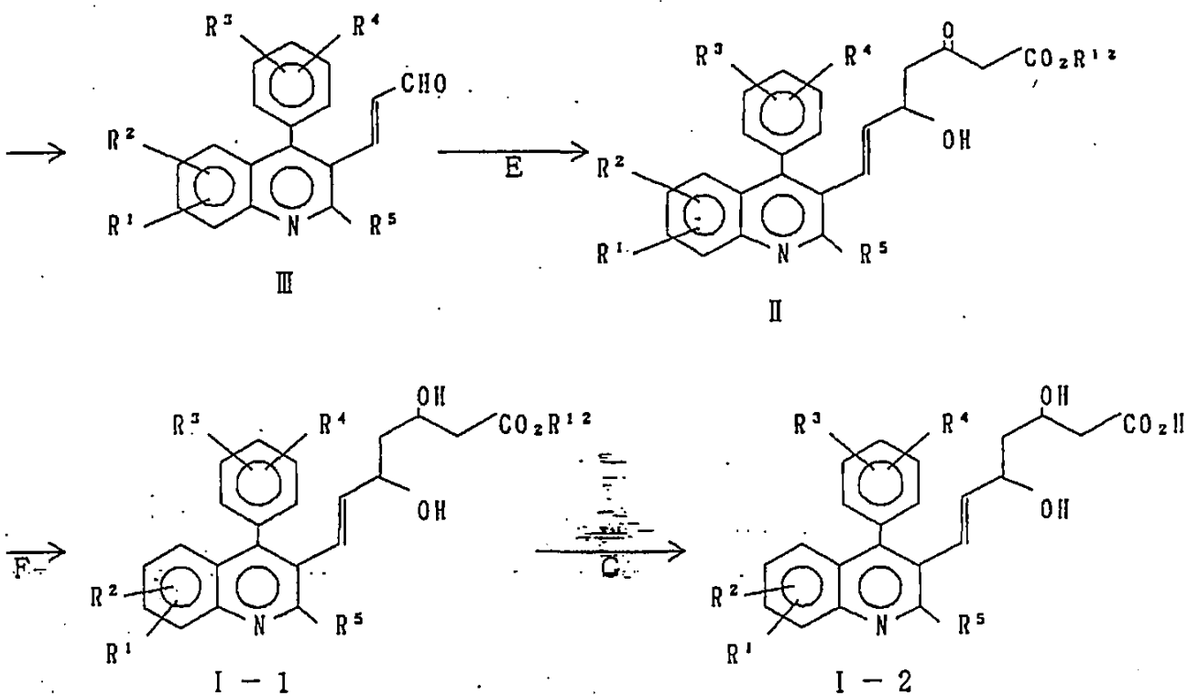
Phenyl-$(CH_2)_m$- for R^5 includes, for example, benzyl, ß-phenylethyl and γ-phenylpropyl.

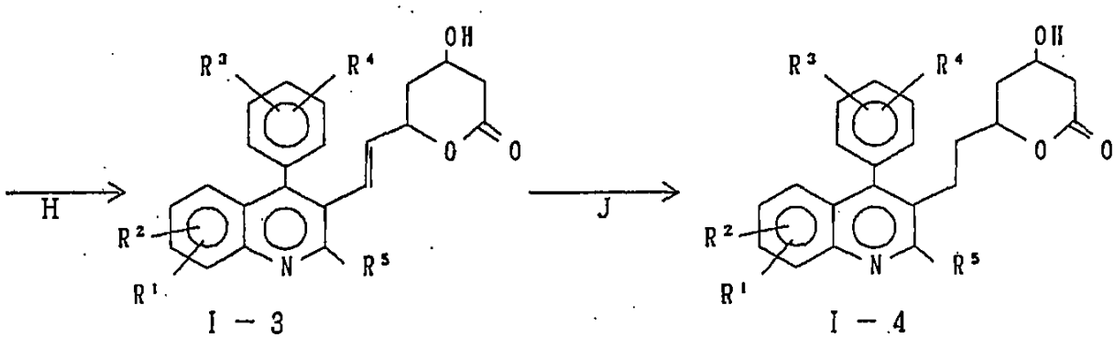
The mevalonolactones of the formula I can be prepared by the following reaction scheme.



VII VI

V IV


R3
R4
CHO
R2
R1
N
R5
Ⅲ
E
O
CO2R12
OH
Ⅱ
F
OH
CO2R12
G
CO2H
I－1
I－2



I − 3　　I − 4

In the above reaction scheme, R^1, R^2, R^3, R^4, R^5 and R^{12} are as defined above with respect to the formula I, and R^{21} represents 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 and dimethyl sulfoxide (Swern oxidation).

Step C represents a synthesis of a hydroxyvinyl ether, 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 hydroxyvinyl ether 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 IV and an acetoacetate. Such condensation reaction is preferably conducted by using sodium hydride and n-butyl lithium as the base in tetrahydrofuran at -78°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.

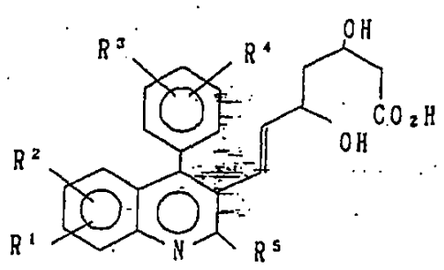
Step G is a step for hydrolyzing the ester. The hydrolysis can be conducted by using an equimolar amount of a base, preferably potassium hydroxide or sodium hydroxide, in a solvent mixture of water and methanol or ethanol at a temperature of from 10 to 25°C. The free acid hereby obtained may be converted 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.

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.

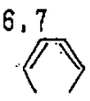
In addition to the compounds disclosed in Examples given hereinafter, compounds of the formulas I-2 given in Table 1 can be prepared by the process of the present invention.

Table 1



(I − 2)

R^1	R^2	R^3	R^4	R^5
7−Me	H	H	H	i−Pr
6−OMe	H	H	H	i−Pr
6−Br	H	4−F	H	i−Pr
6−Cℓ	8−Cℓ	4−F	H	i−Pr
6−Me	8−Me	4−F	H	i−Pr
7−OMe	8−OMe	4−F	H	i−Pr
H	H	4−CH_3	H	i−Pr
H	H	4−Cℓ	H	i−Pr

R^1	R^2	R^3	R^4	R^5
H	H	2－F	H	i－Pr
6－Br	H	2－F	H	i－Pr
6－Cℓ	H	2－Cℓ	H	i－Pr
H	H	4－OMe	H	i－Pr
H	H	3－Me	5－Me	i－Pr
H	H	3－Me	4－F	i－Pr
H	H	4－OPh	H	i－Pr
6,7 		4－F	H	i－Pr
H	H	4－F	H	
H	H	4－F	H	
H	H	4－Ph	H	i－Pr
H	H	4－$PhCH_2$	H	i－Pr
H	H	4－F	H	Et

Further, pharmaceutically acceptable salts such as sodium 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. Thus, the compounds of the present invention are useful as curing agents against hyperlipoproteinemia and atherosclerosis.

These active components 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 binder such as syrup, gum arabic, gelatin, sorbitol, tragacanth gum or

polyvinyl pyrrolidone, an excipient such as lactose, sugar, corn starch, calcium phosphate, sorbitol or glycine, 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.

Further, the compounds of the present invention may be combined with basic anion-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 0.05 to 30 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 VI 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 VI and the processes for their production.

[Examples]

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.

Test A: Inhibition of cholesterol biosynthesis from acetate in vitro

Enzyme solution was prepared from liver of male Wistar rat (weighing from 200 to 250 g) cannulated to the bile-duct and discharged bile for over 24 hours. Liver was cut out at mid-dark and microsome and 105000 xg 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).

By the cannulation to the bile-duct of rats, it has been confirmed that the ability for cholesterol biosynthesis is increased from a few to 10 times. The measurement of the ability for cholesterol biosynthesis was conducted in accordance with a method of Endo, The Metabolism, 16, 1757 (1979). Namely, microsome (0.1 mg protein) and sup fraction (1.0 mg protein) were incubated for 2 hours at 37°C in 200 µl of reaction mixture containing ATP; 1 mM, Glutathione; 6 mM and 0.2 mM [2-^{14}C] sodium acetate (0.2 µCi) with 4 µl of test compound solution

in water or dimethyl sulfoxide (DMSO). 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 IC_{50}, which is the concentration for inhibiting radioactivity incorporated in the nonsaponifiable lipids at the level of 50%.

Test B: Inhibition of cholesterol biosynthesis in culture cells

Human liver cancer cells (Hep G2 cells) at from several to several tens passage were seeded to 6 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 and the incubation was continued. By changing the FBS containing medium to the LpDS containing medium, it has been confirmed that the ability for cholesterol biosynthesis in vivo increases about 1.4 times. After 24 hrs incubation the medium was removed, 0.5 ml of DME medium containing 5% LpDS was added fresh and 1.5 µl of test compound solution dissolved in water or DMSO was added. 0.5 µCi of [2-^{14}C]sodium

acetate 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 three times. Cells were scraped with rubber policeman and collected to tubes. To the resulting cell pellet, 200 µl of 0.5 NKOH was added and the cells were digested by heating them overnight. Aliquot of the digestion was saponified with 15% EtOH-KOH. 3ß-Hydroxysterol was separated from the resulting nonsaponifiable lipids by precipitation method with digitonin in accordance with the method of Sperry el al., J.Biol Chem., 187, 97 (1950).

On the other hand, the amount of the protein was measured by using the remaining of the cell digestion. The ability of cholesterol biosynthesis was indicated with DPM/mg cell protein. Inhibitory activity of compounds was indicated with IC_{50}, which is the concentration for inhibiting radioactivity incorporated in the digitonide at the level of 50%.

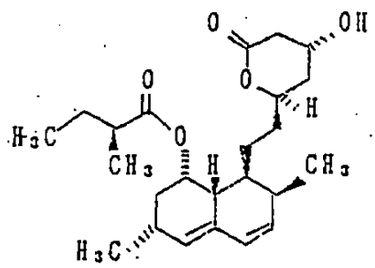
With respect to the compounds of the present invention, the inhibitory activities against HMG-CoA reductase were measured by the above Test A and B. The results are shown in Table 2.

Table 2: Inhibitory activities by Test A

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

Structures of reference compounds:

(1) Mevinolin



(2) CS-514

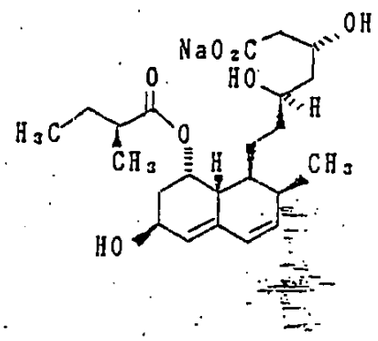


Table 3: Inhibitory activities by Test B-1

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

The compounds of the present invention exhibited activities similar to the reference compound such as CS-514 or Mevinolin in Test A, and exhibited activities superior to CS-514 in Tests B.

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-q)

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 gradually added into a mixture solution of 45 ml of conc. aqueous ammonia and 120 ml of water cooled with ice. 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 thoroughly 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.

NMR δ ppm(in $CDCl_3$)

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

3.7 (m, 1H) 3.7 (q, J=7Hz, 2H)

4.75(t, J=7Hz, 1H) 5.7(m, 1H) 5.95(m, 1H)

7.05~8.2 (m, 8H)

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.

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 under reduced pressure. 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 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 to 0°C. Then, 10 mg (0.263 mmol) of sodium

borohydride was added, and the mixture 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 (in $CDCl_3$) δ ppm:

1.30(t,3H,J=8Hz) 1.39 (d,J=8Hz,6H) 1.4-1.8(m,2H)
2.42(d,J=7Hz,2H) 3.0-3.8 (m,2H) 3.50(m,1H)
3.9-4.6(m,2H) 4.20(q,J=8Hz,2H) 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 (in $CDCl_3$) δ ppm:

1.36(d,J=7Hz,6H) 2.4(m,2H) 3.5(m,1H) 3.45(m,1H)

3.8-4.6(m,2H) 5.40(dd,J_1=19Hz,J_2=8Hz,1H)

6.55 (d,J=19Hz,1H) 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. (Developing solvent: 3% methanol-chloroform)

In the same manner as in Example 1-a, compounds VII-2 to VII-6 were prepared. The physical properties of these compounds are shown in Table 4. (In Table 4, R^1, R^2, R^3, R^4, R^5 and R^{21} correspond to the substituents in compound VII.)

Table 4

Compound	R^1	R^2	R^3	R^4	R^5	R^{21}	m.p. (°C)
VII − 2	H	H	p-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

In the same manner as in Example 1-b, Compounds VI-2 to V-6 were prepared. (In Table 5, R^1, R^2, R^3, R^4 and R^5 correspond to the substituents in Compounds VI and V.)

Table 5

Compound	R^1	R^2	R^3	R^4	R^5	m.p. (°C)
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
V − 6	6-Cℓ	H	H	H	i-Pr	168-169

In the same manner as in Example 1-c, Compounds V-2 to V-6 was prepared. (In Table 6, R^1, R^2, R^3, R^4 and R^5 correspond to the substituents in Compound V.)

Table 6

Compound No.	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

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 in Compound IV.)

Table 7

Compound No.	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-6 were prepared. (In Table 8, R^1, R^2, R^3, R^4 and R^5 correspond to the substituents in Compound III.)

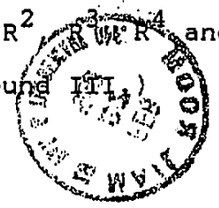


Table 8

Compound No.	R^1	R^2	R^3	R^4	R^5	m.p. (°C)
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

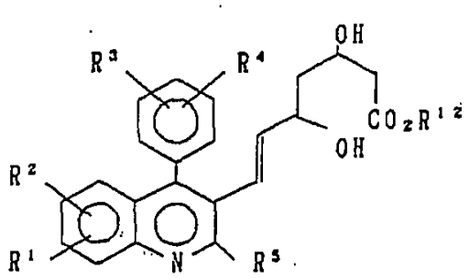
In the same manner as in Example 1-f, Compounds II-2 to II-6 were prepared. (In Table 9, R^1, R^2, R^3, R^4 and R^5 correspond to the substituents in Compound II.)

Table 9

Compound No.	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

In the same manner as in Example 1-g, Compounds I-12 to I-16 were prepared.

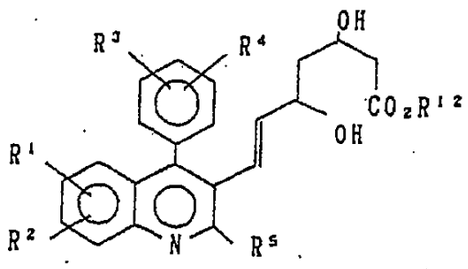
Table 10



Compound No.	R^1	R^2	R^3	R^4	R^5	R^{12}	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

In the same manner as in Example 2, Compounds I-51 to I-55 were prepared.

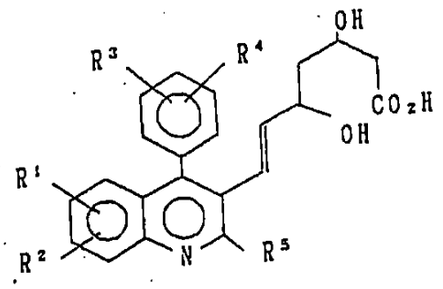
Table 11



Compound No.	R^1	R^2	R^3	R^4	R^5	R^{12}	m. p. (℃)
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)

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

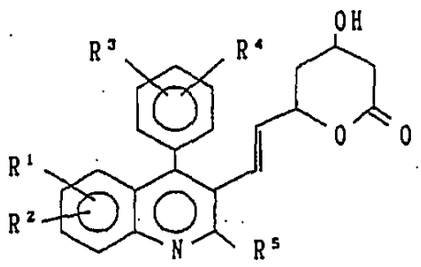
Table 12



Compound No.	R^1	R^2	R^3	R^4	R^5	m.p.(°C) mass spectrum
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



Compound No.	R^1	R^2	R^3	R^4	R^5	m.p. (°C)
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	

Examples of formulations containing the compound of the present invention will be described.

FORMULATION EXAMPLE 1: Tablets

Components (for 100 tablets)

Composition	weight
Compound I-51	1 (g)
Potato starch	20
Carboxymethyl cellulose	2
Polyvinyl alcohol	1.5
Magnesium stearate	0.5
Total	25

The above components were weighed, put into a V-type mixer and mixed uniformly. The mixture powders were formed in tablets by a direct tableting method. The weight per one tablet was 250 mg.

FORMULATION EXAMPLE 2: Soft capsules

Components (for 100 capsules)

Composition	weight
Compound I-51	1 (g)
Olive oil	19
Total	20

The above components were weighed, mixed uniformly, packed in soft capsules each containing 200 mg of the

components, and dried.

FORMULATION EXAMPLE 3: Granules

Components (for 100 packages)

Composition	weight
Compound I-51	1 (g)
Silicic acid anhydride	3
Crystal cellulose powder	9
Lactose	6
Magnesium stearate	1
Total	20

The above components were uniformly mixed, granulated and packaged so that each package contains 200 mg of the components.

FORMULATION EXAMPLE: Suppository

Components (for 100 suppositories)

Composition	weight
Compound I-51	1 (g)
Cacao butter	79
Total	80

The above components were weighed, melt-mixed uniformly at 38°C and poured into suppository containers, which were cooled preliminarily to a slight degree. The weight per one suppository was 0.8 g.

Applicant for Patent: Nissan Chemical Industries Ltd.

United States Court of Appeals for the Federal Circuit

88-1245

IN RE DIANE M. DILLON

James H. Laughlin, Jr., Benoit, Smith & Laughlin, of Arlington, Virginia, argued for appellant. With him on the brief was Gregory F. Wirzbicki, Unocal Corporation, Brea, California, of counsel.

Fred E. McKelvey, Solicitor, Office of the Solicitor, of Arlington, Virginia, argued for appellee. With him on the brief were Richard E. Schafer, Associate Solicitor and Joseph F. Nakamura.

Appealed from: Board of Patent Appeals and Interferences
United States Patent and Trademark Office

United States Court of Appeals for the Federal Circuit

88-1245

IN RE DIANE M. DILLON

DECIDED: December 29, 1989

Before NEWMAN, Circuit Judge, COWEN, Senior Circuit Judge, and ARCHER, Circuit Judge.

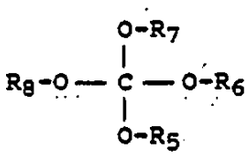
NEWMAN, Circuit Judge.

Diane M. Dillon, assignor to Union Oil Company of California, appeals the decision of the Board of Patent Appeals and Interferences ("Board") of the United States Patent and Trademark Office ("PTO"), November 25, 1987, rejecting claims 2 through 14, 16 through 22, and 24 through 37, all the remaining claims of patent application Serial No. 06/671,570 entitled "Hydrocarbon Fuel Composition". We reverse.

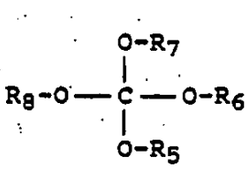
The Invention

Dillon's patent application describes and claims her discovery that the inclusion of certain tetra-orthoester compounds in hydrocarbon fuel compositions will reduce the emission of solid particulates (i.e., soot) during combustion of the fuel. In this appeal Dillon presents claims to hydrocarbon fuel

compositions containing these tetra-orthoesters, and to the method of use of these compositions to reduce particulate emissions during combustion. Claim 2 is the broadest composition claim:

> 2. A composition comprising: a hydrocarbon fuel; and a sufficient amount of at least one orthoester so as to reduce the particulate emissions from the combustion of the hydrocarbon fuel, wherein the orthoester is of the formula:
>
> 
>
> wherein R_5, R_6, R_7 and R_8 are the same or different mono-valent organic radical comprising 1 to about 20 carbon atoms.

The broadest method claim is claim 24:

> 24. A method of reducing the particulate emissions from the combustion of a hydrocarbon fuel comprising combusting a mixture of the hydrocarbon fuel and a sufficient amount of at least one orthoester so as to reduce the particulate emissions, wherein the orthoester is of the formula:
>
> 
>
> wherein R_5, R_6, R_7 and R_8 are the same or different mono-valent organic radical comprising 1 to about 20 carbon atoms.

The other claims are narrower in scope and/or contain additional limitations. In view of our decision, the other claims need not be separately considered.

The tetra-orthoesters are a known class of chemical compounds. It is undisputed that their combination with hydro-

carbon fuel, for any purpose, is not shown in the prior art, and that their use to reduce particulate emissions from combustion of hydrocarbon fuel is not shown or suggested in the prior art.

The Rejection

The Board held all of the claims to be unpatentable on the ground of obviousness, 35 U.S.C. § 103, in view of certain primary and secondary references. As primary references the Board relied on two Sweeney United States Patents, Nos. 4,390,417 and 4,395,267. Sweeney '417 describes hydrocarbon fuel compositions containing specified chemical compounds, i.e., ketals, acetals, and tri-orthoesters,[1/] used for "dewatering" the fuels. Sweeney '267 describes three-component compositions of hydrocarbon fuels heavier than gasoline, immiscible alcohols, and tri-orthoesters, wherein the tri-orthoesters serve as co-solvents to prevent phase separation between fuel and alcohol. The Board explicitly found: "The Sweeney patents do not teach the use of the orthoesters recited in appellant's claims."

