

SPECIFICATION

ACTIVATING AGENT FOR PEROXISOME PROLIFERATOR ACTIVATED RECEPTOR δ

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Technical field

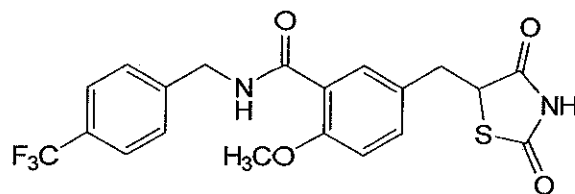
The present invention relates to an activator of peroxisome proliferator activated receptor (PPAR).

10 Prior art

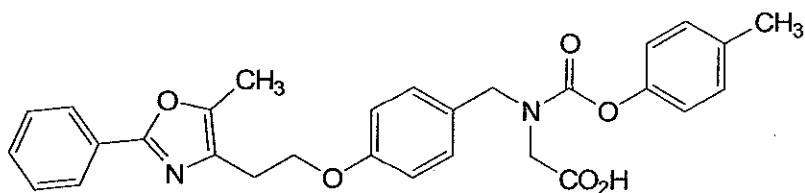
As the activator of peroxisome proliferator activated receptor (PPAR), three subtypes, namely PPAR α , PPAR γ and PPAR δ have been identified (Proc. Natl. Acad. Sci. USA, 91, p7335-7359, 1994).

15 Various compounds have been reported with respect to functions of activating transcription of the PPAR subtypes, lowering blood sugar level, or improving metabolism of lipid. For example, GW-590735 (GSK), KRP-101 (Kyorin) and NS-220 (Roche-Nippon Shinyaku) have been reported as a selective α -agonist having the function of improving metabolism of lipid (J Pharmacol Exp Ther 20 309(3): 970, Jun 2001).

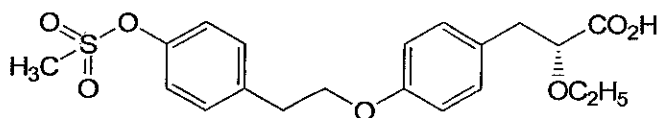
Other agents have a function as a dual agonist for PPAR γ and PPAR α . For example, TZD (thiazolidinedione) derivatives such as KRP-297 (Kyorin) and others such as 25 Muraglitazar (BMS) and Tesaglitazar (AstraZeneca), which are shown below, have been known as the agents have the function. The compounds have been developed as agents for treatment of diabetes to have a main function for PPAR α . 30 Therefore, it is reported that the compounds do not have a strong function for PPAR γ .



KRP-297 (Kyorin)

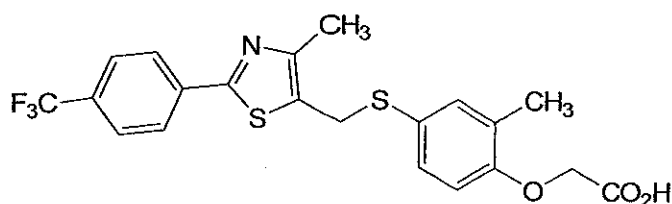


Muraglitazar (BMS)

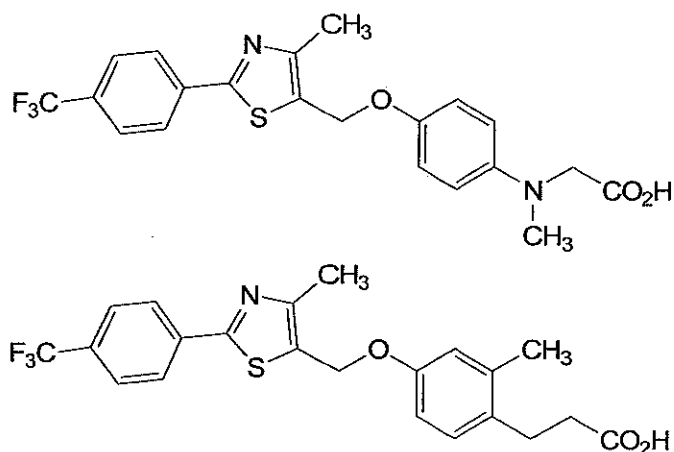


Tesaglitazar (AstraZeneca)

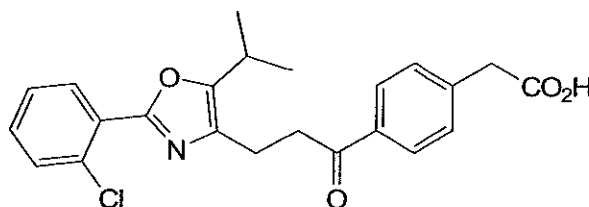
As a selective agonist for PPAR δ , GW-501516 (GSK) having the following formula of phenoxyacetic acid type has been known. WO 01/603 and Bioorg Med Chem Lett 13 (2003) 1517-1521 report that the compound has been developed as an agent for improving metabolism of lipid.



WO 01/603 further discloses the following compounds of phenylglycine type and phenylpropionic acid type.



The present inventors have filed WO 02/76957, which
5 describes that the following compound of phenylacetic
acid type has a function of activating transcription of
PPAR δ .



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The present inventors have further filed WO
03/16291, which describes that a compound of substituted
phenoxyacetic acid type also has an excellent function of
activating transcription of PPAR δ .

15 WO 04/63184 has recently discloses a compound of
phenylpropionic acid type having thiophene in its formula
as a PPAR modulator.

Bioorg Med Chem Lett 13 (2003) 1517-1521 describes
that the activating function of phenylpropionic acid type
20 for PPAR δ is about 30 times weaker than the function of
phenoxyacetic acid type.

WO 01/603 and Bioorg Med Chem Lett 13 (2003) 1517-
1521 are silent with respect to a metical effect of the
phenylglycine type.

The compounds represented by the formula (I), (II) and (III) according to the present invention differ from the above-mentioned compounds such as GW-501516. The above-mentioned documents are silent with respect to the compounds.

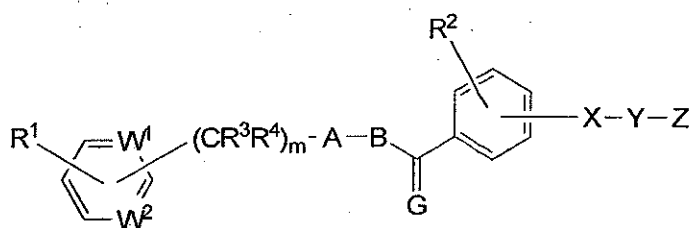
Disclosure of invention

An object of the invention is to provide compounds represented by the formula (I), (II) and (III), which have a function of activating peroxisome proliferator activated receptor.

The present inventors have studied and discovered that compounds of phenylpropionic acid type unexpectedly has an excellent function of activating peroxisome proliferator activated receptor δ , which is different from the descriptions in Bioorg Med Chem Lett 13 (2003) 1517-1521. The present invention has been completed based on the discovery.

The present invention resides in a compound having the following formula (I) or a salt thereof:

(I)



wherein each of W^1 and W^2 independently is CH or nitrogen;

X is NR^5 or CR^6R^7 , wherein R^5 is hydrogen, C_{1-8} alkyl, C_{1-8} alkyl substituted with halogen, C_{1-8} alkyl substituted with C_{1-8} alkoxy, cycloalkyl of three-membered to seven-membered ring, C_{1-8} alkyl substituted with cycloalkyl of three-membered to seven-membered ring, C_{1-8} alkyl

substituted with phenyl, C₂₋₈ acyl, or C₂₋₈ alkenyl, and each of R⁶ and R⁷ independently is hydrogen or C₁₋₈ alkyl;

Y is -(CR⁸R⁹)_n-, wherein each of R⁸ and R⁹ independently is hydrogen or C₁₋₈ alkyl, and n is 1 to 4; or

5 X and Y are combined to form -CR¹⁰=CR¹¹- or ethynylene, wherein each of R¹⁰ and R¹¹ independently is hydrogen or C₁₋₈ alkyl;

Z is carboxyl or tetrazolyl;

10 G is O, S or CR¹²R¹³, wherein each of R¹² and R¹³ independently is hydrogen or C₁₋₈ alkyl;

A is five-membered heterocyclic ring selected from the group consisting of thiazole, oxazole, imidazole, pyrazole, thiophene, furan, and pyrrole, which can be substituted with a substituent selected from the group
15 consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₈ alkoxy, halogen, C₁₋₈ alkyl substituted with halogen, C₁₋₈ alkoxy substituted with halogen, hydroxyl, nitro, C₂₋₈ acyl, C₆₋₁₀ aryl, and a five-membered or six-membered heterocyclic group;

20 B is a C₁₋₈ alkylene, C₂₋₈ alkenylene or C₂₋₈ alkynylene chain, wherein the chain can be substituted with a substituent selected from the group consisting of C₁₋₈ alkyl, cycloalkyl of three-membered to seven-membered ring, C₁₋₈ alkoxy, and halogen;

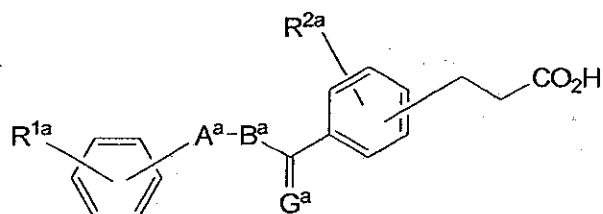
25 each of R¹ and R² independently is hydrogen, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₈ alkoxy, halogen, C₁₋₈ alkyl substituted with halogen, C₁₋₈ alkoxy substituted with halogen, hydroxyl, nitro, C₂₋₈ acyl, C₆₋₁₀ aryl, or a five-membered or six-membered heterocyclic group;

30 each of R³ and R⁴ independently is hydrogen or C₁₋₈ alkyl; and

m is an integer of 0 to 3.

The invention also resides in a compound having the following formula (II) or a salt thereof:

(II)



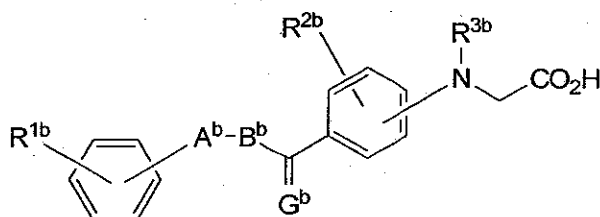
wherein G^a is O, S or CH_2 ;

5 A^a is five-membered heterocyclic ring selected from the group consisting of thiazole, oxazole, and thiophene, which can be substituted with a substituent selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, halogen, C_{1-8} alkyl substituted with halogen, C_{1-8} alkoxy substituted with halogen, hydroxyl, nitro, and C_{2-8} acyl;

10 B^a is a C_{1-8} alkylene or C_{2-8} alkenylene chain; and each of R^{1a} and R^{2a} independently is hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, halogen, C_{1-8} alkyl substituted with halogen, C_{1-8} alkoxy substituted with halogen, hydroxyl, 15 nitro, or C_{2-8} acyl.

The invention further resides in a compound having the following formula (III) or a salt thereof:

(III)



20

wherein G^b is O, S or CH_2 ;

A^b is five-membered heterocyclic ring selected from the group consisting of thiazole, oxazole, and thiophene, which can be substituted with a substituent selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, halogen, 25 C_{1-8} alkyl substituted with halogen, C_{1-8} alkoxy substituted with halogen, hydroxyl, nitro, and C_{2-8} acyl;

B^b is a C₁₋₈ alkylene or C₂₋₈ alkenylene chain;
each of R^{1b} and R^{2b} independently is hydrogen, C₁₋₈
alkyl, C₁₋₈ alkoxy, halogen, C₁₋₈ alkyl substituted with
halogen, C₁₋₈ alkoxy substituted with halogen, hydroxyl,
5 nitro, or C₂₋₈ acyl; and
R^{3b} is hydrogen or C₁₋₈ alkyl.

The present invention relates to an activator of
peroxisome proliferator activated receptor δ which con-
tains as an effective component a compound having the
10 formula (I), (II), or (III) or a salt thereof.

The invention also relates to a method of activating
peroxisome proliferator activated receptor δ , character-
ized in that effective dose of a compound having the for-
mula (I), (II), or (III) or a salt thereof is adminis-
15 tered as an effective component.

The invention further relates to a method for treat-
ment and/or prophylaxis of a disease mediated by per-
oxisome proliferator activated receptor δ , such as dyslip-
idemia, metabolic syndrome, obesity including internal-
20 organs fat type, atherosclerosis or disease associated
therewith, or diabetes, characterized in that effective
dose of a compound having the formula (I), (II), or (III)
or a salt thereof is administered as an effective compo-
nent.

25 The invention furthermore relates to use of a com-
pound having the formula (I), (II), or (III) or a salt
thereof for treatment and/or prophylaxis of a disease me-
diated by peroxisome proliferator activated receptor δ ,
such as dyslipidemia, metabolic syndrome, obesity includ-
30 ing internal-organs fat type, atherosclerosis or disease
associated therewith, or diabetes.

Best embodiments of invention

The present invention is described below in more de-
35 tail.

In the formula (I), R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , a substituent of the five-membered heterocyclic ring represented by A, and a substituent of the C_{1-8} alkylene, C_{2-8} alkenylene or C_{2-8} alkynylene chain represented by B can be C_{1-8} alkyl. Examples of the C_{1-8} alkyl include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl and hexyl.

R^1 , R^2 , R^5 , and a substituent of the five-membered heterocyclic ring represented by A can be C_{2-8} alkenyl. Examples of the C_{2-8} alkenyl include vinyl and allyl.

R^1 , R^2 , and a substituent of the five-membered heterocyclic ring represented by A can be C_{2-8} alkynyl. Examples of the C_{2-8} alkynyl include propargyl.

R^1 , R^2 , a substituent of the five-membered heterocyclic ring represented by A, and a substituent of the C_{1-8} alkylene, C_{2-8} alkenylene or C_{2-8} alkynylene chain represented by B can be C_{1-8} alkoxy. Examples of the C_{1-8} alkoxy include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentyloxy, and hexyloxy.

R^1 , R^2 , a substituent of the five-membered heterocyclic ring represented by A, and a substituent of the C_{1-8} alkylene, C_{2-8} alkenylene or C_{2-8} alkynylene chain represented by B can be halogen. Examples of the halogen include fluorine, chlorine, and bromine.

R^1 , R^2 , R^5 , and a substituent of the five-membered heterocyclic ring represented by A can be C_{1-8} alkyl substituted with halogen. Examples of the C_{1-8} alkyl substituted with halogen include methyl, ethyl, propyl, isopropyl, butyl, and t-butyl which are substituted with 1-3 halogens such as fluorine, chlorine, and bromine. Preferred are trifluoromethyl, chloromethyl, 2-chloroethyl, 2-bromoethyl, and 2-fluoroethyl.

R^1 , R^2 , and a substituent of the five-membered heterocyclic ring represented by A can be C_{1-8} alkoxy substituted with halogen. Examples of the C_{1-8} alkoxy substi-

tuted with halogen include methoxy, ethoxy, propoxy, isopropoxy, butoxy, and t-butoxy which are substituted with 1-3 halogen atoms such as fluorine atom, chlorine atom, or bromine atom. Preferred are trifluoromethoxy, chloromethoxy, 2-chloroethoxy, 2-bromoethoxy, and 2-fluoroethoxy.

R^1 , R^2 , R^5 , and a substituent of the five-membered heterocyclic ring represented by A can be C_{2-8} acyl. Examples of the C_{2-8} acyl include acetyl and propionyl.

10 R^1 , R^2 , and a substituent of the five-membered heterocyclic ring represented by A can be C_{6-10} aryl. Examples of the C_{6-10} aryl include phenyl.

R^1 , R^2 , and a substituent of the five-membered heterocyclic ring represented by A can be a five-membered or 15 six-membered heterocyclic group. Examples of the five-membered or six-membered heterocyclic group include pyridyl.

R^5 can be C_{1-8} alkyl substituted with C_{1-8} alkoxy. Examples of the C_{1-8} alkyl substituted with C_{1-8} alkoxy 20 include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl and hexyl which are substituted with methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentyloxy, or hexyloxy.

R^5 can be cycloalkyl of three-membered to seven-membered ring. Examples of the cycloalkyl of three-membered to seven-membered ring include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

R^5 can be C_{1-8} alkyl substituted with cycloalkyl of three-membered to seven-membered ring. Examples of the 30 C_{1-8} alkyl substituted with cycloalkyl of three-membered to seven-membered ring include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl and hexyl which are substituted with cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

R⁵ can be C₁₋₈ alkyl substituted with phenyl. Examples of the C₁₋₈ alkyl substituted with phenyl include benzyl and phenethyl.

5 A substituent of the C₁₋₈ alkylene, C₂₋₈ alkenylene or C₂₋₈ alkynylene chain represented by B can be cycloalkyl of three-membered to seven-membered ring. Examples of the cycloalkyl of three-membered to seven-membered ring include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

10 In the formula (II), R^{1a}, R^{2a}, and a substituent of five-membered heterocyclic ring represented by A^a can be C₁₋₈ alkyl, C₁₋₈ alkoxy, halogen, C₁₋₈ alkyl substituted with halogen, C₁₋₈ alkoxy substituted with halogen, and C₂₋₈ acyl. Examples of them are the same as the examples
15 of R¹, R², and the substituent of the five-membered heterocyclic ring represented by A in the formula (I).

In the formula (III), R^{1b}, R^{2b}, and a substituent of five-membered heterocyclic ring represented by A^b can be C₁₋₈ alkyl, C₁₋₈ alkoxy, halogen, C₁₋₈ alkyl substituted
20 with halogen, C₁₋₈ alkoxy substituted with halogen, and C₂₋₈ acyl. Examples of them are the same as the examples of R¹, R², and the substituent of the five-membered heterocyclic ring represented by A in the formula (I).

In the formula (III), R^{3b} can be C₁₋₈ alkyl. Examples
25 are the same as the examples of R⁵ in the formula (I).

Each of R¹, R² in the formula (I), R^{1a}, R^{2a} in the formula (II), R^{1b} and R^{2b} in the formula (III) can be one to three groups attached to the rings, such as benzene ring. The two or three groups can be different from each
30 other.

Preferred compounds of the present invention are shown below.

(1) A compound having the formula (I) or a salt thereof, wherein each of W¹ and W² is CH

(2) A compound having the formula (I), a salt thereof, a compound defined in (1), or a salt thereof, wherein X is CR^6R^7

(3) A compound having the formula (I), a salt thereof, a compound defined in (1), or a salt thereof, wherein X is CH_2

(4) A compound having the formula (I), a salt thereof, a compound defined in (1), or a salt thereof, wherein X is NR^5

(5) A compound having the formula (I), a salt thereof, a compound defined in (1), or a salt thereof, wherein X is NH

(6) A compound having the formula (I), a salt thereof, a compound defined in (1), or a salt thereof, wherein X is NR^5 , and R^5 is C_{1-8} alkyl

(7) A compound having the formula (I), a salt thereof, a compound defined in one of (1) to (6), or a salt thereof, wherein Y is CH_2

(8) A compound having the formula (I), a salt thereof, a compound defined in one of (1) to (7), or a salt thereof, wherein Z is carboxyl

(9) A compound having the formula (I), a salt thereof, a compound defined in one of (1) to (8), or a salt thereof, wherein G is O

(10) A compound having the formula (I), a salt thereof, a compound defined in one of (1) to (9), or a salt thereof, wherein A is thiazole, which can be substituted with a substituent selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, halogen, C_{1-8} alkyl substituted with halogen, C_{1-8} alkoxy substituted with halogen, hydroxyl, nitro, C_{2-8} acyl, C_{6-10} aryl, and a five-membered or six-membered heterocyclic group

(11) A compound having the formula (I), a salt thereof, a compound defined in one of (1) to (10), or a salt thereof, wherein B is ethylene chain

5 (12) A compound having the formula (I), a salt thereof, a compound defined in one of (1) to (11), or a salt thereof, wherein each of R^1 and R^2 independently is hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{1-8} alkoxy, halogen, C_{1-8} alkyl substituted with halogen, or C_{1-8} alkoxy substituted with halogen

10 (13) A compound having the formula (I), a salt thereof, a compound defined in one of (1) to (11), or a salt thereof, wherein each of R^1 and R^2 independently is hydrogen, C_{1-8} alkyl, halogen, or C_{1-8} alkyl substituted with halogen

15 (14) A compound having the formula (I), a salt thereof, a compound defined in one of (1) to (13), or a salt thereof, wherein each of R^3 and R^4 is hydrogen

(15) A compound having the formula (I), a salt thereof, a compound defined in one of (1) to (14), or a salt thereof, wherein m is 0

20 (16) A compound having the formula (II) or a salt thereof, wherein G^a is O.

(17) A compound having the formula (II), a salt thereof, a compound defined in (16), or a salt thereof, wherein A^a is thiazole, which can be substituted with a substituent selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, halogen, C_{1-8} alkyl substituted with halogen, C_{1-8} alkoxy substituted with halogen, hydroxyl, nitro, and C_{2-8} acyl.

30 (18) A compound having the formula (II), a salt thereof, a compound defined in (16) or (17), or a salt thereof, wherein B^a is ethylene chain.

(19) A compound having the formula (II), a salt thereof, a compound defined in one of (16) to (18), or a salt thereof, wherein each of R^{1a} and R^{2a} independently is

hydrogen, C₁₋₈ alkyl, C₁₋₈ alkoxy, halogen, C₁₋₈ alkyl substituted with halogen, or C₁₋₈ alkoxy substituted with halogen.

