

Description



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Carboxylic acid derivative and salt thereof



Technical Filed of the Invention

The present invention relates to a novel carboxylic acid compound useful for prevention or treatment of hyperglycemia, hyperlipemia and inflammatory disease, a salt thereof or a hydrate of them, and to a medicament comprising them.

Prior Art

Diabetes mellitus refers to a durable hyperglycemic condition attributable to the absolute or relative shortage of intrinsic insulin (blood glucose-depressing hormone produced and secreted from Langerhans islet β cells in the pancreas), and in this disease, metabolic abnormalities caused by this condition appear as various morbid states.

Diabetes mellitus is classified roughly into insulin dependent diabetes mellitus (IDDM) that is type 1 diabetes mellitus, for treatment of which insulin administration is absolutely necessary, non insulin dependent diabetes mellitus (NIDDM) that is type 2 diabetes mellitus, and other diabetes mellitus (secondary diabetes mellitus; diabetes mellitus occurs as one symptom of other diseases).

In particular, as life-style is modernized, NIDDM is rapidly increased due to overeating and lack of exercise, thus causing

a social problem. While IDDM occurs mainly in infants, NIDDM occurs in middle-aged or elderly persons, to account for the majority of diabetes mellitus in Japan. It is said that NIDDM occurs owing to insulin function-suppressing factors (insulin resistance) such as overeating, lack of exercise, obesity and stress in addition to hereditary factors.

Since excessive intake of calories and obesity resulting from lack of exercise are related to diabetes mellitus as described above, the therapy is based on 3 kinds of therapies, that is, dietary therapy, exercise therapy and chemotherapy.

However, there are not a few cases where dietary therapy and exercise therapy are hardly to conduct because of an increase in the number of persons of advanced age in this aging society in recent years.

In chemotherapy of NIDDM, sulfonyl urea (SU) medicines such as Tolbutamide, Chlorpropamide and Tolazamide and Biguanide (BG) medicines such as Metformin hydrochloride and Buformin have been used as oral blood glucose depressants, but the morbid state of NIDDM is characterized by insulin deficiency and insulin resistance, and it cannot be said that the SU medicines stimulating insulin secretion from pancreatic β cells are effective therapeutic medicines for patients with NIDDM condition, where the insulin secretion potential is well but adequate blood glucose control is not achieved in target organs due to insulin resistance, thus permitting hyperglycemia. Further, the BG medicines may permit the onset of lactic acid

acidosis, so use of such medicines is limited to a certain extent. Further, these chemicals often caused severe hypoglycemia as a side effect.

To solve these problems, development of chemicals with a new working mechanism is advancing, and thiazolidine derivatives such as Troglitazone, Pioglitazone and Rosiglitazone are called insulin sensitizers, and these chemicals recently attract attention because they can ameliorate insulin resistance (or enhance the action of insulin) and lower blood glucose without promoting secretion of insulin from the pancreas.

It has been revealed that these thiazolidine-type chemicals induce differentiation of adipocytes, and exhibit their action via an intranuclear receptor PPAR γ (peroxisome proliferator-activated receptor gamma: a transcriptional factor important for differentiation of adipocytes) (J. Biol. Chem., 270, 12953-12956, 1995). By the differentiation of preadipocytes, immature and small adipocytes with less secretion of TNF α , FFA and leptin are increased thus resulting in amelioration of insulin resistance.

Thiazolidine derivatives such as the above Troglitazone, Pioglitazone and Rosiglitazone also act as agonists for PPAR γ , to exhibit the effect of ameliorating insulin resistance.

Besides PPAR γ , PPAR subtypes such as α , $\beta(\delta)$ etc. have been found, any of which regulate expression of genes involved in lipid metabolism. The homology of each subtype among different biological species is higher than the homology of these subtypes

in the same species, and with respect to distribution of each subtype in tissues, PPAR γ is located substantially in adipose tissues while PPAR α occurs mainly in the liver, heart and kidney, and therefore it was considered that each subtype has an independent function. In recent years, it has been revealed that PPAR γ mainly mediates lipid anabolism by promoting expression of a group of genes for LPL, acyl-CoA carboxylase, GPDH etc. to convert glucose into lipid and storing the lipid, while PPAR α mediates lipid catabolism by regulating expression of a gene group involved in intake of fatty acids into cells and oxidation thereof to decompose lipid.

Moreover, researches concerning relationships between particular subtypes of PPAR and various diseases have been widely conducted in recent years (J.Med.Chem., 2000, 43(4), 527-550; Trends Cardiovasc. Med., 2000, 10, p238-245).

As thiazolidine derivatives acting as PPAR γ and α dual agonists, compounds disclosed in e.g. JP-A 9-48771 are known.

Further, some compounds are known as insulin sensitizers having a carboxylic acid moiety in their structure (Current Pharmaceutical Design, 2, No.1, p85-102, 1996; Bioorganic & Medicinal Chemistry Letters, 6, No.17, p2121-2126, 1996; WO200075103; WO9918066; WO9916758).

However, it has been reported that some chemicals acting as PPAR γ agonists cause hepatic damage and thus should be carefully used, so chemicals satisfactory in both therapeutic effects and side effects such as toxicity are still not obtained.

Further, compounds having a carboxyl group instead of a thiazolidinyl group are merely presented in literatures and not marketed. Further, there is no report showing that such compounds can be used as PPAR γ and α dual agonists, and as a matter of course, their γ , α and $\beta(\delta)$ triple agonist action is not known. However, it is also estimated that the toxicity of PPAR γ agonists described above is the unique one derived from the thiazolidine moiety, and if a compound exhibiting the above action with a new structure in place of the above structure can be found, the compound can be expected to solve the problem of toxicity, and is thus very useful.

The conventional chemicals are still unsatisfactory in respect of neutral fat (triglyceride (TG)) related closely to arteriosclerosis.

Further, the action of PPAR $\beta(\delta)$ to induce differentiation of adipocytes is known (J. Biol. Chem., 274, No. 31, pp. 21920-21925), and by this action, cholesterol levels are reported to be lowered (WO9904815), and if a compound having an agonist action for this subtype can be found, this compound can be expected to exhibit a higher activity than that of the conventional insulin sensitizers and to reduce side effects such as hepatic toxicity.

Furthermore, as a PRAR receptor ligand, diarylic acid derivatives are disclosed in WO00/64888A and triarylic acid derivatives in WO00/64876A.

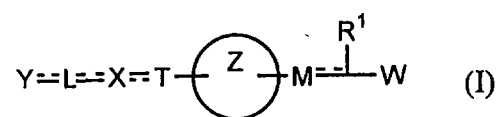
From the foregoing aspects, there is demand for development of excellent chemicals.

Disclosure of the Invention

For the purpose of providing a medicament effective in prevention or treatment of hyperglycemia, which satisfies these various requirements, the present inventors made extensive study and, as a result, they found that a carboxylic acid derivative having a novel structure has an excellent anti-hyperglycemia and anti-hyperlipemia action, thus completing the present invention.

That is, the present invention relates to:

- 1) a carboxylic acid compound represented by the following formula:

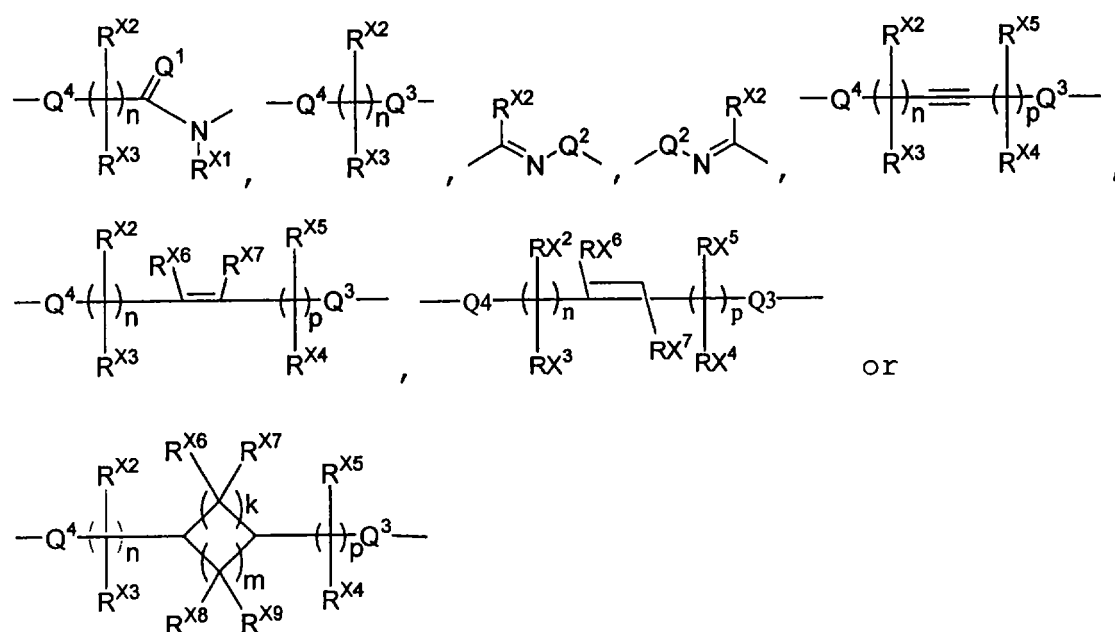


(wherein R^1 represents a hydrogen atom, hydroxyl group, halogen, carboxyl group, or a C_{1-6} alkyl group, a C_{1-6} alkoxy group, a C_{1-6} alkylthio group, a C_{1-6} hydroxyalkyl group, a C_{1-6} hydroxyalkoxy group, a C_{1-6} hydroxyalkylthio group, a C_{1-6} aminoalkyl group, an amino C_{1-6} alkoxy group, an amino C_{1-6} alkylthio group, a halogeno C_{1-6} alkyl group, a halogeno C_{1-6} alkoxy group, a halogeno- C_{1-6} alkylthio group, a C_{2-12} alkoxyalkyl group, a C_{2-12} alkoxyalkoxy group, a C_{2-12} alkoxyalkylthio group, a C_{3-7} cycloalkyl group, a C_{3-7} cycloalkyloxy group, a C_{4-13} cycloalkylalkyloxy group, a C_{3-7} cycloalkylthio group, a C_{2-6} alkenyl group, a C_{2-6} alkenyloxy group, C_{2-6} alkenylthio group, a C_{2-6} alkynyl group, a C_{2-6} alkynyloxy group, a C_{2-6} alkynylthio group, a C_{6-12} aryl group,

a C₆₋₁₂ aryloxy group, a C₆₋₁₂ arylthio group, a C₇₋₁₈ alkylaryl group, a C₇₋₁₈ alkylaryloxy group, a C₇₋₁₈ alkylarylthio group, a C₇₋₁₈ aralkyl group, a C₇₋₁₈ aralkyloxy group or a C₇₋₁₈ aralkylthio group, each of which may have one or more substituents; L represents a single bond, or a C₁₋₆ alkylene group, a C₂₋₆ alkenylene group or a C₂₋₆ alkynylene group, each of which may have one or more substituents; M represents a single bond, or a C₁₋₆ alkylene group, a C₂₋₆ alkenylene group or a C₂₋₆ alkynylene group, each of which may have one or more substituents; T represents a single bond, or a C₁₋₃ alkylene group, a C₂₋₃ alkenylene group or a C₂₋₃ alkynylene group, each of which may have one or more substituents; W represents a carboxyl group;

represents a single bond or a double bond; X represents a single bond, oxygen atom, a group represented by -NR^{X1}CQ¹O- (wherein Q¹ represents an oxygen atom or sulfur atom; and R^{X1} represents a hydrogen atom, formyl group, or a C₁₋₆ alkyl group, a C₁₋₆ hydroxyalkyl group, a C₁₋₆ aminoalkyl group, a halogeno C₁₋₆ alkyl group, a C₂₋₁₂ alkoxyalkyl group, a C₃₋₇ cycloalkyl group, a C₂₋₆ alkenyl group, a C₂₋₆ alkynyl group, a C₆₋₁₂ aryl group, a C₇₋₁₈ alkylaryl group, a C₇₋₁₈ aralkyl group, a C₂₋₇ aliphatic acyl group or a C₇₋₁₉ aromatic acyl group, each of which may have one or more substituents), -OCQ¹NR^{X1}- (wherein Q¹ and R^{X1} are as defined above), -CQ¹NR^{X1}O- (wherein Q¹ and R^{X1} are as defined above), ONR^{X1}CQ¹- (wherein Q¹ and R^{X1} are as defined above), -Q²SO₂- (wherein Q² is an oxygen atom or -NR^{X10}- (wherein R^{X10} represents a hydrogen

atom, formyl group, or a C₁₋₆ alkyl group, a C₁₋₆ hydroxyalkyl group, a C₁₋₆ aminoalkyl group, a halogeno-C₁₋₆ alkyl group, a C₂₋₁₂ alkoxyalkyl group, a C₃₋₇ cycloalkyl group, a C₂₋₆ alkenyl group, a C₂₋₆ alkynyl group, a C₆₋₁₂ aryl group, a C₇₋₁₈ alkylaryl group, a C₇₋₁₈ aralkyl group, a C₂₋₇ aliphatic acyl group or a C₇₋₁₉ aromatic acyl group, each of which may have one or more substituents)) or -SO₂Q²- (wherein Q² is as defined above), or a group represented by the formula:



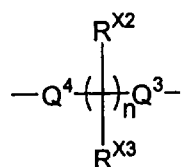
(wherein Q¹, Q² and R^{X1} are as defined above; k represents 0 to 5; m represents 1 to 5; n and p are the same as or different from each other and each represents 1 to 5; R^{X2}, R^{X3}, R^{X4}, R^{X5}, R^{X6}, R^{X7}, R^{X8} and R^{X9} are the same as or different from each other and each represents a hydrogen atom, hydroxy group, halogen, -N(R^{X11})R^{X12}- (wherein R^{X11} and R^{X12} are the same as or different from each other and each represents a hydrogen atom, formyl group, or a C₁₋₆ alkyl group, a C₁₋₆ hydroxyalkyl group, a C₁₋₆ aminoalkyl

group, a halogeno-C₁₋₆ alkyl group, a C₂₋₁₂ alkoxyalkyl group, a C₃₋₇ cycloalkyl group, a C₂₋₆ alkenyl group, a C₂₋₆ alkynyl group, a C₆₋₁₂ aryl group, a C₇₋₁₈ alkylaryl group, a C₇₋₁₈ aralkyl group, a C₂₋₇ aliphatic acyl group or a C₇₋₁₉ aromatic acyl group, each of which may have one or more substituents), or a C₁₋₆ alkyl group, C₁₋₆ alkoxy group, a C₁₋₆ alkylthio group, a C₁₋₆ hydroxyalkyl group, a C₁₋₆ hydroxyalkoxy group, a C₁₋₆ hydroxyalkylthio group, a C₁₋₆ aminoalkyl group, a C₁₋₆ aminoalkoxy group, a C₁₋₆ aminoalkylthio group, a halogeno-C₁₋₆ alkyl group, a halogeno-C₁₋₆ alkoxy group, a halogeno-C₁₋₆ alkylthio group, a C₂₋₁₂ alkoxyalkyl group, a C₂₋₁₂ alkoxyalkoxy group, a C₂₋₁₂ alkoxyalkylthio group, a C₃₋₇ cycloalkyl group, a C₃₋₇ cycloalkyloxy group, a C₄₋₁₃ cycloalkylalkyloxy group, a C₃₋₇ cycloalkylthio group, a C₂₋₆ alkenyl group, a C₂₋₆ alkenyloxy group, a C₂₋₆ alkenylthio group, a C₂₋₆ alkynyl group, a C₂₋₆ alkynyloxy group, a C₂₋₆ alkynylthio group, a C₆₋₁₂ aryl group, a C₆₋₁₂ aryloxy group, a C₆₋₁₂ arylthio group, a C₇₋₁₈ alkylaryl group, a C₇₋₁₈ alkylaryloxy group, a C₇₋₁₈ alkylarylthio group, a C₇₋₁₈ aralkyl group, a C₇₋₁₈ aralkyloxy group or a C₇₋₁₈ aralkylthio group, each of which may have one or more substituents, provided that R^{x2} and R^{x3}, and/or R^{x4} and R^{x5} may together form a ring; and Q³ and Q⁴ are the same as or different from each other and each represents an oxygen atom, (O)S(O) or NR^{x10} (wherein NR^{x10} is as defined above); Y represents a 5- to 14-membered aromatic group or a C₃₋₇ alicyclic hydrocarbon group, each of which may have one or more substituents and one or more hetero atoms; and the ring Z represents a 5- to 14-membered

R^{X9} are as defined above;

4) the carboxylic acid compound according to any one of 1) to 3), a salt thereof, an ester thereof or a hydrate of them, wherein in the formula (I), X is $-NR^{X1}CQ^1O-$ (wherein Q^1 and R^{X1} are as defined above) or $-OCQ^1NR^{X1}-$ (Q^1 and R^{X1} are as defined above);

5) the carboxylic acid compound according to any one of 1) to 3), a salt thereof, an ester thereof or a hydrate of them, wherein in the formula (I), X is a group represented by the formula:

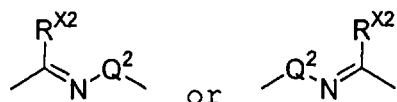


wherein n, Q^3 , Q^4 , R^{X2} and R^{X3} are as defined above;