The Board cited Elliott et al. United States Patent No. 3,903,006 (and certain other patents, not here significant) as secondary references. Elliott describes tri-orthoesters and tetra-orthoesters for use as water scavengers in hydraulic

1/ Tri-orthoesters have three orthoester (-OR) groups bonded to a central carbon atom, and the fourth carbon bond is to hydrogen or a hydrocarbon radical (-R); they are represented as $C(R)(OR)_3$. Tetra-orthoesters have four -OR groups bonded to a central carbon atom, and are represented as $C(OR)_4$; see Dillon's claims, supra.

(non-hydrocarbon) fluids. The Board stated that the Elliott reference shows equivalence between tetra-orthoesters and tri-orthoesters, and that "it is clear from the combined teachings of these references that [Dillon's tetra-orthoesters] would operate to remove water from non-aqueous liquids by the same mechanism as the orthoesters of Sweeney".

The Board stated that there was a "reasonable expectation" that the tri- and tetra-orthoesters would have similar properties, based on "close structural and chemical similarity" and the fact that both the prior art and Dillon use these compounds as "fuel additives". The Board stated that since the tetra-orthoesters were known to serve as water scavengers in hydraulic fluids, "there is a reasonable expectation that the prior art compositions will have properties similar to the claim compositions"; that is, that the tri-orthoesters would be expected to reduce particulate emissions. Although no reference was cited as suggesting the use of any orthoester to reduce particulate emissions,[2/] or to show a relationship between the property of water scavenging and the property of reducing particulate emissions from combustion, the Board concluded, and the Solicitor argues on appeal, that the claimed composition and method "would have been prima facie obvious from

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2/ Although it was not cited or relied on by the Board, the Solicitor cites Moy et al. U.S. Patent No. 3,817,720, for its showing as "smoke-suppressant" in fuels, the combination of a hydroquinone ether, isopropyl alcohol, and diacetone alcohol. The Solicitor cites Moy only to show that particulate emission was a problem known to the art, as Dillon had stated in her specification.

the combined teachings of the references." On this reasoning, the Board held that unless Dillon showed some unexpected advantage or superiority of her claimed tetra-orthoester fuel compositions as compared with tri-orthoester fuel compositions, Dillon's new compositions as well as their new use to reduce particulate emissions were unpatentable for obviousness.

The Board then analyzed Dillon's specification, wherein Dillon had disclosed that both tri- and tetra-orthoesters are effective in reducing particulate emissions from combustion of hydrocarbon fuels, and presented data to illustrate this property. The Board held that because these data do not show the unexpected particulate-reduction superiority of the tetra-orthoester compositions as compared with the tri-orthoester compositions, Dillon had not overcome the prima facie case of obviousness.

The Solicitor maintains that it is not of controlling weight, or even pertinent, that there is no prior art suggesting Dillon's use of reducing particulate emissions, for any compositions similar to those claimed by Dillon. The Solicitor maintains that the existence of the tri-orthoester compositions of Sweeney, which are taught to have an entirely unrelated property and use, suffice to make a prima facie case of obviousness as to Dillon's method as well as her composition claims.

The Issue

The issue is the patentability in terms of 35 U.S.C. § 103 of claims to Dillon's new composition and claims to its new method of use, when the components of the new composition are

deemed to be structurally similar to components of known compositions, but the new use discovered by Dillon for her new composition is neither taught nor suggested in the prior art. The threshold question is whether, under such circumstances, a prima facie case of unpatentability for obviousness is deemed made.[3/]

I

The Composition Claims

The facts as to the prior art are not in dispute; only the conclusions drawn therefrom are at issue. Sweeney shows compositions of tri-orthoesters in hydrocarbon fuels for the purpose of scavenging water in the fuels; Elliott shows that both tri- and tetra-orthoesters have the property of scavenging water in hydraulic liquids. No reference shows compositions of tetra-orthoesters in hydrocarbon fuels for any purpose, and no reference shows any orthoester fuel composition having the property and utility of reducing particulate emissions from combustion of fuels.

The Board held that a prima facie case of obviousness was made despite the fact that Dillon's compositions were new, and despite the absence of any suggestion in the prior art that these compositions would have the property and use discovered by Dillon. In view of this retrenchment by the Board from the weight of precedent, we have undertaken to review the history of this jurisprudence.

3/ Dillon's position is that evidence of unexpected results was not required in this case. Thus the Board's decision was based on Dillon's specification and the prior art, prima facie.

A

The variety of factual situations that have arisen, in the Court of Customs and Patent Appeals, the Court of Claims, and in the Federal Circuit, has produced a rich body of precedent, as the courts sought to identify unifying criteria and apply consistent reasoning to determinations of the question of obviousness of composition and compound claims. Procedural as well as substantive rules were established, to facilitate the uniform application of 35 U.S.C. § 103 despite great diversity in technological facts and in the relationship of the prior art to the inventions at issue.

Thus, as the first step in the examination process, the PTO determines whether a prima facie case of obviousness is deemed made, based on the specification, the prior art, and any other evidence before the examiner. If a prima facie case is made, the applicant may adduce evidence and present argument in rebuttal, following which the determination of obviousness is made on all the evidence. If a prima facie case is not made, no rebuttal is necessary. See the discussion in In re Piasecki, 745 F.2d 1468, 223 USPQ 785 (Fed. Cir. 1984); In re Rinehart, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976); and cases cited therein.

As we will discuss, some early CCPA cases held that a prima facie case of obviousness could be made based solely on similarity of structure, independent of properties and use; but by the 1960's, and thereafter, the weight of CCPA and Federal Circuit authority is that the chemical structure and the properties or

utility must all be considered in determining whether a prima facie case of obviousness has been made. The early status was explained in In re Lunsford, 357 F.2d 380, 382 n.2, 148 USPQ 716, 718 n.2 (CCPA 1966):

> Just how one finds the compounds "obvious" in the first instance, the examiner does not say, but apparently he envisions a comparison of structures only. That such an approach is not sanctioned by this court, although concededly the law was less well-defined in June 1961, the date of the Examiner's Answer, can be seen, e.g., in In re Kraznski, 347 F.2d 656, 146 USPQ 25; In re Ruschig, 343 F.2d 965, 145 USPQ 274; In re Ward, 329 F.2d 1021, 141 USPQ 227; In re Lunsford, 327 F.2d 526, 140 USPQ 425; In re Riden, Jr., 318 F.2d 761, 138 USPQ 112; In re Papesch, 315 F.2d 381, 137 USPQ 43; In re Petering, 301 F.2d 676, 133 USPQ 275; In re Lamboov, 300 F.2d 950, 133 USPQ 270. [Emphasis in original.]

It behooves the PTO, in the first step of patent examination, to ascertain the similarities and differences in structure and properties or utility, and any other pertinent evidence before the examiner, to determine whether in any particular case a prima facie case of obviousness is made. See Piasecki, 745 F.2d at 1472, 223 USPQ at 788 (prima facie obviousness is but a legal inference drawn from uncontradicted evidence).

B

In determining whether an invention would have been obvious under section 103, based either on the application as filed (i.e., prima facie) or with additional evidence if such is adduced, the statute is applied in view of the record and the prior art. As illustrated in precedent, appropriate weight is given to considerations such as the closeness to the field of

the invention of the arts from which the cited references are drawn, the motivation or suggestion in the prior art to combine the cited references, the problem confronting the inventor, the nature of the improvement as compared with the prior art, and a variety of other criteria, all as may arise in any particular case. No single case may involve all these issues, but when present, they can not be ignored.

The Commissioner's position in this case is that it is immaterial, in determining whether a prima facie case of obviousness has been made as to Dillon's composition claims, that no reference shows any relationship between use as a dewatering agent and use to reduce soot formation during combustion. Thus the Commissioner would hold Dillon's invention unpatentable because Dillon did not prove that her tetra-orthoester fuel compositions were superior in soot-reduction to the tri-orthoesters, although there is no suggestion in the prior art that either compound would have any soot-reducing properties at all. That idea comes solely from Dillon's specification, wherein she disclosed that both tri- and tetra-orthoesters are useful to reduce soot-formation from combustion of hydrocarbon fuels.

There is extensive precedent on these points. We review this precedent in light of the Board's decision and the Commissioner's arguments.

In determining whether a prima facie case of obviousness is made by the teachings of the prior art, the weight of precedent of the Federal Circuit and our predecessor courts requires that consideration be given to the properties and utility, as well

as the structure, of a claimed new chemical compound or composition.[4/] This precedent simply implements the requirement of section 103 that the invention be viewed as a whole, and of section 101 that the invention be "new and useful".

This requirement has been consistently upheld in the precedent of this court. For example, in Lunsford the examiner had taken the position that:

> The argument that the 'subject matter as a whole' under 35 U.S.C. § 103 includes the compound and its utility is considered to be without merit.

357 F.2d at 391, 148 USPQ at 725. The CCPA responded:

> [I]t is reasonably clear that the examiner considered only the difference in structures between the claimed compounds and the prior art compounds.
>
> Appellant was entitled to have differences between the claimed invention, the subject matter as a whole, and the prior art references of record evaluated. [Emphases in original.]

Id. (citing In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)). See also Lindemann Maschinenfabrik GmbH v. American Hoist and Derrick Co., 730 F.2d 1452, 1462, 221 USPQ 481, 488 (Fed. Cir. 1984) (it is error to focus inquiry "'solely on the product created, rather than on the obviousness or nonobviousness of its creation'") (quoting General Motors Corp. v. United

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4/ Although Dillon's invention is a new composition, the Board as well as the Solicitor have cited cases dealing with new compounds and new compositions, and also new mechanical devices. For completeness we will discuss these classes of subject matter, although the cases are not entirely interchangeable: for example, few machines have no statutory utility or are directed to the solution of no problem, in contrast to chemical compounds which may be of solely scientific interest.

States Int'l Trade Comm'n, 687 F.2d 476, 482-83, 215 USPQ 484, 489 (CCPA 1982), cert. denied, 459 U.S. 1105 (1983)).

The Board required Dillon to show not only that her discovered utility was unobvious in light of what was taught or suggested in the prior art, but also that her new tetra-orthoester compositions possessed differences or advantages that were not possessed by the prior art compositions, irrespective of whether the prior art itself would lead one to expect that the prior art compositions would have the properties and use discovered by Dillon. That is, the Board required Dillon to show, by comparative experimental data, that the tri-orthoester fuel compositions did not have the property of reducing particulates in combustion -- although the prior art itself is silent as to this property or any suggestion thereof, for either tri- or tetra-orthoester compositions.

Review of precedent shows that while specific factual situations may have justified requiring this type of showing, as discussed infra, in general the CCPA and the Federal Circuit have declined to establish such a requirement as a general basis for patentability of new compounds and compositions. The weight of precedent is to the effect that when the claimed subject matter is a new chemical compound or composition, a prima facie case of obviousness is not deemed made unless both (1) the new compound or composition is structurally similar to the reference compound or composition and (2) there is some suggestion or expectation in the prior art that the new compound or composi-

tion will have the same or a similar utility as that discovered by the applicant. In re Grabiak, 769 F.2d 729, 731, 226 USPQ 870, 871 (Fed. Cir. 1985):

> When chemical compounds have "very close" structural similarities and similar utilities, without more a prima facie case may be made.

In re Rosselet, 347 F.2d 847, 850, 146 USPQ 183, 185 (CCPA 1965):

> [W]e think appellants have failed to present adequate evidence to overcome a prima facie showing of obviousness by reason of the admitted "gross structural similarities" of the art compounds, coupled with the fact that those compounds are shown to have utility in the same area of pharmacological activity. [Emphasis in original.]

The question of whether a prima facie case of obviousness has been made by the prior art turns on the specific technological similarities and differences, as to both structure and properties or utility, between the claimed compounds or compositions and those taught in the prior art. See, e.g., In re Chupp, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987) (new compound useful as herbicide was prima facie obvious from structurally similar prior art compounds useful as herbicides); Grabiak, 769 F.2d at 731-32, 226 USPQ at 871-72 (although similar utility was disclosed for prior art compounds and claimed compounds, structural similarity was insufficient to make prima facie case); In re Payne, 606 F.2d 303, 314, 203 USPQ 245, 254-55 (CCPA 1979) (new compounds useful as pesticides were prima facie obvious from structurally similar prior art compounds known as pesticides).

This precedent has evolved on analysis of a diversity of factual situations. One way that the courts have explained their reasoning is by pointing out that there must be a suggestion in the prior art that would have led a person of ordinary skill to the same solution of the problem facing the applicant: the prior art must provide a motivation whereby one of ordinary skill would be led to do that which the applicant has done. Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983):

> The scope of the prior art has been defined as that "reasonably pertinent to the particular problem with which the inventor was involved."

(quoting In re Wood, 599 F.2d 1032, 1036, 202 USPQ 171, 174 (CCPA 1979)). Payne, 606 F.2d at 314, 203 USPQ at 255:

> When prior art compounds essentially "bracketing" the claimed compounds in structural similarity are all known as pesticides, one of ordinary skill in the art would clearly be motivated to make those same compounds in searching for new pesticides.

In re Swan Wood, 582 F.2d 638, 641, 199 USPQ 137, 139 (CCPA 1978):

> In view of the close structural similarity [and disclosed] antimicrobial activity, we believe that one skilled in the art would have been, prima facie, motivated to make the claimed compounds in the expectation that they, too, would possess antimicrobial activity.

These are simply other ways of explaining that the decision-maker must consider the problem confronting the applicant in order to ascertain how a person of ordinary skill would view the problem and its solution. In re Gyurik, 596 F.2d 1012, 1018, 201 USPQ 552, 557 (CCPA 1979):

> An element in determining obviousness of a new chemical compound is the motivation of one having ordinary skill in the art to make it. That motivation is not abstract, but practical, and is always related to the properties or uses one skilled in the art would expect the compound to have, if made.

In re Cable, 347 F.2d 872, 874, 146 USPQ 175, 177 (CCPA 1965):

> Patentability of appellant's invention under 35 U.S.C. § 103 must be evaluated against the background of the highly developed and specific art to which it relates and this background includes an understanding of those unsolved problems persisting in the art which appellant asserts have been solved by his invention. See Eibel Process Co. v. Minnesota & Ontario Paper Co., 261 U.S. 45, 43 S. Ct. 322, 67 L. Ed. 523 (1923).

Although the Solicitor appears unenthusiastic about this criterion,[5/] it is well established, and has been expressed in various ways. E.g., In re Deminski, 796 F.2d 436, 443, 230 USPQ 313, 316 (Fed. Cir. 1986):

> [The prior art] does not address Deminski's problem of how to remove a large and heavy assembly as a unit. . . . There was no suggestion in the prior art to provide Deminski with the motivation to design the valve assembly [for this reason]. [Emphasis in original.]

Fromson v. Advance Offset Plate, Inc., 755 F.2d 1549, 1556, 225 USPQ 26, 31 (Fed. Cir. 1985):

> The critical inquiry is whether "there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination." [Emphasis in original.]

5/ The Solicitor asked the court to review its holding in In re Wright, 848 F.2d 1216, 6 USPQ2d 1959 (Fed. Cir. 1988), wherein the court stated that it is appropriate to consider the problem facing the inventor in adjudging whether a novel structure would have been obvious in terms of 35 U.S.C. § 103. Wright is discussed post.

(quoting Lindemann Maschinenfabrik GmbH, 730 F.2d at 1462, 221 USPQ at 488); In re Lalu, 747 F.2d 703, 707, 223 USPQ 1257, 1260 (Fed. Cir. 1984) (obviousness analysis requires inquiry as to whether the known uses of the prior art compounds as intermediates provide adequate motivation to one of ordinary skill to investigate these compounds "with an expectation of arriving at" appellants' compounds for the uses described by appellants); In re Fine, 837 F.2d 1071, 1075-76, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) (although the applicant's temperature range overlaps the range shown in a reference, the applicant's purpose in using the claimed temperature range was not taught or appreciated in the prior art); In re Geiger, 815 F.2d 686, 688, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987) (although the prior art disclosed the components of the claimed composition for different uses, prima facie case not established "absent some teaching, suggestion or incentive supporting the combination"); In re Donovan, 509 F.2d 554, 562, 184 USPQ 414, 421 (CCPA 1975):

> That [the prior art] might incorporate elements which could be used in appellants' system does not render appellants' claims obvious when there is no suggestion of using these elements in substantially the same manner as appellants use them.

In re Ratti, 270 F.2d 810, 813, 123 USPQ 349, 352 (CCPA 1959) (the prior art did not teach "how to solve the problems" faced by the inventor); In re Hortman, 264 F.2d 911, 913, 121 USPQ 218, 219 (CCPA 1959):

> For, though the structure may be a simple expedient when the novel concept is realized, that structure may not be obvious to the skilled

> worker in the art where the prior art has failed to suggest the problem or conceive of the idea for its elimination.

These are not abstract criteria. They have often been applied to determinations of the question of unobviousness in the common situation illustrated herein, where Dillon's claimed subject matter is a new composition based on a chemical compound that is different from, but similar in structure to, a known compound, but the invention is based on a property or use not known or obvious from the prior art. Consideration of the problem facing the inventor is an element of perceptive analysis of whether the invention as a whole would have been obvious to a person of ordinary skill. It is not a new parameter in obviousness determinations.

The problem facing the inventor is directly related to the utility of the invention. Particularly in cases where the structures are closely related, the obviousness analysis is aided by consideration of the problem facing the inventor and the improvement he is seeking. See, for example, In re Benno, 768 F.2d 1340, 1346, 226 USPQ 683, 687 (Fed. Cir. 1985), wherein this court observed that "[n]o reason is suggested why anyone would be led to 'modify'" the prior art in the way done by the inventor to solve his problem. The court stated:

> Neither reference has a word to say about the instability . . . under . . . tension . . . [the problem faced by the inventor]. This is not a situation calling for comparative tests, or a showing of "unexpected results," to which the Solicitor has referred. There is no prima facie obviousness to be overcome and hence no need for that type of evidence.

Id. at 1347, 226 USPQ at 688. See also, e.g., Ryco, Inc. v. Ag-Bag Corp., 857 F.2d 1418, 1424, 8 USPQ2d 1323, 1328 (Fed. Cir. 1988):

> Beater Bars as such were certainly old in the agricultural art, having been used on agricultural machines such as manure spreaders and balers. . . . Ryco has shown nothing in the prior art, however, which would suggest the use of the beater bar as a feeder in a bagging machine as in claim 15.

Diversitech Corp. v. Century Steps, Inc., 850 F.2d 675, 679, 7 USPQ2d 1315, 1318 (Fed. Cir. 1988):

> The problem confronted by the inventor must be considered in determining whether it would have been obvious to combine references in order to solve that problem.

Lindemann Maschinenfabrik GmbH, 730 F.2d at 1462, 221 USPQ at 488:

> Nothing in the references alone or together suggests the claimed invention as a solution to the problem of crushing rigidly massive scrap.

Union Carbide Corp. v. American Can Co., 724 F.2d 1567, 1572, 220 USPQ 584, 588 (Fed. Cir. 1984):

> Appellant does not dispute that a basis for determining whether art is analogous under the standards of the Court of Customs and Patent Appeals is to look at whether it deals with a problem similar to that being addressed by the inventor.

Orthopedic Equipment Co. v. United States, 702 F.2d 1005, 1009, 217 USPQ 193, 196 (Fed. Cir. 1983) (five judge panel):

> In determining the relevant art of the claims in suit one looks to the nature of the problem confronting the inventor.

Weather Engineering Corp. of America v. United States, 614 F.2d 281, 287, 204 USPQ 41, 46-47 (Ct. Cl. 1980):

> The near unanimous approach by the courts is that "[t]he prior art that is relevant in evaluating a claim of obviousness is defined by the nature of the problem confronting the would-be-inventor."

(quoting Louis A. Grant, Inc. v. Keibler Indus., Inc., 541 F.2d 284, 191 USPQ 424, 426 (7th Cir. 1976)); In re Rinehart, 531 F.2d at 1054, 189 USPQ at 149 (the problem facing the inventor was not alluded to in the references, nor was there any suggestion to combine features of each reference); In re Sponnoble, 405 F.2d 578, 585, 160 USPQ 237, 243 (CCPA 1969) ("discovery of the source of a problem" is part of the "subject matter as a whole" to be considered in determining obviousness); In re Pye, 355 F.2d 641, 645, 148 USPQ 426, 429 (CCPA 1966):

> Neither reference is directed to the problem solved by the appellant's invention, namely, developing a cleaning composition for the skin having improved lubricity characteristics. In our view, only appellant's specification suggests any reason for combining the teachings of the prior art but use of such suggestion is, of course, improper under the mandate of 35 U.S.C. 103.

In re Cable, 347 F.2d 872, 879, 146 USPQ 175, 181 (CCPA 1965):

> We have been unable to find in any reference of record a recognition of the fracture and cracking problem solved by applicant, or a solution therefor, or a suggestion of the many additional new results flowing from the appellant's invention.