5 (20) A compound having the formula (III) or a salt thereof, wherein G^b is O.

(21) A compound having the formula (III), a salt thereof, a compound defined in (20), or a salt thereof, wherein A^b is thiazole, which can be substituted with a substituent selected from the group consisting of C₁₋₈ al-
10 kyl, C₁₋₈ alkoxy, halogen, C₁₋₈ alkyl substituted with halogen, C₁₋₈ alkoxy substituted with halogen, hydroxyl, nitro, and C₂₋₈ acyl.

(22) A compound having the formula (III), a salt thereof, a compound defined in (20) or (21), or a salt thereof, wherein B^b is ethylene chain.
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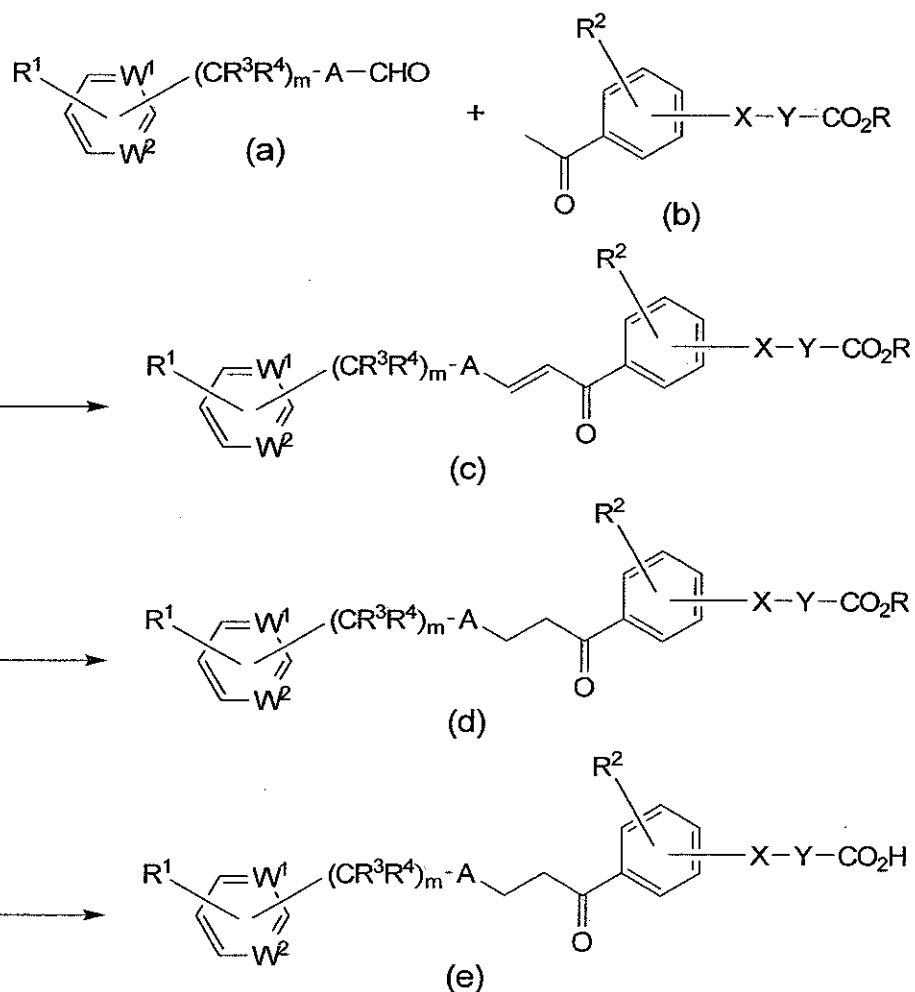
(23) A compound having the formula (III), a salt thereof, a compound defined in one of (20) to (22), or a salt thereof, wherein each of R^{1b} and R^{2b} independently is hydrogen, C₁₋₈ alkyl, C₁₋₈ alkoxy, halogen, C₁₋₈ alkyl substituted with halogen, or C₁₋₈ alkoxy substituted with halogen.
20

The compound having the formula (I), (II), or (III) can be present in the form of a pharmaceutically acceptable salt. Examples of the salt include an alkali metal
25 salt, such as sodium salt, potassium salt and lithium salt.

The compound of the present invention can also be present in the form of an optical isomer such as enantiomer or racemic body, or a geometrical isomer such as cis
30 or trans. These isomers are included in the scope of the present invention.

The processes for preparing the compound of the formula (I) according to the invention are described below.

Synthetic process 1 (wherein G is O, B is ethylene, and Z is carboxyl)



In the formulas, R is lower alkyl, and each of W¹, W², X, Y, A, R¹, R², R³, R⁴, and m are described above.

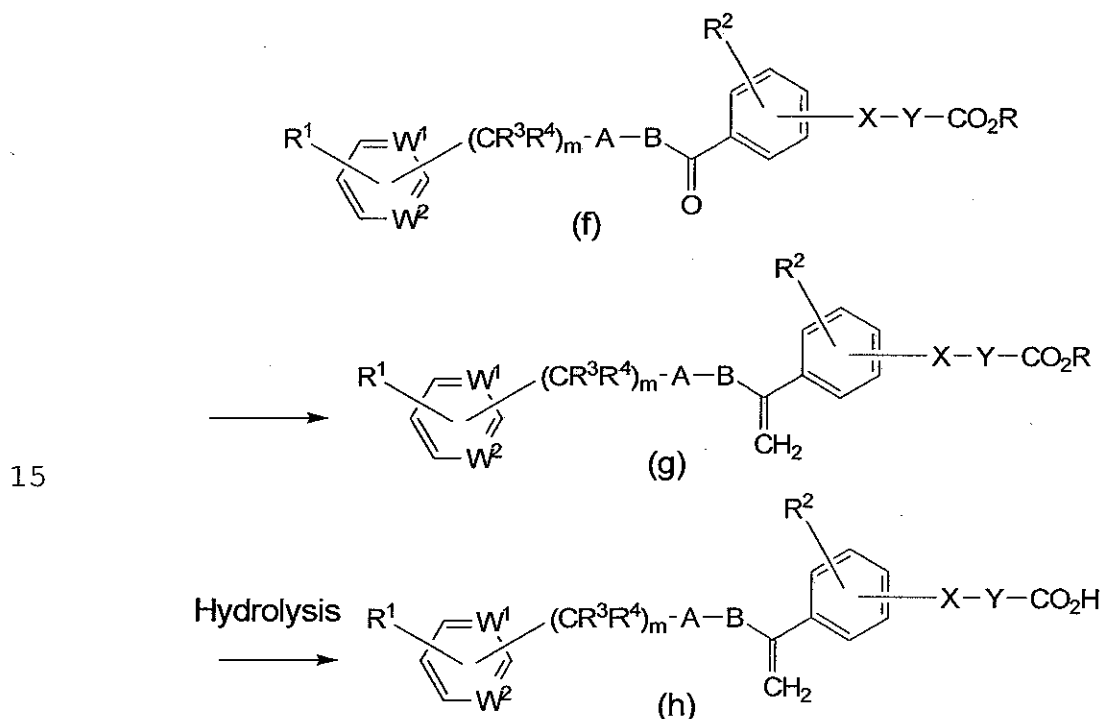
The compound of the formula (c) can be prepared by reacting the aldehyde of the formula (a) with the acetophenone derivative of the formula (b) in the presence of a base such as sodium methoxide or sodium ethoxide in an inert solvent such as THF, methanol, or ethanol.

A catalytic hydrogen reduction reaction of the obtained compound of the formula (c) is carried out in the presence of palladium-active carbon in an inert solvent

such as THF or methanol to obtain an ester of the formula (d). A hydrolytic reaction of the ester of the formula (d) is carried out in the presence of lithium hydroxide or the like to obtain the compound of the formula (e) according to the present invention.

In the case that X-Y-CO₂H is propionic acid, an acrylic ester can be used as the compound of the formula (b). In this case, the acrylic ester is reduced to the propionic ester at the step of reducing the formula (c) to obtain the formula (d).

Synthetic process 2 (wherein G is CH₂, and Z is carboxyl)

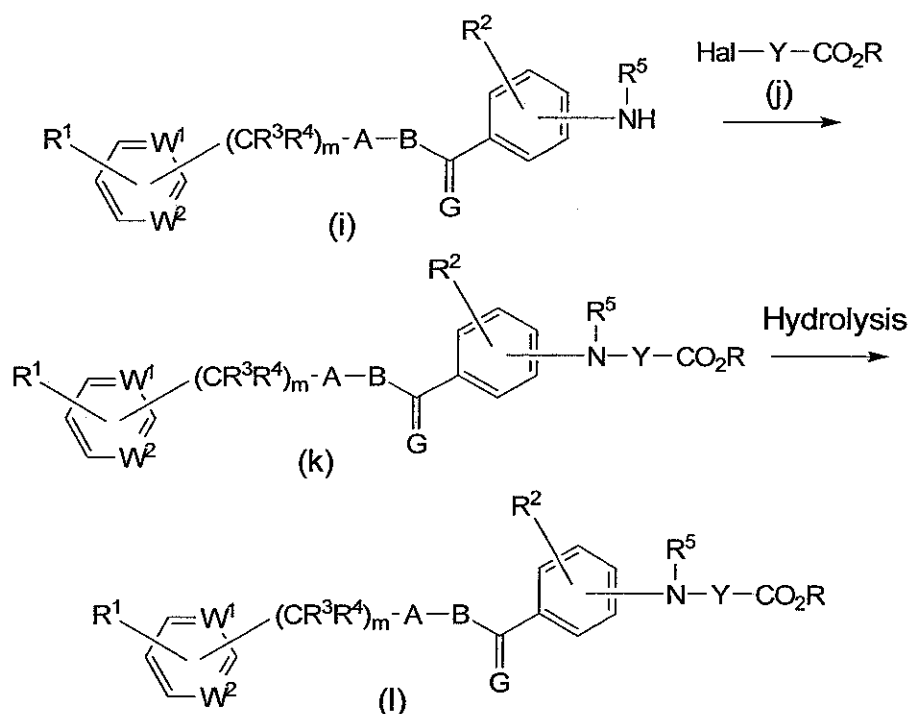


In the formulas, R is lower alkyl, and each of W¹, W², X, Y, A, B, R¹, R², R³, R⁴, and m are described above.

The ester of the formula (g) can be prepared by reacting the ketone of the formula (f) with methyl-triphenylphosphonium bromide, sodium amide in an inert solvent such as THF. A hydrolytic reaction of the ester

of the formula (g) is carried out in the presence of lithium hydroxide to obtain the compound of the formula (h) according to the present invention.

5 Synthetic process 3 (wherein X is NR^5 , and Z is carboxyl)



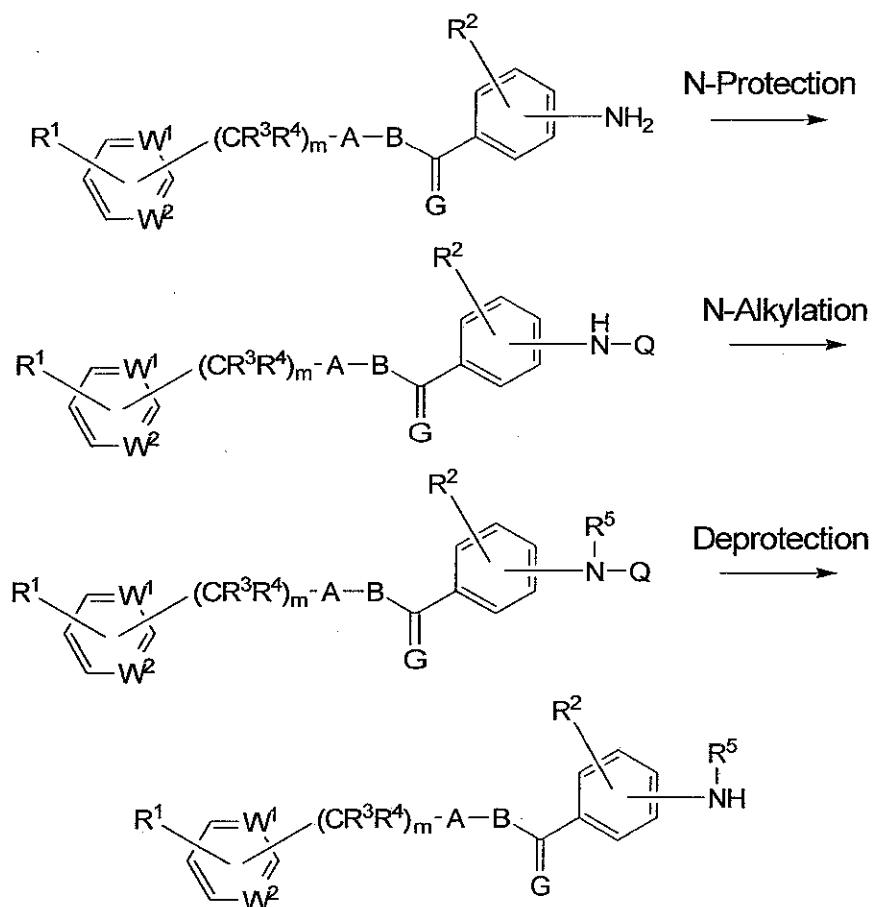
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In the formulas, R is lower alkyl, hal is halogen, and each of W^1 , W^2 , Y, A, B, R^1 , R^2 , R^3 , R^4 , R^5 , and m are described above.

The ester of the formula (k) can be prepared by reacting the amine of the formula (i) with the aliphatic ester of the formula (j). A hydrolytic reaction of the ester of the formula (k) is carried out to obtain the compound of (l) according to the present invention.

The amine of the formula (i) as a starting material in which R^5 is alkyl can be prepared according to the following reaction.

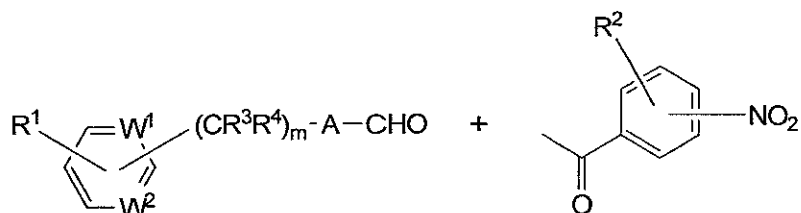
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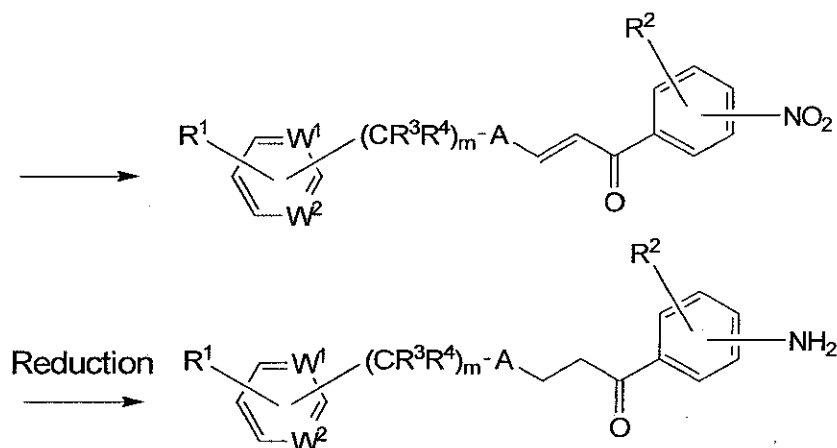


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In the formulas, R⁵ is alkyl, Q is a protective group for o-nitrobenzenesulfonyl or the like, and each of W¹, W², A, B, R¹, R², R³, R⁴, and m are described above.

The amine of the formula (i) as a starting material in which R⁵ is H can be prepared according to the following reaction.



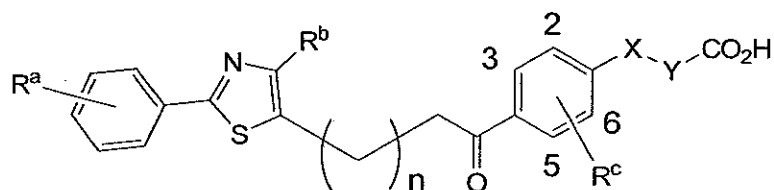


In the formulas, each of W^1 , W^2 , A, R^1 , R^2 , R^3 , R^4 ,
 5 and m are described above.

The compound of the present invention of the formula
 (I), (II) or (III) can be prepared by referring to the
 above-mentioned synthetic processes, the below-mentioned
 examples, and the above-mentioned patent or known docu-
 10 ments.

Examples of the compounds of the present invention
 are shown in the following Tables 1 to 37.

(1)



15

In the formula, X, Y, R^a , R^b , R^c , and n are set forth
 in Tables 1 to 3.

TABLE 1

X	Y	R ^a	R ^b	R ^c	n
CH ₂	CH ₂	4-CF ₃	Isopropyl	2-CH ₃	1
CH ₂	CH ₂	4-CH ₃	Hexyl	2-CH ₃	1
CH ₂	C(CH ₃) ₂	4-CF ₃	Propyl	2-CH ₃	1
CH ₂	CH(CH ₃)	4-CF ₃	sec-Butyl	3-CH ₃	1
CH ₂	CH(C ₂ H ₅)	4-CF ₃	tert-Butyl	3-CH ₃	2
CH ₂	CH(Propyl)	4-CF ₃	Hexyl	2,6-CH ₃	3
CH ₂	(CH ₂) ₂	4-CF ₃	Isopropyl	2-CH ₃	3
CH ₂	(CH ₂) ₂	4-CF ₃	Cyclopropyl	3,5-CH ₃	3
CH(CH ₃)	CH ₂	4-CF ₃	Cyclopropylmethyl	2-Allyl	1
CH ₂	CH ₂	4-CF ₃	4-CF ₃ -Phenyl	2-Propyl	2
CH ₂	CH ₂	2,4-Cl	CH ₃ OCH ₂ CH ₂	2-CH ₃ O	2
CH ₂	CH ₂	2-OH, 4-CF ₃	Isopropyl	2-Cl	1

TABLE 2

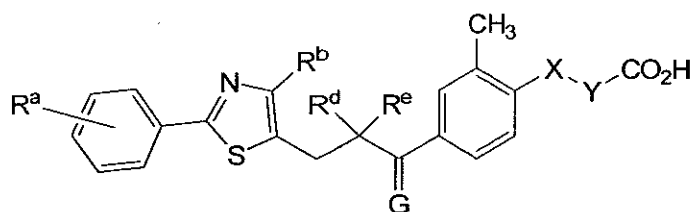
5

X	Y	R ^a	R ^b	R ^c	n
CH ₂	CH ₂	4-CH ₃	Heptyl	2,6-CH ₃	1
NH	CH ₂	4-CF ₃	Isopropyl	H	1
N(CH ₃)	CH ₂	4-CF ₃	Isopropyl	H	1
N(CH ₃)	CH ₂	4-CF ₃	Isopropyl	2-CH ₃	1
N(C ₂ H ₅)	CH ₂	4-CF ₃	Isopropyl	2-CH ₃	1
N(Allyl)	CH ₂	4-CF ₃	Isopropyl	2-CH ₃	1
N(Acetyl)	CH ₂	2-OH, 4-Cl	Isopropyl	3-CH ₃	3
NH	CH ₂	4-CF ₃	Isopropyl	2-CH ₃	1
N(CH ₃)	(CH ₂) ₂	4-CF ₃	Isopropyl	2-CH ₃	1
CH ₂	CH ₂	4-CN	Isopropyl	2-OH	2
CH ₂	CH ₂	4-t-Butyl	Isopropyl	2-Acetyl	1
CH ₂	CH ₂	4-Isopropyl	Isopropyl	2-CF ₃	1

TABLE 3

X	Y	R ^a	R ^b	R ^c	n
CH ₂	(CH ₂) ₃	4-CF ₃ O	Butyl-OCH ₂	2-CH ₃	2
CH ₂	CH ₂	4-CF ₃	Butyl-OCH ₂	2-CH ₃	3
CH ₂	CH ₂	4-CF ₃ O	CH ₃ O(CH ₂) ₅	2-CH ₃ O	3
NH	CH ₂	4-CF ₃ O	CH ₃ O(CH ₂) ₅	2-CH ₃ O	1
N(CH ₃)	CH ₂	4-t-Butyl	Cyclohexyl	2-F	2
N(CH ₃)	CH ₂	4-CF ₃	Hexyl	2-F	1
N(C ₂ H ₅)	CH ₂	4-CF ₃	(CH ₃) ₂ CH(CH ₂) ₅	2,5-CH ₃	1
N(Allyl)	CH ₂	4-CF ₃	4-CF ₃ -Benzyl	2,5-CH ₃	1
N(Ac)	CH ₂	2,4-CH ₃	Isopropyl	2-CH ₃	1
N(CH ₃)	(CH ₂) ₂	4-Acetyl	Isopropyl	2-CH ₃	2

5 (2)

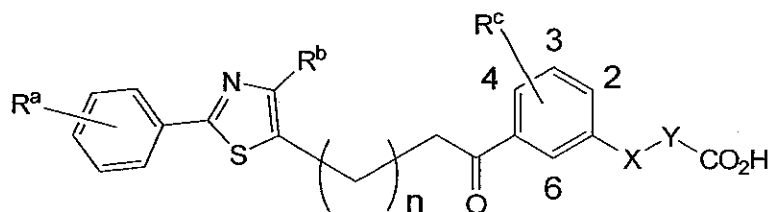


In the formula, X, Y, R^a, R^b, R^d, R^e, and G are set forth in Table 4.