6) the carboxylic acid compound according to 1), a salt thereof, an ester thereof or a hydrate of them, wherein in the formula (I), L is a single bond or a C_{1-6} alkylene group which may have one or more substituents; X is a single bond or oxygen atom; and T is a C_{2-6} alkynylene group which may have one or more substituents;

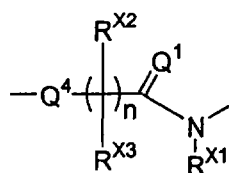
7) the carboxylic acid compound according to 1), a salt thereof, an ester thereof or a hydrate of them, wherein in the formula (I), L is a C_{2-6} alkynylene which may have one or more substituents; X is a single bond or oxygen atom; and T is a single bond or a C_{1-6} alkylene group which may have one or more substituents;

8) the carboxylic acid compound according to 1), a salt thereof, an ester thereof or a hydrate of them, wherein in the formula (I), X is a group represented by the formula:



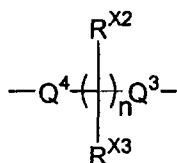
wherein Q^2 and $\text{R}^{\text{X}2}$ are as defined above;

9) the carboxylic acid compound according to 1), a salt thereof, an ester thereof or a hydrate of them, wherein in the formula (I), X is a group represented by the formula:



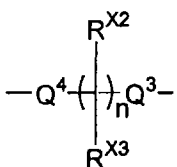
wherein n , Q^1 , Q^4 , $\text{R}^{\text{X}1}$, $\text{R}^{\text{X}2}$ and $\text{R}^{\text{X}3}$ are as defined above;

10) the carboxylic acid compound according to 1), a salt thereof, an ester thereof or a hydrate of them, wherein in the formula (I), X is a group represented by the formula:



wherein Q^3 and Q^4 represent an oxygen atom; and n , $\text{R}^{\text{X}2}$ and $\text{R}^{\text{X}3}$ are as defined above;

11) the carboxylic acid according to 10), a salt thereof, an ester thereof or a hydrate of them, wherein in the formula (I), X is a group represented by the formula:

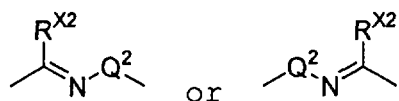


(wherein Q^3 and Q^4 represent an oxygen atom; n represents 2 to 5; and $\text{R}^{\text{X}2}$ and $\text{R}^{\text{X}3}$ are as defined above, provided that either

one of R^{X2} and R^{X3} should be a group other than a hydrogen atom);
 L is a single bond or a C_{1-3} alkylene group which may have one or more substituents; and T is a single bond or a C_{1-3} alkylene group which may have one or more substituents;

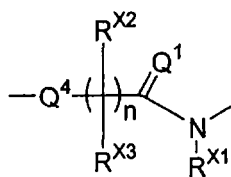
12) the carboxylic acid compound according to 4), a salt thereof, an ester thereof or a hydrate of them, wherein in the formula (I), X is a group represented by the formula $-NR^{X1}CQ^1O-$ (wherein Q^1 represents an oxygen atom, R^{X1} is as defined above) or $-OCQ^1NR^{X1}-$ (wherein Q^1 represents an oxygen atom, R^{X1} is as defined above), L is a single bond or a C_{1-3} alkylene group which may have one or more substituents, and T is a single bond or a C_{1-3} alkylene group which may have one or more substituents;

13) the carboxylic acid compound according to 8), a salt thereof, an ester thereof or a hydrate of them, wherein in the formula (I), X is a group represented by the formula:



(wherein, Q^2 represents an oxygen atom and R^{X2} is as defined above);
 L is a single bond or a C_{1-3} alkylene group which may have one or more substituents; and T is a single bond or a C_{1-3} alkylene group which may have one or more substituents;

14) the carboxylic acid compound according to 9), a salt thereof, an ester thereof or a hydrate of them, wherein in the formula (I), X is a group represented by the formula:



(wherein, Q^1 and Q^4 represent an oxygen atom; $\text{R}^{\text{X}1}$, $\text{R}^{\text{X}2}$ and $\text{R}^{\text{X}3}$ are as defined above; and n represents 1 to 5); L is a single bond or a C_{1-3} alkylene group which may have one or more substituents; and T is a single bond or a C_{1-3} alkylene group which may have one or more substituents;

15) the carboxylic acid compound according to 3), a salt thereof, an ester thereof or a hydrate of them, wherein in the formula (I), X is $-\text{Q}^2\text{SO}_2-$ or $-\text{SO}_2\text{Q}^2-$ (wherein Q^2 represents an oxygen atom); L is a single bond or a C_{1-3} alkylene group which may have one or more substituents; and T is a single bond or a C_{1-3} alkylene group which may have one or more substituents;

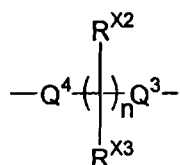
16) the carboxylic acid compound according to 3), a salt thereof, an ester thereof or a hydrate of them, wherein in the formula (I), X is $-\text{CQ}^1\text{NR}^{\text{X}1}\text{O}-$ or $-\text{ONR}^{\text{X}1}\text{CQ}^1-$ (wherein Q^1 represents an oxygen atom; and $\text{R}^{\text{X}1}$ is as defined above); L is a single bond or a C_{1-3} alkylene group which may have one or more substituents; and T is a single bond or a C_{1-3} alkylene group which may have one or more substituents;

17) the carboxylic acid compound according to 11), a salt thereof, an ester thereof or a hydrate of them, wherein in the formula (I), wherein M is a C_{1-6} alkylene group; R^1 is a carboxyl group, or a C_{1-6} alkyl group, a C_{1-6} alkoxy group, a C_{1-6} alkylthio group, a C_{6-12} aryloxy group or a C_{7-18} aralkyloxy group, each of which

may have one or more substituents;

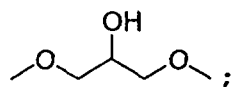
18) the carboxylic acid compound according to 17), a salt thereof, an ester thereof or a hydrate of them, wherein in the formula (I), the ring Z is a 1,3-phenylene group which may have 1 to 4 substituents;

19) the carboxylic acid compound according to 11) or 18), a salt thereof, an ester thereof or a hydrate of them, wherein in the formula (I), X is a group represented by the formula:

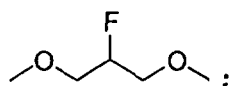


wherein Q³ and Q⁴ represent an oxygen atom; n represents 3 to 5; and R^{X2} and R^{X3} represent a hydrogen atom, hydroxyl group or fluorine atom, provided that either one of R^{X2} and R^{X3} should be a group other than a hydrogen atom;

20) the carboxylic acid compound according to 19), a salt thereof, an ester thereof or a hydrate of them, wherein in the formula (I), X is represented by the formula:



21) the carboxylic acid compound according to 19), a salt thereof, an ester thereof or a hydrate of them, wherein in the formula (I), X is represented by the formula:



22) the carboxylic acid compound according to any one of 19)

to 21), a salt thereof, an ester thereof or a hydrate of them, wherein in the formula (I), M is a methylene group; and R¹ is a C₁₋₆ alkoxy group which may have one or more substituents;

23) the carboxylic acid compound according to 12), a salt thereof, an ester thereof or a hydrate of them, wherein in the formula (I), M is a C₁₋₆ alkylene group; and R¹ is a carboxyl group, or a C₁₋₆ alkyl group, a C₁₋₆ alkoxy group, a C₁₋₆ alkylthio group, a C₆₋₁₂ aryloxy group or a C₇₋₁₈ aralkyloxy group, each of which may have one or more substituents;

24) the carboxylic acid compound according to 23), a salt thereof, an ester thereof or a hydrate of them, wherein in the formula (I), L is a C₁₋₃ alkylene group which may have one or more substituents; and T is a C₁₋₃ alkylene group which may have one or more substituents;

25) the carboxylic acid compound according to 24), a salt thereof, an ester thereof or a hydrate of them, wherein in the formula (I), the ring Z is a 1,3-phenylene group which may have 1 to 4 substituents;

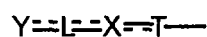
26) the carboxylic acid compound according to 25), a salt thereof, an ester thereof or a hydrate of them, wherein in the formula (I), M is a methylene group; and R¹ is a C₁₋₆ alkoxy group which may have one or more substituents;

27) the carboxylic acid compound according to any one of 13) to 16), a salt thereof, an ester thereof or a hydrate of them, wherein in the formula (I), M is a C₁₋₆ alkylene group; R¹ is a carboxyl group, or a C₁₋₆ alkyl group, a C₁₋₆ alkoxy group, a

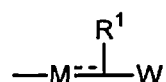
C₁₋₆ alkylthio group, a C₆₋₁₂ aryloxy group or a C₇₋₁₈ aralkyloxy group, each of which may have one or more substituents;

28) the carboxylic acid compound according to any one of 11) to 27), a salt thereof, an ester thereof or a hydrate of them, wherein in the formula (I), Y is a phenyl group which may have 1 or 2 substituents;