In re Shaffer, 229 F.2d 476, 480, 108 USPQ 326, 329 (CCPA 1956) (references which never recognized applicant's problem would not have suggested its solution). Shaffer was discussed in In re Martin, 372 F.2d 556, 152 USPQ 610, (CCPA 1967), decided the same day as In re Gershon, 372 F.2d 535, 152 USPQ 602 (CCPA

1967), on which the dissent relies. In Martin the court stated:

> We think apposite here the statement of this court in In re Shaffer, 229 F.2d 476, 480, 43 CCPA 758, 762:
> * * * a person having the references before him who was not cognizant of appellant's disclosure would not be informed that the problems solved by appellant ever existed. Therefore, can it be said that these references which never recognized appellant's problem would have suggested its solution? We think not, and therefore feel that the references were improperly combined since there is no suggestion in either of the references that they can be combined to produce appellant's result.

Martin, 372 F.2d at 562, 152 USPQ at 615. Shaffer was also quoted and followed in In re Skoll, 523 F.2d 1392, 1396, 187 USPQ 481, 484 (CCPA 1975), as was Gershon, showing that the CCPA saw no inconsistency between Shaffer and Gershon.

Indeed, 35 U.S.C. § 103 requires recognition of the context in which the invention was made. Comparison between the prior art and the subject matter as a whole can not be achieved if the desired utility, the problem for which a solution was sought, is excised from the analysis. In re Graf, 343 F.2d 774, 777, 145 USPQ 197, 199 (CCPA 1965):

> While a selection of certain facts in this case tend to a conclusion of nonobviousness and others taken alone may show obviousness, the conclusion required under section 103 must be grounded on a weighing of all the facts. . . . While merely for the purpose of obtaining uniformity of dyeing, the process may appear to be non-obvious, such a view does not accord weight to all the facts. Obviousness is not to be determined on the basis of purpose alone. [Emphasis in original.]

In re Rothermel, 276 F.2d 393, 397, 125 USPQ 328, 332 (CCPA 1960):

> Where the invention for which a patent is sought solves a problem which persisted in the art, we must look to the problem as well as to its solution if we are to properly appraise what was done and to evaluate it against what would be obvious to one having the ordinary skills of the art.

The vast precedent, well exceeding our sampling, contradicts the Solicitor's position that prima facie obviousness must be determined "regardless of the properties disclosed in the inventor's application." Indeed, the cases relied on by the Solicitor (and by the dissent hereto), as we shall discuss, do not support this position; they do, however, illustrate the evolution of the law, the fact-dependency of obviousness determinations, and the need to exercise judgment.

In In re Stemniski, 444 F.2d 581, 584-85, 170 USPQ 343, 346-47 (CCPA 1971), for example, the court focused on prior art compounds of closely related structure to the claimed compounds, where no significant properties or utility were disclosed for the prior art compounds, other than as intermediates. The court explained that the prior art provided no motivation to make the claimed compounds for applicant's purpose, although "one of ordinary skill would suppose the properties or potential uses of the two groups of compounds would be similar." Id. at 585, 170 USPQ at 347. The court in Stemniski observed that In re Henze, 181 F.2d 196, 85 USPQ 261 (CCPA 1950), and In re Riden, 318 F.2d 761, 138 USPQ 112 (CCPA 1963), held that structure alone could support a presumption of obviousness, and stated that:

> To the extent that Henze and Riden are inconsistent with the views expressed herein, they no longer will be followed, and are overruled.

Id. at 587, 170 USPQ at 348. Henze had already been limited to adjacent homologs of known compounds, i.e., compounds differing by one methylene (CH_2) group, by the courts in In re Mills, 281 F.2d 218, 126 USPQ 513 (CCPA 1960) and In re Elpern, 326 F.2d 762, 140 USPQ 224 (CCPA 1964). See Stemniski, 444 F.2d at 584 n.9, 170 USPQ at 346 n.9. As the CCPA stated in Mills, 281 F.2d at 224, 126 USPQ at 518:

> Homology per se should, therefore, be treated as a chemist would treat it, being nothing more than a fact which must be considered with all other relevant facts before arriving at the conclusion of "obviousness" specified in 35 U.S.C. § 103.

See also In re Shetty, 566 F.2d 81, 86, 195 USPQ 753, 756 (CCPA 1977) (adjacent homolog held "structurally similar" to prior art compound, requiring evidence of actual difference of properties as to compound claim, but not for method claims), and In re Ruschig, 343 F.2d 965, 977, 145 USPQ 274, 285 (CCPA 1965), wherein the court said:

> What is important is the fact that the utility discovered by the appellants is not disclosed in the prior art. [Emphasis in original.][6/]

6/ The dissent lists a number of cases cited by the majority, and implies that these cases are somehow inapt. The cases selected by the dissent cover several different section 103 considerations, and simply illustrate various applications of the law, as follows: In re Fine, 837 F.2d 1071, 1075-76, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) (although the temperature ranges of the prior art and the invention overlap, "the purposes of the two temperature ranges are entirely unrelated") (emphasis added); In re Grabiak, 769 F.2d 729, 732, 226 USPQ 870, 872 (Fed. Cir. 1985) (although similar utility was disclosed for the compounds of the prior art, no suggestion to combine references and no prima facie case was made) (emphasis

[Footnote continued]

The court in In re Albrecht, 514 F.2d 1389, 185 USPQ 585 (CCPA 1975) answered a question indistinguishable from that posed today by the Commissioner, stating:

> We are of the opinion that a novel chemical compound can be nonobvious to one having ordinary skill in the art notwithstanding that it may possess a known property in common with a known structurally similar compound. [Emphasis in original.]

Id. at 1395-96, 185 USPQ at 590. The Albrecht court emphasized

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6/ [Footnote continued]

added); In re Lalu, 747 F.2d 703, 707, 223 USPQ 1257, 1260 (Fed. Cir. 1984) (no prima facie case because use of the prior art compounds as intermediates is "not motivation sufficient to support the structural obviousness rejection") (emphasis added); In re Naber, 494 F.2d 1405, 1407, 181 USPQ 639, 641 (CCPA 1974) ("no evidence that those skilled in the art were aware of the problem . . . which is the primary objective of appellants' invention") (emphasis added); In re Stemniski, 444 F.2d 581, 586, 170 USPQ 343, 347 (CCPA 1971) ("of what significance is [a reasonable expectation of] similarities in significant properties or uses, if in fact no one prior to appellant's entry into the field knew what any of those properties or uses are?"); In re Ruschig, 343 F.2d 965, 977, 145 USPQ 274, 285 (CCPA 1965) ("the vague 'basket' disclosure of possible uses in the [prior art] are unimportant. What is important is the fact that the utility discovered by the appellants is not disclosed in the prior art.") (emphasis in original); In re De Lajarte, 337 F.2d 870, 875, 143 USPQ 256, 259 (CCPA 1964) ("If one were making a colorless glass free of carbon and sulfur, there would be little reason for using the [prior art] formula since it was primarily designed to enhance color stability") (emphasis added); In re Elpern, 326 F.2d 762, 767, 140 USPQ 224, 228 (CCPA 1964) (differences in the structural formulae between the compounds of the references and the claims "are sufficient to make appellant's compounds unobvious") (emphasis added); In re Mills, 281 F.2d 218, 221, 126 USPQ 513, 516-17 (CCPA 1960) (utility for the compounds of the prior art and the claims was identical, but there was no "legal presumption" of obviousness for a compound of a homologous series from a disclosure in the prior art of a non-adjacent member of the series) (emphasis added).

The dissent's position appears to be that precedent requires return to the overruled holdings of Henze and Riden.

the need to

> compar[e] the old and new compounds as wholes, inclusive of their properties.

Id. at 1394, 185 USPQ at 589, citing Papesch, supra, (a compound and its properties are inseparable).

The Albrecht court pointed out that the Solicitor was misinterpreting some of the CCPA's prior decisions, including In re Mod, 408 F.2d 1055, 161 USPQ 281 (CCPA 1969). The court in Albrecht observed that the properties discovered for the new compounds claimed in Albrecht were

> totally dissimilar to any activity previously disclosed for the prior art analogs. A newly discovered activity of a claimed novel compound which bears no material relationship to the activity disclosed for the prior art analogs is further evidence, not to be ignored, of the nonobviousness of the claimed invention.

Id. at 1396, 185 USPQ at 590.

Thus the CCPA established, and the Federal Circuit has followed, the general rule that similarity of structure alone does not make a prima facie case of obviousness; there must be some reason, arising in the prior art, to expect that the claimed compounds or compositions will have the properties found by the applicant. This rule finds pragmatic support in today's state of chemical science, wherein few new compounds are of such imaginative structure that "structurally similar" compounds are not to be found in the prior art.[7/]

7/ In 1980 the Supreme Court noted that over 4,848,000 chemical compounds had been listed by the Chemical Abstracts Service, and that the list was then growing at the rate of 350,000 compounds per year. Dawson Chemical Co. v. Rohm & Haas Co., 448 U.S. 176, 221 n.23, 206 USPQ 385, 407 n.23 (1980).

Since the Solicitor today cites Mod for the same principle for which Mod was criticized in Albrecht, we repeat the admonition that Mod must be understood "in a given factual setting". Albrecht, 514 F.2d at 1395, 185 USPQ at 589; In re Lainson, 339 F.2d 252, 254, 144 USPQ 19, 21 (CCPA 1964):

> The question of obviousness, however, is so closely tied to the facts of each particular case that prior decisions in cases involving different facts are ordinarily of little value in reaching a decision.

An example of the strong fact-dependence of § 103 decisions is seen in In re Hoch, 428 F.2d 1341, 166 USPQ 406 (CCPA 1970), a case relied on by the Solicitor. In Hoch the prior art disclosed utility of a known compound for treatment of plant diseases, and the court held that a prima facie case of obviousness was made as to applicant's use of a structurally similar analog as a herbicide. Stating that it was unclear whether there was a difference between use in treatment of plant diseases and use as a herbicide, the court required evidence of unexpected differences from the prior art compounds. Id. at 1343, 1344, 166 USPQ at 408-09, 409. But the court did consider, in deciding whether a prima facie case had been made, the differences in structure and properties between the claimed compounds and those in the prior art "notwithstanding appellant's failure to establish actual differences in properties". Id. at 1344 n.6, 166 USPQ at 409 n.6. See also Geiger, 815 F.2d at 688, 2 USPQ2d at 1278 (holding that since a prima facie case of obviousness was not established, it was unnecessary to show unexpected results); and compare In re

Wilder, 563 F.2d 457, 195 USPQ 426 (CCPA 1977) with In re Wilder, 429 F.2d 447, 166 USPQ 545 (CCPA 1970) (cases reaching contrary results as to composition and compound claims).

Another example of the strong fact-dependence of obviousness determinations is seen in In re Heck, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039-40 (Fed. Cir. 1983), where the issue related to the differing rates of wear between softer outer metal surfaces and harder inner metal surfaces on a camshaft (Heck's invention), and the weight and pertinence of a reference (Maybach) showing harder metal used to protect softer metal on a camshaft during grinding. Acknowledging that Maybach dealt with a different specific problem within the narrow subject matter of cast iron camshafts, the court found that the prior art was "very narrow, directly related to the automotive camshafts with which Heck's invention is concerned, and zeroes in on the difference in the wearing-away of hardened and less hardened materials of cams". Id. at 1333, 216 USPQ at 1040. The court considered the relation of Maybach's teachings to the problem confronting the inventor, including the problem solved by Maybach, and held that despite Maybach's different particular use, the broader disclosures of Maybach made Heck's use obvious. Id.

The Solicitor relies strongly on In re Lintner, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972), in support of the rejection of Dillon's claims as prima facie obvious. The Lintner compositions were detergent compositions that contained, inter alia, a specific fabric softener and a sugar. The prior art showed

detergent compositions that also contained a fabric softener and a sugar. The prior art described the sugar as a filler, whereas Lintner stated that his sugar improved compatibility. The court affirmed that Lintner's detergent compositions were prima facie obvious, concluding that "there is no departure from the prior art in terms of the result achieved by the addition of sugar." Id. at 1016, 173 USPQ at 563. Lintner is in accord with the main body of precedent, for the court looked to the result achieved by the applicant, and saw no difference compared with that shown in the prior art.

Lintner was placed in perspective in Solder Removal Co. v. United States Int'l Trade Comm'n, 582 F.2d 628, 635, 199 USPQ 129, 135 (CCPA 1978), wherein the court stated:

> The ALJ appears to have viewed arguments that an invention solved a problem not previously recognized, and that nonobviousness may be evidenced by discovery of a problem source, as irrelevant. That view would be incorrect. The ALJ appears also to have felt that where a practice is suggested by the prior art to solve one problem, a conclusion of nonobviousness cannot be supported on the ground that it also solves another problem, previously recognized or not. That position would be too broad. Where the reason for the practice suggested by the prior art is much less significant than the reason derived from the inventor's solution to another problem, the results may be so unexpected as to support a conclusion of nonobviousness. Cf. In re Lintner, 458 F.2d 1013, 59 CCPA 1004, 173 USPQ 560 (1972). [Citations omitted.]

That the use of similar compositions to solve different problems may be unobvious, while the use of similar compositions to solve similar problems may be obvious, depending on the particular

circumstances, accommodates Lintner's facts as well as those of Solder Removal.

The Solicitor also relies on In re Kronig, 539 F.2d 1300, 190 USPQ 425 (CCPA 1976), a case that, like Lintner, turns on its facts. The appellants in Kronig claimed a process using a palladium/alkali metal/iron catalyst in an aqueous acetic acid system to produce allyl acetate. Various references showed the use of palladium catalysts containing alkali metal and iron compounds, and the use of palladium catalysts with aqueous acetic acid, the references disclosing that the inclusion of water and iron compounds served to increase yields and catalyst stability. Appellants argued that the prior art failed to disclose the addition of water to improve catalyst life; however, the court found that using water and an iron compound in the manner shown by the art suggested the appellant's result. Id. at 1304, 190 USPQ at 427. Indeed, it is hard to discern the reason for the Solicitor's emphasis on Kronig, which turns on the usual criterion of whether it would have been obvious to combine the elements of prior art references to achieve the result "suggested by" or "expected" from the teachings of the prior art. Id. at 1304, 190 USPQ at 428.

The other cases pressed by the Solicitor similarly turn on their facts. In In re de Montmollin, 344 F.2d 976, 145 USPQ 416 (CCPA 1965), the claimed invention was a new compound, described by the applicant as useful for dyeing wool and cotton. The reference showed structurally similar compounds and that they were useful for dyeing wool. The court concluded

that the additional ability of the claimed compound to dye cotton was not "sufficient to render the subject matter as a whole unobvious". Id. at 979, 145 USPQ at 417-18.

This decision, like the others selected by the dissent as showing exceptions to the general rule, simply illustrates determination of the question of obviousness by comparing the differences between the structures and properties or uses taught in the art, and those disclosed by the applicant, including consideration of the problems solved, and making a judgment based on "all evidence of record". Id. at 978, 145 USPQ 417. See, e.g., In re Lohr, 317 F.2d 388, 392, 137 USPQ 548, 551 (CCPA 1963):

> Considering all of the evidence in the record: the close structural similarity, the similar method of making the compounds, the similar properties, the same use, and the inconclusive showing of the affidavit, we are constrained to agree with the Board of Appeals that the claimed compounds and compositions are obvious in view of the prior art.

Despite the weight of precedent to the contrary, the Solicitor states that the correct law is as follows:

> [I]f the prior art suggests an inventor's compound or composition per se, that compound or composition would be prima facie obvious, regardless of the properties disclosed in the inventor's application.

Commissioner's brief at 24. We have illustrated precedent with decisions in the chemical arts, as appropriate to considering Dillon's invention. Nevertheless, applying similar reasoning to mechanical devices, the Commissioner asks the court to review its reasoning in In re Wright. See n.4 supra. In Wright the court held patentable a new structure for a car-

penter's level, having the new property and use of enhanced pitch-measuring capability. Although Wright's new structure was a combination of elements that were in the prior art, there was no suggestion in the prior art that this combination if made would have the property and use discovered by Wright. The court explained that there was no suggestion or motivation to make this combination in order to solve the problem of increasing pitch-measuring capability. Wright, 848 F.2d at 1220, 6 USPQ2d at 1962. The Solicitor expresses concern about the statement that it is appropriate to view the question of obviousness in light of the problem facing the inventor,[8/] and states that Wright is "inconsistent, and cannot be reconciled, with the Mod, de Montmollin, Kronig and other cases which have never been expressly overruled". (Footnote omitted.)

These cases, which we have discussed ante, illustrate how the court has treated different factual situations, based on the actual similarities and differences in structure and properties between the claimed compounds or compositions and the prior art. We join the CCPA in deploring "the formal exercise of squeezing new factual situations into preestablished pigeonholes". In re Yates, 663 F.2d 1054, 1056 n.4, 211 USPQ 1149, 1151 n.4 (CCPA 1981). See also In re Shannon, 356 F.2d

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8/ The court stated: "The problem solved by the invention is always relevant. The entirety of a claimed invention, including the combination viewed as a whole, the elements thereof, and the properties and purpose of the invention, must be considered." Wright, 848 F.2d at 1219, 6 USPQ2d at 1962.

548, 551, 148 USPQ 504, 507 (CCPA 1966) (the facts of a prior decision "do not permit our determination there to be raised to a rule of law governing the factual situation here").

The weight of precedent provides a mainstream of consistent authority, applicable broadly to chemical compositions and mechanical devices. The decision in Wright does not depart from that mainstream. The CCPA has well explained the factual dependency of those decisions that tested the boundaries of the prima facie case. Review of de Montmollin and Kronig shows that these cases are not outside the mainstream, despite their factual specificity. In recognition of the vast range encompassed by human creativity, neither judges nor administrators can decree that all inventions will fit "into preestablished pigeonholes". Yates, supra. Authority establishes that all the facts, including both structure and utility, must be considered in determining whether a prima facie case has been made, as was done in Wright.9/

C

Applying the guidance of precedent to Dillon's claimed tetra-orthoester fuel compositions: the compositions are new, and their property and use of reducing particulate emissions is

9/ Apparently misperceiving the reasoning in Wright, see n.5 supra, the dissent urges that Wright be "forthrightly overruled". The dissent thus would overrule the reasoning in Stratoflex, Lindemann, Grabiak, Payne, Weather Engineering, Orthopedic Equipment, Swan Wood, Gyurik, Cable, Deminski, Lalu, Fine, Geiger, Ratti, Hortman, Benno, Diversitech, Union Carbide, Rinehart, Sponnoble, Pye, Shaffer, Martin, Rothermel, Skoll, all cited herein, and many others.

not taught or suggested in the prior art. There is no objective teaching in the prior art that would have led one of ordinary skill to make the claimed compositions in order to solve the problem that was confronting Dillon. There is no reasonable basis in the prior art for expecting that Dillon's new compositions would have the particulate-reducing properties that she discovered. As we have discussed, structure, properties and use must be considered in determining whether a prima facie case of obviousness has been made.

The Commissioner suggests that whether Dillon's compositions are new compositions, or are known compositions used as water scavengers, in either case a prima facie case of obviousness is made as to Dillon's claims.[10/] The Commissioner errs in drawing no distinction between new and known compositions. If the compositions are known, for any use or no use, they are not patentable as compositions, by force of 35 U.S.C. § 102. Titanium Metals Corp. v. Banner, 778 F.2d 775, 780, 227 USPQ 773, 777-78 (Fed. Cir. 1985); Wilder, 429 F.2d at 450, 166 USPQ at 548 ("claims cannot be obtained to that which is not new"). Only if the compositions are new may they be patentable, if the requirements of section 103 are met. (As dis-

10/ Although the dissent states that the issue raised by the Board's decision is not whether a prima facie case was made by the prior art, the Commissioner's brief states: "The claimed subject matter would have been prima facie obvious from the combined teachings of the references". It was on this basis that the Board searched Dillon's specification for unobvious results between the two classes disclosed by Dillon, the tri- and tetra-orthoesters. (Only the tetra-orthoesters are claimed herein.)

cussed post, known as well as new compositions may be the subject of method claims under 35 U.S.C. § 101(b).)

Dillon raises the question of whether the Sweeney and Elliott references are properly combinable, that they are not in analogous arts. We need not decide this question, for even when combined these references offer no recognition of a solution to the problem of reducing particulate-emissions from combustion. See In re Naber, 494 F.2d 1405, 1407, 181 USPQ 639, 641 (CCPA 1974) ("even if one of ordinary skill in the art were moved to combine the references, there would be no recognition that the problem of combustible deposits had been solved").

The Board stated that it is inherent in Dillon's compositions that they would reduce particulate emissions, that Dillon "merely recited a newly discovered function inherently possessed" by the prior art. The courts have not upheld arguments based on "inherent" properties when there is no supporting teaching in the prior art. Inherency and obviousness are distinct concepts. W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 1555, 220 USPQ 303, 314 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984); In re Spormann, 363 F.2d 444, 448, 150 USPQ 449, 452 (CCPA 1966) ("the inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.") When the PTO asserts that there is an explicit or implicit teaching or suggestion in the prior art, the PTO must produce supporting references. Yates, 663 F.2d at 1057, 211 USPQ at 1151.

The Board required Dillon to show unobvious particulate-reduction properties of her tetra-orthoester compositions over her own teaching that the tri-orthoester compositions have the property of reducing particulates, not over any prior art teaching. This requirement has been improper since the CCPA held in In re Ruff, 256 F.2d 590, 598, 118 USPQ 340, 347 (CCPA 1958), that:

> To rely on an equivalence known only to the applicant to establish obviousness is to assume that his disclosure is a part of the prior art. The mere statement of this proposition reveals its fallaciousness. [Emphasis in original.]