TABLE 4

X	Y	R ^a	R ^b	R ^d /R ^e	G
CH ₂	CH ₂	4-CF ₃	Isopropyl	H/H	CH ₂
CH(CH ₃)	CH ₂	4-CF ₃	Cyclopropylmethyl	H/H	S
CH ₂	CH ₂	4-CF ₃	4-CF ₃ -Phenyl	H/H	C(CH ₃) ₂
CH ₂	CH ₂	4-CH ₃	Heptyl	H/H	CH ₂
NH	CH ₂	4-CF ₃	Isopropyl	H/H	S
N(CH ₃)	(CH ₂) ₂	4-CF ₃	Isopropyl	H/H	CH ₂
CH ₂	CH ₂	4-CN	Isopropyl	H/H	C(CH ₃) ₂
CH ₂	(CH ₂) ₃	4-CF ₃ O	Butyl-OCH ₂	CH ₃ /H	CH ₂
CH ₂	CH ₂	4-CF ₃ O	CH ₃ O(CH ₂) ₅	CH ₃ /H	O
N(CH ₃)	CH ₂	4-t-Butyl	Cyclohexyl	Propyl/H	O
N(C ₂ H ₅)	CH ₂	4-CF ₃	(CH ₃) ₂ CH(CH ₂) ₅	CH ₃ /H	O
N(Allyl)	CH ₂	4-CF ₃	4-CF ₃ -Benzyl	H/H	S
N(Acetyl)	CH ₂	2,4-CH ₃	Isopropyl	CH ₃ /CH ₃	CH ₂

(3)



5

In the formula, X, Y, R^a, R^b, R^c, and n are set forth in Tables 5 and 6.

TABLE 5

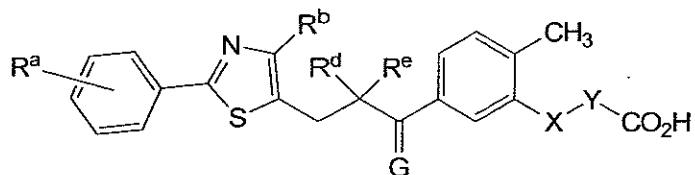
X	Y	R ^a	R ^b	R ^c	n
CH ₂	CH ₂	4-CF ₃	Isopropyl	2-CH ₃	2
CH ₂	CH ₂	4-CH ₃	Hexyl	2-CH ₃	2
CH ₂	C(CH ₃) ₂	4-CF ₃	Propyl	2-CH ₃	1
CH ₂	CH(CH ₃)	4-CF ₃	sec-Butyl	3-CH ₃	1
CH ₂	CH(C ₂ H ₅)	4-CF ₃	tert-Butyl	3-CH ₃	2
CH ₂	CH(Propyl)	4-CF ₃	Hexyl	2,6-CH ₃	3
CH ₂	(CH ₂) ₃	4-CF ₃	Isopropyl	4-CH ₃	1
CH ₂	(CH ₂) ₃	4-CF ₃	Cyclopropyl	3,6-CH ₃	1
CH ₂	CH ₂	2-OH, 4-CF ₃	Isopropyl	2-Cl	1
NH	CH ₂	4-CF ₃	Isopropyl	H	1

TABLE 6

5

X	Y	R ^a	R ^b	R ^c	n
N(CH ₃)	CH ₂	4-CF ₃	Isopropyl	H	1
N(CH ₃)	CH ₂	4-CF ₃	Isopropyl	CH ₃	1
N(C ₂ H ₅)	CH ₂	4-CF ₃	Isopropyl	H	1
N(Allyl)	CH ₂	4-CF ₃	Isopropyl	H	1
N(Acetyl)	CH ₂	2-OH, 4-Cl	Isopropyl	3-CH ₃	3
CH ₂	CH ₂	4-Isopropyl	Isopropyl	2-CF ₃	1
CH ₂	CH ₂	4-CF ₃	Butyl-OCH ₂	2-CH ₃	3
NH	CH ₂	4-CF ₃ O	CH ₃ O(CH ₂) ₅	2-CH ₃ O	1
N(CH ₃)	CH ₂	4-CF ₃	Hexyl	2-F	1
N(CH ₃)	(CH ₂) ₂	4-Acetyl	Isopropyl	2-CH ₃	2

(4)

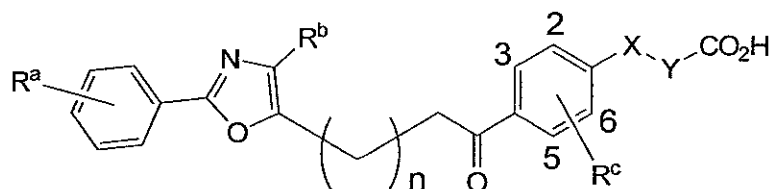


In the formula, X, Y, R^a , R^b , R^d , R^e , and G are set forth in Table 7.

TABLE 7

X	Y	R^a	R^b	R^d/R^e	G
CH ₂	CH ₂	4-CF ₃	Isopropyl	H/H	CH ₂
CH(CH ₃)	CH ₂	4-CF ₃	Cyclopropylmethyl	H/H	S
CH ₂	CH ₂	4-CF ₃	4-CF ₃ -Phenyl	H/H	C(CH ₃) ₂
CH ₂	CH ₂	4-CH ₃	Heptyl	H/H	CH ₂
NH	CH ₂	4-CF ₃	Isopropyl	H/H	S
N(CH ₃)	(CH ₂) ₂	4-CF ₃	Isopropyl	H/H	CH ₂
CH ₂	CH ₂	4-CN	Isopropyl	H/H	C(CH ₃) ₂
CH ₂	(CH ₂) ₃	4-CF ₃ O	Butyl-OCH ₂	CH ₃ /CH ₃	CH ₂
N(Allyl)	CH ₂	4-CF ₃	4-CF ₃ -Benzyl	H/H	S
N(Acetyl)	CH ₂	2,4-CH ₃	Isopropyl	CH ₃ /CH ₃	CH ₂

10 (5)



In the formula, X, Y, R^a , R^b , R^c , and n are set forth in Tables 8 and 9.

15

TABLE 8

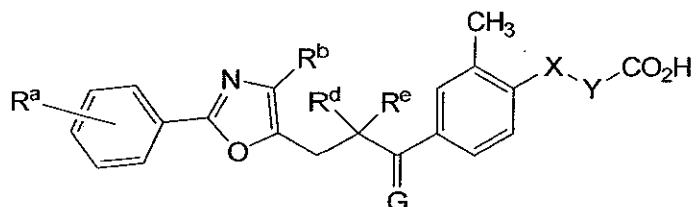
X	Y	R ^a	R ^b	R ^c	n
CH ₂	CH ₂	4-CF ₃	Isopropyl	2-CH ₃	1
CH ₂	CH ₂	4-CH ₃	Hexyl	2-CH ₃	1
CH ₂	C(CH ₃) ₂	4-CF ₃	Propyl	2-CH ₃	1
CH ₂	CH(CH ₃)	4-CF ₃	sec-Butyl	3-CH ₃	1
CH ₂	CH(C ₂ H ₅)	4-CF ₃	tert-Butyl	3-CH ₃	2
CH ₂	CH(Propyl)	4-CF ₃	Hexyl	2,6-CH ₃	3
CH ₂	(CH ₂) ₂	4-CF ₃	Isopropyl	3-CH ₃	3
CH ₂	(CH ₂) ₂	4-CF ₃	Cyclopropyl	3,5-CH ₃	3
CH ₂	CH ₂	2-OH, 4-CF ₃	Isopropyl	2-Cl	1
NH	CH ₂	4-CF ₃	Isopropyl	H	1

TABLE 9

5

X	Y	R ^a	R ^b	R ^c	n
N(CH ₃)	CH ₂	4-CF ₃	Isopropyl	H	1
N(CH ₃)	CH ₂	4-CF ₃	Isopropyl	2-CH ₃	1
N(C ₂ H ₅)	CH ₂	4-CF ₃	Isopropyl	H	1
N(Allyl)	CH ₂	4-CF ₃	Isopropyl	H	1
N(Acetyl)	CH ₂	2-OH, 4-Cl	Isopropyl	H	3
CH ₂	CH ₂	4-Isopropyl	Isopropyl	2-CF ₃	1
CH ₂	CH ₂	4-CF ₃	Butyl-OCH ₂	2-CH ₃	3
NH	CH ₂	4-CF ₃ O	CH ₃ O(CH ₂) ₅	2-CH ₃ O	1
N(CH ₃)	CH ₂	4-CF ₃	Hexyl	2-F	1
N(CH ₃)	(CH ₂) ₂	4-Acetyl	Isopropyl	2-CH ₃	2

(6)

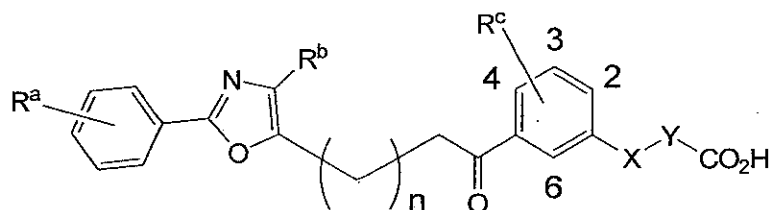


In the formula, X, Y, R^a, R^d, R^e, and G are set forth
5 in Table 10.

TABLE 10

X	Y	R ^a	R ^b	R ^d /R ^e	G
CH ₂	CH ₂	4-CF ₃	Isopropyl	H/H	CH ₂
CH(CH ₃)	CH ₂	4-CF ₃	Cyclopropylmethyl	H/H	S
CH ₂	CH ₂	4-CF ₃	4-CF ₃ -Phenyl	H/H	C(CH ₃) ₂
CH ₂	CH ₂	2,4-Cl	CH ₃ OCH ₂ CH ₂	CH ₃ /H	O
CH ₂	CH ₂	4-CH ₃	Heptyl	H/H	CH ₂
NH	CH ₂	4-CF ₃	Isopropyl	H/H	S
N(CH ₃)	(CH ₂) ₂	4-CF ₃	Isopropyl	H/H	CH ₂
CH ₂	CH ₂	4-CN	Isopropyl	H/H	C(CH ₃) ₂
CH ₂	CH ₂	4-t-Butyl	Isopropyl	C ₂ H ₅ /H	O
CH ₂	(CH ₂) ₃	4-CF ₃ O	Butyl-OCH ₂	CH ₃ /CH ₃	CH ₂
CH ₂	CH ₂	4-CF ₃ O	CH ₃ O(CH ₂) ₅	CH ₃ /CH ₃	O
N(CH ₃)	CH ₂	4-t-Butyl	Cyclohexyl	CH ₃ /CH ₃	O
N(C ₂ H ₅)	CH ₂	4-CF ₃	(CH ₃) ₂ CH(CH ₂) ₅	CH ₃ /CH ₃	O
N(Allyl)	CH ₂	4-CF ₃	4-CF ₃ -Benzyl	H/H	S
N(Acetyl)	CH ₂	2,4-CH ₃	Isopropyl	CH ₃ /CH ₃	CH ₂

(7)



In the formula, X, Y, R^a, R^b, R^c, and n are set forth
5 in Tables 11 to 13.

TABLE 11

X	Y	R ^a	R ^b	R ^c	n
CH ₂	CH ₂	4-CF ₃	Isopropyl	2-CH ₃	1
CH ₂	CH ₂	4-CH ₃	Hexyl	2-CH ₃	1
CH ₂	CH ₂	4-CF ₃	Isopropyl	2-CH ₃	2
CH ₂	C(CH ₃) ₂	4-CF ₃	Propyl	2-CH ₃	1
CH ₂	CH(CH ₃)	4-CF ₃	sec-Butyl	3-CH ₃	1
CH ₂	CH(C ₂ H ₅)	4-CF ₃	tert-Butyl	3-CH ₃	2
CH ₂	CH(Propyl)	4-CF ₃	Hexyl	2,6-CH ₃	3
CH ₂	(CH ₂) ₂	4-CF ₃	Isopropyl	2-CH ₃	1
CH ₂	(CH ₂) ₂	4-CF ₃	Cyclopropyl	3,4-CH ₃	3
CH(CH ₃)	CH ₂	4-CF ₃	Cyclopropylmethyl	2-Allyl	1
CH ₂	CH ₂	4-CF ₃	4-CF ₃ -Phenyl	2-Propyl	2
CH ₂	CH ₂	2,4-Cl	CH ₃ OCH ₂ CH ₂	2-CH ₃ O	2

TABLE 12

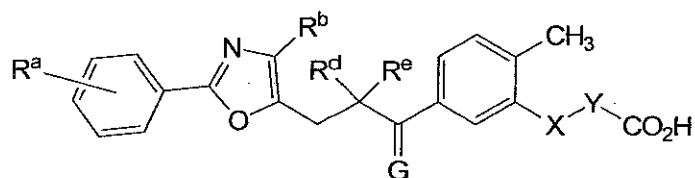
X	Y	R ^a	R ^b	R ^c	n
CH ₂	CH ₂	2-OH, 4-CF ₃	Isopropyl	2-Cl	1
CH ₂	CH ₂	4-CH ₃	Heptyl	2,6-CH ₃	1
NH	CH ₂	4-CF ₃	Isopropyl	H	1
N(CH ₃)	CH ₂	4-CF ₃	Isopropyl	H	1
N(CH ₃)	CH ₂	4-CF ₃	Isopropyl	2-CH ₃	1
N(C ₂ H ₅)	CH ₂	4-CF ₃	Isopropyl	H	1
N(Allyl)	CH ₂	4-CF ₃	Isopropyl	H	1
N(Acetyl)	CH ₂	2-OH, 4-Cl	Isopropyl	H	3
NH	CH ₂	4-CF ₃	Isopropyl	2-CH ₃	1
N(CH ₃)	(CH ₂) ₂	4-CF ₃	Isopropyl	2-CH ₃	1
CH ₂	CH ₂	4-CN	Isopropyl	2-OH	2
CH ₂	CH ₂	4-t-Butyl	Isopropyl	2-Acetyl	1

TABLE 13

5

X	Y	R ^a	R ^b	R ^c	n
CH ₂	CH ₂	4-Isopropyl	Isopropyl	2-CF ₃	1
CH ₂	(CH ₂) ₃	4-CF ₃ O	Butyl-OCH ₂	2-CH ₃	2
CH ₂	CH ₂	4-CF ₃	Butyl-OCH ₂	2-CH ₃	3
CH ₂	CH ₂	4-CF ₃ O	CH ₃ O(CH ₂) ₅	2-CH ₃ O	3
NH	CH ₂	4-CF ₃ O	CH ₃ O(CH ₂) ₅	2-CH ₃ O	1
N(CH ₃)	CH ₂	4-t-Butyl	Cyclohexyl	2-F	2
N(CH ₃)	CH ₂	4-CF ₃	Hexyl	2-F	1
N(C ₂ H ₅)	CH ₂	4-CF ₃	(CH ₃) ₂ CH(CH ₂) ₅	2,6-CH ₃	1
N(Allyl)	CH ₂	4-CF ₃	4-CF ₃ -Benzyl	2,6-CH ₃	1
N(Acetyl)	CH ₂	2,4-CH ₃	Isopropyl	2-CH ₃	1
N(CH ₃)	(CH ₂) ₂	4-Acetyl	Isopropyl	2-CH ₃	2

(8)

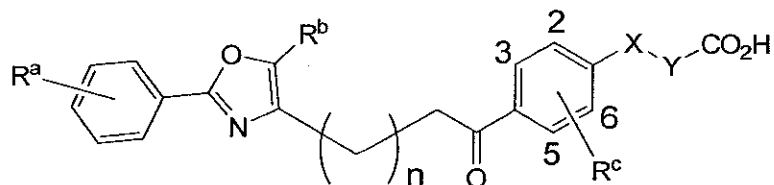


In the formula, X, Y, R^a, R^b, R^d, R^e, and G are set
5 forth in Table 14.

TABLE 14

X	Y	R ^a	R ^b	R ^d /R ^e	G
CH ₂	CH ₂	4-CF ₃	Isopropyl	H/H	CH ₂
CH(CH ₃)	CH ₂	4-CF ₃	Cyclopropylmethyl	H/H	S
CH ₂	CH ₂	4-CF ₃	4-CF ₃ -Phenyl	H/H	C(CH ₃) ₂
CH ₂	CH ₂	2,4-Cl	CH ₃ OCH ₂ CH ₂	CH ₃ /H	O
CH ₂	CH ₂	4-CH ₃	Heptyl	H/H	CH ₂
NH	CH ₂	4-CF ₃	Isopropyl	H/H	S
N(CH ₃)	(CH ₂) ₂	4-CF ₃	Isopropyl	H/H	CH ₂
CH ₂	CH ₂	4-CN	Isopropyl	H/H	C(CH ₃) ₂
CH ₂	CH ₂	4-t-Butyl	Isopropyl	C ₂ H ₅ /H	O
CH ₂	(CH ₂) ₃	4-CF ₃ O	Butyl-OCH ₂	CH ₃ /H	CH ₂
CH ₂	CH ₂	4-CF ₃ O	CH ₃ O(CH ₂) ₅	CH ₃ /H	O
N(CH ₃)	CH ₂	4-t-Butyl	Cyclohexyl	CH ₃ /H	O
N(C ₂ H ₅)	CH ₂	4-CF ₃	(CH ₃) ₂ CH(CH ₂) ₅	CH ₃ /CH ₃	O
N(Allyl)	CH ₂	4-CF ₃	4-CF ₃ -Benzyl	H/H	S
N(Acetyl)	CH ₂	2,4-CH ₃	Isopropyl	CH ₃ /CH ₃	CH ₂

(9)



In the formula, X, Y, R^a, R^b, R^c, and n are set forth
5 in Tables 15 to 17.

TABLE 15

X	Y	R ^a	R ^b	R ^c	n
CH ₂	CH ₂	H	Isopropyl	2-CH ₃	1
CH ₂	CH ₂	2-OH, 4-Cl	Hexyl	2-CH ₃	1
CH ₂	CH ₂	2-OH, 4-CF ₃	Isopropyl	2-CH ₃	1
CH ₂	C(CH ₃) ₂	2, 4-Cl	Propyl	2-CH ₃	1
CH ₂	CH(CH ₃)	4-CF ₃	sec-Butyl	3-CH ₃	1
CH ₂	CH(C ₂ H ₅)	4-CF ₃	tert-Butyl	3-CH ₃	2
CH ₂	CH(Propyl)	4-CF ₃	Hexyl	2, 6-CH ₃	3
CH ₂	(CH ₂) ₂	4-CF ₃	Isopropyl	3-CH ₃	3
CH ₂	(CH ₂) ₂	4-CF ₃	Cyclopropyl	3, 5-CH ₃	3
CH(CH ₃)	CH ₂	4-CF ₃	Cyclopropylmethyl	2-Allyl	1
CH ₂	CH ₂	4-CF ₃	4-CF ₃ -Phenyl	2-Propyl	2
CH ₂	CH ₂	2, 4-Cl	CH ₃ OCH ₂ CH ₂	2-CH ₃ O	2

TABLE 16

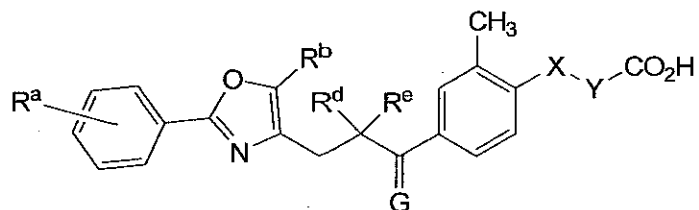
X	Y	R ^a	R ^b	R ^c	n
CH ₂	CH ₂	2-OH, 4-CF ₃	Isopropyl	2-Cl	1
CH ₂	CH ₂	4-CH ₃	Heptyl	2, 6-CH ₃	1
NH	CH ₂	4-CF ₃	Isopropyl	H	1
N(CH ₃)	CH ₂	4-CF ₃	Isopropyl	H	1
N(CH ₃)	CH ₂	4-CF ₃	Isopropyl	2-CH ₃	1
N(C ₂ H ₅)	CH ₂	4-CF ₃	Isopropyl	H	1
N(Allyl)	CH ₂	4-CF ₃	Isopropyl	H	1
N(CH ₃)	CH ₂	2-OH, 4-Cl	Isopropyl	H	1
NH	CH ₂	4-CF ₃	Isopropyl	2-CH ₃	1
N(CH ₃)	(CH ₂) ₂	4-CF ₃	Isopropyl	2-CH ₃	1
CH ₂	CH ₂	4-CN	Isopropyl	2-OH	2
CH ₂	CH ₂	4-t-Butyl	Isopropyl	2-Acetyl	1

TABLE 17

5

X	Y	R ^a	R ^b	R ^c	n
CH ₂	CH ₂	4-Isopropyl	Isopropyl	2-CF ₃	1
CH ₂	(CH ₂) ₃	4-CF ₃ O	Butyl-OCH ₂	2-CH ₃	2
CH ₂	CH ₂	4-CF ₃	Butyl-OCH ₂	2-CH ₃	3
CH ₂	CH ₂	4-CF ₃ O	CH ₃ O(CH ₂) ₅	2-CH ₃ O	3
NH	CH ₂	4-CF ₃ O	CH ₃ O(CH ₂) ₅	2-CH ₃ O	1
N(CH ₃)	CH ₂	4-t-Butyl	Cyclohexyl	2-F	2
N(CH ₃)	CH ₂	4-CF ₃	Hexyl	2-F	1
N(C ₂ H ₅)	CH ₂	4-CF ₃	(CH ₃) ₂ CH(CH ₂) ₅	2, 5-CH ₃	1
N(Allyl)	CH ₂	4-CF ₃	4-CF ₃ -Benzyl	2, 5-CH ₃	1
N(Acetyl)	CH ₂	2, 4-CH ₃	Isopropyl	2-CH ₃	1
N(CH ₃)	(CH ₂) ₂	4-Acetyl	Isopropyl	2-CH ₃	2

(10)

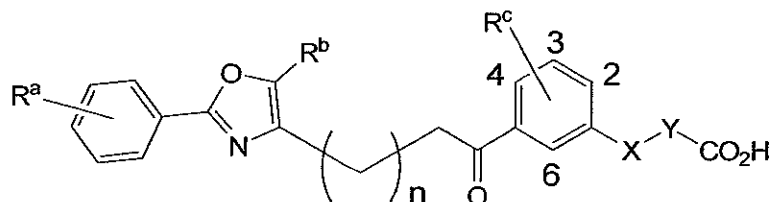


In the formula, X, Y, R^a, R^b, R^d, R^e, and G are set forth in Table 18.