29) the carboxylic acid compound according to 1), a salt thereof, an ester thereof or a hydrate of them, wherein in the formula (I), a group represented by the formula:



(wherein each symbol represents a group as defined above) and a group represented by the formula:



(wherein each symbol represents a group as defined above) are bound with each other on the ring Z via from 2 to 8 atoms;

30) the carboxylic acid compound according to 1), a salt thereof, an ester thereof or a hydrate of them, wherein the compound represented by the formula (I) is one selected from:

(1) 2-isopropoxy-3-(3-[3-(2,4-dichlorophenyl)-2-propynyl]oxyphenyl)propanoic acid;

(2) 3-3-[3-(4-trifluoromethylphenyl)-1-hydroxy-1-methyl-2-propynyl]phenyl-2-isopropoxypropanoic acid;

(3) 2-isopropoxy-3-[3-([4-(trifluoromethyl)benzyl]-oxyehtaneimidoyl)phenyl]propanoic acid;

(4) 2-ethoxy-3-{3-[2-([4-(trifluoromethyl)anilino]-

carbonyl)oxy)ethyl]phenyl]propanoic acid;

(5) 3-{3-[3-(4-chloro-2-cyanophenoxy)-2-hydroxypropoxy]phenyl}-2-isopropoxypropanoic acid;

(6) 2-isopropoxy-3-(3-{{{4-trifluoromethoxybenzyl}-oxy}carbonyl)amino)methyl]phenyl]propanoic acid;

(7) 3-{3-[3-(2,4-dichlorophenoxy)-2(S)-hydroxypropoxy]phenyl}-2(S)-isopropoxypropanoic acid;

(8) 3-{3-[3-(4-chloro-2-cyanophenoxy)-2(S)-hydroxypropoxy]phenyl}-2(S)-isopropoxypropanoic acid;

(9)

3-(3-{2(S)-hydroxy-3-[3-(1-hydroxy-1-methylethyl)-phenoxy]-propoxy}phenyl)-2(S)-isopropoxypropanoic acid;

(10) 3-(3-{2(R)-hydroxy-3-[4-chlorophenoxy]propoxy}-phenyl)-2(S)-isopropoxypropanoic acid;

(11) 3-(3-{2(S)-hydroxy-3-[2,4-dimethylphenoxy]-propoxy}phenyl)-2(S)-isopropoxypropanoic acid;

(12) 3-(3-{2(S)-hydroxy-3-[4-chloro-2-fluorophenoxy]-propoxy}phenyl)-2(S)-isopropoxypropanoic acid;

(13) 3-{3-[3-(2,4-dichlorophenoxy)-2(R)-hydroxypropoxy]phenyl}-2(S)-isopropoxypropanoic acid;

(14) 3-{3-[3-(4-chloro-2-cyanophenoxy)-2(R)-hydroxypropoxy]phenyl}-2(S)-isopropoxypropanoic acid;

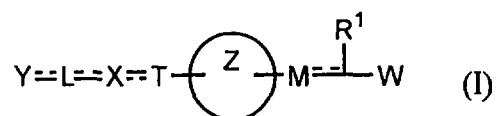
(15) 3-(3-{2(R)-hydroxy-3-[2,4-dimethylphenoxy]-propoxy}phenyl)-2(S)-isopropoxypropanoic acid;

(16) 3-{3-[3-(2,4-dichlorophenoxy)-2(R)-fluoropropyl]phenyl}-2(S)-isopropoxypropanoic acid;

- (17) 3-{3-[3-(4-chlorophenoxy)-2(S)-fluoropropyl]phenyl}-2(S)-isopropoxypropanoic acid;
- (18) 3-{3-[3-(4-chloro-2-cyanophenoxy)-2(R)-fluoropropyl]phenyl}-2(S)-isopropoxypropanoic acid;
- (19) 3-{3-[3-(2,4-dichlorophenoxy)-2(S)-fluoropropyl]phenyl}-2(S)-isopropoxypropanoic acid;
- (20) 3-{3-[3-(4-chlorophenoxy)-2(R)-fluoropropyl]phenyl}-2(S)-isopropoxypropanoic acid;
- (21) 3-{3-[3-(4-chloro-2-cyanophenoxy)-2(S)-fluoropropyl]phenyl}-2(S)-isopropoxypropanoic acid;
- (22) 3-{3-[3-(2,4-dimethylphenoxy)-2(S)-fluoropropyl]phenyl}-2(S)-isopropoxypropanoic acid;
- (23) 2(S)-isopropoxy-3-{3-[4-trifluoromethylbenzyloxycarbonylamino)methyl]phenyl}-propanoic acid;
- (24) 2(S)-isopropoxy-3-{3-[3-trifluoromethylbenzyloxycarbonylamino)methyl]phenyl}-propanoic acid;
- (25) 2(S)-isopropoxy-3-{3-[4-trifluoromethoxybenzyloxycarbonylamino)methyl]phenyl}-propanoic acid;
- (26) 3-(3-{[4-(1-hydroxy-1-methylethyl)-benzyloxycarbonylamino]methyl}phenyl)-2(S)-isopropoxypropanoic acid;
- (27) 3-(3-{[2,5-dichlorobenzyloxycarbonylamino]methyl}phenyl)-2(S)-isopropoxypropanoic acid;

- (28) 3-(3-([4-ethoxybenzyloxycarbonylamino]methyl)-phenyl)-2(S)-isopropoxypropanoic acid;
- (29) 3-(3-([3-trifluoromethoxybenzyloxycarbonylamino]methyl)phenyl)-2(S)-isopropoxypropanoic acid;
- (30) 3-(3-([2-(4-chlorophenyl)ethoxycarbonylamino]methyl)phenyl)-2(S)-isopropoxypropanoic acid;
- (31) 2(S)-isopropoxy-3-{3-[(quinolin-2-ylmethoxycarbonylamino)methyl]phenyl}propanoic acid;
- (32) 3-{[3-(2,4-dichlorophenyl)carbamoyloxymethyl-4-ethoxy]phenyl}-2-isopropoxypropanoic acid;
- (33) 3-([4-[5-(benzo[1,3]dioxolyl)]-carbamoyloxymethyl]phenyl)-2-isopropoxypropanoic acid;
- (34) 3-{3-[3-(2,4-dichlorophenoxy)-1-propynyl]phenyl}-2(S)-isopropoxypropanoic acid;
- (35) 3-{3-[3-(2,4-dichlorophenyl)-2-propionyloxy]phenyl}-2(S)-isopropoxypropanoic acid;
- (36) 3-{3-[3-(4-chlorophenyl)-2-propionyloxy]phenyl}-2(S)-isopropoxypropanoic acid;
- (37) 2(S)-3-{[3-(2,4-dichlorophenyl)carbamoyloxymethyl-4-ethoxy]phenyl}-2-isopropoxypropanoic acid;
- (38) 3-{3-[2-(4-chlorophenoxy)acetylamino]-4-ethoxyphenyl}-2-isopropoxypropanoic acid;
- (39) 3-{3-[2-(2,4-dichlorophenoxy)acetylamino]-4-ethoxyphenyl}-2-isopropoxypropanoic acid; and
- (40) 3-{4-[3-(4-chloro-2-cyanophenoxy)-2-hydroxypropoxy]phenyl}-2-isopropoxypropanoic acid;

31) a medicament comprising a carboxylic acid compound represented by the following formula:



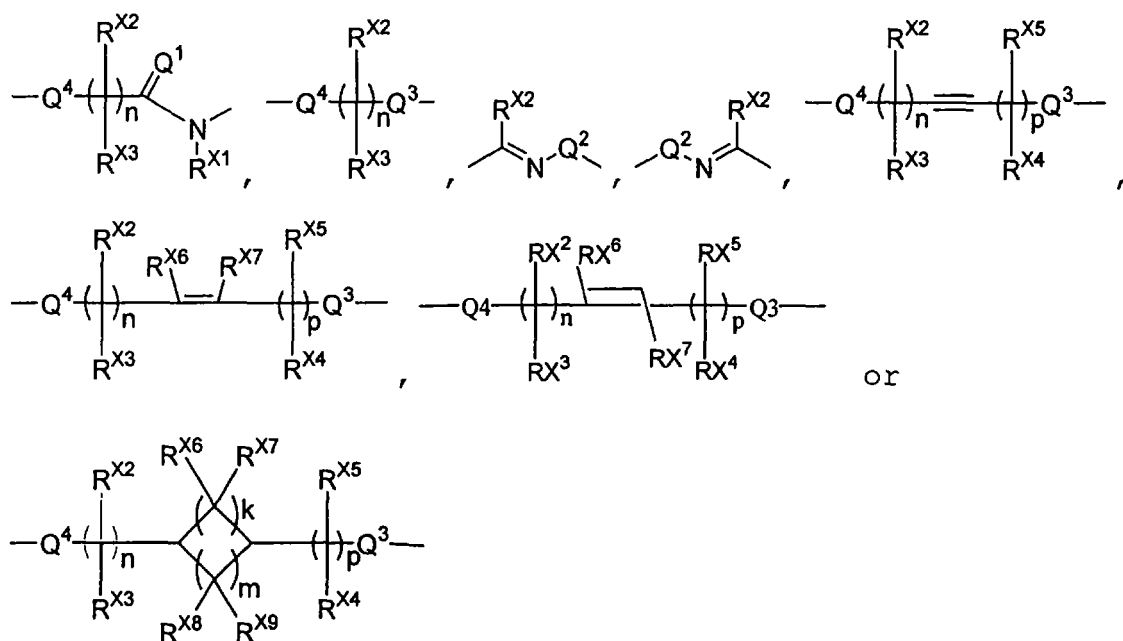
(wherein R^1 represents a hydrogen atom, hydroxyl group, halogen, carboxyl group, or a C_{1-6} alkyl group, a C_{1-6} alkoxy group, a C_{1-6} alkylthio group, a C_{1-6} hydroxyalkyl group, a C_{1-6} hydroxyalkoxy group, a C_{1-6} hydroxyalkylthio group, a C_{1-6} aminoalkyl group, an amino C_{1-6} alkoxy group, an amino C_{1-6} alkylthio group, a halogeno C_{1-6} alkyl group, a halogeno C_{1-6} alkoxy group, a halogeno- C_{1-6} alkylthio group, a C_{2-12} alkoxyalkyl group, a C_{2-12} alkoxyalkoxy group, a C_{2-12} alkoxyalkylthio group, a C_{3-7} cycloalkyl group, a C_{3-7} cycloalkyloxy group, a C_{4-13} cycloalkylalkyloxy group, a C_{3-7} cycloalkylthio group, a C_{2-6} alkenyl group, a C_{2-6} alkenyloxy group, C_{2-6} alkenylthio group, a C_{2-6} alkynyl group, a C_{2-6} alkynyloxy group, a C_{2-6} alkynylthio group, a C_{6-12} aryl group, a C_{6-12} aryloxy group, a C_{6-12} arylthio group, a C_{7-18} alkylaryl group, a C_{7-18} alkylaryloxy group, a C_{7-18} alkylarylthio group, a C_{7-18} aralkyl group, a C_{7-18} aralkyloxy group or a C_{7-18} aralkylthio group, each of which may have one or more substituents; L represents a single bond, or a C_{1-6} alkylene group, a C_{2-6} alkenylene group or a C_{2-6} alkynylene group, each of which may have one or more substituents; M represents a single bond, or a C_{1-6} alkylene group, a C_{2-6} alkenylene group or a C_{2-6} alkynylene group, each of which may have one or more substituents; T represents a single bond, or a C_{1-3} alkylene group, a C_{2-3} alkenylene group or a C_{2-3}

alkynylene group, each of which may have one or more substituents;

W represents a carboxyl group;

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represents a single bond or a double bond; X represents a single bond, oxygen atom, a group represented by $-NR^{X1}CQ^1O-$ (wherein Q^1 represents an oxygen atom or sulfur atom; and R^{X1} represents a hydrogen atom, formyl group, or a C_{1-6} alkyl group, a C_{1-6} hydroxyalkyl group, a C_{1-6} aminoalkyl group, a halogeno C_{1-6} alkyl group, a C_{2-12} alkoxyalkyl group, a C_{3-7} cycloalkyl group, a C_{2-6} alkenyl group, a C_{2-6} alkynyl group, a C_{6-12} aryl group, a C_{7-18} alkylaryl group, a C_{7-18} aralkyl group, a C_{2-7} aliphatic acyl group or a C_{7-19} aromatic acyl group, each of which may have one or more substituents), $-OCQ^1NR^{X1}-$ (wherein Q^1 and R^{X1} are as defined above), $-CQ^1NR^{X1}O-$ (wherein Q^1 and R^{X1} are as defined above), $ONR^{X1}CQ^1-$ (wherein Q^1 and R^{X1} are as defined above), $-Q^2SO_2-$ (wherein Q^2 is an oxygen atom or $-NR^{X10}-$ (wherein R^{X10} represents a hydrogen atom, formyl group, or a C_{1-6} alkyl group, a C_{1-6} hydroxyalkyl group, a C_{1-6} aminoalkyl group, a halogeno- C_{1-6} alkyl group, a C_{2-12} alkoxyalkyl group, a C_{3-7} cycloalkyl group, a C_{2-6} alkenyl group, a C_{2-6} alkynyl group, a C_{6-12} aryl group, a C_{7-18} alkylaryl group, a C_{7-18} aralkyl group, a C_{2-7} aliphatic acyl group or a C_{7-19} aromatic acyl group, each of which may have one or more substituents)) or $-SO_2Q^2-$ (wherein Q^2 is as defined above), or a group represented by the formula:



(wherein Q^1 , Q^2 and R^{X1} are as defined above; k represents 0 to 5; m represents 1 to 5; n and p are the same as or different from each other and each represents 1 to 5; R^{X2} , R^{X3} , R^{X4} , R^{X5} , R^{X6} , R^{X7} , R^{X8} and R^{X9} are the same as or different from each other and each represents a hydrogen atom, hydroxy group, halogen, $-N(R^{X11})R^{X12}-$ (wherein R^{X11} and R^{X12} are the same as or different from each other and each represents a hydrogen atom, formyl group, or a C_{1-6} alkyl group, a C_{1-6} hydroxyalkyl group, a C_{1-6} aminoalkyl group, a halogeno- C_{1-6} alkyl group, a C_{2-12} alkoxyalkyl group, a C_{3-7} cycloalkyl group, a C_{2-6} alkenyl group, a C_{2-6} alkynyl group, a C_{6-12} aryl group, a C_{7-18} alkylaryl group, a C_{7-18} aralkyl group, a C_{2-7} aliphatic acyl group or a C_{7-19} aromatic acyl group, each of which may have one or more substituents), or a C_{1-6} alkyl group, C_{1-6} alkoxy group, a C_{1-6} alkylthio group, a C_{1-6} hydroxyalkyl group, a C_{1-6} hydroxyalkoxy group, a C_{1-6} hydroxyalkylthio group, a C_{1-6} aminoalkyl group, a C_{1-6} aminoalkoxy group, a C_{1-6} aminoalkylthio

group, a halogeno-C₁₋₆ alkyl group, a halogeno-C₁₋₆ alkoxy group, a halogeno-C₁₋₆ alkylthio group, a C₂₋₁₂ alkoxyalkyl group, a C₂₋₁₂ alkoxyalkoxy group, a C₂₋₁₂ alkoxyalkylthio group, a C₃₋₇ cycloalkyl group, a C₃₋₇ cycloalkyloxy group, a C₄₋₁₃ cycloalkylalkyloxy group, a C₃₋₇ cycloalkylthio group, a C₂₋₆ alkenyl group, a C₂₋₆ alkenyloxy group, a C₂₋₆ alkenylthio group, a C₂₋₆ alkynyl group, a C₂₋₆ alkynyloxy group, a C₂₋₆ alkynylthio group, a C₆₋₁₂ aryl group, a C₆₋₁₂ aryloxy group, a C₆₋₁₂ arylthio group, a C₇₋₁₈ alkylaryl group, a C₇₋₁₈ alkylaryloxy group, a C₇₋₁₈ alkylarylthio group, a C₇₋₁₈ aralkyl group, a C₇₋₁₈ aralkyloxy group or a C₇₋₁₈ aralkylthio group, each of which may have one or more substituents, provided that R^{X2} and R^{X3}, and/or R^{X4} and R^{X5} may together form a ring; and Q³ and Q⁴ are the same as or different from each other and each represents an oxygen atom, (O)S(O) or NR^{X10} (wherein NR^{X10} is as defined above)); Y represents a 5- to 14-membered aromatic group or a C₃₋₇ alicyclic hydrocarbon group, each of which may have one or more substituents and one or more hetero atoms; and the ring Z represents a 5- to 14-membered aromatic group which may have 1 to 4 substituents and one or more hetero atoms, and wherein part of the ring may be saturated), a salt thereof, an ester thereof or a hydrate of them;

32) the medicament according to 31), which is based on PPAR α and γ dual agonism;

33) the medicament according to 31), which is based on PPAR α , $\beta(\delta)$ and γ triple agonism;

34) the medicament according to any one of 31) to 33), which

is an insulin sensitizer;

35) the medicament according to any one of 31) to 33), which is an agent for preventing or treating diabetes mellitus;

36) the medicament according to any one of 31) to 33), which is an agent for preventing or treating syndrome X;

37) the medicament according to any one of 31) to 33), which is an agent for preventing or treating diabetic complications;