See also In re Wertheim, 541 F.2d 257, 269, 191 USPQ 90, 102 (CCPA 1976) (applicant's own disclosures can not be used to support a rejection of the claims "absent some admission that matter disclosed in the specification is in the prior art").

The Solicitor raises the argument that Dillon is simply removing from the public an obvious variant of Sweeney's tri-orthoester compositions, presumably a variant that might be useful to scavenge water in fuels. To the extent that this argument raises policy considerations, the patentability of a new composition having a new and unobvious utility is firmly established in precedent, and the policy of a statute that authorizes such patentability has been tested and proven over decades of experience. Patentability is decided by applying the law to the facts specific to each case; this reasoned approach long ago transcended deciding the question of obviousness as a matter of immutable policy. In Mills, 281 F.2d at 222-23, 126 USPQ at 517, the court cautioned again

against "the observed tendency of the Patent Office to freeze into legal rules of general application what, at best, are statements applicable to particular fact situations."

Granting Dillon a patent on her new compositions, based on her discovery of a new and unobvious property and utility, takes away nothing that the public already has. See Ruschig, 343 F.2d at 979, 145 USPQ at 286 (favoring the provision of adequate patent protection for applicant's compounds over the "mere possibility that someone might wish to use some of them for some such purpose" unrelated to applicant's purpose). The public receives not only the knowledge of Dillon's discovery, for abandoned patent applications are maintained in secrecy, but Dillon is not deprived of an incentive to commercialize this new product for this new use. The statute, and underlying policy, do not bar Dillon from patenting her invention simply because her new compositions might also possess a property shared by a known composition.

There is merit to the classical explanation that the incentive to study new variations of known compounds and compositions, in order to search for new uses, would be diminished if such new compounds and compositions can not be patented despite discovery of new and unobvious properties. The contrary view carries scant counter-balancing public benefit. Nor is it in accord with the weight of CCPA and Federal Circuit precedent.

We conclude that the prior art does not constitute a prima facie case of obviousness of Dillon's compositions. Since Dillon's claimed invention meets the statutory criteria of

patentability, the rejection of composition claims 2-14, 16-22, and 36-37 is reversed.

II

The Method Claims

The Board drew no distinction between patentability of Dillon's composition and method claims. At oral argument the Solicitor, responding to a question from the bench, stated that Dillon has no way of claiming her invention, either as a new composition or as a new use, despite the absence of prior art pertinent to Dillon's use. The Solicitor stated: "I don't know how to suggest an allowable claim apart from any other art that might exist in this particular case."

A new use of a composition is claimed in the form of a process or method. This style of claiming was codified in 35 U.S.C. § 100(b):

> The term "process" means process, art or method, and includes a new use of a known process, machine, manufacture, composition of matter, or material.

See In re Fong, 288 F.2d 932, 933, 129 USPQ 264, 266 (CCPA 1961) ("because the law does not permit the claiming of such an invention in terms of use, the claims are directed to a process . . . or a composition . . . , conventional and recognized ways of claiming inventions predicated on the discovery of a new use"); In re Moreton, 288 F.2d 708, 709, 129 USPQ 227, 228 (CCPA 1961) ("This mere matter of form [i.e., claiming a new use as a method] should have no effect on patentability.") This claim form applies to a newly discovered use of a composition, whether a known or new composition. See generally 1 D. Chisum, Patents,

§ 1.03[8][c] at 1-174 to -179 (1989) and 2 D. Chisum, Patents, § 5.04[8][a] at 5-359 to -365 (1989); 2 E. Lipscomb, Walker on Patents, § 6:54 at 340 to 342 (1985).

The only question for the decision-maker is whether the claimed method of use would have been obvious to a person of ordinary skill in the field of the invention. In evaluating the patentability of Dillon's method claims it is not pertinent whether the compositions themselves are known or new or unobvious. The issue is solely whether the utility discovered by Dillon, the reduction of particulate emissions from combustion, would have been obvious in light of the prior art.

Perhaps recognizing the dearth of prior art before the Board as to the method claims, the Solicitor argues on appeal, for the first time, that Dillon's method claims are drawn simply to combustion. The Solicitor states that it would have been obvious to combust Dillon's fuel composition, even if the composition itself and its properties would not have been obvious. As support the Solicitor cites In re Durden, 763 F.2d 1406, 226 USPQ 359 (Fed. Cir. 1985), wherein the court held that the substitution of new reactants into a well known chemical process of making carbamate compounds did not, in that case, render unobvious the chemical reaction itself, which, except for the specific reactants, was disclosed in a reference.

The holding in Durden does not support the Commissioner's thesis. Durden's process claim was not to a new method of use, but to a known process of making a compound. Dillon is not claiming a chemical reaction; she is claiming a new use of a

composition, in the form of method claims. Dillon's invention is not a new process of combustion, but a new method of reducing particulates from combustion. After decades of this style of claiming a new use as a method, the Commissioner's position that the claims are unpatentable because "[t]he principal use of any fuel is combustion" is frivolous.

No reference or combination of references describes or suggests the use of any orthoester to reduce particulates in combustion of hydrocarbon fuels. Indeed, Dillon has consistently objected to the Board's attempt to compare her invention with her own disclosure. Dillon simply takes the position that her invention of particulate reducing compositions and method is unexpected as compared with the prior art, because nothing in the prior art teaches or suggests it. Considering Dillon's method claims, prior art that neither teaches nor suggests the use of these compositions to reduce particulate emissions in combustion is inadequate to make a prima facie case of obviousness.

The Board cited In re Merck & Co., Inc., 800 F.2d 1091, 1097, 231 USPQ 375, 379 (Fed Cir. 1986), in arguing that obviousness does not require absolute predictability. Obviousness does, however, require some relationship between the use taught in the reference and the use discovered by the applicant. In Merck the reference compound and the claim compound were both known, and the uses were similar; the court held that the claimed use would be expected prima facie in light of the known use of the reference compound. Applying this reasoning to

Dillon's claims leads to the opposite conclusion, for Dillon's use is unrelated to the known utility of the prior art compositions. See, e.g., In re May, 574 F.2d 1082, 1093, 197 USPQ 601, 610 (CCPA 1978) (claims to use as non-addictive analgesics for May's compounds held unobvious from the known use of the prior art compounds as addictive analgesics, in view of the unpredictable nature of this property).

We conclude that a prima facie case of obviousness as to the method claims has not been made. The rejection of claims 24-35 is reversed.

Conclusion

The rejection of claims 2 through 14, 16 through 22, and 24 through 37 is

REVERSED.

United States Court of Appeals for the Federal Circuit

88-1245

IN RE DIANE M. DILLON

ARCHER, Circuit Judge, dissenting.

The majority reverses the Board's decision solely because in its view prima facie obviousness under 35 U.S.C. § 103 (1982 & Supp. IV) can never be established when the specific problem and use described by the inventor are not addressed or suggested in the prior art.[1/] In this case, the prior art clearly would have motivated or taught the skilled artisan to produce the composition and method claimed by Dillon and, due to the absence of evidence showing non-obviousness, the Board determined, correctly in my view, that Dillon's invention was not patentable. I therefore dissent.

Preliminarily, I disagree with the way that the majority has framed the issue presented in this appeal. The majority opinion states that "[t]he threshhold question is whether, under such circumstances, a prima facie case of unpatentability for obviousness is deemed made." Slip op. at 6. As

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1/ The majority states: "There is no objective teaching in the prior art that would have led one of ordinary skill to make the claimed combinations in order to solve the problem that was confronting Dillon. There is no reasonable basis in the prior art for expecting that Dillon's new compositions would have the particulate-reducing properties that she discovered." Slip op. at 29-30 (emphasis added).

this court has made clear, "[t]he concept of prima facie obviousness in ex parte patent examination is but a procedural mechanism to allocate in an orderly way the burdens of going forward and of persuasion as between the examiner and the applicant." In re Piasecki, 745 F.2d 1468, 1471-72, 223 USPQ 785, 787-88 (Fed. Cir. 1984). This being so, once the full evidentiary record is established, as it is before the Board and on appeal to this court, the presumptions associated with the intermediate procedural burdens drop from the case, and the decisionmaker must focus solely upon the ultimate question to be decided. Id. at 1472-73, 223 USPQ at 788; In re Rinehart, 531 F.2d 1048, 1052, 189 USPQ 143, 147 (CCPA 1976); cf. United States Postal Serv. Board of Governors v. Aikens, 460 U.S. 711, 714-17 (1983) (in discrimination cases under Title VII the prima facie case method is a procedural device for the orderly production of evidence, but once the evidentiary record is established it is error to focus solely "on the question of prima facie case rather than directly on the question of discrimination."). Accordingly, the issue here is not whether a prima facie case was made, but rather whether Dillon's claimed composition and method would have been obvious on the record as a whole.

The facts underlying this appeal are set forth in the majority's opinion and will not be repeated here. The claimed composition and method are suggested by the prior

art, albeit for a reason different from that which Dillon has disclosed.[2/] Under the rationale identified by the examiner and affirmed by the Board, the prior art taught adding tetra-orthoesters to hydrocarbon fuels, whereas Dillon was concerned with reducing the amount of particulate emissions produced by the combustion of the same fuels.

Under 35 U.S.C. § 103 it is the claimed composition which must be patentable, not the motivation or subjective idea upon which that composition is based. Jones v. Hardy, 727 F.2d 1524, 1527-28, 220 USPQ 1021, 1024 (Fed. Cir. 1984). Accordingly, an additional or different reason for doing what the prior art suggests should be done does not prevent a conclusion that a claimed invention would have been obvious to one skilled in the art. In re Kronig, 539 F.2d 1300, 1304, 190 USPQ 425, 427-28 (CCPA 1976) ("Appellants further allege that the effect of water addition which they disclose (to lengthen the service life of the catalyst) is different from the effect of water addition disclosed in Yasui et al. Nevertheless, Yasui et al. provide ample motivation to add water in order to increase product yields, and we do not view

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2/ Dillon challenges the combination of the Sweeney and Elliott patents arguing that because Elliott deals with the dewatering of hydraulic fluids rather than hydrocarbon fuel, its teachings are related to a nonanalogous art area. Dillon's argument is unavailing here because Elliott's teachings are related to solving a problem Sweeney has indicated is pertinent to the hydrocarbon fuel art. See In re Deminski, 796 F.2d 436, 442, 230 USPQ 313, 315 (Fed. Cir. 1986); cf. In re Kronig, 539 F.2d 1300, 1303-04, 190 USPQ 425, 427 (CCPA 1976).

the rejection as deficient merely because the appellants allege a different advantage resulting from the addition of water. . . . [I]t is sufficient here that Yasui et al. clearly suggests doing what appellants have done, viz., adding water." (emphasis added)); In re Lintner, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972) ("The fact that appellant uses sugar for a different purpose does not alter the conclusion that its use in a prior art composition would be prima facie obvious from the purpose disclosed in the references." (emphasis added))[3/]; see also In re Heck, 699 F.2d 1331, 1333, 216 USPQ 1038, 1040 (Fed. Cir. 1983) ("[I]t would have been obvious to those skilled in the art to use them together when a differential in wearing away quality was desired, even though appellant's particular purpose was different from that of [the prior art]." (emphasis added)); In re Graf, 343 F.2d 774, 777, 145 USPQ 197,

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3/ The majority attempts to avoid the holding of Lintner by characterizing its facts as being accommodated by Solder Removal Co. v. United States Int'l Trade Comm'n, 582 F.2d 628, 635, 199 USPQ 129, 135 (CCPA 1978), which required a weighing and balancing of all the facts, including the significance of the problem suggested by the prior art versus the inventor's solution to another problem ("where the results may be so unexpected as to support a conclusion of nonobviousness") in making the ultimate determination with respect to obviousness. Slip op. at 24-26. Kronig, Lintner, and Heck are each consistent with the weighing or balancing approach articulated in Solder Removal. While appearing to adopt that approach by citing and quoting from Solder Removal, the majority instead holds that the only suggestion or motivation from the prior art which can be sufficient to establish even a prima facie case of obviousness is that which Dillon says was instrumental to her discovery of the claimed invention. See quote from majority opinion in footnote 1, supra.

199 (CCPA 1965) ("Obviousness is not to be determined on the basis of purpose alone.").

Obviousness is determined not on the basis of argument, but on evidence produced in the record. See In re De Blauwe, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984). Hence, when the examiner has shown that the prior art suggests the claimed invention for a particular purpose, the applicant cannot upset that showing merely by asserting, without proof, that the purpose behind or the properties of the claimed invention are different. Instead, it is necessary for the applicant to demonstrate by evidence of nonobviousness, such as unexpected novel or greatly enhanced results, commercial success, long felt need, etc., that the claimed invention would not have been obvious to the skilled artisan. In In re Lintner the court stated:

> The fact that appellant uses sugar for a different purpose does not alter the conclusion that its use in a prior art composition would be prima facie obvious from the purpose disclosed in the references.
>
> Differences between a patent applicant's and the prior art's motivation for adding an element to a composition may be reflected in the composition ultimately produced. A claimed composition may possess unexpectedly superior properties or advantages as compared to prior art compositions. In this way, the conclusion of prima facie obviousness may be rebutted and the claimed subject matter ultimately held to be legally nonobvious.

458 F.2d at 1016, 173 USPQ at 562 (CCPA 1972) (emphasis added). See also 2 D. Chisum, Patents, § 5.04[6] at 5-325 (1989) ("The fact that the prior art 'suggests' the modification for a

different purpose is irrelevant to the issue of prima facie obviousness though it is relevant to rebuttal of prima facie obviousness.").

In addition, the specific problem facing the applicant need not be recognized in all cases by the prior art before obviousness may be established.[4/] In In re Gershon, 372 F.2d 535, 152 USPQ 602 (CCPA 1967), the court stated:

> Although the cited prior art does fail to disclose or suggest either the existence of appellants' problem or its cause, we cannot agree that the art does not teach or suggest a solution to the problem. The cited art, especially the Gershon article, unquestionably teaches the superiority of "buffered acidic fluoride solutions" in effectively reducing dental enamel solubility in vitro. We think that one of ordinary skill in the dentifrice art would thus be persuaded to use buffered acidic fluoride dentifrices for the purpose of reducing dental enamel solubility in vivo. Such obvious use of buffered dentifrices would inherently provide a solution to appellants' problem, even though an adequate theoretical explanation of the reason why incorporation of buffering agents in acidic fluoride dentifrices achieves superior RES values is not found in the cited art. We think it is sufficient that the prior art clearly suggests doing what the applicants have done, although an underlying explanation of exactly why this should

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4/ The majority notes that the discovery of the source of a problem plaguing the prior art is a part of the "subject matter as a whole" to be considered in determining obviousness, citing In re Sponnoble, 405 F.2d 578, 585, 160 USPQ 237, 243 (CCPA 1969). Slip op. at 17. See also Eibel Process Co. v. Minnesota & Ontario Paper Co., 261 U.S. 45, 67-68 (1923). That doctrine has no application in this case, however, where Dillon has not indicated that she has discovered the source of the particulate emission problem, thereby making its solution simple. See 2 D. Chisum, Patents, § 5.04[7] at 5-353 (1989) ("The Eibel doctrine applies only where the inventor has discovered the source of a recognized problem." (emphasis in original)).

> be done, other than to obtain the expected superior beneficial results, is not taught or suggested in the cited references.[5/]

Id. at 538-39, 152 USPQ at 605 (emphasis in original). In the present case, the use of tetra-orthoesters as water scavengers in fuel mixtures as suggested by Sweeney and Elliott would have inherently solved Dillon's problem concerning particulate emissions.

Dillon's specification sets forth several examples that must be considered in making the obviousness determination. These examples are especially pertinent here because they provide a comparison between a composition disclosed by the Sweeney reference alone (although Dillon apparently was not aware of this reference, having originally claimed that same composition) and the composition encompassed by Dillon's claims and thus could provide evidence showing the nonobviousness of Dillon's invention. In Examples III through XII, trimethyl-orthoacetate (an orthoester of the formula taught by Sweeney) was shown to reduce the amount of particulate emissions from #2 diesel fuel by 14.61, 10.26, 29.90, 18.57, 12.01, 18.09, 11.30,

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5/ The majority points to In re Shaffer, 229 F.2d 476, 480, 108 USPQ 326, 329 (CCPA 1956), to suggest that the problem confronting the inventor must be addressed by the prior art in order for obviousness to be established. Slip op. at 17. Shaffer, however, is easily distinguished from this case. In Shaffer, the court found that the prior art did not suggest the equivalency between the amplifiers of the primary and secondary references. Id. at 479, 108 USPQ at 328-29. Accordingly, there was no suggestion to replace the amplifier of the primary reference with that of the secondary art. In this case, however, it is beyond dispute that Elliott teaches the equivalency between tri- and tetra-orthoesters as water scavengers.

(0), 27, and 27 percent, respectively. In Examples XIII through XVIII, tetra-methyl-orthocarbonate (a claimed tetra-orthoester) reduced particulate emissions by only 6.7, 7.9, 10.8, 16.6, 12.8, and 10.3 percent, respectively. This evidence, as the Board found, does not tend to prove the nonobviousness of the claimed invention. It, instead, shows only that a composition within Sweeney's disclosure tends to exhibit an even greater particulate-reducing ability than does the composition Dillon claims.

Accordingly, in light of the suggestion in the art to employ tetra-orthoesters as water scavengers in fuel mixtures and the absence of any evidence of nonobviousness, the Board's holding that Dillon's composition and method[6/] claims are unpatentable is correct and should be affirmed.

The cases regarding the obviousness of chemical compounds cited by the majority do not require a contrary result. The majority erroneously states that "a prima facie case of obviousness is not deemed made unless both (1) the new compound or composition is structurally similar to the reference compound or composition and (2) there is some suggestion or expectation in the prior art that the new compound or composition will have the same or similar ultility as discovered by the applicant," citing, among others, In re

6/ Dillon's method claims consist solely of the process of combusting the fuel mixture of her composition claims. Since the utility of Sweeney mixtures is as a fuel, combustion of the Sweeney/Elliott mixture would also have been obvious to the skilled artisan.

Grabiak, 769 F.2d 729, 731, 226 USPQ 870, 871 (Fed. Cir. 1985); In re Rosselet, 347 F.2d 847, 850, 146 USPQ 183, 185 (CCPA 1965); In re Chupp, 816 F.2d 643, 645-46, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987); In re Payne, 606 F.2d 303, 314, 203 USPQ 245, 254-55 (CCPA 1979); and In re Swan Wood, 582 F.2d 638, 641, 199 USPQ 137, 139 (CCPA 1978). See slip op. at 11-12. These cases, however, do not support the second prong of the stated test. In Grabiak the court reversed the Board's decision because it found lacking a sufficient structural similarity between the known and claimed compounds upon which to support the examiner's rejection. There was no holding regarding the utility of the claimed and referenced compounds. While in Rosselet, Payne, and Swan Wood the claimed and known compounds were of similar utility, this fact served only to confirm the inference of fact that the claimed compound would have been obvious based on its structural likeness to a useful prior art compound. See Chupp, 816 F.2d at 646, 2 USPQ2d at 1439; In re Mills, 281 F.2d 218, 223, 126 USPQ 513, 517 (CCPA 1960). The similarity in utility between the two compounds was not a teaching taken from the prior art. Likewise, in Chupp, the fact that the claimed and prior art compounds were both herbicides cannot be transformed into a requirement that in all cases the examiner can only base his obviousness determinations on compounds having the same or similar utility as that claimed by the applicant.

In In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963), a most often cited chemical obviousness case, the court reversed

the rejection of the applicant's claims because the Board had failed to consider evidence that the claimed compounds exhibited unexpected advantageous properties not possessed by the related compounds of the prior art. Id. at 391, 137 USPQ at 51. Indeed, such evidence, when of record, must always be considered by the examiner. The Papesch holding, however, does not mean that obviousness cannot be predicated on the structural likeness of the claimed invention to known useful compounds.

The additional cases cited by the majority are consistent with Papesch. In In re Albrecht, 514 F.2d 1385, 185 USPQ 585 (CCPA 1975), the CCPA held that a prima facie case of structural obviousness had been established notwithstanding that the claimed novel compound was disclosed for a totally different utility as compared to the referenced compound (local anesthetic versus antiviral agent).[7/] In this case, the claimed compounds were ultimately held to be nonobvious, but only after the examiner's obviousness rejection was rebutted by evidence that the novel compounds actually possessed unexpected properties not exhibited by those disclosed in the cited reference.

7/ This flatly contradicts the majority's holding that in order to establish "a prima facie case of obviousness[,] there must be some reason, arising in the prior art, to expect that the claimed compounds or compositions will have the properties found by the applicant." Slip op. at 22. The prior art relied upon in Albrecht clearly gave no such an expection, yet the court expressly indicated that obviousness, at that stage of the prosecution, had been established.