TABLE 18

X	Y	R ^a	R ^b	R ^d /R ^e	G
CH ₂	CH ₂	2-OH, 4-CF ₃	Isopropyl	H/H	CH ₂
CH(CH ₃)	CH ₂	4-CF ₃	Cyclopropylmethyl	H/H	S
CH ₂	CH ₂	4-CF ₃	4-CF ₃ -Phenyl	H/H	C(CH ₃) ₂
CH ₂	CH ₂	2, 4-Cl	CH ₃ OCH ₂ CH ₂	CH ₃ /H	O
CH ₂	CH ₂	4-CH ₃	Heptyl	H/H	CH ₂
NH	CH ₂	4-CF ₃	Isopropyl	H/H	S
N(CH ₃)	(CH ₂) ₂	4-CF ₃	Isopropyl	H/H	CH ₂
CH ₂	CH ₂	4-CN	Isopropyl	H/H	C(CH ₃) ₂
CH ₂	CH ₂	4-t-Butyl	Isopropyl	C ₂ H ₅ /H	O
CH ₂	(CH ₂) ₃	4-CF ₃ O	Butyl-OCH ₂	CH ₃ /CH ₃	CH ₂
CH ₂	CH ₂	4-CF ₃ O	CH ₃ O(CH ₂) ₅	CH ₃ /CH ₃	O
N(CH ₃)	CH ₂	4-t-Butyl	Cyclohexyl	CH ₃ /CH ₃	O
N(C ₂ H ₅)	CH ₂	4-CF ₃	(CH ₃) ₂ CH(CH ₂) ₅	CH ₃ /CH ₃	O
N(Allyl)	CH ₂	4-CF ₃	4-CF ₃ -Benzyl	H/H	S
N(Acetyl)	CH ₂	2, 4-CH ₃	Isopropyl	CH ₃ /CH ₃	CH ₂

(11)



In the formula, X, Y, R^a , R^b , R^c , and n are set forth
5 in Tables 19 and 20.

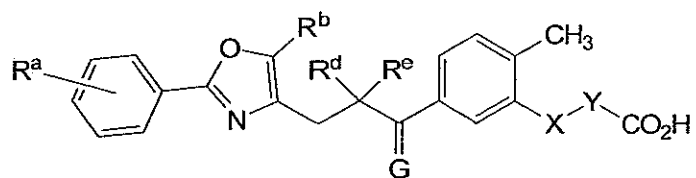
TABLE 19

X	Y	R^a	R^b	R^c	n
CH ₂	CH ₂	H	Isopropyl	2-CH ₃	1
CH ₂	CH ₂	2-OH, 4-Cl	Hexyl	2-CH ₃	1
CH ₂	C(CH ₃) ₂	2, 4-Cl	Propyl	2-CH ₃	1
CH ₂	CH(CH ₃)	4-CF ₃	sec-Butyl	3-CH ₃	1
CH ₂	CH(C ₂ H ₅)	4-CF ₃	tert-Butyl	3-CH ₃	2
CH ₂	CH(Propyl)	4-CF ₃	Hexyl	2, 6-CH ₃	3
CH ₂	(CH ₂) ₂	4-CF ₃	Isopropyl	3-CH ₃	3
CH ₂	(CH ₂) ₂	4-CF ₃	Cyclopropyl	3, 6-CH ₃	3
CH ₂	CH ₂	2-OH, 4-CF ₃	Isopropyl	2-Cl	1
NH	CH ₂	4-CF ₃	Isopropyl	H	1

TABLE 20

X	Y	R ^a	R ^b	R ^c	n
N(CH ₃)	CH ₂	4-CF ₃	Isopropyl	H	1
N(CH ₃)	CH ₂	4-CF ₃	Isopropyl	2-CH ₃	1
N(C ₂ H ₅)	CH ₂	4-CF ₃	Isopropyl	H	1
N(Allyl)	CH ₂	4-CF ₃	Isopropyl	H	1
N(Acetyl)	CH ₂	2-OH, 4-Cl	Isopropyl	H	3
CH ₂	CH ₂	4-Isopropyl	Isopropyl	2-CF ₃	1
CH ₂	CH ₂	4-CF ₃	Butyl-OCH ₂	2-CH ₃	3
NH	CH ₂	4-CF ₃ O	CH ₃ O(CH ₂) ₅	2-CH ₃ O	1
N(CH ₃)	CH ₂	4-CF ₃	Hexyl	2-F	1
N(CH ₃)	(CH ₂) ₂	4-Acetyl	Isopropyl	2-CH ₃	2

(12)



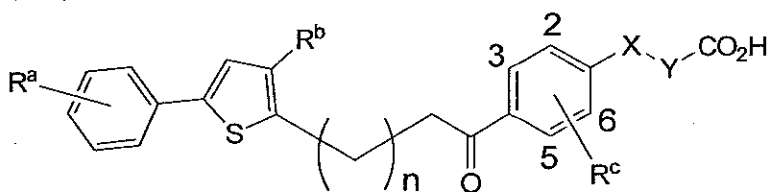
5

In the formula, X, Y, R^a, R^b, R^d, R^e, and G are set forth in Table 21.

TABLE 21

X	Y	R ^a	R ^b	R ^d /R ^e	G
CH ₂	CH ₂	2-OH, 4-CF ₃	Isopropyl	H/H	CH ₂
CH(CH ₃)	CH ₂	4-CF ₃	Cyclopropylmethyl	H/H	S
CH ₂	CH ₂	4-CF ₃	4-CF ₃ -Phenyl	H/H	C(CH ₃) ₂
CH ₂	CH ₂	2, 4-Cl	CH ₃ OCH ₂ CH ₂	CH ₃ /H	O
CH ₂	CH ₂	4-CH ₃	Heptyl	H/H	CH ₂
NH	CH ₂	4-CF ₃	Isopropyl	H/H	S
N(CH ₃)	(CH ₂) ₂	4-CF ₃	Isopropyl	H/H	CH ₂
CH ₂	CH ₂	4-CN	Isopropyl	H/H	C(CH ₃) ₂
CH ₂	CH ₂	4-t-Butyl	Isopropyl	C ₂ H ₅ /H	O
CH ₂	(CH ₂) ₃	4-CF ₃ O	Butyl-OCH ₂	CH ₃ /CH ₃	CH ₂
CH ₂	CH ₂	4-CF ₃ O	CH ₃ O(CH ₂) ₅	CH ₃ /CH ₃	O
N(CH ₃)	CH ₂	4-t-Butyl	Cyclohexyl	CH ₃ /CH ₃	O
N(C ₂ H ₅)	CH ₂	4-CF ₃	(CH ₃) ₂ CH(CH ₂) ₅	CH ₃ /CH ₃	O
N(Allyl)	CH ₂	4-CF ₃	4-CF ₃ -Benzyl	H/H	S
N(Acetyl)	CH ₂	2, 4-CH ₃	Isopropyl	CH ₃ /CH ₃	CH ₂

(13)



5

In the formula, X, Y, R^a, R^b, R^c, and n are set forth in Tables 22 and 23.

TABLE 22

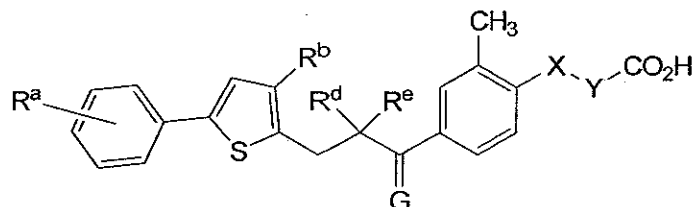
X	Y	R ^a	R ^b	R ^c	n
CH ₂	CH ₂	4-CF ₃	Isopropyl	2-CH ₃	1
CH ₂	CH ₂	2-OH, 4-Cl	Hexyl	2-CH ₃	1
CH ₂	C(CH ₃) ₂	2, 4-Cl	Propyl	2-CH ₃	1
CH ₂	CH(CH ₃)	4-CF ₃	sec-Butyl	3-CH ₃	1
CH ₂	CH(C ₂ H ₅)	4-CF ₃	tert-Butyl	3-CH ₃	2
CH ₂	CH(Propyl)	4-CF ₃	Hexyl	2, 6-CH ₃	3
CH ₂	(CH ₂) ₂	4-CF ₃	Isopropyl	3-CH ₃	3
CH ₂	(CH ₂) ₂	4-CF ₃	Cyclopropyl	3, 5-CH ₃	3
CH ₂	CH ₂	2-OH, 4-CF ₃	Isopropyl	2-Cl	1
NH	CH ₂	4-CF ₃	Isopropyl	H	1
N(CH ₃)	CH ₂	4-CF ₃	Isopropyl	H	1

TABLE 23

5

X	Y	R ^a	R ^b	R ^c	n
N(CH ₃)	CH ₂	4-CF ₃	Isopropyl	2-CH ₃	1
N(C ₂ H ₅)	CH ₂	4-CF ₃	Isopropyl	H	1
N(Allyl)	CH ₂	4-CF ₃	Isopropyl	H	1
N(Acetyl)	CH ₂	2-OH, 4-Cl	Isopropyl	H	3
N(CH ₃)	CH ₂	4-CF ₃	Isopropyl	2-CH ₃	1
CH ₂	CH ₂	4-Isopropyl	Isopropyl	2-CF ₃	1
CH ₂	CH ₂	4-CF ₃	Butyl-OCH ₂	2-CH ₃	3
NH	CH ₂	4-CF ₃ O	CH ₃ O(CH ₂) ₅	2-CH ₃ O	1
N(CH ₃)	CH ₂	4-CF ₃	Hexyl	2-F	1
N(CH ₃)	(CH ₂) ₂	4-Acetyl	Isopropyl	2-CH ₃	2

(14)

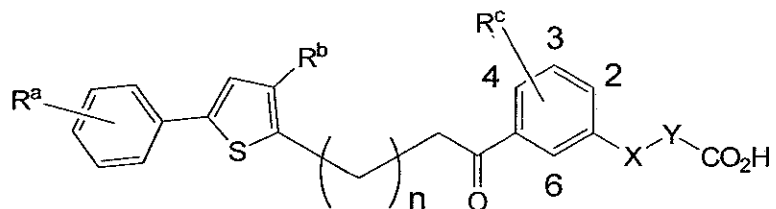


In the formula, X, Y, R^a, R^b, R^d, R^e, and G are set
5 forth in Table 24.

TABLE 24

X	Y	R ^a	R ^b	R ^d /R ^e	G
CH ₂	CH ₂	2-OH, 4-CF ₃	Isopropyl	H/H	CH ₂
CH(CH ₃)	CH ₂	4-CF ₃	Cyclopropylmethyl	H/H	S
CH ₂	CH ₂	4-CF ₃	4-CF ₃ -Phenyl	H/H	C(CH ₃) ₂
CH ₂	CH ₂	2, 4-Cl	CH ₃ OCH ₂ CH ₂	CH ₃ /H	O
CH ₂	CH ₂	4-CH ₃	Heptyl	H/H	CH ₂
NH	CH ₂	4-CF ₃	Isopropyl	H/H	S
N(CH ₃)	(CH ₂) ₂	4-CF ₃	Isopropyl	H/H	CH ₂
CH ₂	CH ₂	4-CN	Isopropyl	H/H	C(CH ₃) ₂
CH ₂	CH ₂	4-t-Butyl	Isopropyl	C ₂ H ₅ /H	O
CH ₂	(CH ₂) ₃	4-CF ₃ O	Butyl-OCH ₂	CH ₃ /CH ₃	CH ₂
CH ₂	CH ₂	4-CF ₃ O	CH ₃ O(CH ₂) ₅	CH ₃ /CH ₃	O
N(CH ₃)	CH ₂	4-t-Butyl	Cyclohexyl	CH ₃ /CH ₃	O
N(C ₂ H ₅)	CH ₂	4-CF ₃	(CH ₃) ₂ CH(CH ₂) ₅	CH ₃ /CH ₃	O
N(Allyl)	CH ₂	4-CF ₃	4-CF ₃ -Benzyl	H/H	S
N(Acetyl)	CH ₂	2, 4-CH ₃	Isopropyl	CH ₃ /CH ₃	CH ₂

(15)



In the formula, X, Y, R^a, R^b, R^c, and n are set forth
5 in Tables 25 and 26.

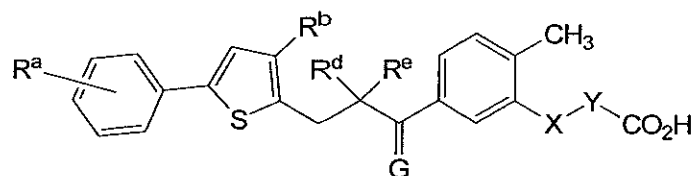
TABLE 25

X	Y	R ^a	R ^b	R ^c	n
CH ₂	CH ₂	4-CF ₃	Isopropyl	2-CH ₃	1
CH ₂	CH ₂	2-OH, 4-Cl	Hexyl	2-CH ₃	1
CH ₂	C(CH ₃) ₂	2, 4-Cl	Propyl	2-CH ₃	1
CH ₂	CH(CH ₃)	4-CF ₃	sec-Butyl	3-CH ₃	1
CH ₂	CH(C ₂ H ₅)	4-CF ₃	tert-Butyl	3-CH ₃	2
CH ₂	CH(Propyl)	4-CF ₃	Hexyl	2, 6-CH ₃	3
CH ₂	(CH ₂) ₂	4-CF ₃	Isopropyl	3-CH ₃	3
CH ₂	(CH ₂) ₂	4-CF ₃	Cyclopropyl	3, 6-CH ₃	3
CH ₂	CH ₂	2-OH, 4-CF ₃	Isopropyl	2-Cl	1
NH	CH ₂	4-CF ₃	Isopropyl	H	1
N(CH ₃)	CH ₂	4-CF ₃	Isopropyl	H	1

TABLE 26

X	Y	R ^a	R ^b	R ^c	n
N(CH ₃)	CH ₂	4-CF ₃	Isopropyl	2-CH ₃	1
N(C ₂ H ₅)	CH ₂	4-CF ₃	Isopropyl	2-CH ₃	1
N(Allyl)	CH ₂	4-CF ₃	Isopropyl	2-CH ₃	1
N(Acetyl)	CH ₂	2-OH, 4-Cl	Isopropyl	3-CH ₃	3
CH ₂	CH ₂	4-Isopropyl	Isopropyl	2-CF ₃	1
CH ₂	CH ₂	4-CF ₃	Butyl-OCH ₂	2-CH ₃	3
NH	CH ₂	4-CF ₃ O	CH ₃ O(CH ₂) ₅	2-CH ₃ O	1
N(CH ₃)	CH ₂	4-CF ₃	Hexyl	2-F	1
N(CH ₃)	(CH ₂) ₂	4-Acetyl	Isopropyl	2-CH ₃	2

(16)



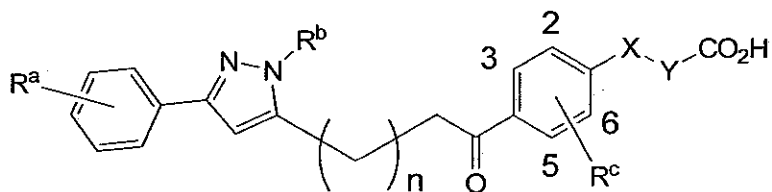
5

In the formula, X, Y, R^a, R^b, R^d, R^e, and G are set forth in Table 27.

TABLE 27

X	Y	R ^a	R ^b	R ^d /R ^e	G
CH ₂	CH ₂	2-OH, 4-CF ₃	Isopropyl	H/H	CH ₂
CH(CH ₃)	CH ₂	4-CF ₃	Cyclopropylmethyl	H/H	S
CH ₂	CH ₂	4-CF ₃	4-CF ₃ -Phenyl	H/H	C(CH ₃) ₂
CH ₂	CH ₂	2, 4-Cl	CH ₃ OCH ₂ CH ₂	CH ₃ /H	O
CH ₂	CH ₂	4-CH ₃	Heptyl	H/H	CH ₂
NH	CH ₂	4-CF ₃	Isopropyl	H/H	S
N(CH ₃)	(CH ₂) ₂	4-CF ₃	Isopropyl	H/H	CH ₂
CH ₂	CH ₂	4-CN	Isopropyl	H/H	C(CH ₃) ₂
CH ₂	CH ₂	4-t-Butyl	Isopropyl	C ₂ H ₅ /H	O
CH ₂	(CH ₂) ₃	4-CF ₃ O	Butyl-OCH ₂	CH ₃ /CH ₃	CH ₂
CH ₂	CH ₂	4-CF ₃ O	CH ₃ O(CH ₂) ₅	CH ₃ /CH ₃	O
N(CH ₃)	CH ₂	4-t-Butyl	Cyclohexyl	CH ₃ /CH ₃	O
N(C ₂ H ₅)	CH ₂	4-CF ₃	(CH ₃) ₂ CH(CH ₂) ₅	CH ₃ /CH ₃	O
N(Allyl)	CH ₂	4-CF ₃	4-CF ₃ -Benzyl	H/H	S
N(Acetyl)	CH ₂	2, 4-CH ₃	Isopropyl	CH ₃ /CH ₃	CH ₂

(17)



5

In the formula, X, Y, R^a, R^b, R^c, and n are set forth in Tables 28 and 29.

TABLE 28

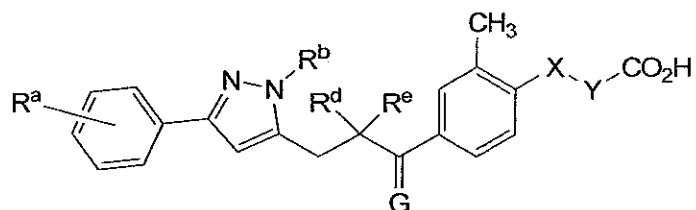
X	Y	R ^a	R ^b	R ^c	n
CH ₂	CH ₂	H	Isopropyl	2-CH ₃	1
CH ₂	CH ₂	2-OH, 4-Cl	Hexyl	2-CH ₃	1
CH ₂	C(CH ₃) ₂	2, 4-Cl	Propyl	2-CH ₃	1
CH ₂	CH(CH ₃)	4-CF ₃	sec-Butyl	3-CH ₃	1
CH ₂	CH(C ₂ H ₅)	4-CF ₃	tert-Butyl	3-CH ₃	2
CH ₂	CH(Propyl)	4-CF ₃	Hexyl	2, 6-CH ₃	3
CH ₂	(CH ₂) ₂	4-CF ₃	Isopropyl	3-CH ₃	3
CH ₂	(CH ₂) ₂	4-CF ₃	Cyclopropyl	3, 6-CH ₃	3
CH ₂	CH ₂	2-OH, 4-CF ₃	Isopropyl	2-Cl	1
NH	CH ₂	4-CF ₃	Isopropyl	H	1

TABLE 29

5

X	Y	R ^a	R ^b	R ^c	n
N(CH ₃)	CH ₂	4-CF ₃	Isopropyl	H	1
N(CH ₃)	CH ₂	4-CF ₃	Isopropyl	2-CH ₃	1
N(C ₂ H ₅)	CH ₂	4-CF ₃	Isopropyl	H	1
N(Allyl)	CH ₂	4-CF ₃	Isopropyl	H	1
N(Acetyl)	CH ₂	2-OH, 4-Cl	Isopropyl	H	3
CH ₂	CH ₂	4-Isopropyl	Isopropyl	2-CF ₃	1
CH ₂	CH ₂	4-CF ₃	Butyl-OCH ₂	2-CH ₃	3
NH	CH ₂	4-CF ₃ O	CH ₃ O(CH ₂) ₅	2-CH ₃ O	1
N(CH ₃)	CH ₂	4-CF ₃	Hexyl	2-F	1
N(CH ₃)	(CH ₂) ₂	4-Acetyl	Isopropyl	2-CH ₃	2

(18)

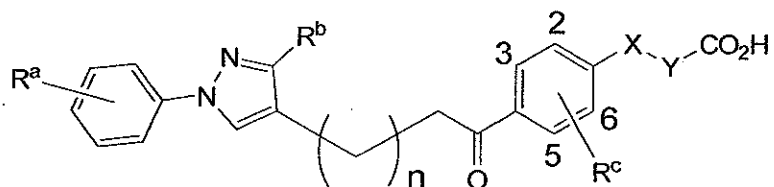


In the formula, X, Y, R^a, R^b, R^d, R^e, and G are set forth in Table 30.