38) the medicament according to any one of 31) to 33), which is an agent for preventing or treating hyperlipemia;

39) the medicament according to any one of 31) to 33), which is a lipid-lowering agent;

40) the medicament according to any one of 31) to 33), which is an agent for preventing or treating obesity;

41) the medicament according to any one of 31) to 33), which is an agent for treating osteoporosis;

42) the medicament according to any one of 31) to 33), which is an anti-inflammatory agent;

43) the medicament according to any one of 31) to 33), which is an agent for preventing or treating digestive disease;

44) the medicament according to 43), wherein the digestive disease is a disease selected from the group consisting of 1) inflammatory diseases of the digestive organs; 2) proliferative diseases of the digestive organs; and 3) ulcerative diseases of the digestive organs;

45) the medicament according to 44), wherein the inflammatory disease of the digestive organs is a disease selected from the

group consisting of 1) ulcerative colitis; 2) Crohn's disease;
3) pancreatitis; and (4) gastritis;

46) the medicament according to 44), wherein the inflammatory disease of the digestive organs is ulcerative colitis;

47) an agent for preventing or treating a disease against which an insulin sensitizing action is efficacious, which comprises the compound according to any one of 1) to 30) as the active ingredient;

48) the agent for preventing or treating digestive disease according to 44), wherein the proliferative diseases of the digestive organs is a disease selected from the group consisting of 1) benign tumor of the digestive organs; 2) digestive polyp; 3) hereditary polyposis syndrome; 4) colon cancer; 5) rectum cancer and 6) stomach cancer;

49) the medicament according to any one of 31) to 33) whose action is improving energy metabolism, which is an agent for preventing or treating 1) stenocardia and myocardial infarction, and sequelae thereof; 2) senile dementia; or 3) cerebrovascular dementia;

50) the medicament according to any one of 31) to 33) which is an immunomodulatory agent;

51) the medicament according to any one of 31) to 33) which is an agent for preventing or treating cancer;

52) a method of preventing or treating a disease against which an insulin sensitizing action is efficacious, which comprises administering to a patient a pharmaceutically effective amount

of the carboxylic acid compound according to any one of 1) to 30), a salt thereof, an ester thereof or a hydrate of them; and 53) use of the carboxylic acid compound according to any one of 1) to 30), a salt thereof, an ester thereof or a hydrate of them, for producing an agent for preventing or treating a disease against which an insulin sensitizing action is efficacious.

The present invention provides a pharmaceutical composition comprising a carboxylic acid compound represented by the formula (I), a salt thereof, an ester thereof or a hydrate of them, and a pharmaceutically acceptable carrier.

The present invention also provides a method of preventing or treating a disease against which PPAR α and γ dual agonism or PPAR α , $\beta(\delta)$ and γ triple agonism is efficacious, which comprises administering to a patient a pharmaceutically effective amount of the carboxylic acid compound according to any one of 1) to 30), a salt thereof, an ester thereof or a hydrate of them.

Further, the present invention provides use of the carboxylic acid compound according to any one of 1) to 30), a salt thereof, an ester thereof or a hydrate of them, for producing an agent for preventing or treating a disease against which PPAR α and γ dual agonism or PPAR α , $\beta(\delta)$ and γ triple agonism is efficacious.

In the present invention, "disease against which PPAR α and γ dual agonism or PPAR α , $\beta(\delta)$ and γ triple agonism is efficacious" includes diabetes mellitus; syndrome X; diabetic

complications; hyperlipemia; a disease against which a lipid-lowering action is efficacious; obesity; osteoporosis; a disease against which an anti-inflammatory action is efficacious, digestive diseases including 1) inflammatory diseases of digestive organs including ulcerative colitis, Crohn's disease, pancreatitis and gastritis; 2) the proliferative diseases of digestive organs including benign tumor of digestive organs, digestive polyp, hereditary polyposis syndrome, colon cancer, rectum cancer and stomach cancer; and 3) ulcerative diseases of digestive organs; 1) stenocardia and myocardial infarction, and sequelae thereof; 2) senile dementia; or 3) cerebrovascular dementia based on energy metabolism improving effect, respectively, a disease against which an immunomodulatory action is efficacious, and tumor disease.

In this specification, the structural formulae of the compounds may, for convenience' sake, indicate a certain isomer, but the present invention encompasses every possible isomer such as geometric isomer, optical isomer based on asymmetric carbon, stereoisomer and tautomer, which can occur in the structures of the compounds of the present invention, and mixtures of these isomers, and therefore, the compounds of the present invention are not limited by the formulae shown for convenience' sake.

Now, the terms used in this specification are described in detail.

When R^1 , R^{x1} , R^{x2} , R^{x3} , R^{x4} , R^{x5} , R^{x6} , R^{x7} , R^{x8} , R^{x9} and R^{x10} each represents a C_{1-6} alkyl group which may have one or more

substituents, the alkyl group means a C₁₋₆ linear or branched alkyl group, and specific examples thereof include methyl group, ethyl group, n-propyl group, i-propyl group, n-butyl group, i-butyl group, sec-butyl group, t-butyl group, n-pentyl group, i-pentyl group, sec-pentyl group, t-pentyl group, neopentyl group, 1-methylbutyl group, 2-methylbutyl group, 1,1-dimethylpropyl group, 1,2-dimethylpropyl group, n-hexyl group, i-hexyl group, 1-methylpentyl group, 2-methylpentyl group, 3-methylpentyl group, 1,1-dimethylbutyl group, 1,2-dimethylbutyl group, 2,2-dimethylbutyl group, 1,3-dimethylbutyl group, 2,3-dimethylbutyl group, 3,3-dimethylbutyl group, 1-ethylbutyl group, 2-ethylbutyl group, 1,1,2-trimethylpropyl group, 1,2,2-trimethylpropyl group, 1-ethyl-1-methylpropyl group and 1-ethyl-2-methylpropyl group, preferably methyl group, ethyl group, n-propyl group, i-propyl group, n-butyl group, i-butyl group, sec-butyl group, t-butyl group, n-pentyl group, i-pentyl group, sec-pentyl group, t-pentyl group, neopentyl group, 1-methylbutyl group, 2-methylbutyl group, 1,1-dimethylpropyl group, 1,2-dimethylpropyl group, n-hexyl group and i-hexyl group, more preferably methyl group, ethyl group, n-propyl group, i-propyl group, n-butyl group, i-butyl group, sec-butyl group, t-butyl group, n-pentyl group, i-pentyl group, sec-pentyl group, t-pentyl group, neopentyl group, 1-methylbutyl group, 2-methylbutyl group, 1,1-dimethylpropyl group and 1,2-dimethylpropyl group, further preferably methyl group,

ethyl group, n-propyl group, i-propyl group, n-butyl group, i-butyl group, sec-butyl group and t-butyl group, and most preferably methyl group, ethyl group, n-propyl group and i-propyl group.

Herein, the phrase "which may have a substituent" specifically means that the group may be substituted with a substituent such as hydroxyl group; thiol group; nitro group; morpholino group; thiomorpholino group; a halogen atom such as fluorine atom, chlorine atom, bromine atom and iodine atom; nitrile group; azide group; formyl group; alkyl group such as methyl group, ethyl group, propyl group, isopropyl group and butyl group; alkenyl group such as vinyl group, allyl group and propenyl group; alkynyl group such as ethynyl group, butynyl group and propargyl group; alkoxy group such as methoxy group, ethoxy group, propoxy group and butoxy group corresponding to the lower alkyl group; halogenoalkyl group such as fluoromethyl group, difluoromethyl group, trifluoromethyl group and fluoroethyl group; hydroxyalkyl group such as hydroxymethyl group, hydroxyethyl group and hydroxypropyl group; guanidino group; formimidoyl group; acetoimidoyl group; carbamoyl group; thiocarbamoyl group; carbamoylalkyl group such as carbamoylmethyl group and carbamoylethyl group; alkyl carbamoyl group such as methylcarbamoyl group and dimethylcarbamoyl group; carbamide group; alkanoyl group such as acetyl group; amino group; alkylamino group such as methylamino group, ethylamino group and isopropylamino group; dialkylamino group such as