In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); In re Lalu, 747 F.2d 703, 223 USPQ 1257 (Fed. Cir. 1984); In re Grabiak, 769 F.2d 729, 226 USPQ 870 (Fed. Cir. 1985); In re Naber, 494 F.2d 1405, 181 USPQ 639 (CCPA 1974); In re Stemniski, 444 F.2d 581, 170 USPQ 343 (CCPA 1971); In re Ruschig, 343 F.2d 965, 145 USPQ 274 (CCPA 1965); In re De Lajarte, 337 F.2d 870, 143 USPQ 256 (CCPA 1964); In re Elpern, 326 F.2d 762, 140 USPQ 224 (CCPA 1964); and In re Mills, 281 F.2d 218, 126 USPQ 513 (CCPA 1960), do not hold otherwise. Although in each of these cases the court reversed the Board's decision that the claimed inventions would have been obvious, it did so because there was no suggestion in the art whatsoever to produce the claimed invention. Not one of these cases stands for the proposition advanced by the majority that a validly suggested reason for producing the claimed invention is insufficient for the purposes of section 103 because it does not address the problem of the inventor or because the prior art does not disclose or predict the alleged but unproven benefits of the claimed invention.[8/]

In sum, the myriad of chemical obviousness cases cited by the majority stand only for the unremarkable proposition that a novel compound may be unpatentable when it is shown to be structurally similar to another known and useful compound. In

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8/ In Lalu, Naber, Stemniski and Ruschig, the court indicated that structural obviousness could not be established where the prior art disclosed no utility whatsoever (or other than as an intermediate in a chemical (footnote continued)

such a case, the inference of obviousness may be overcome by a showing by the applicant that the claimed compound actually "possesses unobvious or unexpected beneficial properties not actually possessed by the prior art [structurally similar compound]." In re Mills, 281 F.2d at 222, 126 USPQ at 516 (partial emphasis added). These cases do not, however, require or suggest, as the majority holds, that chemical obviousness can only be predicated on prior art compounds which have the same or similar utility as the claimed compound. See In re Albrecht, 514 F.2d at 1388, 185 USPQ at 593.

Lastly, the majority cites the decision of this court in In re Wright, 848 F.2d 1216, 6 USPQ2d 1959 (Fed. Cir. 1988 support of its decision. While Wright[9/] supports the result

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8/ (continued)

process) for the referenced compound. These holdings do not support the majority's holding that the prior art must show the same or similar utility as does the applicant for the claimed invention in order to establish obviousness. On the contrary, the lack of disclosed utility in these cases may be likened to the lack of any reason or suggestion to combine various prior art teachings in a typical "reason to combine" case. In a "reason to combine" case, there must be "some" teaching or suggestion to combine the prior art. See Uniroyal, Inc. v. Rudkin-Wiley Corp., 837 F.2d 1044, 1051, 5 USPQ2d 1434, 1438 (Fed. Cir. 1988). Likewise, in structural obviousness cases, "some" utility for the referenced compound is sufficient to infer obviousness. In re Albrecht, 514 F.2d at 1388.

9/ Wright has been cited by this court in Diversitech Corp. v. Century Steps, Inc., 850 F.2d 675, 679, 7 USPQ2d 1315, 1318 (Fed. Cir. 1988), and In re Newell, slip op. at 7 (Fed. Cir. Dec. 12, 1989). These cases are distinguishable from this one because of either the existence of considerable objective evidence of nonobviousness or the lack of any suggestion in the prior art for the claimed invention. Thus, Wright's preclusion of obviousness where the inventor's problem and properties were not addressed or disclosed by the prior art was not in issue.

the majority reaches in this case, I do not find comfort in this fact because Wright, in my view, is in direct conflict with our precedent.[10/] As shown ante, that precedent does not make the subjective motivation or purpose disclosed by the inventor for producing the claimed invention an overriding factor in determining whether obviousness can be established from the teachings of the prior art. In Wright, the court held that although the prior art suggested the claimed invention for one purpose, because it did not suggest the invention for Wright's purpose or as a solution to the problem confronting him, it did not establish prima facie obviousness of the claimed invention. Such a holding is based solely on subjective criteria and is wholly at odds with the objective evidence-based analysis required by 35 U.S.C. § 103 and with the decisions of the CCPA and this court which disregard the

---

10/ The majority states that I have "misperceiv[ed] the reasoning in Wright" and would overrule some 25, or more, prior holdings of this and our predecessor court. Slip op. at 30 n.9. Contrary to the majority's view, however, it is the reasoning in Wright which represents the departure from our prior jurisprudence. See Adelman, Patent Law Perspectives, § 2.6[1], 2-406.2 (1989) ("In In re Wright[] the Federal Circuit wrongly failed to properly balance expected and unexpected properties in connection with a mechanical invention."); Rollins, "PTO Practice: Was Wright Wrong?", 71 J. Pat. & Tm. Off. Soc. 39 (1989) (Wright "diverges from prior precedent in a manner which, if intentional, represents a rather substantial change in the law."; Kayton, Patent Practice, 5-36 (4th ed. 1989) ("The highwater mark in the law of what is and is not prima facie obvious is In re Wright . . . ."); Brantley, Patent Law Handbook, 231-35 (1989-90) (Wright provides a "new approach[] to arguments attempting to rebut a rejection under section 103.").

mere articulation of the purpose or motivation behind the invention insofar as obviousness is concerned.

Consequently, because a panel of this court is without power to overrule the binding precedent of this court and its predecessors, the decision in Wright does not control this appeal and merits no following. It should be limited to its facts if not forthrightly overruled.

I would affirm the Board's decision.

12D 3-7-90
12: 071
D Springer

Grp 129

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1910-1982

PATENT, TRADEMARK AND COPYRIGHT LAW
AND RELATED FEDERAL AND ITC LITIGATION

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°REGISTERED PATENT AGENT

DOCKET NO.: 49-111-0

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231

IN RE APPLICATION OF:
YOSHIHIRO FUJIKAWA ET AL **GROUP ART UNIT: 129**
SERIAL NO.: 07/233,752 **EXAMINER: SPRINGER**
FILED: AUGUST 19, 1988
FOR: QUINOLINE TYPE MEVALONOLACTONES

SIR:

Attached hereto for filing are the following papers:

Supplemental Amendment

Our check in the amount of $ -0- 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,

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

Norman F. Oblon
Registration No.: 24,618

Steven B. Kelber
Registration No.: 30,073

49-111-0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

13/E
EBW
5-4-90

IN RE APPLICATION OF:	:	
YOSHIHIRO FUJIKAWA ET AL	:	GROUP ART UNIT: 129
SERIAL NO.: 07/233,752	:	EXAMINER: SPRINGER
FILED: AUGUST 19, 1988	:	
FOR: QUINOLINE TYPE MEVALONOLACTONES	:	

SUPPLEMENTAL AMENDMENT

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231

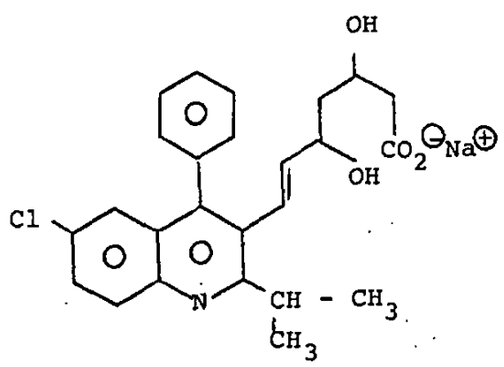
SIR:

Supplementing Applicants' response of February 27, 1990, introduction of the following amendment is respectfully requested.

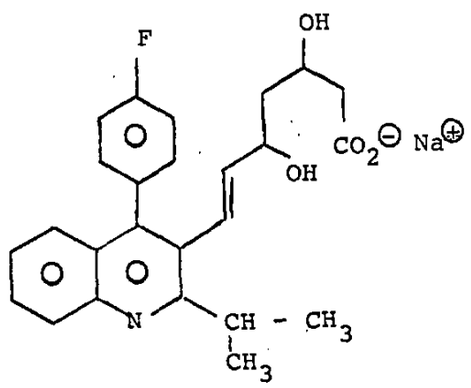
IN THE CLAIMS:

Please introduce the following new Claims 39 and 40.

--39. A compound of the formula:



40. A compound of the formula:



REMARKS:

Applicants have introduced Claims 39 and 40, directed to species disclosed in the invention. Claim 39 corresponds to compound I-56 set forth on page 70 of the application. The compound of Claim 40 is disclosed in Example 2, page 41 of the application, and is referred to on page 32 and 34, Tables 2 and 3.

These claims also find literal support in Japanese Patent Application 207224/1987, benefit of the filing date thereof, August 20, 1987, having been claimed by applicants pursuant to 35 U.S.C. §119. Referring to the certified English translation of that priority application, filed with applicants' response of February 27, 1990, the compound of Claim 39 is set forth on page 33, Table 11. The compound of Claim 40 corresponds to example 2, pages 26-27, and is referred to in Tables 2 and 3, pages 18 and 20 of the translation.

These claims are introduced in anticipation of the requested Interference. As no new matter is introduced by the claims, entry is respectfully requested. Upon entry, Claims 1-40 remain pending in the case.

Claims 39 and 40 are patentable over the prior art of record in the application, essentially for the reasons set forth in the response of February 27, 1990. These claims would further

correspond to the Count of the Interference proposed by applicants.

Entry, consideration and appropriate Declaration of Interference is respectfully requested.

Respectfully submitted,

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

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Steven B. Kelber
Registration No.: 30,073
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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.
07/233,752	08/19/88	FUJIKAWA Y	39111-0

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EXAMINER	
SPRINGER, D	
ART UNIT	**PAPER NUMBER**
121	14

DATE MAILED: 06/21/90

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

2/27/90 2f

☐ This application has been examined ☒ Responsive to communication filed on 4/27/90 ☐ 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 1-40 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-40 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

FILE

Claims 1-40 are pending.

Claims 1-40 are rejected as claims 1-38 were previously rejected over the Merck Frost Canada, European patent which teach quinoline compounds of the type claimed; no patentable distinction thereover is apparent since in the species claims presented it is apparent that the "y" group of the Merck Frost patent and the identical quinoline rings instantly leave the examiner unpersuaded of any patentable distinction thereover. Also the phenyl ring therein is analogous to applicants delta lactone as in species claim 36.

Springer: ach

05/22/90

David B. Springer

DAVID B. SPRINGER
PRIMARY EXAMINER
ART UNIT 121

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.
233,752	8/19/88	Fujikawa et al	49-111-0

EXAMINER	
D. Springer	
ART UNIT	PAPER NUMBER
12	15

DATE MAILED:

EXAMINER INTERVIEW SUMMARY RECORD

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

(1) Mr. Steve Kelber, Atty (3) _____

(2) Mr David Springer (4) _____

Date of interview 8/27/90

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 with respect to some or all of the claims in question. ☐ was not reached.

Claims discussed: All

Identification of prior art discussed: Frost et al Canada

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: Exmr. indicated that claims were no longer rejected over the Frost reference and that claims are all considered to be allowable. An interference with Picard et al will be declared in the near future.

(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.)

Unless the paragraphs below have 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 (e.g., items 1–7 on the reverse side of this form). If a response to the last Office action has already been filed, then applicant is given one month from this interview date to provide a statement of the substance of the interview.

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

☐ 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.

D. Springer
Examiner's Signature

PTOL-413 (REV. 1-84)

ORIGINAL - FOR INSERTION IN RIGHT HAND FLAP OF FILE WRAPPER

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*REGISTERED PATENT AGENT

#16
EBW
3-12-91

DOCKET NO.: 49-111-0

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231

12M
12E
9/17/90
Springer 041

IN RE APPLICATION OF:
YOSHIHIRO FUJIKAWA ET AL **GROUP ART UNIT: 121**
SERIAL NO.: 07/233,752 **EXAMINER: SPRINGER**
FILED: AUGUST 19, 1988
FOR: QUINOLINE TYPE MEVALONOLACTONES
SIR:

Attached hereto for filing are the following papers:

Amendment

Our check in the amount of $ -0- 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,

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

Norman F. Oblon
Registration No.: 24,618

Steven B. Kelber
Registration No.: 30,073

DS20027 03/13/91 07233752 15-0030 020 117 730.00CH

MISSING PAGE(S)

FROM THE U.S. PATENT OFFICE

OFFICIAL FILE WRAPPER

Petition For Ext of Time

49-111-0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

17/F
EBW
3-12-9

IN RE APPLICATION OF:	:	
YOSHIHIRO FUJIKAWA ET AL	:	GROUP ART UNIT: 129
SERIAL NO.: 07/233,752	:	EXAMINER: SPRINGER
FILED: AUGUST 19, 1988	:	
FOR: QUINOLINE TYPE MEVALONOLACTONES	:	

AMENDMENT

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231

SIR:

Supplementing the decision finding all claims allowable reflected in the Interview Summary Sheet of August 27, 1990, and pending the Declaration of Interference referred to in the Interview Summary Sheet, applicants respectfully request entry of the following amendment.

IN THE CLAIMS:

Please cancel Claim 10.

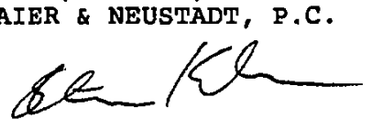
REMARKS:

Applicants have cancelled Claim 10 of the above-captioned patent application, the subject matter of which is being pursued in a divisional application, filed simultaneously herewith. Applicants have discovered that the subject matter of Claim 10, and related subject matter, exhibits unobvious and distinguishing properties, with respect to the genus circumscribed by the remaining claims of the above-captioned application, as well as the claims of the patent with which an Interference is to be declared. Accordingly, that claim will be pursued in a separate application.

Applicants look forward to the Declaration of Interference in the above-captioned application.

Respectfully submitted,

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



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Registration No.: 24,618

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

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703-521-5940

Dear Client:

This is the best copy available, of the attached page(s), due to the condition of the source document.

Please be assured that every effort has been made to supply you with the highest quality documentation.

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.
07/233,752	08/19/88	FUJIKAWA Y	49-111-0.

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MC CLELLAND & MAIER
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ARLINGTON, VA 22202

EXAMINER	
RICHTER, J	
ART UNIT	**PAPER NUMBER**
121	

DATE MAILED: 05/20/91

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 4 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 Johann Richter whose telephone number is (703) 308-0546.

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.

Between the 5th of June and the 12th of June 1991, Examining Group 120 will be moving from Crystal Plaza Building 2 to Crystal Mall Building 1. During and after this transition period the

Examiner can be reached through the Group 120 receptionist (703) 308-1235 which number will remain unchanged after the move. Subsequent to the move the examiner can be reached at (703) 308-4532.

RICHTER:drb
May 15, 1991

JOHANN RICHTER
EXAMINER
ART UNIT 121

FORM PTO-122
(REV. 12-87)

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

TITLE REPORT

PAPER NO. 19

A. APPLICATION FILE DATA

1. SERIAL NO. 07/233752

2. FILED 08-19-88

3. INVENTOR(S) - FULL NAME(S)

Yoshikiro Fujikawa
Mikio Suzuki
Hiroshi Masaki Etc

4. DIVISION OF

5. CONTINUATION OF

6. REISSUE OF

7. SUBSTITUTE OF

B. ASSIGNMENT RECORD DATA

The assignment records reveal that the Title appears to be vested in:

☐ (1.) Inventor(s)

☐ (2.) As endorsed

☐ (3.) As the record now stands, the patent, when granted, will issue in the name of the inventor(s).

☒ (4.) Other Nissan Chemical Industries Ltd.

EXAMINED UP TO AND INCLUDING	THIS CERTIFICATE DATED	09-23-91

BRANCH CHIEF OF ASSIGNMENT SEARCH BRANCH

Shirley M. Royall

PATENT NUMBER: ISSUE DATE: 00/00/00
SERIAL NUMBER: 07/233752 FILING DATE: 08/19/88
RELATED PATENT NUMBERS: 5011930
TITLE: QUINOLINE TYPE MEVALONOLACTONES
APPLICANT: FUJIKAWA, YOSHIHIRO ; SUZUKI, MIKIO
IWASAKI, HIROSHI ; SAKASHITA, MITSUAKI
KITAHARA, MASAKI

REEL: 4960 FRAME: 0609 DATE RECORDED: 10/18/88 NUMBER OF PAGES: 002
ASSIGNOR: FUJIKAWA, YOSHIHIRO
EXC DATE: 10/03/88
SUZUKI, MIKIO
EXC DATE: 10/03/88
IWASAKI, HIROSHI
EXC DATE: 10/03/88
SAKASHITA, MITSUAKI
EXC DATE: 10/03/88
KITAHARA, MASAKI
EXC DATE: 10/03/88
ASSIGNEE: NISSAN CHEMICAL INDUSTRIES LTD., 7-1, 3-CHOME, KANDA-NISHIKI-C
CHIYODA-KU, TOKYO, JAPAN

YOU HAVE MORE SCREENS,PRESS THE ASSNR KEYS & SEND FOR NEXT SCREEN
BRIEF:
ASSIGNMENT OF ASSIGNORS INTEREST
RETURN ADDRESS: OBLON, FISHER, SPIVAK,
MC CLELLAND & MAIER
1755 S. JEFF. DAVIS HWY.
CRYSTAL SQ. FIVE-STE. 400
ARLINGTON, VA 22202

NO MORE INFORMATION FOR THIS SERIAL NUMBER

Paper No. 20

All communications respecting this case should identify it by number and names of parties.

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PAT. & T.M. OFFICE
BOARD OF PATENT APPEALS
AND INTERFERENCES

Applicants: Fujikawa et al.
Serial No.: 07/233,752
Filed: 08/19/88
For: Quinoline Type
Mevalonolactones

Accorded Benefit of: Japan Serial Nos. 207224 filed 08/20/87 and 15585 filed 01/26/88

The case referred to above has been forwarded to the Board of Patent Appeals and Interferences because it is adjudged to interfere with other cases hereafter specified. Attention is directed to the fact that this interference is declared pursuant to 37 CFR 1.601 et seq., effective February 11, 1985 (49 F.R. 48416. 1050 O.G. 385). The interference is designated as No. 102,648.

By direction of the Commissioner of Patents and Trademarks and as required by 35 USC 135(c), notice is hereby given the parties of the requirement of the law for filing in the Patent and Trademark Office a copy of any agreement "in connection with or in contemplation of the termination of the interference."

The cases involved in this interference are:

Junior Party

Applicant: Sompong Wattanasin

Address: 11 Divito Trail Hopatcong, New Jersey 07843

Serial No.: 07/498,301 filed 03/23/90

For: Quinoline Analogs Of Mevalonolactone And Derivatives Thereof

Assignees: None

Attorneys of Record: Gerald D. Sharkin, Robert S. Honor, Richard E. Villa, Walter F. Jewell, Thomas O. McGovern, Thomas C. Doyle, Melvyn M. Kassenoff, Joseph J. Borovian, Joanne M. Giesser and Diane E. Furman

Associate Attorney: None

Accorded Benefit of: U.S. Serial No. 07/318,773 filed 03/03/89

Address: Gerald D. Sharkin
Sandoz Corp.
59 Route 10
E. Hanover, NJ 07936

Junior Party

Patentees: Joseph A. Picard, Bruce D. Roth and Drago R. Sliskovic

Addresses: 3545 Greenbrier Apt. 65C, Ann Arbor, Michigan 48105
1440 King George Blvd., Ann Arbor, Michigan 48104
4860 Cole Blvd., Ypsilanti, Michigan 48197

Serial No.: 07/129,516 filed 12/07/87, Patent No. 4,761,419 issued 08/02/88

For: 6-(((Substituted)Quinolinyl)Ethyl)-And Ethenyl)Tetrahydeo-4-Hydroxypyran-2-One Inhibitors Of Cholesterol Biosynthesis

Assignees: Warner-Lambert Company, A Corp. of DE

Attorneys of Record: Elizabeth M. Anderson, Ronald A. Daignault, Charles Gaglia, Jerry F. Janssen, Henry Jeanette, Anne M. Kelly, Gary M. Nath, Howard Olevsky, Stephen Raines, Daniel A. Scola and Joan Thierstein

Associate Attorney: None

Accorded Benefit of: None

Address: Jerry F. Janssen
Warner-Lambert Co.
2800 Plymouth Road
Ann Arbor, MI 48105

Senior Party

Applicants: Yoshihiro Fujikawa, Mikio Suzuki, Hiroshi Iwasaki, Mitsuaki Sakashita and Masaki Kitahara

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

Serial No.: 07/233,752 filed 08/19/88

For: Quinoline Type Mevalonolactones

Assignees: Nissan Chemical Industries Ltd., Tokyo, Japan

Attorneys of Record: Norman F. Oblon, Stanley P. Fisher, Marvin J. Spivak, C. Irvin McClelland, Gregory J. Maier, Arthur I. Neustadt, Robert C. Miller, Richard D. Kelly, James D. Hamilton, Eckhard H. Kuesters, Robert T. Pous, Charles L. Gholz, Vincent J. Sunderdick, William E. Beaumont and Steven B. Kelber

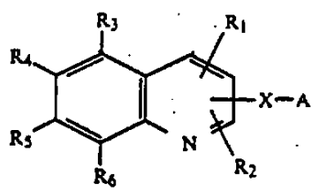
Associate Attorney: None

Accorded Benefit of: Japan Serial Nos. 207224 filed 08/20/87 and 15585 filed 01/26/88

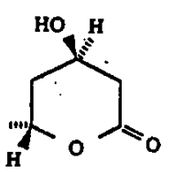
Address: Oblon, Fisher, Spivak,
McClelland & Maier
1755 S. Jeff. Davis Hwy.
Crystal Square 5, Ste. 400
Arlington, VA 22202

Count 1

A compound of structural Formula I

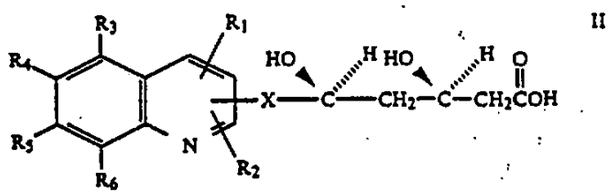


wherein A is



X is —CH2CH2— or —CH=CH—;
R_1 and R_2 are independently
hydrogen;
alkyl of from one to six carbons;
trifluoromethyl;
cyclopropyl;
cyclohexyl;
cyclohexylmethyl;
phenyl;
phenyl substituted with
fluorine,
chlorine,
bromine,
hydroxy,
trifluoromethyl,
alkyl of from one to four carbon atoms, or
alkoxy of from one to four carbon atoms;
phenylmethyl;
phenylmethyl substituted with
fluorine,
chlorine,
bromine,
hydroxy,
trifluoromethyl,
alkyl of from one to four carbon atoms, or
alkoxy of from one to four carbon atoms;
2-, 3-, or 4-pyridinyl; or
2-, 4-, or 5-pyrimidinyl;

R_3, R_4, R_5, R_6 are independently selected from
hydrogen;
alkyl of from one to six carbon atoms;
trifluoromethyl;
cyclopropyl;
fluorine;
chlorine;
bromine;
hydroxy;
alkoxy of from one to four carbon atoms;
cyano;
nitro;
amino;
acetylamino;
aminomethyl;
phenyl;
phenyl substituted with
fluorine,
chlorine,
bromine,
hydroxy,
trifluoromethyl,
alkyl of from one to four carbon atoms, or
alkoxy of from one to four carbon atoms;
phenylmethyl; or
phenylmethyl substituted with
fluorine,
chlorine,
bromine,
hydroxy,
trifluoromethyl, or
alkyl of from one to four carbon atoms;
provided that when X is in the 2-position, Rl is hydrogen and is attached in the 4-position;
or a corresponding 3,5-dihydroxyacid of Formula II



II

wherein A, X, R_1, R_2, R_3, R_4, and R_5 are as defined above, or a pharmaceutically acceptable salt thereof.