TABLE 30

X	Y	R ^a	R ^b	R ^d /R ^e	G
CH ₂	CH ₂	2-OH, 4-CF ₃	Isopropyl	H/H	CH ₂
CH(CH ₃)	CH ₂	4-CF ₃	Cyclopropylmethyl	H/H	S
CH ₂	CH ₂	4-CF ₃	4-CF ₃ -Phenyl	H/H	C(CH ₃) ₂
CH ₂	CH ₂	2, 4-Cl	CH ₃ OCH ₂ CH ₂	CH ₃ /H	O
CH ₂	CH ₂	4-CH ₃	Heptyl	H/H	CH ₂
NH	CH ₂	4-CF ₃	Isopropyl	H/H	S
N(CH ₃)	(CH ₂) ₂	4-CF ₃	Isopropyl	H/H	CH ₂
CH ₂	CH ₂	4-CN	Isopropyl	H/H	C(CH ₃) ₂
CH ₂	CH ₂	4-t-Butyl	Isopropyl	C ₂ H ₅ /H	O
CH ₂	(CH ₂) ₃	4-CF ₃ O	Butyl-OCH ₂	CH ₃ /H	CH ₂
CH ₂	CH ₂	4-CF ₃ O	CH ₃ O(CH ₂) ₅	CH ₃ /H	O
N(CH ₃)	CH ₂	4-t-Butyl	Cyclohexyl	CH ₃ /H	O
N(C ₂ H ₅)	CH ₂	4-CF ₃	(CH ₃) ₂ CH(CH ₂) ₅	CH ₃ /CH ₃	O
N(Allyl)	CH ₂	4-CF ₃	4-CF ₃ -Benzyl	H/H	S
N(Acetyl)	CH ₂	2, 4-CH ₃	Isopropyl	CH ₃ /CH ₃	CH ₂

(19)



In the formula, X, Y, R^a , R^b , R^c , and n are set forth
5 in Tables 31 and 32.

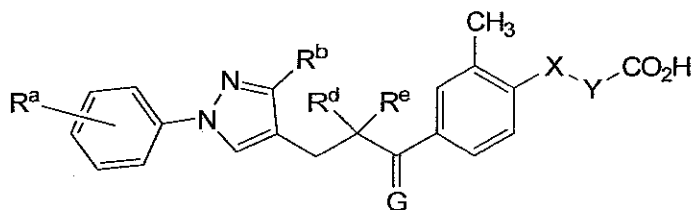
TABLE 31

X	Y	R^a	R^b	R^c	n
CH ₂	CH ₂	4-CF ₃	Isopropyl	2-CH ₃	1
CH ₂	CH ₂	2-OH, 4-Cl	Hexyl	2-CH ₃	1
CH ₂	C(CH ₃) ₂	2,4-Cl	Propyl	2-CH ₃	1
CH ₂	CH(CH ₃)	4-CF ₃	sec-Butyl	3-CH ₃	1
CH ₂	CH(C ₂ H ₅)	4-CF ₃	tert-Butyl	3-CH ₃	2
CH ₂	CH(Propyl)	4-CF ₃	Hexyl	2,6-CH ₃	3
CH ₂	(CH ₂) ₂	4-CF ₃	Isopropyl	3-CH ₃	3
CH ₂	(CH ₂) ₂	4-CF ₃	Cyclopropyl	3,6-CH ₃	3
CH ₂	CH ₂	2-OH, 4-CF ₃	Isopropyl	2-Cl	1
NH	CH ₂	4-CF ₃	Isopropyl	H	1

TABLE 32

X	Y	R ^a	R ^b	R ^c	n
N(CH ₃)	CH ₂	4-CF ₃	Isopropyl	H	1
N(CH ₃)	CH ₂	4-CF ₃	Isopropyl	2-CH ₃	1
N(C ₂ H ₅)	CH ₂	4-CF ₃	Isopropyl	H	1
N(Allyl)	CH ₂	4-CF ₃	Isopropyl	H	1
N(Acetyl)	CH ₂	2-OH, 4-Cl	Isopropyl	H	3
CH ₂	CH ₂	4-Isopropyl	Isopropyl	2-CF ₃	1
CH ₂	CH ₂	4-CF ₃	Butyl-OCH ₂	2-CH ₃	3
NH	CH ₂	4-CF ₃ O	CH ₃ O(CH ₂) ₅	2-CH ₃ O	1
N(CH ₃)	CH ₂	4-CF ₃	Hexyl	2-F	1
N(CH ₃)	(CH ₂) ₂	4-Acetyl	Isopropyl	2-CH ₃	2

(20)



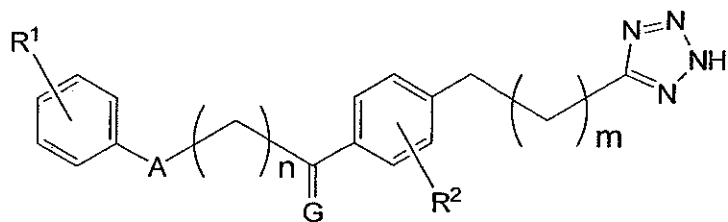
5

In the formula, X, Y, R^a, R^b, R^d, R^e, and G are set forth in Table 33.

TABLE 33

X	Y	R ^a	R ^b	R ^d /R ^e	G
CH ₂	CH ₂	2-OH, 4-CF ₃	Isopropyl	H/H	CH ₂
CH(CH ₃)	CH ₂	4-CF ₃	Cyclopropylmethyl	H/H	S
CH ₂	CH ₂	4-CF ₃	4-CF ₃ -Phenyl	H/H	C(CH ₃) ₂
CH ₂	CH ₂	2, 4-Cl	CH ₃ OCH ₂ CH ₂	CH ₃ /H	O
CH ₂	CH ₂	4-CH ₃	Heptyl	H/H	CH ₂
NH	CH ₂	4-CF ₃	Isopropyl	H/H	S
N(CH ₃)	(CH ₂) ₂	4-CF ₃	Isopropyl	H/H	CH ₂
CH ₂	CH ₂	4-CN	Isopropyl	H/H	C(CH ₃) ₂
CH ₂	CH ₂	4-t-Butyl	Isopropyl	C ₂ H ₅ /H	O
CH ₂	(CH ₂) ₃	4-CF ₃ O	Butyl-OCH ₂	CH ₃ /CH ₃	CH ₂
CH ₂	CH ₂	4-CF ₃ O	CH ₃ O(CH ₂) ₅	CH ₃ /CH ₃	O
N(CH ₃)	CH ₂	4-t-Butyl	Cyclohexyl	CH ₃ /CH ₃	O
N(C ₂ H ₅)	CH ₂	4-CF ₃	(CH ₃) ₂ CH(CH ₂) ₅	CH ₃ /CH ₃	O
N(Allyl)	CH ₂	4-CF ₃	4-CF ₃ -Benzyl	H/H	S
N(Acetyl)	CH ₂	2, 4-CH ₃	Isopropyl	CH ₃ /CH ₃	CH ₂

(21)



5

In the formula, A, R¹, R², m, n, and G are set forth in Tables 34 and 35.

TABLE 34

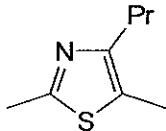
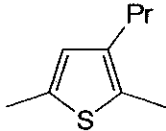
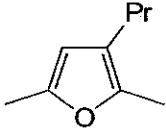
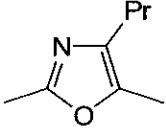
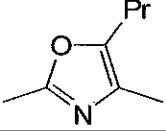
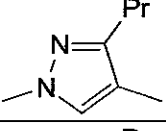
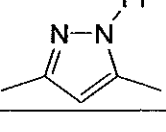
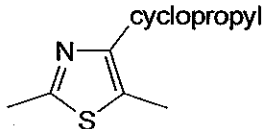
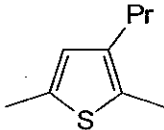
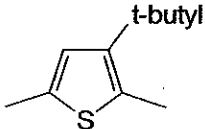
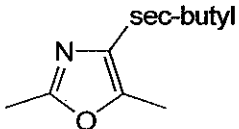
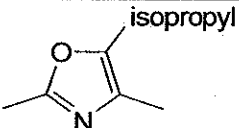
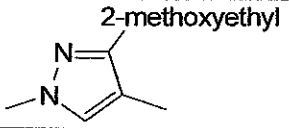
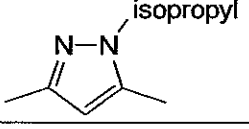
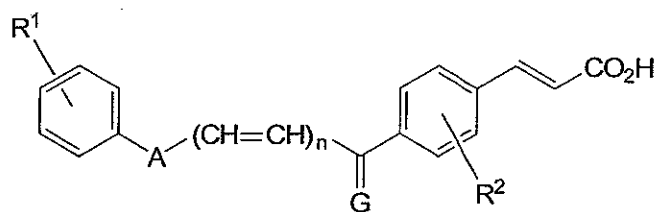
A	R ¹	R ²	m	n	G
	4-CF ₃	2-CH ₃	2	1	O
	4-CF ₃	2-CH ₃	2	1	O
	4-CF ₃	2-CH ₃	3	1	CH ₂
	4-CF ₃	2-CH ₃	2	1	O
	2-OH, 4-Cl	3-CH ₃	2	1	O
	4-CF ₃	3-CH ₃	2	2	O
	4-CF ₃	2, 6-CH ₃	2	3	O

TABLE 35

A	R ¹	R ²	m	n	G
	4-CF ₃	2-CH ₃	3	1	O
	4-CF ₃	2-CH ₃	2	1	O
	4-CF ₃	2-CH ₃	2	1	CH ₂
	2-OH, 4-Cl	3-CH ₃	3	1	O
	4-CH ₃	3-CH ₃	1	1	O
	4-CF ₃	3-CH ₃	2	2	O
	4-CF ₃	2, 6-CH ₃	2	3	O

(22)



5

In the formula, A, R¹, R², n, and G are set forth in Tables 36 and 37.

TABLE 36

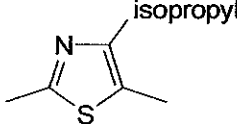
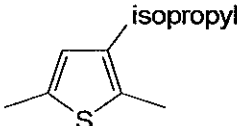
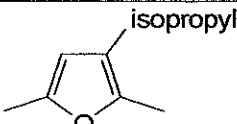
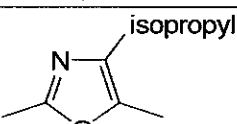
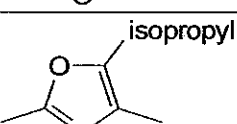
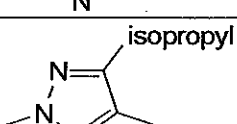
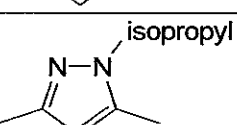
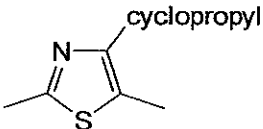
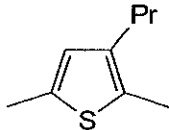
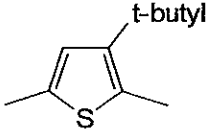
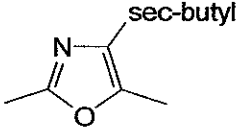
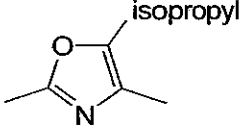
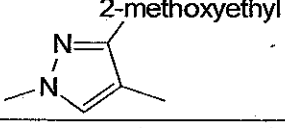
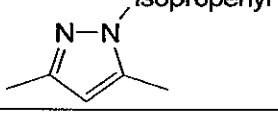
A	R ¹	R ²	n	G
	4-CF ₃	2-CH ₃	1	O
	4-CF ₃	2-CH ₃	1	O
	4-CF ₃	2-CH ₃	2	CH ₂
	4-CF ₃	2-CH ₃	2	O
	2-OH, 4-Cl	3-CH ₃	2	O
	4-CF ₃	3-CH ₃	2	O
	4-CF ₃	2, 6-CH ₃	2	O

TABLE 37

A	R ¹	R ²	n	G
	4-CF ₃	2-CH ₃	3	O
	4-CF ₃	2-CH ₃	2	O
	4-CF ₃	2-CH ₃	2	CH ₂
	2-OH, 4-Cl	3-CH ₃	3	O
	4-CH ₃	3-CH ₃	1	O
	4-CF ₃	3-CH ₃	2	O
	4-CF ₃	2, 6-CH ₃	2	O

The pharmacological effects of the invention are described below.

The PPAR activating effect of the compound of the invention was determined by the following method:

A receptor expression plasmid (pSG5-GAL4-hPPAR α or γ or δ (LBD)), a luciferase expression plasmid (MH100 $\times$ 4-TK-Luc), and a β -galactosidase expression plasmid (pCMX- β -GAL) are transfected into CV-1 cells (ATCC) (Kliwer, S.A. et al., (1992) Nature, 358: 771-774). After the gene transfer is conducted by utilizing a lipofection reagent

(Lipofectamine 2000, Invitrogen), it is incubated for about 40 hours in the presence of a compound to be tested. The luciferase activity and β -GAL activity are measured on the soluble cells.

5 The luciferase activity is calibrated by the β -GAL activity. A relative ligand activity is calculated under the condition that the luciferase activity of the cells treated by GW-590735 for PPAR α , Rosiglitazone for PPAR γ , or GW-501516 for PPAR δ is set to 100% to determine EC₅₀
10 (see the below-mentioned Examples 14 and 15).

 In contrast to the description of Bioorg Med Chem Lett 13 (2003) 1517-1521 that the activating function of phenylpropionic acid type for PPAR δ is weak, the compounds of the invention show an excellent activating effect for
15 transcription of PPAR δ , as is shown in Tables 38 and 39. As is described above, the compounds represented by the formula (I), (II), and (III) are strong PPAR δ agonists.

 A medicament of the PPAR δ agonist of the present invention is effective for treatment or prophylaxis of diseases mediated by PPAR δ . The diseases include hyperlipidemia, dyslipidemia, hypercholesterolemia, hypertriglyceridemia, HDL hypocholesterolemia, LDL hypercholesterolemia and/or HLD non-cholesterolemia, VLDL hyperproteinemia, dyslipoproteinemia, apolipoprotein A-I hypoproteinemia, atherosclerosis, disease of arterial sclerosis,
20 disease of cardiovascular systems, cerebrovascular disease, peripheral circulatory disease, metabolic syndrome, syndrome X, obesity including internal-organs fat type, diabetes, hyperglycemia, insulin resistance, impaired
25 glucose tolerance, hyperinsulinism, diabetic complication, cardiac insufficiency, cardiac infarction, cardiomyopathy, hypertension, fatty liver, non-alcoholic fatty hepatitis, thrombus, Alzheimer disease, neurodegenerative disease, demyelinating disease, multiple sclerosis, adrenal leukodystrophy, dermatitis, psoriasis, acne, skin ag-
30 35

ing, trichosis, inflammation, arthritis, asthma, hyper-sensitive intestine syndrome, ulcerative colitis, Crohn's disease, pancreatitis, or cancer including colon cancer, large intestine cancer, skin cancer, cancer of the
5 breast, carcinoma of the prostate, ovary cancer, and lung cancer.

The compound of the invention can be administered to human beings by ordinary administration methods such as oral administration or parenteral administration.

10 The compound can be granulated in ordinary manners for the preparation of pharmaceuticals. For instance, the compound can be processed to give pellets, granule, powder, capsule, suspension, injection, suppository, and the like.

15 For the preparation of these pharmaceuticals, ordinary additives such as vehicles, disintegrators, binders, lubricants, dyes, and diluents can be used. As the vehicles, lactose, D-mannitol, crystalline cellulose and glucose can be mentioned. Further, there can be mentioned
20 starch and carboxymethylcellulose calcium (CMC-Ca) as the disintegrators, magnesium stearate and talc as the lubricants, and hydroxypropylcellulose (HPC), gelatin and polyvinylpyrrolidone (PVP) as the binders.

The compound of the invention can be administered to
25 an adult generally in an amount of 0.1 mg to 100 mg a day by parenteral administration and 1 mg to 2,000 mg a day by oral administration. The dosage can be adjusted in consideration of age and conditions of the patient.

The invention is further described by the following
30 non-limiting examples.

Examples

Example 1

35 3-[4-[3-[4-Hexyl-2-(4-methylphenyl)thiazol-5-yl]propionyl]-2-methylphenyl]propionic acid

(1) 4-Hexyl-2-(4-methylphenyl)thiazole-5-carboaldehyde
[4-Hexyl-2-(4-methylphenyl)thiazol-5-yl]methanol
(500 mg, 1.727 mmol) was dissolved in anhydrous methylene
5 chloride (6 mL). Molecular sieve (3A powder, 890 mg) and
pyridinium chlorochromate (745 mg, 3.455 mmol) were added
to the solution. The mixture was stirred at room tempera-
ture for 30 minutes. Diethyl ether (20 mL) and Silica gel
(Wako-gel, C-300HG, 2 g) were added to the mixture. The
10 resulting mixture was further stirred at room temperature
for 10 minutes. The reaction mixture was filtrated
through glass filter. The residue was washed with diethyl
ether. The solvent was removed from the obtained filtrate
under reduced pressure. The obtained residue was purified
15 by silica gel column chromatography with hexane/ethyl
acetate (8:1, v/v) to give the desired compound (346 mg)
as white crystalline product (yield 70%).

^1H NMR (CDCl_3 , 400MHz): δ =
0.89 (3H, t, J=7Hz),
20 1.3-1.4 (6H, m),
1.8-1.9 (2H, m),
2.41 (3H, s),
3.09 (2H, t, J=7Hz),
7.27 (2H, d, J=8Hz),
25 7.90 (2H, d, J=8Hz),
10.08 (1H, s).

(2) Methyl 3-(4-acetyl-2-methylphenyl)-2-bromopropionate
1-(4-Amino-3-methylphenyl)ethanone (1.70 g, 11.39
30 mmol) was dissolved in methanol (15 mL)-acetone (38 mL).
The solution was cooled to 0°C. 48% Hydrobromic acid
(5.15 mL, 45.56 mmol) was dropwise added to the solution
for 1 minute. A solution of sodium nitrite (943 mg, 13.67
mmol) in water (1.8 mL) was further added to the solu-
35 tion. The mixture was stirred at the same temperature for

30 minutes. The mixture was left to room temperature. Methyl acrylate (7.23 mL, 80.30 mmol) and copper(I) oxide (117 mg) were added to the mixture. The resulting mixture was stirred at 40°C for 30 minutes. The solvent was removed under reduced pressure. Ice-cold water (150 mL) was added to the residue. The mixture was neutralized with ammonia water, and extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried with anhydrous sodium sulfate. The solvent was removed under reduced pressure to give the desired compound (2.79 g) as brown oil (yield 82%).

^1H NMR(CDCl_3 , 400MHz): δ =

2.41 (3H, s),

2.58 (3H, s),

3.33 (1H, dd, $J=7, 15\text{Hz}$),

3.52 (1H, dd, $J=7, 15\text{Hz}$),

3.74 (3H, s),

4.43 (1H, t, $J=7\text{Hz}$),

7.2-7.9 (3H, m).

(3) 3-(4-Acetyl-2-methylphenyl)acrylic acid

The obtained methyl 3-(4-acetyl-2-methylphenyl)-2-bromopropionate (2.79g, 9.33 mmol) was dissolved in methanol (80 mL). The solution was cooled to 5°C. Sodium methoxide (1.51 g, 27.98 mmol) was added to the solution. The mixture was stirred at room temperature for 20 minutes, refluxed for 1 hour, cooled to room temperature, and acidized with 1N hydrochloric acid. Water (50 mL) was added to the mixture. The mixture was extracted with chloroform. The organic layer was dried with anhydrous sodium sulfate. The solvent was removed under reduced pressure to give 657 mg of the desired compound as yellow crystalline product (yield 34%).

^1H NMR(CD_3OD , 400MHz): δ =

2.49 (3H, s),

2.59 (3H, s),
6.49 (1H, d, J=16Hz),
7.73 (1H, d, J=8Hz),
7.8-7.9 (3H, m),
5 7.97 (1H, d, J=16Hz).

(4) Methyl 3-(4-acetyl-2-methylphenyl)acrylate

The obtained 3-(4-acetyl-2-methylphenyl)acrylic acid (657 mg, 3.22 mmol) was dissolved in methanol (20 mL).
10 Concentrated sulfuric acid (250 μ L) was added to the solution. The mixture was refluxed for 2 hours, and cooled to room temperature. Water (50 mL) was added to the solution. Methanol was removed under reduced pressure. The solution was extracted with ethyl acetate, washed with
15 saturated aqueous sodium bicarbonate solution and saturated brine. The organic layer was dried with anhydrous sodium sulfate. The solvent was removed under reduced pressure. The obtained residue was purified by silica gel column chromatography with hexane/ethyl acetate (9:1,
20 v/v) to give the desired compound (665 mg) as yellow crystalline product (yield 95%).

^1H NMR (CDCl_3 , 400MHz): δ =

2.49 (3H, s),
2.60 (3H, s),
25 3.83 (3H, s),
6.43 (1H, d, J=16Hz),
7.62 (1H, d, J=9Hz),
7.7-7.8 (2H, m),
7.96 (1H, d, J=16Hz).