dimethylamino group, methylethylamino group and diethylamino group; amino alkyl group such as aminomethyl group, aminoethyl group and aminopropyl group; carboxyl group; alkoxycarbonyl group such as methoxycarbonyl group, ethoxycarbonyl group and propoxycarbonyl group; alkoxycarbonylalkyl group such as methoxycarbonylmethyl group, ethoxycarbonylmethyl group, propoxycarbonylmethyl group, methoxycarbonylethyl group, ethoxycarbonylethyl group and propoxycarbonylethyl group; alkyloxyalkyl group such as methyloxymethyl group, methyloxyethyl group, ethyloxymethyl group and ethyloxyethyl group; alkylthioalkyl group such as methylthiomethyl group, methylthioethyl group, ethylthiomethyl group and ethylthioethyl group; aminoalkylaminoalkyl group such as aminomethylaminomethyl group and aminoethylaminomethyl group; alkylcarbonyloxy group such as methylcarbonyloxy group, ethylcarbonyloxy group and isopropylcarbonyloxy group; arylalkoxyalkoxyalkyl group such as oxymethyl group and benzyloxyethyloxyethyl group; hydroxyalkoxyalkyl group such as hydroxyethyloxymethyl group and hydroxyethyloxyethyl group; arylalkoxyalkyl group such as benzyloxymethyl group, benzyloxyethyl group and benzyloxypropyl group; quaternary ammonio group such as trimethylammonio group, methylethylmethylanmonio group and triethyl ammonio group; cycloalkyl group such as cyclopropyl group, cyclobutyl group, cyclopentyl group and cyclohexyl group; cycloalkenyl group such as cyclopropenyl group, cyclobutenyl group, cyclopentenyl group

and cyclohexenyl group; aryl group such as phenyl group, pyridinyl group, thienyl group, furyl group and pyrrolyl group; alkylthio group such as methylthio group, ethylthio group, propylthio group and butylthio group; arylthio group such as phenylthio group, pyridinylthio group, thienylthio group, furylthio group and pyrrolylthio group; aryl lower alkyl group such as benzyl group, trityl group and dimethoxytrityl group; substituted sulfonyl group such as sulfonyl group, mesyl group and p-toluene sulfonyl group; aryloyl group such as benzoyl group; halogenoaryl group such as fluorophenyl group and bromophenyl group; and oxyalkoxy group such as methylene dioxy group.

The phrase "which may have one or more substituents" means that the group may have one or more of these groups in an arbitrary combination, and includes e.g. an alkyl group, alkenyl group, alkynyl group and alkoxy group substituted with hydroxyl group, thiol group, nitro group, morpholino group, thiomorpholino group, a halogen atom, nitrile group, azide group, formyl group, amino group, alkylamino group, dialkylamino group, carbamoyl group and sulfonyl group.

Hereinafter, the phrases "which may have a substituent" and "which may have one or more substituents" in the present invention have the meanings as defined above.

When R^1 , R^{x2} , R^{x3} , R^{x4} , R^{x5} , R^{x6} , R^{x7} , R^{x8} and R^{x9} represents a C_{1-6} alkoxy group which may have one or more substituents, the alkoxy group means a C_{1-6} linear or branched alkoxy group and refers to a group having an oxygen atom bound to the end of the

alkyl group. Specific examples thereof include methoxy group, ethoxy group, n-propoxy group, i-propoxy group, n-butoxy group, i-butoxy group, sec-butoxy group, t-butoxy group, n-pentyloxy group, i-pentyloxy group, sec-pentyloxy group, t-pentyloxy group, neopentyloxy group, 1-methylbutoxy group, 2-methylbutoxy group, 1,1-dimethylpropoxy group, 1,2-dimethylpropoxy group, n-hexyloxy group, i-hexyloxy group, 1-methylpentyloxy group, 2-methylpentyloxy group, 3-methylpentyloxy group, 1,1-dimethylbutoxy group, 1,2-dimethylbutoxy group, 2,2-dimethylbutoxy group, 1,3-dimethylbutoxy group, 2,3-dimethylbutoxy group, 3,3-dimethylbutoxy group, 1-ethylbutoxy group, 2-ethylbutoxy group, 1,1,2-trimethylpropoxy group, 1,2,2-trimethylpropoxy group, 1-ethyl-1-methylpropoxy group and 1-ethyl-2-methylpropoxy group; preferably methoxy group, ethoxy group, n-propoxy group, i-propoxy group, n-butoxy group, i-butoxy group, sec-butoxy group, t-butoxy group, n-pentyloxy group, i-pentyloxy group, sec-pentyloxy group, t-pentyloxy group, neopentyloxy group, 1-methylbutoxy group, 2-methylbutoxy group, 1,1-dimethylpropoxy group, 1,2-dimethylpropoxy group, n-hexyloxy group and i-hexyloxy group; more preferably methoxy group, ethoxy group, n-propoxy group, i-propoxy group, n-butoxy group, i-butoxy group, sec-butoxy group, t-butoxy group, n-pentyloxy group, i-pentyloxy group, sec-pentyloxy group, t-pentyloxy group, neopentyloxy group, 1-methylbutoxy group, 2-methylbutoxy group,

1,1-dimethylpropoxy group and 1,2-dimethylpropoxy group; further preferably methoxy group, ethoxy group, n-propoxy group, i-propoxy group, n-butoxy group, i-butoxy group, sec-butoxy group and t-butoxy group; and most preferably a methoxy group, ethoxy group, n-propoxy group and i-propoxy group.

When R^1 , R^{x2} , R^{x3} , R^{x4} , R^{x5} , R^{x6} , R^{x7} , R^{x8} and R^{x9} represent a C_{1-6} alkylthio group which may have one or more substituents, the alkylthio group represents a C_{1-6} linear or branched alkylthio group and refers to a group having a sulfur atom bound to the end of the alkyl group. Specific examples thereof include methylthio group, ethylthio group, n-propylthio group, i-propylthio group, n-butylthio group, i-butylthio group, sec-butylthio group, t-butylthio group, n-pentylthio group, i-pentylthio group, sec-pentylthio group, t-pentylthio group, neopentylthio group, 1-methylbutylthio group, 2-methylbutylthio group, 1,1-dimethylpropylthio group, 1,2-dimethylpropylthio group, n-hexylthio group, i-hexylthio group, 1-methylpentylthio group, 2-methylpentylthio group, 3-methylpentylthio group, 1,1-dimethylbutylthio group, 1,2-dimethylbutylthio group, 2,2-dimethylbutylthio group, 1,3-dimethylbutylthio group, 2,3-dimethylbutylthio group, 3,3-dimethylbutylthio group, 1-ethylbutylthio group, 2-ethylbutylthio group, 1,1,2-trimethylpropylthio group, 1,2,2-trimethylpropylthio group, 1-ethyl-1-methylpropylthio group and 1-ethyl-2-methylpropylthio group, preferably methylthio group, ethylthio group, n-propylthio group,

i-propylthio group, n-butylthio group, i-butylthio group, sec-butylthio group, t-butylthio group, n-pentylthio group, i-pentylthio group, sec-pentylthio group, t-pentylthio group, neopentylthio group, 1-methylbutylthio group, 2-methylbutylthio group, 1,1-dimethylpropylthio group, 1,2-dimethylpropylthio group, n-hexylthio group and i-hexylthio group; more preferably methylthio group, ethylthio group, n-propylthio group, i-propylthio group, n-butylthio group, i-butylthio group, sec-butylthio group, t-butylthio group, n-pentylthio group, i-pentylthio group, sec-pentylthio group, t-pentylthio group, neopentylthio group, 1-methylbutylthio group, 2-methylbutylthio group, 1,1-dimethylpropylthio group and 1,2-dimethylpropylthio group; further preferably methylthio group, ethylthio group, n-propylthio group, i-propylthio group, n-butylthio group, i-butylthio group, sec-butylthio group and t-butylthio group; and most preferably a methylthio group, ethylthio group, n-propylthio group and i-propylthio group.

When R^1 , R^{X1} , R^{X2} , R^{X3} , R^{X4} , R^{X5} , R^{X6} , R^{X7} , R^{X8} , R^{X9} and R^{X10} represent a C_{1-6} hydroxyalkyl group which may have one or more substituents, the hydroxyalkyl group represents a group having the C_{1-6} linear or branched alkyl group substituted at a substitutable site with a hydroxy group. Specific examples thereof include hydroxymethyl group, 2-hydroxyethyl group and 1-hydroxyethyl group.

Similarly, when R^1 , R^{X2} , R^{X3} , R^{X4} , R^{X5} , R^{X6} , R^{X7} , R^{X8} and R^{X9}

represent a C₁₋₆ hydroxyalkoxy group which may have one or more substituents, the hydroxyalkoxy group represents a group having the C₁₋₆ linear or branched alkoxy group substituted at a substitutable site with a hydroxy group. Specific examples thereof include hydroxymethoxy group, 2-hydroxyethoxy group and 1-hydroxyethoxy group.

Similarly, when R¹, R^{x2}, R^{x3}, R^{x4}, R^{x5}, R^{x6}, R^{x7}, R^{x8} and R^{x9} represent a C₁₋₆ hydroxyalkylthio group which may have one or more substituents, the hydroxyalkylthio group represents a group having the C₁₋₆ linear or branched alkylthio group substituted at a substitutable site with a hydroxy group. Specific examples thereof include hydroxymethylthio group, 2-hydroxyethylthio group and 1-hydroxyethylthio group.