The claims of the parties which correspond to Count 1 are:

Wattanasin : Claims 1-7 and 10

Picard et al. : Claims 1 and 2-14

Fujikawa et al.: Claims 1-9, 11-34, 36, 39 and 40

Count 2

A method of inhibiting cholesterol biosynthesis in a patient in need of said treatment comprising administering a cholesterol synthesis inhibiting amount of a compound as defined by count 1 in combination with pharmaceutically acceptable carrier.

The claims of the parties which correspond to Count 2 are:

Wattanasin : Claims 8 and 9

Picard et al. : Claim 15

Fujikawa et al.: Claims 35, 37 and 38

Michael Sofocleous
Examiner-in-Chief
(703) 557-4066

gjh

FORM PTO-222
(REV. 1-90)

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

INTERFERENCE DIGEST

Interference No. 102,648 Paper No. 21

Name, Yoshihiro Fujikawa et al.

Serial No. 07/233,752 Patent No. _____

Title, QUINOLINE TYPE MEVALONOLACTONES

Filed, 08/19/88

Interference with Wattanasin and Picard et al.

DECISION ON MOTIONS

Examiner-in-Chief, _____ Dated, _____

FINAL DECISION

Board of Patent Appeals and Interferences, adverse Dated, 1/31/95

Court, _____ Dated, _____

REMARKS

Adverse as to Picard et al 4/10/92

This should be placed in each application or patent involved in interference in addition to the interference letters.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: :

YOSHIHORI FUJIKAWA ET AL : GROUP ART UNIT: 129

SERIAL NUMBER: 07/233,752 : EXAMINER: SPRINGER

FILED: AUGUST 19, 1988 :

FOR: QUINOLINE TYPE MEVALONOLACTONES

AMENDMENT--37 CFR §1.633(C)

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231

SIR:

Pursuant to the provision of the above-captioned Rule and Rule 637(c)(1)(ii), entry of the following amendments to the above-captioned patent application are respectfully requested.

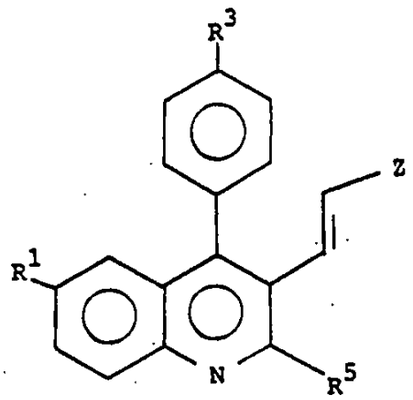
IN THE CLAIMS:

Please add the following new Claims 41-44.

G1

--41. A compound of the formula:

G1 cont'd



wherein R^1 = H

R^3 = F

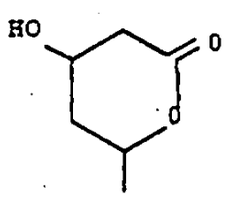
R^5 = cyclopropyl (c-Pr) and Z is selected from the group consisting of

$-CH(OH)-CH_2-CH(OH)-CH_2-COOH$

$-CH(OH)-CH_2-CH(OH)-CH_2-COONa$

$-CH(OH)-CH_2-CH(OH)-CH_2COO\frac{1}{2}Ca$

$-CH(OH)-CH_2-CH(OH)-CH_2COOR$, wherein R is C_{1-3}, alkyl and



42. The compound of Claim 41, wherein Z is $-CH(OH)-CH_2-CH(OH)-CH_2-COONa$.

43. The compound of Claim 41, wherein Z is $-CH(OH)-CH_2-CH(OH)-CH_2-COO\frac{1}{2}Ca$.

44. A method of inhibiting cholesterol biosynthesis in a patient in need of said treatment comprising administering a cholesterol synthesis inhibiting amount of a compound of Claim 41 in combination with a pharmaceutically acceptable carrier.--

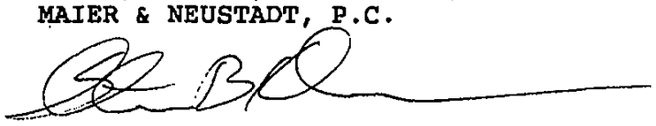
REMARKS:

Applicants have amended the claims herein to present claims narrowly drawn to the subject matter of Counts 3 and 4 set forth in Fujikawa et al's Motion to Redefine the Interference, Rule 633(c) by addition of Counts 3 and 4. No new matter is added by the amendment. All support necessary for the claims appears in Claims

1 and 35 as originally filed, see also added Claims 37 and 38. Moreover, each of the selections is taught by one or more of the examples set forth in the specification. As the claims do not introduce new matter, permit Fujikawa to contest priority as to Counts 3 and 4 directed to patentably distinct subject matter, and otherwise are unobjectionable under the Rules, entry is respectfully requested. Upon entry, Claims 1-9 and 11-44 remain pending in the case, with Claims 41-43 corresponding to Count 3, and Claim 44 corresponding to Count 4.

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

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF:	:	
YOSHIHIRO FUJIKAWA ET AL	:	GROUP ART UNIT: 129
SERIAL NO.: 07/07/233,752	:	
FILED: AUGUST 19, 1988	:	EXAMINER: SPRINGER
FOR: QUINOKINE TYPE MEVALONOLACTONES	:	

DECLARATION

HONORABLE COMMISSIONER OF PATENTS & TRADEMARKS

WASHINGTON, D.C. 20231

SIR:

Now comes MIDORIKO MATSUDA who deposes and says:

That my name is MIDORIKO MATSUDA;

That my address is 11-3, Kamiosaki 2-chome, Shinagawa-ku, Tokyo, Japan;

That I know well both the English and Japanese languages;

That the attached English language translation is true and correct translation of Japanese Patent Application No. 193606/1988 filed on August 3, 1988 to the best of my knowledge and belief;

I hereby declare further that all statements made herein of 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 this application or any patent issuing thereon.

FURTHER DEPONENT SAITH NOT.

January 19, 1990 — Midoriko Matsuda

Date — Midoriko Matsuda

MISSING PAGE(S)

FROM THE U.S. PATENT OFFICE

OFFICIAL FILE WRAPPER

For Translation
See Paper #12

Paper No. 24

All communications respecting this case should identify it by number and names of parties.

U.S. DEPARTMENT OF COMMERCE
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Telephone: (703)557-4007
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PAT. & T.M. OFFICE
BOARD OF PATENT APPEALS
AND INTERFERENCES

Patentees: Fujikawa et al.
Serial No.: 07/233,752
Filed: 08/19/88
For: Quinoline Type
Mevalonolactones

Accorded Benefit of: Japan Serial Nos. 207224 filed 08/20/87 and 15585 filed 01/26/88

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By direction of the Commissioner of Patents and Trademarks and as required by 35 USC 135(c), notice is hereby given the parties of the requirement of the law for filing in the Patent and Trademark Office a copy of any agreement "in connection with or in contemplation of the termination of the interference."

The cases involved in this interference are:

Junior Party

Applicant: Sompong Wattanasin

Address: 11 Divito Trail Hopatcong, New Jersey 07843

Serial No.: 07/498,301 filed 03/23/90

For: Quinoline Analogs Of Mevalonolactone And Derivatives Thereof

Assignees: None

Attorneys of Record: Gerald D. Sharkin, Robert S. Honor, Richard E. Villa, Walter F. Jewell, Thomas O. McGovern, Thomas C. Doyle, Melvyn M. Kassenoff, Joseph J. Borovian, Joanne M. Giesser and Diane E. Furman

Associate Attorney: None

Accorded Benefit of: U.S. Serial No. 07/318,773 filed 03/03/89

Address: Gerald D. Sharkin
Sandoz Corp.
59 Route 10
E. Hanover, NJ 07936

Junior Party

Applicants: Yoshihiro Fujikawa, Mikio Suzuki, Hiroshi Iwasaki, Mitsuaki Sakashita and Masaki Kitahara

Addresses: Nissan Chemical Industries, Ltd, Chuo Kenkyusho, 722-1, Tsuboi-cho, Funabashi-shi, Chiba-ken, Japan Respectfully

Serial No.: 07/483,720 filed 02/23/90, Patent No. 5,011,930 issued 04/30/91

For: Quinoline Type Mevalonolactones

Assignees: Nissan Chemical Industries Ltd., Tokyo, Japan

Attorneys of Record: Norman F. Oblon, Stanley P. Fisher, Marvin J. Spivak, C. Irvin McClelland, Gregory J. Maier, Arthur I. Neustadt, Robert C. Miller, Richard D. Kelly, James D. Hamilton, Eckhard H. Kuesters, Robert T.

Pous, Charles L. Gholz, Vincent J. Sunderdick, William E. Beaumont and Steven B. Kelber

Associate Attorney: None

Accorded Benefit of: Japan Serial Nos. 207224 filed 08/20/87, 15585 filed 01/26/88 and U.S. Serial No. 07/233,752 filed 08/19/88

Address: Steven B. Kelber
Oblon, Fisher, Spivak,
McClelland & Maier
1755 S. Jeff. Davis Hwy.
Crystal Square 5, Ste. 400
Arlington, VA 22202

Senior Party

Applicants: Yoshihiro Fujikawa, Mikio Suzuki, Hiroshi Iwasaki, Mitsuaki Sakashita and Masaki Kitahara

Addresses: Nissan Chemical Industries, Ltd, Chuo Kenkyusho, 722-1, Tsuboi-cho, Funabashi-shi, Chiba-ken, Japan Respectfully

Serial No.: 07/233,752 filed 08/19/88

For: Quinoline Type Mevalonolactones

Assignees: Nissan Chemical Industries Ltd., Tokyo, Japan

Attorneys of Record: Norman F. Oblon, Stanley P. Fisher, Marvin J. Spivak, C. Irvin McClelland, Gregory J. Maier, Arthur I. Neustadt, Robert C. Miller, Richard D. Kelly, James D. Hamilton, Eckhard H. Kuesters, Robert T. Pous, Charles L. Gholz, Vincent J. Sunderdick, William E. Beaumont and Steven B. Kelber

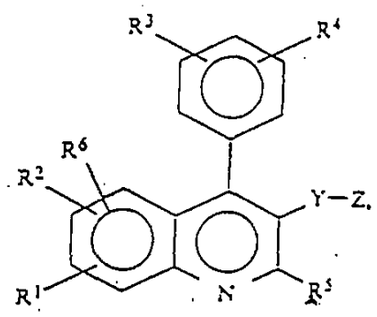
Associate Attorney: None

Accorded Benefit of: Japan Serial Nos. 207224 filed 08/20/87 and 15585 filed 01/26/88

Address: **Oblon, Fisher, Spivak,
McClelland & Maier
1755 S. Jeff. Davis Hwy.
Crystal Square 5, Ste. 400
Arlington, VA 22202**

Count 1

A compound of the formula:



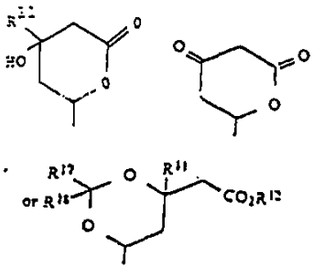
wherein R^1, R^2, R^3, R^4 and R^6 are independently
hydrogen,
C_{1-6} alkyl,
C_{1-6} cycloalkyl,
C_{1-3} alkoxy,
n-butoxy,
i-butoxy,
sec-butoxy,
R^7R^8N- (wherein R^7 and R^8 are independently hydrogen or C_{1-3} alkyl),

trifluoromethyl,
trifluoromethoxy,
difluoromethoxy,
fluoro,
chloro,
bromo,
phenyl,
phenoxy,
benzyloxy,
hydroxy,
hydroxymethyl,
$-O(CH_2)_\alpha OR^{19}$ (wherein R^{19} is hydrogen or C_{1-3}alkyl and α is 1, 2 or 3),
or when located at the ortho position to each other, R^3 and R^4 together optionally form $-CH=CH-CH=CH-$;

R^5 is hydrogen,
C_{1-6} alkyl,
C_{2-3} alkenyl,
C_{3-6} cycloalkyl,
phenyl substituted by R^9 (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).

Y is
$-CH_2-$,
$-CH_2CH_2-$,
$-CH=CH-$,
$-CH_2-CH=CH-$, or
$-CH=CH-CH_2-$;

Z is



or $-Q-CH_2WCH_2-CO_2R^{12}$ (where R^{12} is hydrogen or R^{14});

Q is $-CH(OH)-$.
$-C(O)-$, or
$-C(OR^{13})_2-$;

W is $-C(R^{11})(OH)-$ (where R^{11} is hydrogen or C_{1-3} alkyl),
$-C(O)-$, or
$-C(OR^{13})_2-$;

the 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^{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); and

R^{17} and R^{18} are independently hydrogen or C_{1-3} alkyl;

The claims of the parties which correspond to Count 1 are:

Wattanasin : Claims 1-7 and 10

Fujikawa et al. '930 : Claim 1

Fujikawa et al.: Claims 1-9, 11-34, 36, 39 and 40

Michael Sofocleous
Examiner-in-Chief
(703) 557-4066

gjh

FORM PTO-222
(REV. 1-90)

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

INTERFERENCE DIGEST

Interference No. 102,975 Paper No. 25

Name, Yoshihiro Fujikawa et al.

Serial No. 07/233,752 Patent No. _____

Title, Quinoline Type Mevalonolactones

Filed, 08/19/88

Interference with Wattanasin and Fujikawa et al.

DECISION ON MOTIONS

Examiner-in-Chief, _____ Dated, _____

FINAL DECISION

Board of Patent Appeals and Interferences, adverse Dated, 1/31/95

Court, _____ Dated, _____

REMARKS

This should be placed in each application or patent involved in interference in addition to the interference letters.

Paper No. 26

All communications respecting this case should identify it by number and names of parties

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

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Commissioner of Patents and Trademarks
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PAT. & T.M. OFFICE
BOARD OF PATENT APPEALS
AND INTERFERENCES

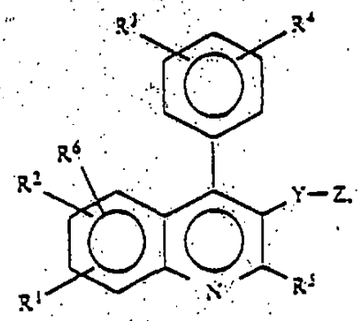
Interference No. 102,648
Applicants: Fujikawa et al.
Serial No.: 07/233,752
Filed: 08/19/88
For: Quinoline Type Mevalonolactones
Accorded Benefit of: Japan Serial Nos. 207224 filed 08/20/87 and 15585 filed 01/26/88

The above identified interference is hereby redeclared as follows:

Counts 1 and 2 is stricken, and count 3 is added.

Count 3

A method of inhibiting cholesterol biosynthesis in a patient in need of said treatment comprising administering a cholesterol synthesis inhibiting amount of a compound of the formula:



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,

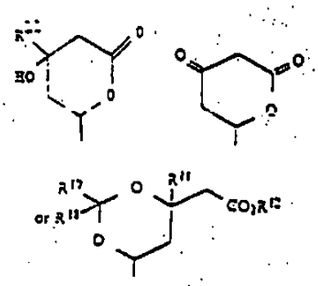
sec-butoxy,

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,
hydroxymethyl,
$-O(CH_2)_\alpha OR^{19}$ (wherein R^{19} is hydrogen or C_{1-3}alkyl and α is 1, 2 or 3),
or when located at the ortho position to each other, R^3 and R^4 together optionally form $-CH=CH-CH=CH-$;

R^5 is hydrogen,
C_{1-6} alkyl,
C_{2-3} alkenyl,
C_{3-6} cycloalkyl,
phenyl substituted by R^9 (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).

Y is
$-CH_2-$,
$-CH_2CH_2-$,
$-CH=CH-$,
$-CH_2-CH=CH-$, or
$-CH=CH-CH_2-$;

Z is



or $-Q-CH_2WCH_2-CO_2R^{12}$ (where R^{12} is hydrogen or R^{14});

Q is $-CH(OH)-$.
$-C(O)-$, or
$-C(OR^{13})_2-$;

W is $-C(R^{11})(OH)-$ (where R^{11} is hydrogen or C_{1-3} alkyl),
$-C(O)-$, or
$-C(OR^{13})_2-$;

the 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^{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); and

R^{17} and R^{18} are independently hydrogen or C_{1-3} alkyl;

as defined in combination with pharmaceutically acceptable carrier.

The claims of the parties which correspond to count 3 are:

Wattanasin : Claims 8 and 9

Fujikawa et al.: Claims 35, 37 and 38

Michael Sofocleous
Examiner-in-Chief
(703) 557-4066

gjh

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United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
07/233,752	08/19/1988	YOSHIHIRO FUJIKAWA	49-111-0	9698

22850 7590 06/12/2003

OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER	
MCKANE, JOSEPH K	

ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 06/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Notice of Abandonment	Application No.	Applicant(s)	
	07/233,752	FUJIKAWA ET AL.	
	Examiner	Art Unit	
	Joseph K. McKane	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

This application is abandoned in view of:

1. ☐ Applicant's failure to timely file a proper reply to the Office letter mailed on _____.
   (a) ☐ A reply was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply (including a total extension of time of _____ month(s)) which expired on _____.
   (b) ☐ A proposed reply was received on _____, but it does not constitute a proper reply under 37 CFR 1.113 (a) to the final rejection.
   (A proper reply under 37 CFR 1.113 to a final rejection consists only of: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114).
   (c) ☐ A reply was received on _____ but it does not constitute a proper reply, or a bona fide attempt at a proper reply, to the non-final rejection. See 37 CFR 1.85(a) and 1.111. (See explanation in box 7 below).
   (d) ☐ No reply has been received.

2. ☐ Applicant's failure to timely pay the required issue fee and publication fee, if applicable, within the statutory period of three months from the mailing date of the Notice of Allowance (PTOL-85).
   (a) ☐ The issue fee and publication fee, if applicable, was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the statutory period for payment of the issue fee (and publication fee) set in the Notice of Allowance (PTOL-85).
   (b) ☐ The submitted fee of $_____ is insufficient. A balance of $_____ is due.
   The issue fee required by 37 CFR 1.18 is $_____. The publication fee, if required by 37 CFR 1.18(d), is $_____.
   (c) ☐ The issue fee and publication fee, if applicable, has not been received.

3. ☐ Applicant's failure to timely file corrected drawings as required by, and within the three-month period set in, the Notice of Allowability (PTO-37).
   (a) ☐ Proposed corrected drawings were received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply.
   (b) ☐ No corrected drawings have been received.

4. ☐ The letter of express abandonment which is signed by the attorney or agent of record, the assignee of the entire interest, or all of the applicants.

5. ☐ The letter of express abandonment which is signed by an attorney or agent (acting in a representative capacity under 37 CFR 1.34(a)) upon the filing of a continuing application.

6. ☒ The decision by the Board of Patent Appeals and Interference rendered on *1-31-95* and because the period for seeking court review of the decision has expired and there are no allowed claims.

7. ☐ The reason(s) below:

Joseph K McKane

JOSEPH K. McKANE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Petitions to revive under 37 CFR 1.137(a) or (b), or requests to withdraw the holding of abandonment under 37 CFR 1.181, should be promptly filed to minimize any negative effects on patent term.