30 (5) Methyl 3-[4-[3-[4-hexyl-2-(4-methylphenyl)thiazol-5-yl]propenoyl]-2-methylphenyl]acrylate

The obtained methyl 3-(4-acetyl-2-methylphenyl)acrylate (200 mg, 0.916 mmol) was dissolved
35 in anhydrous tetrahydrofuran (1 mL) under nitrogen atmos-

phere. Molecular sieve (3A powder, 200 mg) was added to the solution. 0.5 M solution of sodium methoxide in methanol (1.83 mL, 0.916 mmol) was added to the solution cooled with ice while stirring. The mixture was stirred at the same temperature for 10 minutes. A solution (1 mL) of 4-hexyl-2-(4-methylphenyl)thiazole-5-carboaldehyde obtained at (1) of Example 1 (132 mg, 0.458 mmol) in anhydrous tetrahydrofuran was slowly added to the mixture. The resulting mixture was stirred while cooling with ice for 3 hours. The organic layer was dried with anhydrous sodium sulfate. The solvent was removed under reduced pressure. The residue was recrystallized with hexane and ethyl acetate to give the desired compound (185 mg) as yellow crystalline product (yield 83%).

¹H NMR(CDCl₃, 400MHz): δ=

0.89(3H, t, J=7Hz),
1.3-1.5(6H, m),
1.7-1.8(2H, m),
2.41(3H, s),
2.53(3H, s),
2.93(2H, t, J=7Hz),
3.84(3H, s),
6.46(1H, d, J=16Hz),
7.20(1H, d, J=16Hz),
7.8-7.9(2H, m),
7.66(1H, d, J=8Hz),
7.8-7.9(4H, m),
7.99(1H, d, J=16Hz),
8.02(1H, d, J=16Hz).

(6) Methyl 3-[4-[3-[4-hexyl-2-(4-methylphenyl)thiazol-5-yl]propionyl]-2-methylphenyl]propionate

The obtained methyl 3-[4-[3-[4-hexyl-2-(4-methylphenyl)thiazol-5-yl]propenoyl]-2-

methylphenyl]acrylate (112 mg, 0.230 mmol) was dissolved

in methanol (1 mL) and tetrahydrofuran (1 mL). 10% palladium carbon (22 mg) was added to the solution to cause replacement of hydrogen in the system. The mixture was stirred at room temperature for 3 hours. The reaction mixture was filtrated with Celite. The filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography with hexane/ethyl acetate (5:1, v/v) to give the desired compound (46 mg) as colorless oil (yield 41%).

¹H NMR(CDCl₃, 400MHz): δ=

0.88 (3H, t, J=7Hz),

1.2-1.4 (6H, m),

1.6-1.8 (2H, m),

2.37 (3H, s),

2.38 (3H, s),

2.61 (2H, t, J=8Hz),

2.72 (2H, t, J=8Hz),

2.99 (2H, t, J=8Hz),

3.2-3.3 (4H, m),

3.68 (3H, s),

7.19 (2H, d, J=8Hz),

7.23 (1H, d, J=8Hz),

7.7-7.8 (4H, m).

(7) 3-[4-[3-[4-Hexyl-2-(4-methylphenyl)thiazol-5-yl]propionyl]-2-methylphenyl]propionic acid

The obtained methyl 3-[4-[3-[4-hexyl-2-(4-methylphenyl)thiazol-5-yl]propionyl]-2-

methylphenyl]propionate (45 mg, 0.0915 mmol) was sus-

pended in ethanol (2 mL) and water (1 mL). Lithium hydroxide monohydrate (12 mg, 0.275 mmol) was added to the suspension. The mixture was refluxed for 1 hour. 1N hydrochloric acid (5 mL) and ice-cooled water (2 mL) were added to the mixture. The mixture was extracted with ethyl acetate. The organic layer was washed with brine,

and dried with anhydrous sodium sulfate. The solvent was removed under reduced pressure. The obtained residue was recrystallized with hexane and ethyl acetate to give the desired compound (38 mg) as white crystalline product

5 (yield 87%).

FAB-MS (m/e): 478 (M+1)

¹H NMR (CDCl₃, 400MHz): δ=

0.88 (3H, t, J=7Hz),

1.3-1.4 (6H, m),

10 1.6-1.8 (2H, m),

2.37 (3H, s),

2.38 (3H, s),

2.6-2.8 (4H, m),

3.00 (2H, t, J=8Hz),

15 3.1-3.3 (4H, m),

7.19 (2H, d, J=8Hz),

7.24 (1H, s),

7.7-7.8 (4H, m).

20 Example 2

3-[4-[3-[3-Isopropyl-5-[4-(trifluoromethyl)phenyl]thiophen-2-yl]propionyl]-2-methylphenyl]propionic acid

25 (1) 3-Isopropyl-5-[4-(trifluoromethyl)phenyl]thiophene-2-carboaldehyde

The subject compound was obtained in an analogous manner to (1) of Example 1 from [3-Isopropyl-5-[4-(trifluoromethyl)phenyl]thiophen-2-yl]methanol.

30 Pale yellow crystalline product

Yield 57%

¹H NMR (CDCl₃, 400MHz): δ=

1.39 (6H, d, J=7Hz),

3.6-3.8 (1H, m),

35 7.37 (1H, s),

7.68 (2H, d, J=8Hz) ,
7.77 (2H, d, J=8Hz) ,
10.11 (1H, s) .

- 5 (2) Methyl 3-[4-[3-[3-isopropyl-5-[4-(trifluoromethyl)phenyl]thiophene-2-yl]propenoyl]-2-methylphenyl]acrylate

The subject compound was obtained in an analogous manner to (5) of Example 1.

10 Yellow crystalline product

Yield 67%

^1H NMR(CDCl₃, 400MHz): δ =

1.32 (6H, d, J=7Hz) ,
2.54 (3H, s) ,
15 3.3-3.5 (1H, m) ,
3.84 (3H, s) ,
6.46 (1H, d, J=16Hz) ,
7.3-7.4 (1H, m) ,
7.6-7.9 (8H, m) ,
20 8.00 (1H, d, J=15Hz) ,
8.11 (1H, d, J=15Hz) .

- (3) Methyl 3-[4-[3-[3-isopropyl-5-[4-(trifluoromethyl)phenyl]thiophene-2-yl]propionyl]-2-methylphenyl]propionate

The subject compound was obtained in an analogous manner to (6) of Example 1.

Pale yellow crystalline product

Yield 58%

30 ^1H NMR(CDCl₃, 400MHz): δ =

1.26 (6H, d, J=7Hz) ,
2.38 (3H, s) ,
2.61 (2H, t, J=8Hz) ,
2.99 (2H, t, J=8Hz) ,
35 3.0-3.1 (1H, m) ,

3.2-3.4 (4H, m),
3.68 (3H, s),
7.20 (1H, s),
7.23 (1H, d, J=8Hz),
5 7.58 (2H, d, J=8Hz),
7.64 (2H, d, J=8Hz),
7.7-7.8 (2H, m).

(4) 3-[4-[3-[3-Isopropyl-5-[4-
10 (trifluoromethyl)phenyl]thiophene-2-yl]propionyl]-2-
methylphenyl]propionic acid

The subject compound was obtained in an analogous
manner to (7) of Example 1.

White crystalline product

15 Yield 79%

FAB-MS (m/e) : 488 (M)

¹H NMR (CDCl₃, 400MHz) : δ=

1.25 (6H, d, J=7Hz),
2.38 (3H, s),
20 2.67 (2H, t, J=8Hz),
3.01 (2H, t, J=8Hz),
3.0-3.1 (1H, m),
3.2-3.4 (4H, m),
7.20 (1H, s),
25 7.24 (1H, s),
7.58 (2H, d, J=8Hz),
7.64 (2H, d, J=8Hz),
7.7-7.8 (1H, m),
7.77 (1H, s).

30

Example 3

3-[4-[3-(5-Isopropyl-2-phenyl-4-oxazolyl)propionyl]-
2-methylphenyl]propionic acid

(1) 5-Isopropyl-2-(2,4-dichlorophenyl)oxazole-4-carboaldehyde

The subject compound was obtained in an analogous manner to (1) of Example 1 from 5-isopropyl-2-(2,4-dichlorophenyl)oxazole-4-methanol.

Pale yellow crystalline product

^1H NMR(CDCl_3 , 400MHz): δ =

1.39 (6H, d, $J=7\text{Hz}$),

3.72 (1H, dq, $J=7, 7\text{Hz}$),

10 7.37 (1H, dd, $J=2, 8\text{Hz}$),

7.55 (1H, d, $J=2\text{Hz}$),

7.99 (1H, d, $J=8\text{Hz}$),

10.06 (1H, s).

15 (2) Methyl 3-[4-[3-[5-isopropyl-2-(2,4-dichlorophenyl)-4-oxazolyl]propenoyl]-2-methylphenyl]acrylate

The subject compound was obtained in an analogous manner to (5) of Example 1 from the obtained 5-isopropyl-2-(2,4-dichlorophenyl)oxazole-4-carboaldehyde and methyl 20 3-(4-acetyl-2-methylphenyl)acrylate.

Pale yellow crystalline product

^1H NMR(CDCl_3 , 400MHz): δ =

1.39 (6H, d, $J=7\text{Hz}$),

2.52 (3H, s),

25 3.39 (1H, dq, $J=7, 7\text{Hz}$),

3.83 (3H, s),

6.46 (1H, d, $J=16\text{Hz}$),

7.38 (1H, dd, $J=2, 8\text{Hz}$),

7.55 (1H, d, $J=2\text{Hz}$),

30 7.66 (1H, d, $J=8\text{Hz}$),

7.75 (1H, d, $J=15\text{Hz}$),

7.80 (1H, d, $J=15\text{Hz}$),

7.9-8.0 (2H, m),

7.99 (1H, d, $J=16\text{Hz}$),

35 8.01 (1H, d, $J=8\text{Hz}$).

(3) Methyl 3-[4-[3-(5-isopropyl-2-phenyl-4-oxazolyl)propionyl]-2-methylphenyl]propionate

The subject compound was obtained in an analogous
5 manner to (6) of Example 1 from the methyl 3-[4-[3-[5-isopropyl-2-(2,4-dichlorophenyl)-4-oxazolyl]propenoyl]-2-methylphenyl]acrylate.

Colorless oil

^1H NMR(CDCl_3 , 400MHz): δ =

10 1.30 (6H, d, J=7Hz),

2.35 (3H, s),

2.59 (2H, t, J=7Hz),

2.9-3.1 (4H, m),

3.17 (1H, dq, J=7, 7Hz),

15 3.36 (2H, t, J=7Hz),

3.67 (3H, s),

7.20 (1H, d, J=8Hz),

7.3-7.5 (3H, m),

7.7-7.9 (2H, m),

20 7.9-8.1 (2H, m).

(4) 3-[4-[3-(5-Isopropyl-2-phenyl-4-oxazolyl)propionyl]-2-methylphenyl]propionic acid

The subject compound was obtained in an analogous
25 manner to (7) of Example 1 from the methyl 3-[4-[3-(5-isopropyl-2-phenyl-4-oxazolyl)propionyl]-2-methylphenyl]propionate.

Colorless oil

FAB-MS (m/e): 406 (M+1)

30 ^1H NMR(CDCl_3 , 400MHz): δ =

1.30 (6H, d, J=7Hz),

2.35 (3H, s),

2.63 (2H, t, J=7Hz),

2.9-3.1 (4H, m),

35 3.17 (1H, dq, J=7, 7Hz),

3.34 (2H, t, J=7Hz) ,
7.21 (1H, d, J=8Hz) ,
7.3-7.5 (3H, m) ,
7.7-7.9 (2H, m) ,
5 7.9-8.1 (2H, m) .

Example 4

3-[4-[3-[4-Isopropyl-2-[4-
(trifluoromethyl)phenyl]thiazol-5-yl-]propenoyl]-2-
10 methylphenyl]acrylic acid

The desired compound was obtained in an analogous manner to (5) of Example 1 from methyl 3-(4-acetyl-2-methylphenyl)acrylate and [4-isopropyl-2-[4-
15 (trifluoromethyl)phenyl]thiazol-5-yl]carboaldehyde.

Yellow crystalline product

FAB-MS (m/e) : 486 (M+1)
¹H NMR (CDCl₃, 400MHz) : δ=
1.40 (6H, d, J=7Hz) ,
20 2.56 (3H, s) ,
3.4-3.5 (1H, m) ,
6.49 (1H, d, J=16Hz) ,
7.28 (1H, d, J=16Hz) ,
7.7-7.8 (3H, m) ,
25 7.8-7.9 (2H, m) ,
8.0-8.2 (4H, m) .

Example 5

3-[4-[3-[4-Isopropyl-2-[4-
30 (trifluoromethyl)phenyl]thiazol-5-yl]propionyl]-2-
methylphenyl]propionic acid

The desired compound was obtained in an analogous manner as in (6) of Example 1 using the 3-[4-[3-[4-
35 Isopropyl-2-[4-(trifluoromethyl)phenyl]thiazol-5-yl-

]propenoyl]-2-methylphenyl]acrylic acid prepared in Example 4.

White crystalline product

FAB-MS (m/e): 490 (M+1)

5 ^1H NMR (CDCl_3 , 400MHz): δ =

1.33 (6H, d, J=7Hz),

2.38 (3H, s),

2.66 (2H, t, J=8Hz),

3.00 (2H, t, J=8Hz),

10 3.1-3.2 (1H, m),

3.2-3.3 (4H, m),

7.25 (1H, d, J=7Hz),

7.64 (2H, d, J=8Hz),

7.7-7.8 (2H, m),

15 8.00 (2H, d, J=8Hz).

Example 6

20 3-[4-[1-[2-[4-Isopropyl-2-[4-(trifluoromethyl)phenyl]thiazol-5-yl]ethyl]vinyl]-2-methylphenyl]propionic acid

(1) Methyl 3-[4-[1-[2-[4-isopropyl-2-[4-(trifluoromethyl)phenyl]thiazol-5-yl]ethyl]vinyl]-2-methylphenyl]propionate

25 Methyltriphenylphosphonium bromide (89 mg, 0.250 mmol) was suspended in anhydrous tetrahydrofuran (3.5 mL) under nitrogen atmosphere. The suspension was stirred at room temperature for 30 minutes. A solution (1.5 mL) of methyl 3-[4-[3-[4-isopropyl-2-[4-(trifluoromethyl)phenyl]thiazol-5-yl]propionyl]2-methylphenyl]propionate (84 mg, 0.167 mmol) in anhydrous tetrahydrofuran was dropwise added to the suspension. The mixture was stirred at the same temperature for 19 hours. A saturated aqueous ammonium chloride solution was drop-
35 wise added to the mixture. The mixture was extracted with

ethyl acetate. The organic layer was washed with saturated brine, and dried with anhydrous sodium sulfate. The solvent was removed under reduced pressure.

The obtained residue was purified by silica gel column chromatography with hexane/ethyl acetate (8:1, v/v) to give the desired compound (70 mg) as pale yellow oil (yield 84%).

^1H NMR(CDCl_3 , 400MHz): δ =

1.28 (6H, d, $J=7\text{Hz}$),
2.34 (3H, s),
2.5-2.7 (2H, m),
2.8-2.9 (2H, m),
2.9-3.1 (5H, m),
3.69 (3H, s),
5.06 (1H, s),
5.31 (1H, s),
7.13 (1H, d, $J=9\text{Hz}$),
7.1-7.3 (2H, m),
7.64 (2H, d, $J=8\text{Hz}$),
8.01 (2H, d, $J=8\text{Hz}$).

(2) 3-[4-[1-[2-[4-Isopropyl-2-[4-(trifluoromethyl)phenyl]thiazol-5-yl]ethyl]vinyl]-2-methylphenyl]propionic acid

The desired compound was obtained in an analogous manner as in (7) of Example 1.

White crystalline product

FAB-MS (m/e): 488 ($M+1$)

^1H NMR(CDCl_3 , 400MHz): δ =

1.28 (6H, d, $J=7\text{Hz}$),
2.35 (3H, s),
2.66 (2H, dd, $J=7, 8\text{Hz}$)
2.82 (2H, dd, $J=7, 8\text{Hz}$),
2.9-3.0 (5H, m),
5.07 (1H, s),

5.32 (1H, s),
7.1-7.3 (3H, m),
7.64 (2H, d, J=8Hz),
8.00 (2H, d, J=8Hz).

5

Example 7

N-[4-[3-[4-Isopropyl-2-[4-(trifluoromethyl)phenyl]thiazol-5-yl]propionyl]phenyl]-N-methylglycine

10

(1) 3-[4-Isopropyl-2-[4-(trifluoromethyl)phenyl]thiazol-5-yl]-1-(4-nitrophenyl)propenone

4-Isopropyl-2-[4-(trifluoromethyl)phenyl]thiazole-5-carbaldehyde (4.53 g, 15.14 mmol) and 4-nitroacetophenone (2.50 g, 15.14 mmol) were dissolved in a mixture of anhydrous methanol (30 mL) and anhydrous tetrahydrofuran (30 mL). Sodium methoxide (258 mg, 3.79 mmol) was added to the solution. The resulting mixture was stirred at room temperature for 1 hour under nitrogen atmosphere. The solvent was removed under reduced pressure. The mixture was suspended in chloroform. Insoluble matters were filtered, washed with water, a saturated aqueous sodium bicarbonate solution, and saturated brine. The solvent was again removed under reduced pressure. The residue was recrystallized with n-hexane and ethyl acetate (1:1) to give the desired compound (4.08 g) as yellow crystalline produce (yield 60%).

20

25

^1H NMR (CDCl_3 , 400MHz): δ =

30

1.40 (6H, d, J=7Hz),
3.4-3.5 (1H, m),
7.24 (1H, d, J=12Hz),
7.73 (2H, d, J=8Hz),
8.14 (5H, m),
8.37 (2H, d, J=8Hz).

35

(2) 1-(4-Aminophenyl)-3-[4-isopropyl-2-[4-(trifluoromethyl)phenyl]thiazol-5-yl]-propan-1-one

The obtained 3-[4-isopropyl-2-[4-(trifluoromethyl)phenyl]thiazol-5-yl]-1-(4-

5 nitrophenyl)propenone (4.08 g, 9.14 mmol) was dissolved in tetrahydrofuran (120 mL) and methanol (100 mL). 10% suspension (20 mL) of palladium carbon (400 mg) was added to the solution. The mixture was stirred at 60°C for 2 hours under atmosphere of hydrogen. The mixture was
10 cooled to room temperature. Insoluble matters were filtered. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography with hexane/ethyl acetate (7:3, v/v) to give the desired compound (2.31 g) as yellow crystalline product
15 (yield 60%).

^1H NMR(CDCl_3 , 400MHz): δ =

1.33 (6H, d, $J=7\text{Hz}$),
3.1-3.3 (5H, m),
4.12 (2H, br s),
20 6.65 (2H, td, $J=2, 8\text{Hz}$),
7.63 (2H, d, $J=8\text{Hz}$),
7.82 (2H, td, $J=2, 8\text{Hz}$),
8.00 (2H, d, $J=8\text{Hz}$).

25 (3) N-[4-[3-[4-Isopropyl-2-[4-(trifluoromethyl)phenyl]thiazol-5-yl]propionyl]phenyl]-2-nitrobenzenesulfonamide

The obtained 1-(4-aminophenyl)-3-[4-isopropyl-2-[4-(trifluoromethyl)phenyl]thiazol-5-yl]-propan-1-one (250
30 mg, 0.597 mmol) was dissolved in anhydrous pyridine (5 mL). O-nitrophenylsulfonyl chloride (146 mg, 0.659 mmol) was added to the solution. The mixture was stirred at room temperature for 1 hour. The outer temperature was heated to 80°C, and the mixture was further stirred for
35 16 hours. The mixture was cooled to room temperature.

Water was added to the mixture. The mixture was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium bicarbonate solution and saturated brine, and dried with anhydrous sodium sulfate to remove the solvent. The obtained residue was purified by silica gel column chromatography with hexane/ethyl acetate (8:2, v/v) to give the desired compound (265 mg) as yellow crystalline product (yield 74%).

^1H NMR(CDCl_3 , 400MHz): δ =

- 1.32 (6H, d, $J=7\text{Hz}$),
3.0-3.2 (1H, m),
3.2-3.3 (4H, m),
7.32 (2H, d, $J=8\text{Hz}$),
7.45 (1H, s),
7.6-7.7 (4H, m),
7.87 (1H, d, $J=8\text{Hz}$),
7.90 (2H, d, $J=8\text{Hz}$),
7.94 (1H, dd, $J=1, 8\text{Hz}$),
7.99 (2H, d, $J=8\text{Hz}$).

(4) N-[4-[3-[4-Isopropyl-2-[4-(trifluoromethyl)phenyl]thiazol-5-yl]propionyl]phenyl]-N-methyl-2-nitrobenzenesulfonamide

The obtained N-[4-[3-[4-isopropyl-2-[4-(trifluoromethyl)phenyl]thiazol-5-yl]propionyl]phenyl]-2-nitrobenzenesulfonamide (265 mg, 0.439 mmol) was dissolved in anhydrous dimethylformamide (10 mL). Iodomethane (30 μL , 0.483 mmol) and potassium carbonate (121 mg, 0.875 mmol) were added to the solution. The mixture was stirred at room temperature for 16 hours. The mixture was neutralized with 0.2 N aqueous solution of hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium bicarbonate solution and saturated brine, and dried with anhydrous sodium sulfate to remove the solvent. The ob-

tained residue was purified by silica gel column chromatography with hexane/ethyl acetate (7:3, v/v) to give the desired compound (230 mg) as yellow oil (yield 85%).

^1H NMR (CDCl_3 , 400MHz): δ =

- 5 1.34 (6H, d, $J=7\text{Hz}$),
3.1-3.2 (1H, m),
3.2-3.4 (4H, m),
3.41 (3H, s),
7.38 (2H, d, $J=8\text{Hz}$),
10 7.5-7.8 (6H, m),
7.94 (2H, d, $J=8\text{Hz}$),
8.00 (2H, d, $J=8\text{Hz}$).

- (5) 3-[4-Isopropyl-2-[4-(trifluoromethyl)phenyl]thiazol-
15 5-yl]-1-(4-methylaminophenyl)propan-1-one

- The obtained N-[4-[3-[4-isopropyl-2-[4-(trifluoromethyl)phenyl]thiazol-5-yl]propionyl]phenyl]-N-methyl-2-nitrobenzenesulfonamide (230 mg, 0.372 mmol) was dissolved in anhydrous dimethylformamide (5 mL). Potassium carbonate (154 mg, 1.116 mmol) and thiophenol (46 μL , 0.446 mmol) were added to the solution. The mixture was stirred at room temperature for 1 hour. The mixture was diluted with water, and extracted with ethyl acetate. The organic layer was washed with water, a saturated aqueous sodium bicarbonate solution, and saturated brine, and dried with anhydrous sodium sulfate. The solvent was removed under reduced pressure. The obtained residue was purified by silica gel column chromatography with hexane/ethyl acetate (8:2, v/v) to give the desired compound (154 mg) as yellow crystalline product (yield 95%).
- 20
25
30

^1H NMR (CDCl_3 , 400MHz): δ =

- 1.33 (6H, d, $J=7\text{Hz}$),
2.90 (3H, d, $J=5\text{Hz}$),
3.1-3.3 (5H, m),
35 4.26 (1H, br s),

6.56 (2H, d, J=8Hz),
7.63 (2H, d, J=8Hz),
7.85 (2H, d, J=8Hz),
8.00 (2H, d, J=8Hz).

5

(6) Ethyl ester of N-[4-[3-[4-isopropyl-2-[4-(trifluoromethyl)phenyl]thiazol-5-yl]propionyl]phenyl]-N-methylglycine

10 The obtained 3-[4-Isopropyl-2-[4-(trifluoromethyl)phenyl]thiazol-5-yl]-1-(4-methylaminophenyl)propan-1-one (40 mg, 0.0931 mmol) and diisopropylethylamine (80 μ L, 0.462 mmol) were dissolved in anhydrous dimethylformamide (2 mL). Ethyl bromoacetate (66 mg, 0.393 mmol) was added to the solution. The mixture was stirred at 110°C for 16 hours. The mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried with anhydrous sodium sulfate to remove the solvent. The obtained residue was purified by silica gel column chromatography with hexane/chloroform (7:3, v/v) to give the desired compound (56 mg) as yellow crystalline product (yield 47%).

^1H NMR(CDCl₃, 400MHz): δ =

1.25 (3H, t, J=7Hz),
25 1.33 (6H, d, J=7Hz),
3.14 (3H, s),
3.1-3.2 (1H, m),
3.2-3.3 (4H, m),
4.12 (2H, s),
30 4.19 (2H, q, J=7Hz),
6.65 (2H, d, J=8Hz),
7.63 (2H, d, J=8Hz),
7.88 (2H, d, J=8Hz),
8.00 (2H, d, J=8Hz).

35

(7) N-[4-[3-[4-Isopropyl-2-[4-(trifluoromethyl)phenyl]thiazol-5-yl]propionyl]phenyl]-N-methylglycine

The obtained ethyl ester of N-[4-[3-[4-isopropyl-2-
5 [4-(trifluoromethyl)phenyl]thiazol-5-yl]propionyl]phenyl]-N-methylglycine (54 mg, 0.104 mmol) was dissolved in ethanol (1 mL) and THF (1 mL). 1N sodium hydroxide (208 μ L, 0.208 mmol) was added to the solution. The mixture was stirred at room temperature for 20 min-
10 utes, diluted with water (2 mL), neutralized with 1N aqueous solution of hydrochloric acid, and stirred at 5°C for 30 minutes. The precipitate was filtered, washed with water, and dried at 60°C for 2 hours under reduced pressure to give the desired compound (40 mg) as yellow crys-
15 talline product (yield 78%).

FAB-MS(m/e):491(M+1)

^1H NMR(CDCl_3 , 400MHz): δ =

1.32(6H,d,J=7Hz),
3.1-3.2(4H,m),
20 3.2-3.3(4H,m),
4.17(2H,s),
6.66(2H,d,J=8Hz),
7.63(2H,d,J=8Hz),
7.89(2H,d,J=8Hz),
25 7.99(2H,d,J=8Hz).

Example 8

N-[4-[3-[4-Isopropyl-2-[4-
(trifluoromethyl)phenyl]thiazol-5-
30 yl]propionyl]phenyl]glycine

(1) Ethyl ester of N-[4-[3-[4-Isopropyl-2-[4-(trifluoromethyl)phenyl]thiazol-5-yl]propionyl]phenyl]glycine

The desired compound was obtained in an analogous manner to (6) of Example 7 from 1-(4-aminophenyl)-3-[4-isopropyl-2-[4-(trifluoromethyl)phenyl]thiazol-5-yl]-propan-1-one.

5 Pale yellow amorphous

Yield 83%

^1H NMR(CDCl_3 , 400MHz): δ =

1.31 (3H, t, J=7Hz),

1.33 (6H, d, J=7Hz),

10 3.1-3.3 (5H, m),

3.95 (2H, d, J=5Hz),

4.27 (2H, q, J=7Hz),

4.82 (1H, m),

6.58 (2H, d, J=8Hz),

15 7.63 (2H, d, J=8Hz),

7.86 (2H, d, J=8Hz),

8.00 (2H, d, J=8Hz).

(2) N-[4-[3-[4-Isopropyl-2-[4-
20 (trifluoromethyl)phenyl]thiazol-5-
yl]propionyl]phenyl]glycine

The desired compound was obtained in an analogous manner to (7) of Example 7 from ethyl ester of N-[4-[3-[4-Isopropyl-2-[4-(trifluoromethyl)phenyl]thiazol-5-
25 yl]propionyl]phenyl]glycine.

Yellow crystalline product

Yield 75%

^1H NMR(CDCl_3 , 400MHz): δ =

1.33 (6H, d, J=7Hz),

30 2.17 (1H, s),

3.1-3.3 (5H, m),

4.06 (2H, s),

6.60 (2H, d, J=8Hz),

7.63 (2H, d, J=8Hz),

35 7.87 (2H, d, J=8Hz),

7.99 (2H, d, J=8Hz) .

Example 9

5 N-[4-[3-[3-Isopropyl-5-[4-
 (trifluoromethyl)phenyl]thiophen-2-yl]propionyl]phenyl]-
 N-methylglycine

(1) Ethyl ester of N-(4-acetophenyl)-N-methylglycine
 4-Methylaminoacetophenone (277 mg, 1.86 mmol) and
10 diisopropylethylamine (485 μ L, 2.79 mmol) were dissolved
 in anhydrous DMF (10 mL). Ethyl bromoacetate (372 mg,
 2.23 mmol) was added to the solution. The mixture was
 stirred at 110°C for 16 hours under nitrogen atmosphere.
 The mixture was cooled to room temperature. Diisopro-
15 pylethylamine (162 μ L, 0.93 mmol) and ethyl bromoacetate
 (155 mg, 0.93 mmol) were added to the mixture. The re-
 sulting mixture was stirred at 110°C for 16 hours. The
 mixture was cooled to room temperature, diluted with
 ethyl acetate, washed with water, saturated brine, and
20 dried with anhydrous sodium sulfate. The solvent was re-
 moved under reduced pressure. The obtained residue was
 purified by silica gel column chromatography with hex-
 ane/chloroform (1:1, v/v) to give the desired compound
 (274 mg) as brown oil (yield 63%).

25 ^1H NMR(CDCl₃, 400MHz): δ =

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

 2.51 (3H, s),

 3.14 (3H, s),

 4.12 (2H, s),

30 4.20 (2H, q, J=7Hz),

 6.65 (2H, d, J=8Hz),

 7.87 (2H, d, J=8Hz) .

(2) Ethyl ester of N-[4-[3-[3-isopropyl-5-[4-(trifluoromethyl)phenyl]thiophen-2-yl]propenoyl]phenyl]-N-methylglycine

The obtained ethyl ester of N-(4-acetophenyl)-N-methylglycine (92 mg, 0.389 mmol) was dissolved in anhydrous THF (2 mL). Molecular sieve (3A powder, 200 mg) was added to the solution. The mixture was cooled to 5°C. 21 Wt.% ethanol solution of sodium ethoxide (145 μ L, 0.389 mmol) was dropwise added to the mixture under nitrogen atmosphere. The resulting mixture was stirred at the same temperature for 10 minutes. A solution (10 mL) of 3-isopropyl-5-(4-trifluoromethylphenyl)thiophene-2-carbaldehyde (116 mg, 0.389 mmol) in anhydrous THF was added to the mixture. The resulting mixture was stirred at the same temperature for 30 minutes. The mixture was neutralized with 1N aqueous solution of hydrochloric acid, and diluted with chloroform. The insoluble matters were filtered, washed with 0.2 N aqueous solution of hydrochloric acid and saturated brine, and dried with anhydrous sodium sulfate. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography with hexane/ethyl acetate (9:1, v/v) to give the desired compound (100 mg) as crude.

(3) Ethyl ester of N-[4-[3-[3-isopropyl-5-[4-(trifluoromethyl)phenyl]thiophen-2-yl]propionyl]phenyl]-N-methylglycine

The obtained crude of ethyl ester of N-[4-[3-[3-isopropyl-5-[4-(trifluoromethyl)phenyl]thiophen-2-yl]propenoyl]phenyl]-N-methylglycine (100 mg) was dissolved in anhydrous tetrahydrofuran (5 mL) and methanol (4 mL). Methanol suspension (1 mL) of 10% palladium-active carbon (10 mg) was added to the solution. The mixture was stirred at room temperature for 2 hours under hydrogen atmosphere. Insoluble matters were filtered.

The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography with hexane/ethyl acetate (9:1, v/v) to give the desired compound (37 mg) as colorless oil (yield through two steps 18%).

¹H NMR(CDCl₃, 400MHz): δ=

1.2-1.3 (9H, m),

3.0-3.1 (1H, m),

3.14 (3H, s),

3.2-3.3 (4H, m),

4.12 (2H, s),

4.19 (2H, q, J=7Hz),

6.65 (2H, d, J=9Hz),

7.20 (1H, s),

7.57 (2H, d, J=8Hz),

7.64 (2H, d, J=8Hz),

7.90 (2H, d, J=9Hz).

(4) N-[4-[3-[3-Isopropyl-5-[4-

(trifluoromethyl)phenyl]thiophene-2-yl]propionyl]phenyl]-N-methylglycine

The obtained ethyl ester of N-[4-[3-[3-isopropyl-5-[4-(trifluoromethyl)phenyl]thiophen-2-

yl]propionyl]phenyl]-N-methylglycine (37 mg, 0.071 mmol)

was dissolved in ethanol (0.5 mL) and THF (0.5 mL). 1N

sodium hydroxide (143 μL, 0.143 mmol) was added to the

solution. The mixture was stirred at room temperature for

30 minutes, neutralized with 1N aqueous solution of hy-

drochloric acid, and stirred at 5°C for 20 minutes. Pre-

cipitated crystalline was filtered, washed with water and

cooled ethanol, and dried at 50°C for 1 hour under re-

duced pressure to give the desired compound (26 mg) as

white crystalline product (yield 75%).

FAB-MS (m/e): 490 (M+1)

¹H NMR(CDCl₃, 400MHz): δ=

1.25 (6H, d, J=7Hz) ,
3.0-3.1 (1H, m) ,
3.14 (3H, s) ,
3.1-3.3 (4H, m) ,
5 4.18 (2H, s) ,
6.67 (2H, d, J=8Hz) ,
7.19 (1H, s) ,
7.57 (2H, d, J=8Hz) ,
7.63 (2H, d, J=8Hz) ,
10 7.91 (2H, d, J=8Hz) .

Example 10

N-[4-[3-[2-(4-chloro-2-hydroxyphenyl)-5-isopropyl-4-
oxazolyl]propionyl]phenyl]-N-methylglycine

15

(1) Ethyl ester of N-[4-[3-[2-(4-chloro-2-
hydroxyphenyl)-5-isopropyl-4-oxazolyl]propionyl]phenyl]-
N-methylglycine

The desired compound was obtained in an analogous
20 manner to (2) of Example 9 from 2-(4-chloro-2-
hydroxyphenyl)-5-isopropyl-4-oxazole-4-carboaldehyde and
ethyl ester of N-(4-acetophenyl)-N-methylglycine.

Yellowish brown crystalline product

Yield 49%

25 ¹H NMR (CDCl₃, 400MHz) : δ=
1.27 (3H, t, J=7Hz) ,
1.39 (6H, d, J=7Hz) ,
3.18 (3H, s) ,
3.3-3.5 (1H, m) ,
30 4.16 (2H, s) ,
4.22 (2H, q, J=7Hz) ,
6.71 (2H, d, J=9Hz) ,
6.97 (1H, dd, J=2Hz, 8Hz) ,
7.13 (1H, d, J=2Hz) ,
35 7.66 (1H, d, J=15Hz) ,

7.71 (1H, d, J=15Hz),
7.76 (1H, d, J=8Hz),
8.03 (2H, d, J=9Hz),
11.38 (1H, s).

5

(2) Ethyl ester of N-[4-[3-[2-(4-chloro-2-hydroxyphenyl)-5-isopropyl-4-oxazolyl]propionyl]phenyl]-N-methylglycine

The desired compound was obtained in an analogous manner to (3) of Example 9 from the obtained ethyl ester of N-[4-[3-[2-(4-chloro-2-hydroxyphenyl)-5-isopropyl-4-oxazolyl]propionyl]phenyl]-N-methylglycine.

Slightly yellow crystalline product

Yield 53%

15 ¹H NMR (CDCl₃, 400MHz): δ=

1.25 (3H, t, J=7Hz),
1.31 (6H, d, J=7Hz),
2.93 (2H, t, J=7Hz),
3.13 (3H, s),
20 3.1-3.3 (1H, m),
3.25 (2H, t, J=7Hz),
4.11 (2H, s),
4.19 (2H, q, J=7Hz),
6.64 (2H, d, J=9Hz),
25 6.90 (1H, dd, J=1Hz, 8Hz),
7.05 (1H, d, J=1Hz),
7.68 (1H, d, J=8Hz),
7.88 (2H, d, J=9Hz),
11.53 (1H, s).

30

(3) N-[4-[3-[2-(4-chloro-2-hydroxyphenyl)-5-isopropyl-4-oxazolyl]propionyl]phenyl]-N-methylglycine

The desired compound was obtained in an analogous manner to (4) of Example 9 from the obtained ethyl ester

of N-[4-[3-[2-(4-chloro-2-hydroxyphenyl)-5-isopropyl-4-oxazolyl]propionyl]phenyl]-N-methylglycine.

Pale yellow crystalline product

Yield 85%

5 Melting point 166-168°C

FAB-MS (m/e): 457 (M+1)

¹H NMR (CDCl₃, 400MHz): δ=

1.31 (6H, d, J=7Hz),

2.93 (2H, t, J=7Hz),

10 3.14 (3H, s),

3.1-3.3 (1H, m),

3.26 (2H, t, J=7Hz),

4.18 (2H, s),

6.66 (2H, d, J=9Hz),

15 6.90 (1H, dd, J=2Hz, 9Hz),

7.04 (1H, d, J=2Hz),

7.68 (1H, d, J=9Hz),

7.89 (2H, d, J=9Hz).

20 Example 11

3-[4-[3-[4-Isopropyl-2-[4-(trifluoromethyl)phenyl]-5-thiazolyl]propionyl]-2-ethylphenyl]propionic acid

(1) Methyl 3-[2-ethyl-4-[3-[4-isopropyl-2-[4-(trifluoromethyl)phenyl]-5-thiazolyl]propenoyl]phenyl]acrylate

The desired compound was obtained in an analogous manner to (5) of Example 1 from 4-isopropyl-2-[4-(trifluoromethyl)phenyl]thiazole-5-carboaldehyde and

30 methyl 3-(4-acetyl-2-ethylphenyl)acrylate.

Yellow crystalline product

Yield 55% (2 steps)

¹H NMR (CDCl₃, 400MHz): δ=

1.29 (3H, t, J=8Hz),

35 1.39 (6H, d, J=7Hz),

2.88 (2H, q, J=8Hz),
3.4-3.5 (1H, m),
3.84 (3H, s),
6.47 (1H, d, J=15Hz),
5 7.28 (1H, d, J=15Hz),
7.7-7.8 (3H, m),
7.8-7.9 (2H, m),
8.0-8.2 (4H, m).

10 (2) Methyl 3-[2-ethyl-4-[3-[4-isopropyl-2-[4-(trifluoromethyl)phenyl]-5-thiazolyl]propionyl]phenyl]propionate

The desired compound was obtained in an analogous manner to (6) of Example 1 from the obtained methyl 3-[2-ethyl-4-[3-[4-isopropyl-2-[4-(trifluoromethyl)phenyl]-5-thiazolyl]propenoyl]phenyl]acrylate.

Yellow oil

Yield 60%

¹H NMR (CDCl₃, 400MHz): δ=

20 1.26 (3H, t, J=8Hz),
1.34 (6H, d, J=7Hz),
2.61 (2H, t, J=8Hz),
2.72 (2H, q, J=8Hz),
3.02 (2H, t, J=8Hz),
25 3.1-3.2 (1H, m),
3.2-3.4 (4H, m),
3.68 (3H, s),
7.24 (1H, d, J=8Hz),
7.64 (2H, d, J=8Hz),
30 7.73 (1H, dd, J=2Hz, 8Hz),
7.80 (1H, d, J=2Hz),
8.00 (2H, d, J=8Hz).

(3) 3-[4-[3-[4-Isopropyl-2-[4-(trifluoromethyl)phenyl]-5-thiazolyl]propionyl]-2-ethylphenyl]propionic acid

The desired compound was obtained in an analogous manner to (7) of Example 1 from the obtained methyl 3-[2-ethyl-4-[3-[4-isopropyl-2-[4-(trifluoromethyl)phenyl]-5-thiazolyl]propionyl]phenyl]propionate.

5 Pale yellow crystalline product

Yield 74%

FAB-MS (m/e) : 504 (M+1)

¹H NMR (CDCl₃, 400MHz) : δ =

1.26 (3H, t, J=7Hz) ,
10 1.33 (6H, d, J=7Hz) ,
2.6-2.8 (4H, m) ,
3.03 (2H, t, J=8Hz) ,
3.1-3.2 (1H, m) ,
3.2-3.4 (4H, m) ,
15 7.26 (1H, d, 8Hz) ,
7.64 (2H, d, J=8Hz) ,
7.74 (1H, dd, J=8Hz, 2Hz) ,
7.80 (1H, d, J=2Hz) ,
8.00 (2H, d, J=8Hz) .

20

Example 12

3-[4-[3-[2-(4-Chloro-2-hydroxyphenyl)-5-isopropyl-4-oxazolyl]propionyl]-2-methylphenyl]propionic acid

25 (1) Methyl 3-[4-[3-[2-(4-chloro-2-hydroxyphenyl)-5-isopropyl-4-oxazolyl]propenoyl]-2-methylphenyl]acrylate

The desired compound was obtained in an analogous manner to (5) of Example 1 from 2-(4-chloro-2-hydroxyphenyl)-5-isopropyl-4-oxazole-4-carbaldehyde and
30 methyl 3-(4-acetyl-2-ethylphenyl)acrylate.

Pale brown crystalline product

Yield 61%

¹H NMR (CDCl₃, 400MHz) : δ =

1.41 (6H, d, J=7Hz) ,
35 2.54 (3H, s) ,

3.3-3.5 (1H, m),
3.84 (3H, s),
6.47 (1H, d, J=16Hz),
6.98 (1H, dd, J=2Hz, 9Hz),
5 7.13 (1H, d, J=2Hz),
7.64 (1H, d, J=15Hz),
7.67 (1H, d, J=9Hz),
7.73 (1H, d, J=15Hz),
7.77 (1H, d, J=8Hz),
10 7.8-7.9 (2H, m),
7.99 (1H, d, J=16Hz),
11.27 (1H, s).

(2) Methyl 3-[4-[3-[2-(4-chloro-2-hydroxyphenyl)-5-
15 isopropyl-4-oxazolyl]propionyl]-2-methylphenyl]propionate

The desired compound was obtained in an analogous
manner to (6) of Example 1 from the obtained methyl 3-[4-
[3-[2-(4-chloro-2-hydroxyphenyl)-5-isopropyl-4-
oxazolyl]propenoyl]-2-methylphenyl]acrylate.