PTO/SB/68 (02-09)
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Telephone: (703) 308-2733

In re Application of

Application Number	Filed
07-233752	8-19-1988

Paper No. FF28

I hereby request access under 37 CFR 1.14(a)(1)(iv) to the application file record of the above-identified ABANDONED application, which is not within the file jacket of a pending Continued Prosecution Application (CPA) (37 CFR 1.53(d)) and which is identified in, or to which a benefit is claimed, in the following document (as shown in the attachment):

United States Patent Application Publication No. _____, page, _____ line _____,

United States Patent Number 5011930, column _____, line, _____ or

WIPO Pub. No._____, page _____, line _____.

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Farhana Shoaib
Signature

4-06-09
Date

Farhana Shoaib
Typed or printed name

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In re Application of

Application Number	Filed
07/233,752	08-19-88

Paper No. 29

I hereby request access under 37 CFR 1.14(a)(1)(iv) to the application file record of the above-identified ABANDONED application, which is not within the file jacket of a pending Continued Prosecution Application (CPA) (37 CFR 1.53(d)) and which is identified in, or to which a benefit is claimed, in the following document (as shown in the attachment):

United States Patent Application Publication No. 5,011,930, page, _____ line _____,

United States Patent Number _____, column _____, line, _____ or

WIPO Pub. No._____, page _____, line _____.

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Maria
Signature

8-19-09
Date

Marian
Typed or printed name

Registration Number, if applicable

(703) 486-1150
Telephone Number

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AUG 19 2009
(Initials)

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In re Application of

Application Number	Filed
07/233752	Aug 19, 1988

Paper No. #20

I hereby request access under 37 CFR 1.14(a)(1)(iv) to the application file record of the above-identified ABANDONED application, which is not within the file jacket of a pending Continued Prosecution Application (CPA) (37 CFR 1.53(d)) and which is identified in, or to which a benefit is claimed, in the following document (as shown in the attachment):

United States Patent Application Publication No. _____, page, _____ line _____,

United States Patent Number 5859857, column _____, line, _____ or

WIPO Pub. No._____, page _____, line _____.

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(2) If the application is incorporated by reference or otherwise identified in a U.S. patent, a statutory invention registration, a U.S. patent application publication, or an international patent application publication in accordance with PCT Article 21(2), a member of the public may obtain a copy of the pending application as originally filed.

S Gonzalez — 9-15-09

Signature — Date

Sal Gonzalez

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Telephone: (703) 308-2733

In re Application of

Application Number	Filed
07-233752	8-19-88

Paper No. #31

I hereby request access under 37 CFR 1.14(a)(1)(iv) to the application file record of the above-identified ABANDONED application, which is not within the file jacket of a pending Continued Prosecution Application (CPA) (37 CFR 1.53(d)) and which is identified in, or to which a benefit is claimed, in the following document (as shown in the attachment):

United States Patent Application Publication No. _____, page, _____ line _____,

United States Patent Number 5872130, column _____, line, _____ or

WIPO Pub. No._____, page _____, line _____.

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In re Application of	
Application Number: 07/233,752	Filed: 8/19/88

Paper No. #32

I hereby request access under 37 CFR 1.14(a)(1)(iv) to the application file record of the above-identified ABANDONED application, which is not within the file jacket of a pending Continued Prosecution Application (CPA) (37 CFR 1.53(d)) and which is identified in, or to which a benefit is claimed, in the following document (as shown in the attachment):

United States Patent Application Publication No. _____, page, _____ line _____,

United States Patent Number 5011930, column Face, line, _____ or

WIPO Pub. No._____, page _____, line _____.

Related Information About Access to Applications Maintained in the Image File Wrapper System (IFW) and Access to Pending Applications in General

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Michael D. Lieton
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Date

Michael D. Linton
Typed or printed name

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Telephone: (703) 308-2733

In re Application of: Fujikawa

Application Number	Filed
07/233752	Aug. 19, 88

Paper No. #33

I hereby request access under 37 CFR 1.14(a)(1)(iv) to the application file record of the above-identified ABANDONED application, which is not within the file jacket of a pending Continued Prosecution Application (CPA) (37 CFR 1.53(d)) and which is identified in, or to which a benefit is claimed, in the following document (as shown in the attachment):

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Kelvin Rodriguez
Signature

11-3-9
Date

KELVIN Rodriguez
Typed or printed name

Registration Number, if applicable

(703)418-2777
Telephone Number

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In re Application of
Fujikawa

Application Number	Filed
07/233,752	Aug. 19, 88

Paper No. #34

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United States Patent Application Publication No. _____, page, _____ line _____,

United States Patent Number 5102888, column _____, line, _____

WIPO Pub. No. _____, page _____, line _____.

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Thomas Lupo
Signature

5/24/10
Date

Thomas Lupo
Typed of printed name

Registration Number, if applicable

(540) 379, 3881
Telephone Number

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Approved by: D. Bryant
(initials) MAY 24 2010

Unit: _____

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In re Application of

Application Number	Filed
07/233,752	8/19/88

Paper No. #35

I hereby request access under 37 CFR 1.14(a)(1)(iv) to the application file record of the above-identified ABANDONED application, which is not within the file jacket of a pending Continued Prosecution Application (CPA) (37 CFR 1.53(d)) and which is identified in, or to which a benefit is claimed, in the following document (as shown in the attachment):

United States Patent Application Publication No. _____, page, _____ line _____,

United States Patent Number 5011930, column Face, line, _____ or

WIPO Pub. No._____, page _____, line _____.

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Michael D. Linton — Signature

12/6/10 — Date

Michael D. Linton — Typed or printed name

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In re Application of

Application Number	Filed
07/233,752	8/19/88

Paper No. #36

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United States Patent Number 5872130, column _____, line, _____.

WIPO Pub. No. _____, page _____, line _____.

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Azieb Tesfay
Signature

2/3/11
Date

Azieb Tesfay
Typed of printed name

Registration Number, if applicable

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Telephone Number

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In re Application of
Fujikawa

Application Number	Filed
07/233752	8/19/88

Paper No. #37

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Steven Blount
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In re Application of

Application Number	Filed
07/233,752	

Paper No. #38

I hereby request access under 37 CFR 1.14(a)(1)(iv) to the application file record of the above-identified ABANDONED application, which is not within the file jacket of a pending Continued Prosecution Application (CPA) (37 CFR 1.53(d)) and which is identified in, or to which a benefit is claimed, in the following document (as shown in the attachment):

United States Patent Application Publication No. _____, page, _____ line _____,

United States Patent Number US 5,854,259, column _____, line, _____.

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In re Application of
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Application Number	Filed
07/233,752	Aug. 19, 88

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US005854259A

United States Patent [19]

Fujikawa et al.

[11] **Patent Number: 5,854,259**

[45] **Date of Patent: Dec. 29, 1998**

[54] **QUINOLINE TYPE MEVALONOLACTONES**

[75] Inventors: **Yoshihiro Fujikawa; Mikio Suzuki; Hiroshi Iwasaki**, all of Funabashi; **Mitsuaki Sakashita; Masaki Kitahara**, both of Saitama-ken, all of Japan

[73] Assignee: **Nissan Chemical Industries Ltd.**, Tokyo, Japan

[21] Appl. No.: **978,884**

[22] Filed: **Nov. 19, 1992**

Related U.S. Application Data

[62] Division of Ser. No. 883,398, May 15, 1992, which is a division of Ser. No. 631,092, Dec. 19, 1990, which is a continuation of Ser. No. 233,752, Aug. 19, 1988.

[30] **Foreign Application Priority Data**

Aug. 20, 1987	[JP]	Japan	62-207224
Jan. 26, 1988	[JP]	Japan	63-15585
Aug. 3, 1988	[JP]	Japan	63-193606

[51] **Int. Cl.**[6] **A61K 31/47**; C07D 215/12

[52] **U.S. Cl.** **514/311**; 546/173

[58] **Field of Search** 546/173; 514/311

[56] **References Cited**

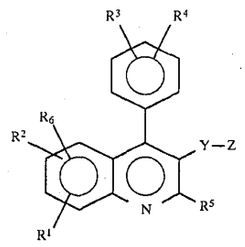
U.S. PATENT DOCUMENTS

5,753,675 5/1998 Wattanasin 514/311

Primary Examiner—Laura L. Stockton
Attorney, Agent, or Firm—Oblon, Spivak, McClelland, Maier & Neustadt, P.C.

[57] **ABSTRACT**

Described herein are mevalonolactone derivatives having a quinoline ring of formula (I)



(I)

wherein the R^1, R^2, R^3, R^4, R^5, Y and Z variables are described therein.

4 Claims, No Drawings

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In re Application of	
Application Number 07/233,752	Filed Aug. 19, 1988

Paper No. #40

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US005872130A

United States Patent [19]

Fujikawa et al.

[11] Patent Number: 5,872,130

[45] Date of Patent: Feb. 16, 1999

[54] QUINOLINE TYPE MEVALONOACTONES

[75] Inventors: Yoshihiro Fujikawa; Mikio Suzuki; Hiroshi Iwasaki, all of Funabashi; Mitsuaki Sakashita; Masaki Kitahara, both of Shiraoka-machi, all of Japan

[73] Assignee: Nissan Chemical Industries Ltd., Tokyo, Japan

[21] Appl. No.: 631,092

[22] Filed: Dec. 19, 1990

Related U.S. Application Data

[63] Continuation of Ser. No. 233,752, Aug. 19, 1988.

[30] Foreign Application Priority Data

Jan. 26, 1988 [JP] Japan 63-15585
Aug. 3, 1988 [JP] Japan 63-193606
Aug. 20, 1997 [JP] Japan 62-207224

[51] Int. Cl.[6] A61K 31/47; C07D 215/12

[52] U.S. Cl. 514/311; 546/173

[58] Field of Search 546/173; 514/311

[56] References Cited

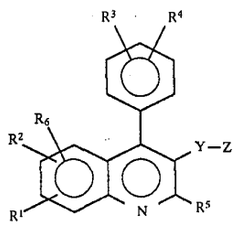
U.S. PATENT DOCUMENTS

5,753,675 5/1998 Wattanasin 514/311

Primary Examiner—Laura L. Stockton
Attorney, Agent, or Firm—Oblon, Spivak, McClelland, Maier & Neustadt, P.C.

[57] ABSTRACT

Described herein are mevalonolactone derivatives having a quinoline ring of formula (I)



(I)

wherein the R^1, R^2, R^3, R^4, R^5, Y and Z variables are described therein.

5 Claims, No Drawings

PTO/SB/68 (04-07)
Approved for use through 9/30/2007. OMB 0651-0031
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In re Application of		
	Application Number	Filed
	07/233,252	8-19-1988

Paper No. #4

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United States Patent Application Publication No. _____, page, _____ line _____

United States Patent Number 5,872,130, column Face, line, _____ or

WIPO Pub. No._____, page _____, line _____.

Related Information About Access to Applications Maintained in the Image File Wrapper System (IFW) and Access to Pending Applications in General

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(1) If the benefit of the pending application is claimed under 35 U.S.C. 119(e), 120, 121, or 365 in another application that has: (a) issued as a U.S. patent, or (b) published as a statutory invention registration, a U.S. patent application publication, or an international patent application publication in accordance with PCT Article 21(2), a member of the public may obtain a copy of: the file contents; the pending application as originally filed; or any document in the file of the pending application.

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Mike Surles — Signature

8-13-13 — Date

Mike Surles — Typed or printed name

Registration Number, if applicable

703-553-0000 — Telephone Number

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US005872130A

United States Patent [19]

Fujikawa et al.

[11] **Patent Number: 5,872,130**

[45] **Date of Patent: Feb. 16, 1999**

[54] **QUINOLINE TYPE MEVALONOACTONES**

[75] Inventors: **Yoshihiro Fujikawa; Mikio Suzuki; Hiroshi Iwasaki,** all of Funabashi; **Mitsuaki Sakashita; Masaki Kitahara,** both of Shiraoka-machi, all of Japan

[73] Assignee: **Nissan Chemical Industries Ltd.,** Tokyo, Japan

[21] Appl. No.: **631,092**

[22] Filed: **Dec. 19, 1990**

Related U.S. Application Data

[63] Continuation of Ser. No. 233,752, Aug. 19, 1988.

[30] **Foreign Application Priority Data**

Jan. 26, 1988	[JP]	Japan	63-15585
Aug. 3, 1988	[JP]	Japan	63-193606
Aug. 20, 1997	[JP]	Japan	62-207224

[51] **Int. Cl.**[6] **A61K 31/47**; C07D 215/12

[52] **U.S. Cl.** **514/311**; 546/173

[58] **Field of Search** 546/173; 514/311

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,753,675 5/1998 Wattanasin 514/311

Primary Examiner—Laura L. Stockton

Attorney, Agent, or Firm—Oblon, Spivak, McClelland, Maier & Neustadt, P.C.

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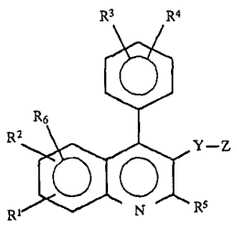

(I)

wherein the R^1, R^2, R^3, R^4, R^5, Y and Z variables are described therein.

5 Claims, No Drawings

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Application Number	Filed
07/233,752	Aug 19, 1988.

Paper No. #42

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United States Patent Application Publication No. 5872130, page, _____ line _____,

United States Patent Number _____, column _____, line, _____.

WIPO Pub. No. _____, page _____, line _____.

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Alexandra Wilbert
Signature

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Date

_____
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Application Number	Filed
07/233,752	Aug. 19, 1988

Paper No. 43

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United States Patent Number 5854259, column _____, line, _____.

WIPO Pub. No. _____, page _____, line _____.

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Signature

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Date

D. H. Lucas
Typed of printed name

Registration Number, if applicable

571-289-0030
Telephone Number

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Application Number	Filed
07/233,752	8/19/88

Paper No. 4444

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Michael D. Linton
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1/28/15
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Michael D. Linton
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US005872130A

United States Patent [19]

Fujikawa et al.

[11] Patent Number: 5,872,130

[45] Date of Patent: Feb. 16, 1999

[54] QUINOLINE TYPE MEVALONOACTONES

[75] Inventors: Yoshihiro Fujikawa; Mikio Suzuki; Hiroshi Iwasaki, all of Funabashi; Mitsuaki Sakashita; Masaki Kitahara, both of Shiraoka-machi, all of Japan

[73] Assignee: Nissan Chemical Industries Ltd., Tokyo, Japan

[21] Appl. No.: 631,092

[22] Filed: Dec. 19, 1990

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[58] Field of Search 546/173; 514/311

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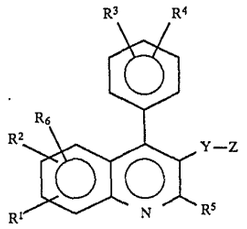

(I)

wherein the R^1, R^2, R^3, R^4, R^5, Y and Z variables are described therein.

5 Claims, No Drawings

MISCELLANEOUS PAGE(S)

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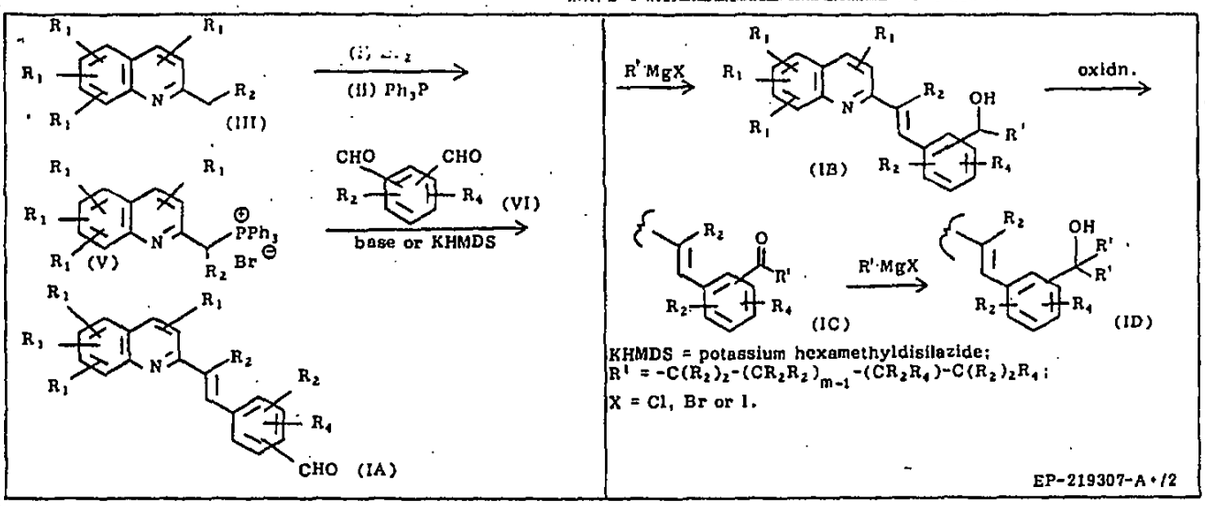


R_2 = H, 1-3C alkyl, 2-3C alkenyl or CF_3.

USE

(I) are antagonists of the slow reacting substance of anaphylaxis (SRS-A), esp. leukotriene D4. They also exhibit moderate inhibition of leukotriene biosynthesis. Thus (I) can be used as antiasthmatic, antiallergic, antiinflammatory and cytoprotective agents, and for treating allergic rhinitis, chronic bronchitis, and skin diseases such as psoriasis and atopic eczema.

(I) are also useful for antagonising or inhibiting the pathological actions of leukotrienes on the cardiovascular and vascular systems which can result in e.g. angina; and for treating inflammatory and allergic diseases of the eye e.g. allergic conjunctivitis.

Diseases which (I) can be used to treat include erosive gastritis, erosive oesophagitis, inflammatory bowel disease, ethanol induced haemorrhagic erosions, hepatic ischaemia, noxious agent induced damage or necrosis of hepatic pancreatic, renal or myocardial tissue, parenchymal damage of the liver caused by hepatotoxic agents such as CCl_4 and D-galactosamine, ischaemic renal failure, disease induced hepatic damage, bile salt induced pancreatic or gastric damage, trauma or stress induced cell damage, glycerol induced renal failure and obstructive airway diseases (e.g. allergic bronchial asthma).

(I) also cause increased resistance of gastrointestinal mucosa to the effects of irritants (e.g. ulcerogenic activity of aspirin and indomethacin) and prevent gastric lesions induced by oral admin. of irritants such as strong acids, strong bases, ethanol and hypertonic saline solns.

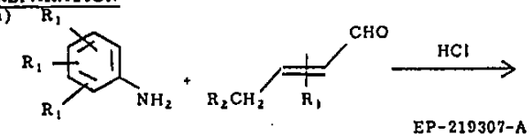
Dose is 0.001-100 (pref. 0.01-10, esp. 0.1-1)mg/kg/day except as cytoprotective; or 0.1-100 (pref. 1-100)mg/kg/day as cytoprotectives.

SPECIFICALLY CLAIMED

10 Cpds. (I) e.g.:
2-(2-(4-(1-hydroxyhexyl)phenyl)ethenyl)quinoline (Ia);
4-(2-(quinolin-2-yl)ethenyl)acetophenone;
3-(2-(quinolin-2-yl)ethenyl)benzaldehyde;
2-(2-(3-(1-hydroxyl-1-methylethyl)phenyl)ethenyl)quinoline; and
7-bromo-2-(2-(3-(1-hydroxypropyl)phenyl)ethenyl)quinoline.

PREPARATION

(a)



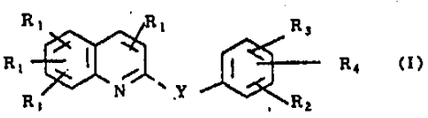
EP-219307-A+/1

87-110236/16 B02 MERI 16.10.85
MERCK FROSST CANADA *EP -219-307-A
16.10.85-US-788180 (22.04.87) A61k-31/47 C07d-215/14

New 2-phenyl:alkenyl or alkynyl-quinoline derivs. - having leukotriene antagonist activity, useful as e.g. anti-asthmatic, antiinflammatory, anti allergic and cyto-protective agents

C87-045822 E(AT BE CH DE FR GB IT LI LU NL SE)

Quinoline derivs. of formula (I) and their pharmaceutically acceptable salts are new:



(I)

Y = $-(CR_2{=}CR_2)_n$ or $(C{\equiv}C)_n$;

R_1 = independently H, halo, 1-8C alkyl, 2-8C alkenyl, 2-8C alkynyl, CF_3, OR_2, SR_2, SOR_2, SO_2R_2, $N(R_2)_2$, CHO, $COCR_2$, CO_2R_2, $C(OH)(R_2)_2$, CN, NO_2 or opt. substd. phenyl, benzyl or phenethyl;

R_2 = H, 1-8C alkyl, 2-8C alkenyl, 2-8C alkynyl, CF_3 or opt. substd. phenyl, benzyl or phenethyl;

B(6-D2, 12-A7, 12-C10, 12-D1, 12-D2, 12-D6, 12-D6A, 12-D7, 12-E6, 12-F1C, 12-F2, 12-G1, 12-G1A, 12-G1B1, 12-G2, 12-G3, 12-J1, 12-J5, 12-K2, 12-K6, 12-L4)

R_3 = $-(A)_m-(CR_1R_2)_m-(CR_2R_4)_m-CR_2R$ (sic); provided that R_3 is not CHO when it is para to Y;

R_4 = H, halo, NO_2, OR_2, SR_2, $N(R_2)_2$ or 1-8C alkyl;
or $(R_4)_2$ = O=;

A = CO or $C(R_2)(OR_6)$;

R_6 = H, 1-6C alkyl, COR_7, phenyl or benzyl;

R_7 = H, 1-8C alkyl, 2-8C alkenyl, 2-8C alkynyl, CF_3, phenyl, benzyl or phenethyl;

each m = 0-8, provided that at least one is not 0;

n = 1-2.