20 Colorless oil

Yield 47%

¹H NMR(CDCl₃, 400MHz): δ=

1.32 (6H, d, J=7Hz),
2.36 (3H, s),
25 2.59 (2H, t, J=8Hz),
2.94 (2H, t, J=7Hz),
2.98 (2H, t, J=8Hz),
3.1-3.3 (1H, m),
3.33 (2H, t, J=7Hz),
30 3.68 (3H, s),
6.90 (1H, dd, J=2Hz, 8Hz),
7.04 (1H, d, J=2Hz),
7.21 (1H, d, J=8Hz),
7.68 (1H, d, J=8Hz),
35 7.7-7.8 (2H, m),

11.47 (1H, s) .

(3) 3-[4-[3-[2-(4-Chloro-2-hydroxyphenyl)-5-isopropyl-4-oxazolyl]propionyl]-2-methylphenyl]propionic acid

5 The desired compound was obtained in an analogous manner to (7) of Example 1 from the obtained methyl 3-[4-[3-[2-(4-chloro-2-hydroxyphenyl)-5-isopropyl-4-oxazolyl]propionyl]-2-methylphenyl]propionate.

White crystalline product

10 Yield 93%

Melting point 141-144°C

FAB-MS (m/e) : 456 (M+1)

¹H NMR (CDCl₃, 400MHz) : δ =

1.32 (6H, d, J=7Hz) ,

15 2.37 (3H, s) ,

2.65 (2H, t, J=8Hz) ,

2.95 (2H, t, J=7Hz) ,

2.99 (2H, t, J=8Hz) ,

3.1-3.3 (1H, m) ,

20 3.33 (2H, t, J=7Hz) ,

6.90 (1H, dd, J=2Hz, 8Hz) ,

7.04 (1H, d, J=2Hz) ,

7.24 (1H, d, J=8Hz) ,

7.68 (1H, d, J=8Hz) ,

25 7.7-7.8 (2H, m) .

Example 13

3-[4-[3-[5-Isopropyl-2-(2-hydroxyphenyl)-4-oxazolyl]propionyl]-2-methylphenyl]propionic acid

30

(1) Methyl 3-[4-[3-[5-isopropyl-2-(2-hydroxyphenyl)-4-oxazolyl]propionyl]-2-methylphenyl]propionate

Methyl 3-[4-[3-[5-isopropyl-2-(2-methoxyphenyl)-4-oxazolyl]propionyl]-2-methylphenyl]propionate (24 mg,

35 0.0534 mmol) was dissolved in methylene chloride (1.2 mL) .

1M dichloromethane solution of trichloroborane (127 μ L, 0.127 mmol) was added to the solution at 0°C. The mixture was stirred at room temperature for 24 hours. Ice-cold water (5 mL) was added to the mixture. The resulting mixture was extracted with chloroform. The organic layer was washed with saturated aqueous solution of sodium carbonate and water, and dried with anhydrous sodium sulfate. The solvent was removed under reduced pressure. The obtained residue was purified by silica gel column chromatography with hexane/ethyl acetate (3:1, v/v) to give the desired compound (4 mg) as white crystalline product (yield 17%).

White crystalline product

Yield 17%

¹H NMR(CDCl₃, 400MHz): δ =
1.32 (6H, d, J=7Hz),
2.36 (3H, s),
2.59 (2H, t, J=7Hz),
2.9-3.0 (4H, m),
3.1-3.3 (1H, m),
3.34 (2H, t, J=7Hz),
3.68 (3H, s),
6.92 (1H, t, J=8Hz),
7.03 (1H, d, J=8Hz),
7.21 (1H, d, J=8Hz),
7.2-7.3 (1H, m),
7.7-7.8 (3H, m).

(2) 3-[4-[3-[5-Isopropyl-2-(2-hydroxyphenyl)-4-oxazolyl]propionyl]-2-methylphenyl]propionic acid

The desired compound was obtained in an analogous manner to (7) of Example 1 from the obtained methyl 3-[4-[3-[5-isopropyl-2-(2-hydroxyphenyl)-4-oxazolyl]propionyl]-2-methylphenyl]propionate.

White powder

Yield 75%

FAB-MS (m/e) : 422 (M+1)

¹H NMR (CDCl₃, 400MHz) : δ =

- 1.32 (6H, d, J=7Hz),
- 5 2.37 (3H, s),
- 2.65 (2H, t, J=7Hz),
- 2.9-3.0 (4H, m),
- 3.1-3.3 (1H, m),
- 3.34 (2H, t, J=7Hz),
- 10 6.92 (1H, t, J=8Hz),
- 7.02 (1H, d, J=8Hz),
- 7.2-7.3 (2H, m),
- 7.7-7.8 (3H, m).

15 Example 14 (Pharmacological tests 1)

I. Method of measurement

PPAR activating functions of test compounds (compounds of Examples) were measured in the manner described below.

- 20 A receptor expression plasmid (pSG5-GAL4-hPPAR α or γ or δ (LBD)), a luciferase expression plasmid (pUC8-MH100 $\times$ 4-TK-Luc), and a β -galactosidase expression plasmid (pCMX- β -GAL) were transfected into CV-1 cells (ATCC) (Kliwer, S.A. et al., (1992) Nature, 358: 771-774). After the gene transfer was conducted by utilizing a lipofection reagent (Lipofectamine 2000, Invitrogen), it was incubated for about 40 hours in the presence of a compound to be tested. The luciferase activity and β -GAL activity were measured on the soluble cells.

- 30 The luciferase activity was calibrated by the β -GAL activity. A relative ligand activity was calculated under the condition that the luciferase activity of the cells treated by GW-590735 for PPAR α , Rosiglitazone for PPAR γ , or GW-501516 for PPAR δ was set to 100% to determine EC₅₀.

II. Results

The results of tests are shown in Table 38.

TABLE 38

5

Test compounds	PPAR activity		
	PPAR α	PPAR γ	PPAR δ
Example 1	Inactive	Inactive	56
Example 2	Inactive	Inactive	88
Example 3	Inactive	Inactive	76
Example 4	Inactive	Inactive	22
Example 5	Inactive	Inactive	114
Example 6	Inactive	Inactive	68
Example 7	Inactive	Inactive	81
Example 8	Inactive	Inactive	61
Example 9	Inactive	Inactive	80

PPAR activity: a relative value using 10^{-7} M of the test compound (control=100%)

α : GW-590735 10^{-6} M

10 γ : Rosiglitazone 10^{-5} M

δ : GW-501516 10^{-7} M

(Except that compounds of Examples 3 and 8 were measured in the amount of 10^{-6} M)

15 As is apparent from Table 38, the test compound show excellent agonist functions for PPAR δ . The compound of Example 5 shows the particularly strong agonist function for PPAR δ .

Example 15 (Pharmacological tests 2)

The tests were conducted in the same manner to Example 14(1).

The results of tests are shown in Table 39.

5

TABLE 39

Test compounds	PPAR activity		
	PPAR α	PPAR γ	PPAR δ
Example 10	Inactive	Inactive	69
Example 11	Inactive	Inactive	89
Example 12	Inactive	Inactive	93
Example 13	Inactive	Inactive	62

10 PPAR activity: a relative value using 10^{-7} M of the test compound (control=100%)

α : GW-590735 10^{-6} M

γ : Rosiglitazone 10^{-5} M

δ : GW-501516 10^{-7} M

15 (Except that compound of Example 13 was measured in the amount of 10^{-6} M)

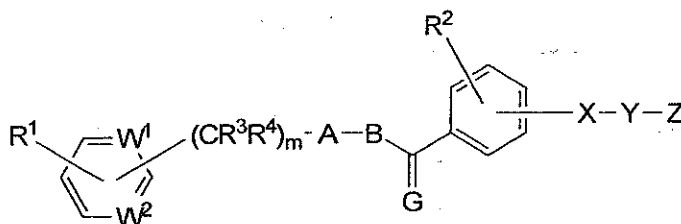
As is apparent from Table 39, the test compound show excellent agonist functions for PPAR δ .

CLAIMS

1. A compound having the following formula (I) or a salt thereof:

5

(I)



wherein each of W¹ and W² independently is CH or nitrogen;

10 X is NR⁵ or CR⁶R⁷, wherein R⁵ is hydrogen, C₁₋₈ alkyl, C₁₋₈ alkyl substituted with halogen, C₁₋₈ alkyl substituted with C₁₋₈ alkoxy, cycloalkyl of three-membered to seven-membered ring, C₁₋₈ alkyl substituted with cycloalkyl of three-membered to seven-membered ring, C₁₋₈ alkyl substituted with phenyl, C₂₋₈ acyl, or C₂₋₈ alkenyl, and
15 each of R⁶ and R⁷ independently is hydrogen or C₁₋₈ alkyl;

Y is -(CR⁸R⁹)_n-, wherein each of R⁸ and R⁹ independently is hydrogen or C₁₋₈ alkyl, and n is 1 to 4; or

X and Y are combined to form -CR¹⁰=CR¹¹- or
20 ethynylene, wherein each of R¹⁰ and R¹¹ independently is hydrogen or C₁₋₈ alkyl;

Z is carboxyl or tetrazolyl;

G is O, S or CR¹²R¹³, wherein each of R¹² and R¹³ independently is hydrogen or C₁₋₈ alkyl;

25 A is five-membered heterocyclic ring selected from the group consisting of thiazole, oxazole, imidazole, pyrazole, thiophene, furan, and pyrrole, which can be substituted with a substituent selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₈ alkoxy, halogen, C₁₋₈ alkyl substituted with halogen, C₁₋₈ alkoxy substituted with halogen, hydroxyl, nitro, C₂₋₈

30

acyl, C₆₋₁₀ aryl, and a five-membered or six-membered heterocyclic group;

B is a C₁₋₈ alkylene, C₂₋₈ alkenylene or C₂₋₈ alkynylene chain, wherein the chain can be substituted with
5 a substituent selected from the group consisting of C₁₋₈ alkyl, cycloalkyl of three-membered to seven-membered ring, C₁₋₈ alkoxy, and halogen;

each of R¹ and R² independently is hydrogen, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₈ alkoxy, halogen, C₁₋₈
10 alkyl substituted with halogen, C₁₋₈ alkoxy substituted with halogen, hydroxyl, nitro, C₂₋₈ acyl, C₆₋₁₀ aryl or a five-membered or six-membered heterocyclic group;

each of R³ and R⁴ independently is hydrogen or C₁₋₈ alkyl; and

15 m is an integer of 0 to 3.

2. A compound or a salt thereof defined in claim 1, wherein each of W¹ and W² is CH.

20 3. A compound or a salt thereof defined in claim 1 or 2, wherein X is CR⁶R⁷.

4. A compound or a salt thereof defined in claim 1 or 2, wherein X is CH₂.

25

5. A compound or a salt thereof defined in claim 1 or 2, wherein X is NR⁵.

6. A compound or a salt thereof defined in claim 1
30 or 2, wherein X is NH.

7. A compound or a salt thereof defined in claim 1 or 2, wherein X is NR⁵, and R⁵ is C₁₋₈ alkyl.

8. A compound or a salt thereof defined in any one of claims 1 to 7, wherein Y is CH₂.

9. A compound or a salt thereof defined in any one of claims 1 to 8, wherein Z is carboxyl.

10. A compound or a salt thereof defined in any one of claims 1 to 9, wherein G is O.

11. A compound or a salt thereof defined in any one of claims 1 to 10, wherein A is thiazole, which can be substituted with a substituent selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₈ alkoxy, halogen, C₁₋₈ alkyl substituted with halogen, C₁₋₈ alkoxy substituted with halogen, hydroxyl, nitro, C₂₋₈ acyl, C₆₋₁₀ aryl, and a five-membered or six-membered heterocyclic group.

12. A compound or a salt thereof defined in any one of claims 1 to 11, wherein B is ethylene chain.

13. A compound or a salt thereof defined in any one of claims 1 to 12, wherein each of R¹ and R² independently is hydrogen, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₁₋₈ alkoxy, halogen, C₁₋₈ alkyl substituted with halogen, or C₁₋₈ alkoxy substituted with halogen.

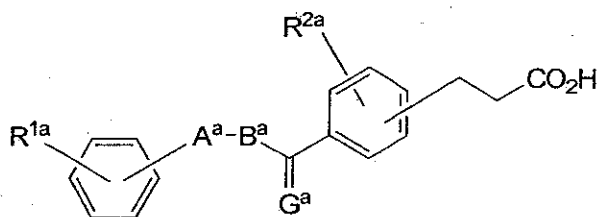
14. A compound or a salt thereof defined in any one of claims 1 to 12, wherein each of R¹ and R² independently is hydrogen, C₁₋₈ alkyl, halogen, or C₁₋₈ alkyl substituted with halogen.

15. A compound or a salt thereof defined in any one of claims 1 to 14, wherein each of R³ and R⁴ is hydrogen.

16. A compound or a salt thereof defined in any one of claims 1 to 14, wherein m is 0.

17. A compound having the following formula (II) or a salt thereof:

(II)



wherein G^a is O, S or CH_2 ;

10 A^a is five-membered heterocyclic ring selected from the group consisting of thiazole, oxazole, and thiophene, which can be substituted with a substituent selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, halogen, C_{1-8} alkyl substituted with halogen, C_{1-8} alkoxy substituted with halogen, hydroxyl, nitro, and C_{2-8} acyl;

15 B^a is a C_{1-8} alkylene or C_{2-8} alkenylene chain; and each of R^{1a} and R^{2a} independently is hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, halogen, C_{1-8} alkyl substituted with halogen, C_{1-8} alkoxy substituted with halogen, hydroxyl, nitro, or C_{2-8} acyl.

18. A compound or a salt thereof defined in claim 17, wherein G^a is O.

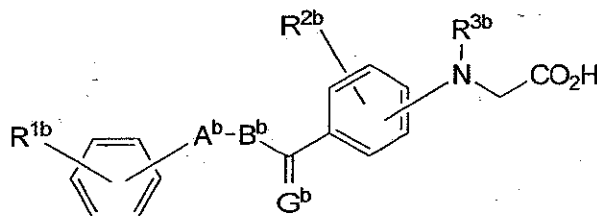
25 19. A compound or a salt thereof defined in claim 17 or 18, wherein A^a is thiazole, which can be substituted with a substituent selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, halogen, C_{1-8} alkyl substituted with halogen, C_{1-8} alkoxy substituted with halogen, hydroxyl, nitro, and C_{2-8} acyl.

20. A compound or a salt thereof defined in any one of claims 17 to 19, wherein B^a is ethylene chain.

21. A compound or a salt thereof defined in any one of claims 17 to 20, wherein each of R^{1a} and R^{2a} independently is hydrogen, C₁₋₈ alkyl, C₁₋₈ alkoxy, halogen, C₁₋₈ alkyl substituted with halogen, or C₁₋₈ alkoxy substituted with halogen.

22. A compound having the following formula (III) or a salt thereof:

(III)



wherein G^b is O, S or CH₂;

A^b is five-membered heterocyclic ring selected from the group consisting of thiazole, oxazole, and thiophene, which can be substituted with a substituent selected from the group consisting of C₁₋₈ alkyl, C₁₋₈ alkoxy, halogen, C₁₋₈ alkyl substituted with halogen, C₁₋₈ alkoxy substituted with halogen, hydroxyl, nitro, and C₂₋₈ acyl;

B^b is a C₁₋₈ alkylene or C₂₋₈ alkenylene chain;

each of R^{1b} and R^{2b} independently is hydrogen, C₁₋₈ alkyl, C₁₋₈ alkoxy, halogen, C₁₋₈ alkyl substituted with halogen, C₁₋₈ alkoxy substituted with halogen, hydroxyl, nitro, or C₂₋₈ acyl; and

R^{3b} is hydrogen or C₁₋₈ alkyl.

23. A compound or a salt thereof defined in claim 22, wherein G^b is O.

24. A compound or a salt thereof defined in claim 22 or 23, wherein A^b is thiazole, which can be substituted with a substituent selected from the group consisting of C₁₋₈ alkyl, C₁₋₈ alkoxy, halogen, C₁₋₈ alkyl substituted with halogen, C₁₋₈ alkoxy substituted with halogen, hydroxyl, nitro, and C₂₋₈ acyl.

25. A compound or a salt thereof defined in any one of claims 22 to 24, wherein B^b is ethylene chain.

26. A compound or a salt thereof defined in any one of claims 22 to 25, wherein each of R^{1b} and R^{2b} independently is hydrogen, C₁₋₈ alkyl, C₁₋₈ alkoxy, halogen, C₁₋₈ alkyl substituted with halogen, or C₁₋₈ alkoxy substituted with halogen.

27. An activator of peroxisome proliferator activated receptor δ which contains as an effective component a compound or a salt thereof defined in any one of claims 1 to 26.

28. A medicament which contains a compound or a salt thereof defined in any one of claims 1 to 26 and a pharmaceutically acceptable vehicle.

29. The use of an effective dose of a compound or a salt thereof defined in any one of claims 1 to 26 in the manufacture of a medicament for activating peroxisome proliferator activated receptor δ .

30. The use of an effective dose of a compound or a salt thereof defined in any one of claims 1 to

26 in the manufacture of a medicament for treatment and/or prophylaxis proliferator activated receptor δ .

31. The use defined in claim 30, wherein a disease
5 mediated by peroxisome proliferator activated receptor δ is
hyperlipidemia, dyslipidemia, hypercholesterolemia,
hypertriglyceridemia, HDL hypocholesterolemia, LDL
hypercholesterolemia and/or HLD non-cholesterolemia, VLDL
hyperproteinemia, dyslipoproteinemia, apolipoprotein A-I
10 hypoproteinemia, atherosclerosis, disease of arterial sclerosis,
disease of cardiovascular systems, cerebrovascular disease,
peripheral circulatory disease, metabolic syndrome, syndrome X,
obesity including internal-organs fat type, diabetes,
hyperglycemia, insulin resistance, impaired glucose tolerance,
15 hyperinsulinism, diabetic complication, cardiac insufficiency,
cardiac infarction, cardiomyopathy, hypertension, fatty liver,
non-alcoholic fatty hepatitis, thrombus, Alzheimer disease,
neurodegenerative disease, demyelinating disease, multiple
sclerosis, adrenal leukodystrophy, dermatitis, psoriasis, acne,
20 skin aging, trichosis, inflammation, arthritis, asthma, hyper-
sensitive intestine syndrome, ulcerative colitis, Crohn's disease,
pancreatitis, or cancer including colon cancer, large intestine
cancer, skin cancer, cancer of the breast, carcinoma of the
prostate, ovary cancer, and lung cancer.

25 32. The use defined in claim 30, wherein a disease mediated
by peroxisome proliferator activated receptor δ is dyslipidemia,
metabolic syndrome, obesity including internal-organs fat type,
atherosclerosis or disease associated therewith, or diabetes.

33. A compound or a salt thereof defined in any one of claims 1 to 26 for use in the manufacture of a medicament for treatment and/or prophylaxis of a disease mediated by peroxisome proliferator activated receptor δ .

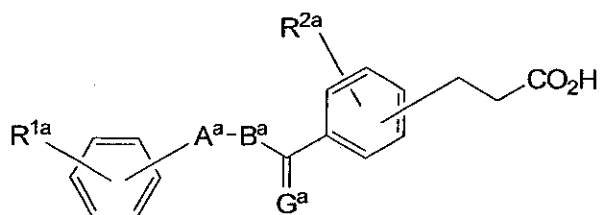
34. A compound or a salt thereof defined in claim 33, wherein a disease mediated by peroxisome proliferator activated receptor δ is hyperlipidemia, dyslipidemia, hypercholesterolemia, hypertriglyceridemia, HDL hypocholesterolemia, LDL hypercholesterolemia and/or HLD non-cholesterolemia, VLDL hyperproteinemia, dyslipoproteinemia, apolipoprotein A-I hypoproteinemia, atherosclerosis, disease of arterial sclerosis, disease of cardiovascular systems, cerebrovascular disease, peripheral circulatory disease, metabolic syndrome, syndrome X, obesity including internal-organs fat type, diabetes, hyperglycemia, insulin resistance, impaired glucose tolerance, hyperinsulinism, diabetic complication, cardiac insufficiency, cardiac infarction, cardiomyopathy, hypertension, fatty liver, non-alcoholic fatty hepatitis, thrombus, Alzheimer disease, neurodegenerative disease, demyelinating disease, multiple sclerosis, adrenal leukodystrophy, dermatitis, psoriasis, acne, skin aging, trichosis, inflammation, arthritis, asthma, hypersensitive intestine syndrome, ulcerative colitis, Crohn's disease, pancreatitis, or cancer including colon cancer, large intestine cancer, skin cancer, cancer of the breast, carcinoma of the prostate, ovary cancer, and lung cancer.

35. A compound or a salt thereof defined in claim 33, wherein a disease mediated by peroxisome proliferator activated receptor δ is dyslipidemia, metabolic syndrome, obesity including internal-organs fat type, atherosclerosis or disease associated therewith, or diabetes.

ABSTRACT

A compound represented by the following general formula (II) or a salt thereof is used as an activator of PPAR δ .

(II)



wherein G^a is O, CH_2 or the like;

10 A^a is thiazole, oxazole, or thiophene, which can have a substituent such as C_{1-8} alkyl, C_{1-8} alkoxy, halogen, C_{1-8} alkyl substituted with halogen or the like;

B^a is a C_{1-8} alkylene or C_{2-8} alkenylene chain; and

each of R^{1a} and R^{2a} independently is hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, halogen, C_{1-8} alkyl substituted with
15 halogen or the like.