Also claimed are compsns. useful for antagonising leukotriene activity in mammals contg. (I) and opt. a non-steroidal antiinflammatory drug, peripheral analgesic, cyclooxygenase inhibitor, leukotriene antagonist, leukotriene inhibitor, H_2 receptor antagonist, antihistaminic, prostaglandin antagonist or thromboxane antagonist.

MORE SPECIFICALLY

Y = $-C(R_2){=}C(R_2)-$ or ethynylene;

R_1 = H, halo, Me, CF_3 or SCF_3;

EP-219307-A+

PATENT APPLICATION FEE DETERMINATION RECORD

Effective December 16, 1991

Application or Docket Number: 233,752

ENTITY

FOR	NUMBER FILED	NUMBER EXTRA	RATE	FEE	OR	RATE	FEE
BASIC FEE				$ 345.00	OR		$ 690.00
TOTAL CLAIMS	40 minus 20 =	*	x $10 =		OR	x $20 =	
INDEPENDENT CLAIMS	3 minus 3 =	*	x 36 =		OR	x 72 =	
MULTIPLE DEPENDENT CLAIM PRESENT			+ 110 =		OR	+ 220 =	
			TOTAL		OR	TOTAL	

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

CLAIMS AS AMENDED - PART II

SMALL ENTITY OR **OTHER THAN SMALL ENTITY**

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE	ADDITIONAL FEE	OR	RATE	ADDITIONAL FEE
Total	* 43	Minus	** 40	= 3	x $10 =		OR	x $20 =	60.00
Independent	* 4	Minus	*** 3	= 1	x 36 =		OR	x 72 =	72.00
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM					+ 110 =		OR	+ 220 =	
					TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	132.00

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE	ADDITIONAL FEE	OR	RATE	ADDITIONAL FEE
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

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE	ADDITIONAL FEE	OR	RATE	ADDITIONAL FEE
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.

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

FORM PTO-875
Rev. 3-83

PATENT APPLICATION FEE DETERMINATION RECORD

SERIAL NO.	FILING DATE
233752	08.19.88
APPLICANT (FIRST NAMED)	
Jay Kanda et al	

CLAIMS AS FILED - PART I

FOR	NO. FILED	NO EXTRA
BASIC FEE		
TOTAL CLAIMS	35 - 20 =	15
INDEP CLAIMS	1 - 1 =	
MULTIPLE DEPENDENT CLAIM PRESENT		

* If the difference in col. 1 is less than zero, enter "0" in col. 2

SMALL ENTITY RATE	SMALL ENTITY FEE		OTHER THAN A SMALL ENTITY RATE	OTHER THAN A SMALL ENTITY FEE
	$ 170	OR		$ 340
x 6	$	OR	x 12	$ 180
x 17	$	OR	x 34	$
x 55	$	OR	x 110	$
TOTAL	$	OR	TOTAL	$ 520

CLAIMS AS AMENDED - PART II

	(1)		(2)	(3)
	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NO PREVIOUSLY PAID FOR	PRESENT EXTRA
AMENDMENT A				
TOTAL	* 36	MINUS	** 35	* 1
INDEP	* 1	MINUS	*** 3	*
FIRST PRESENTATION OF MULTIPLE DEP CLAIM				

SMALL ENTITY RATE	SMALL ENTITY ADDIT FEE		OTHER THAN A SMALL ENTITY RATE	OTHER THAN A SMALL ENTITY ADDIT FEE
$	$	OR	x 12	$ 12
15	$	OR	30 -	$
100	$	OR	100 -	$
TOTAL ADDIT FEE	$	OR	TOTAL	$ 12

	(1)		(2)	(3)
	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NO PREVIOUSLY PAID FOR	PRESENT EXTRA
AMENDMENT B				
TOTAL	* 38	MINUS	** 38	* 2
INDEP	* 1	MINUS	*** 1	*
FIRST PRESENTATION OF MULTIPLE DEP CLAIM				

SMALL ENTITY RATE	SMALL ENTITY ADDIT FEE		OTHER THAN A SMALL ENTITY RATE	OTHER THAN A SMALL ENTITY ADDIT FEE
$	$	OR	12	$ 24
15	$	OR	30	$
100	$	OR	100	$
TOTAL ADDIT FEE	$	OR	TOTAL	$ 24

	(1)		(2)	(3)
	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NO PREVIOUSLY PAID FOR	PRESENT EXTRA
AMENDMENT C				
TOTAL	* 40	MINUS	** 38	* 2
INDEP	* 3	MINUS	*** 3	*
FIRST PRESENTATION OF MULTIPLE DEP CLAIM				

SMALL ENTITY RATE	SMALL ENTITY ADDIT FEE		OTHER THAN A SMALL ENTITY RATE	OTHER THAN A SMALL ENTITY ADDIT FEE
$	$	OR	12	$ 24
15	$	OR	30	$
100	$	OR	100	$
TOTAL ADDIT. FEE	$	OR	TOTAL	$

* If the entry in Col. 1 is less than the entry in Col. 2, write "0" in Col. 3.

** If the "Highest No. Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest No. Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest No. Previously Paid For" IN THIS SPACE is the highest number found in the corresponding box in Col. 1.

PTO-1130 (REV. 8-87)

U.S. DEPARTMENT OF COMMERCE—PATENT & TM OFFICE

PALM III APPLICATION FILE DATA CODING SHEET

PREPARED BY: Everett D | DATE: 9.7.88

FORMAT NO. 2 Serial No. 07/228,752

TYPE APPL	FILING DATE (Month / Day / Year)	SPECIAL HANDLING	GROUP ART UNIT	CLASS	SHEETS OF DRAWINGS	ASGT?	TOTAL CLAIMS	INDEPENDENT CLAIMS	SMALL ENTITY?	FILING FEE RECEIVED	SECURITY CASE?	FOREIGN LICENSE?
1	08 / 19 / 88		125	514		Y	35	1	0	630	N	N

FORMAT NO. 3 ATTORNEY DOCKET NUMBER (12 spaces): 49-111-0 — Atty.'s Reg. Nos. ☑ APPL. PAPERS ☐ CODING SHEET

FORMAT NO. 4 Applicant's Name & Address — ☑ APPL. PAPERS ☐ CODING SHEET

FORMAT NO. 5 Title of Invention — ☑ APPL. PAPERS ☐ CODING SHEET

FORMAT NO. 6&7 Correspondence Address — ☑ APPL. PAPERS ☐ CODING SHEET

FORMAT NO. 8

	RECORD	CONTINUITY CODE	PARENT APPLICATION SERIAL NUMBER	PARENT FILING DATE (Month / Day / Year)	STATUS CODE	PARENT PATENT NUMBER
	801		0			
	802		0			
	803		0			
	804		0			
	805		0			
	806		0			
	807		0			
	808		0			
	809		0			
☐ MORE ON SUPPLEMENTAL CODING SHEET	810		0			

FORMAT NO. 9

	RECORD	COUNTRY CODE	PCT/FOREIGN APPLICATION SERIAL NUMBER	FILING DATE (Month / Day / Year)
	901	JPX	207224	08 / 20 / 87
FOREIGN PRIORITY CLAIMED? ☑ YES ☐ NO	902	JPX	15585	01 / 26 / 88
	903			
	904			
	905			
	906			
☐ APPLICATION PAPERS	907			
	908			
	909			
☐ MORE ON SUPPLEMENTAL CODING SHEET	910			

Staple Issue Slip Here

INDEX OF CLAIMS

Claim		Date
Final	Original	
	1	6-89 11/6
	2	
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	4	
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Claim		Date
Final	Original	
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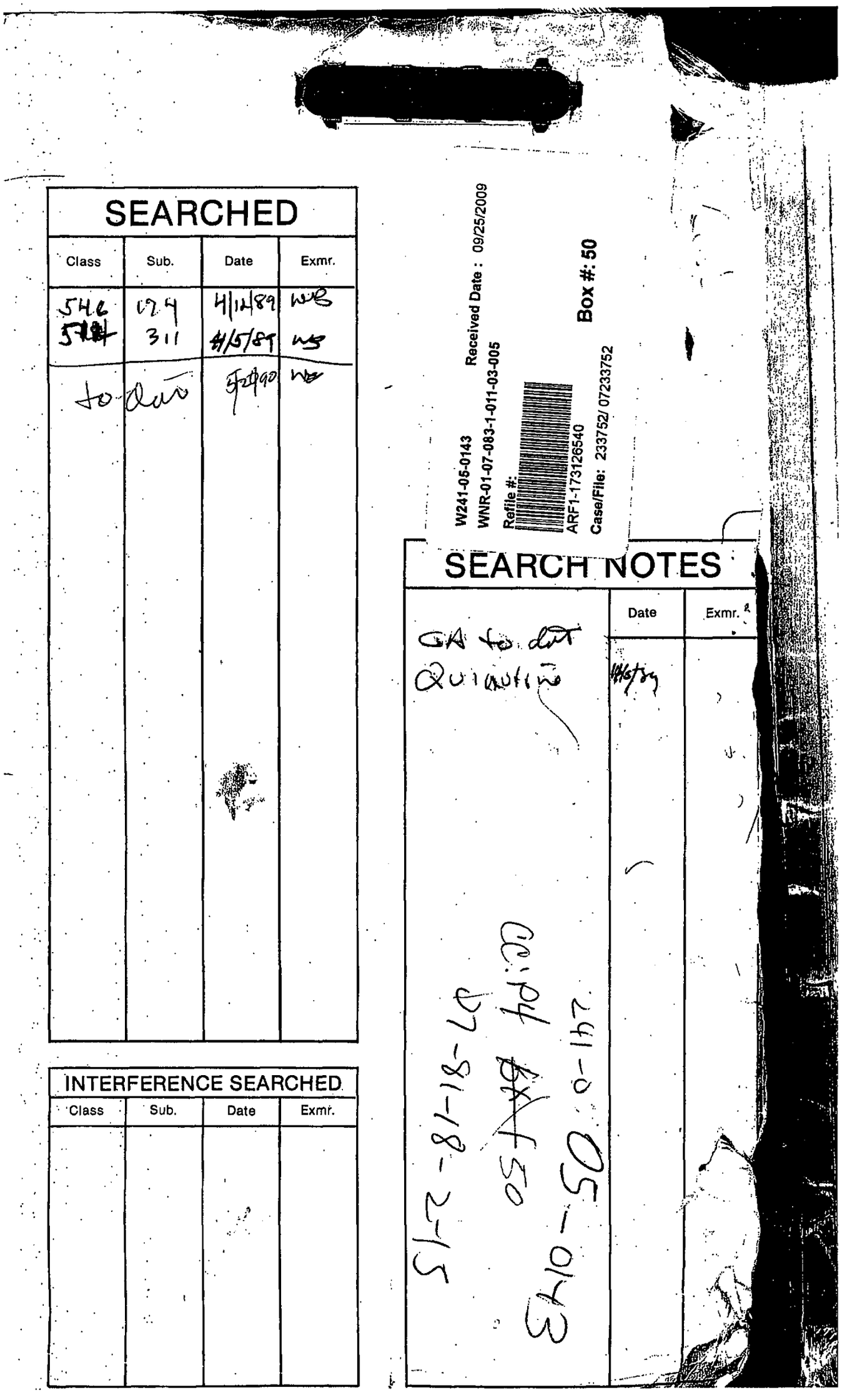


SEARCHED

Class	Sub.	Date	Exmr.
546	179	4/12/89	WB
514	311	4/5/89	WB
to date		5/2/90	WB

INTERFERENCE SEARCHED

Class	Sub.	Date	Exmr.

Received Date : 09/25/2009

W241-05-0143
WNR-01-07-083-1-011-03-005

Refile #:
ARF1-173126540

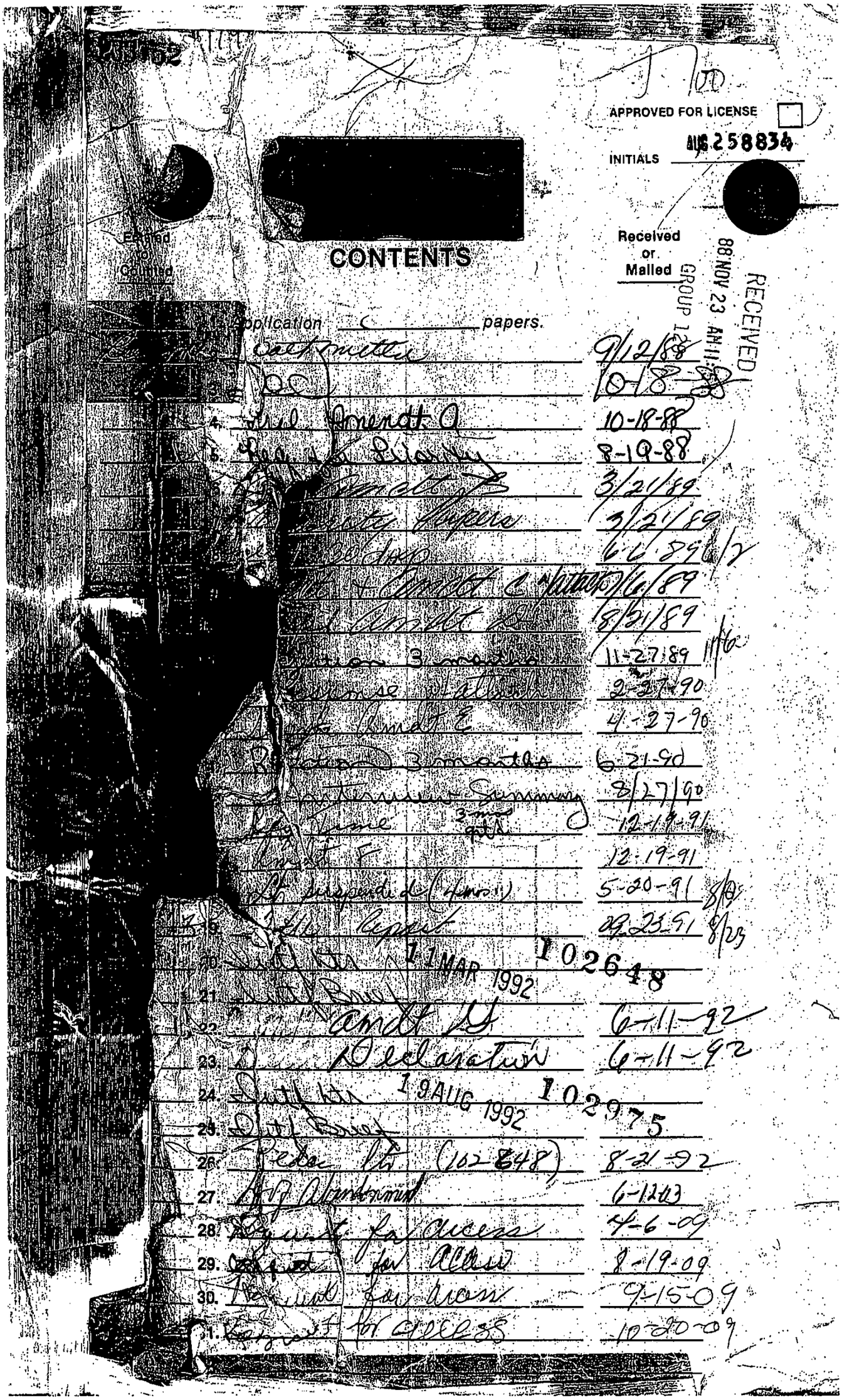
Box #: 50

Case/File: 233752/ 07233752

SEARCH NOTES

	Date	Exmr.
GA to date Quinuclidine	4/6/89	

5-17-81-18-LA
05 AX 50
Diphenyl
210-50.0-167



APPROVED FOR LICENSE ☐

INITIALS AUG 258834

Received or Mailed

RECEIVED
88 NOV 23 AM 11:58
GROUP 1

Entered in Counted

CONTENTS

Application ( ) papers.

1.	Letter		9/12/88
2.	DC		10-18-88
3.	Trial Amend A		10-18-88
4.	Rec'd Priority		8-19-88
5.	Specification		3/21/89
6.	Claims Copies		3/21/89
7.	Oath		6-6-89
8.	Amdt C Withdrawn		8/6/89
9.	Amdt B		8/31/89
10.	Ext 3 months		11-27-89
11.	Response w/Affidavit		2-27-90
12.	Amdt E		4-27-90
13.	Ext 3 months		6-21-90
14.	Petition Suspending		8/27/90
15.	Ext time 3 mos		12-19-91
16.	Amdt F		12-19-91
17.	Pet suspended (4 mos)		5-20-91
18.	Ltr Appeal		08-23-91
19.	Ltr	11 MAR 1992	102648
20.	Ltr Rec'd		
21.	Amdt G		6-11-92
22.	Declaration		6-11-92
23.	Petition	19 AUG 1992	102975
24.	Ltr Rec'd		
25.	Petn Dec (102648)		8-21-92
26.	Abandonment		6-12-03
27.	Request for Access		4-6-09
28.	Grant for Access		8-19-09
29.	Request for Access		9-15-09
30.	Grant for Access		10-20-09

APPROVED FOR LICENSE ☐

INITIALS

AUG 258834

Entered
Counted

Received
or
Mailed

RECEIVED
88 NOV 23 AM 11:58
GROUP 180

CONTENTS

1.	Application ( ) papers.	
2.	Power of Atty	9/12/88
3.	DC	10-18-88
4.	Trial Amendt A	10-18-88
5.	Fee Ltr Licensing	8-19-88
6.	Amendt B	3/21/89
7.	Petty Papers	3/21/89
8.	30 Day	6-6-89 6/7
9.	Ltr + Amdt C w/attach	8/6/89
10.	Ltr Amdt D	8/31/89
11.	Petition 3 months	11-27-89 11/6
12.	Response w/attach	2-27-90
13.	Amendt E	4-27-90
14.	Petition 3 months	6-21-90
15.	Petition Suspending	8/27/90
16.	Appeal Brief 3 mo ext	12-19-91
17.	Amdt F	12-19-91
18.	Ltr suspended (4 mos)	5-20-91 8/9
19.	Petition Appeal	08-23-91 8/23
20.	Petition 11 MAR 1992	102648
21.	Appeal Brief	
22.	Amdt G	6-11-92
23.	Declaration	6-11-92
24.	Petition 19 AUG 1992	102975
25.	Appeal Brief	
26.	Petition (102648)	8-21-92
27.	Ltr Abandonment	6-12-03
28.	Request for Access	4-6-09
29.	Request for Access	8-19-09
30.	Request for Access	9-15-09
31.	Request for Access	10-20-09

[redacted]

APPROVED FOR LICENSE ☐

INITIALS AUG 258834

CONTENTS

Received or Mailed

RECEIVED
88 NOV 23 AM 11:58
GROUP 1 [illegible]

plication (papers.	
[illegible]	9/12/88
[illegible]	10-18-88
mendt A	10-18-88
Priority	8-19-88
mett B	3/21/89
rity Papers	3/21/89
7 30 dxp	6-6-89 6/7
ect + Amett C w/attach	8/6/89
ept Amdt D	8/31/89
ection 3 months	11-27-89 11/6
Response w/attach	2-27-90
Amdt E	4-27-90
ction 3 months	6-21-90
Extension Summary	8/27/90
Time 3-mos qtr	12-14-91
ff F	12-19-91
Suspended (4 mos)	5-20-91 8/23
e Report	08-23-91 8/23
ltr 11 MAR 1992	102648
Brief	
Amdt G	6-11-92
Declaration	6-11-92
ltr 19 AUG 1992	102975
Brief	
ge ltr (102648)	8-21-92
Abandonment	6-12-03
uest for Access	4-6-04
uest for Access	8-19-04
uest for Access	9-1[illegible]-09
[illegible] Access	[illegible]2-09

SEARCHED

Class	Sub.	Date	Exmr.
546	124	4/12/89	WB
546	311	4/5/89	WB
to date		5/29/90	WB

33 Request for Access 11-3-09
34. Request for access 5-24-10
35-Request for access 12/6/10
36) Request for access 2/3/11
37) Request for Access 11/18/11
38) Request for Access 12/21/11
39) Request for Access 7/26/12 GA to date
40) Request for Access 10/24/13 WB
41) Request for access 8-13-13
42) Request for access 6-11-14
43 Request for access. 9-30-14
44) Request for access 1-28-15

INTERFERENCE SEARCHED

Class	Sub.	Date	Exmr.

Received Date : 09/25/2009
W241-05-0143

Received Date : 10/27/2009
W241-05-0143
WNR-01-07-083-1-011-03-005
Refile #:
ARF1-187735315
Case/File: 07/233,752
Box #: 50

SEARCH NOTES

Date	Exmr.
11/6/89	

5-27-81-18-LA
2-10-50-0-167