When R¹, R^{x1}, R^{x2}, R^{x3}, R^{x4}, R^{x5}, R^{x6}, R^{x7}, R^{x8}, R^{x9} and R^{x10} represent a C₁₋₆ aminoalkyl group which may have one or more substituents, the aminoalkyl group represents a group having the C₁₋₆ linear or branched alkyl group substituted at a substitutable site with an amino group. Specific examples thereof include aminomethyl group, 2-aminoethyl group and 1-aminoethyl group.

Similarly, when R¹, R^{x2}, R^{x3}, R^{x4}, R^{x5}, R^{x6}, R^{x7}, R^{x8} and R^{x9} represent a C₁₋₆ aminoalkoxy group which may have one or more substituents, the aminoalkoxy group represents a group having the C₁₋₆ linear or branched alkoxy group substituted at a substitutable site with an amino group. Specific examples thereof include aminomethoxy group, 2-aminoethoxy group and 1-aminoethoxy group.

Similarly, when R^1 , R^{x2} , R^{x3} , R^{x4} , R^{x5} , R^{x6} , R^{x7} , R^{x8} and R^{x9} represent a C_{1-6} aminoalkylthio group which may have one or more substituents, the aminoalkylthio group represents a group having the C_{1-6} linear or branched alkylthio group substituted at a substitutable site with an amino group. Specific examples thereof include aminomethylthio group, 2-aminoethylthio group and 1-aminoethylthio group.

When R^1 , R^{x1} , R^{x2} , R^{x3} , R^{x4} , R^{x5} , R^{x6} , R^{x7} , R^{x8} , R^{x9} and R^{x10} represent a halogeno C_{1-6} alkyl group which may have one or more substituents, the halogenoalkyl group represents a group having the C_{1-6} linear or branched alkyl group substituted at substitutable sites with one or more halogen atoms. Herein, the halogen atoms refer to fluorine atom, chlorine atom, bromine atom and iodine atom. Specific examples of such a group include fluoromethyl group, trifluoromethyl group, 2-fluoroethyl group and 1-fluoroethyl group.

Similarly when R^1 , R^{x2} , R^{x3} , R^{x4} , R^{x5} , R^{x6} , R^{x7} , R^{x8} and R^{x9} represent a C_{1-6} halogenated alkoxy group which may have one or more substituents, the halogenated alkoxy group represents a group having the C_{1-6} linear or branched alkoxy group substituted at substitutable sites with one or more halogen atoms. Specific examples thereof include fluoromethoxy group, trifluoromethoxy group, 2-fluoroethoxy group and 1-fluoroethoxy group.

Similarly, when R^1 , R^{x2} , R^{x3} , R^{x4} , R^{x5} , R^{x6} , R^{x7} , R^{x8} and R^{x9} represent a C_{1-6} halogenated alkylthio group which may have one or more substituents, the halogenated alkylthio group represents

a group having the C₁₋₆ linear or branched alkylthio group substituted at substitutable sites with one or more halogen atoms. Specific examples thereof include fluoromethylthio group, trifluoromethylthio group, 2-fluoroethylthio group and 1-fluoroethylthio group.

When R¹, R^{x1}, R^{x2}, R^{x3}, R^{x4}, R^{x5}, R^{x6}, R^{x7}, R^{x8}, R^{x9} and R^{x10} represent a C₂₋₁₂ alkoxyalkyl group which may have one or more substituents, the alkoxyalkyl group represents a group having the C₁₋₆ linear or branched alkyl group substituted at a substitutable site with the C₁₋₆ linear or branched alkoxy group. Specific examples thereof include methoxymethyl group, ethoxymethyl group, 1-methoxyethyl group, 2-methoxyethyl group, 1-ethoxyethyl group and 2-ethoxyethyl group.

Similarly, when R¹, R^{x2}, R^{x3}, R^{x4}, R^{x5}, R^{x6}, R^{x7}, R^{x8} and R^{x9} represent a C₂₋₁₂ alkoxyalkoxy group which may have one or more substituents, the alkoxyalkoxy group represents a group having the C₁₋₆ linear or branched alkoxy group substituted at a substitutable site with the C₁₋₆ linear or branched alkoxy group. Specific examples thereof include methoxymethoxy group, ethoxymethoxy group, 1-methoxyethoxy group, 2-methoxyethoxy group, 1-ethoxyethoxy group and 2-ethoxyethoxy group.

Similarly, when R¹, R^{x2}, R^{x3}, R^{x4}, R^{x5}, R^{x6}, R^{x7}, R^{x8} and R^{x9} represent a C₂₋₁₂ alkoxyalkylthio group which may have one or more substituents, the alkoxyalkylthio group represents a group having the C₁₋₆ linear or branched alkylthio group substituted at a substitutable site with the C₁₋₆ linear or branched alkoxy

group. Specific examples thereof include methoxymethylthio group, ethoxymethylthio group, 1-methoxyethylthio group, 2-methoxyethylthio group, 1-ethoxyethylthio group and 2-ethoxyethylthio group.

When $R^1, R^{x1}, R^{x2}, R^{x3}, R^{x4}, R^{x5}, R^{x6}, R^{x7}, R^{x8}, R^{x9}$ and R^{x10} represent a C_{3-7} cycloalkyl group which may have one or more substituents, the cycloalkyl group means a C_{3-7} cyclic alkyl group, and specific examples thereof include cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group and cycloheptyl group.

Similarly, when $R^1, R^{x2}, R^{x3}, R^{x4}, R^{x5}, R^{x6}, R^{x7}, R^{x8}$ and R^{x9} represent a C_{3-7} cycloalkyloxy group which may have one or more substituents, the cycloalkyloxy group refers to a group having an oxygen atom bound to the end of the C_{3-7} cyclic alkyl group, and specific examples thereof include cyclopropyloxy group, cyclobutyloxy group, cyclopentyloxy group, cyclohexyloxy group and cycloheptyloxy group.

Similarly, when $R^1, R^{x2}, R^{x3}, R^{x4}, R^{x5}, R^{x6}, R^{x7}, R^{x8}$ and R^{x9} represent C_{3-7} cycloalkylthio group which may have one or more substituents, the cycloalkylthio group refers to a group having a sulfur atom bound to the end of the C_{3-7} cycloalkyl group, and specific examples thereof include cyclopropylthio group, cyclobutylthio group, cyclopentylthio group, cyclohexylthio group and cycloheptylthio group.

When $R^1, R^{x1}, R^{x2}, R^{x3}, R^{x4}, R^{x5}, R^{x6}, R^{x7}, R^{x8}, R^{x9}$ and R^{x10} represent a C_{2-6} alkenyl group which may have one or more substituents, the alkenyl group is a C_{2-6} linear or branched alkenyl group and

refers to a compound residue having a double bond in the alkyl group containing 2 or more carbon atoms. Specific examples of thereof include ethenyl group, 1-propene-1-yl group, 2-propene-1-yl group, 3-propene-1-yl group, 1-butene-1-yl group, 1-butene-2-yl group, 1-butene-3-yl group, 1-butene-4-yl group, 2-butene-1-yl group, 2-butene-2-yl group, 1-methyl-1-propene-1-yl group, 2-methyl-1-propene-1-yl group, 1-methyl-2-propene-1-yl group, 2-methyl-2-propene-1-yl group, 1-methyl-1-butene-1-yl group, 2-methyl-1-butene-1-yl group, 3-methyl-1-butene-1-yl group, 1-methyl-2-butene-1-yl group, 2-methyl-2-butene-1-yl group, 3-methyl-2-butene-1-yl group, 1-methyl-3-butene-1-yl group, 2-methyl-3-butene-1-yl group, 3-methyl-3-butene-1-yl group, 1-ethyl-1-butene-1-yl group, 2-ethyl-1-butene-1-yl group, 3-ethyl-1-butene-1-yl group, 1-ethyl-2-butene-1-yl group, 2-ethyl-2-butene-1-yl group, 3-ethyl-2-butene-1-yl group, 1-ethyl-3-butene-1-yl group, 2-ethyl-3-butene-1-yl group, 3-ethyl-3-butene-1-yl group, 1,1-dimethyl-1-butene-1-yl group, 1,2-dimethyl-1-butene-1-yl group, 1,3-dimethyl-1-butene-1-yl group, 2,2-dimethyl-1-butene-1-yl group, 3,3-dimethyl-1-butene-1-yl group, 1,1-dimethyl-2-butene-1-yl group, 1,2-dimethyl-2-butene-1-yl group, 1,3-dimethyl-2-butene-1-yl group, 2,2-dimethyl-2-butene-1-yl group, 3,3-dimethyl-2-butene-1-yl group, 1,1-dimethyl-3-butene-1-yl group, 1,2-dimethyl-3-butene-1-yl group, 1,3-dimethyl-3-butene-1-yl group, 2,2-dimethyl-3-butene-1-yl

group, 3,3-dimethyl-3-butene-1-yl group, 1-pentene-1-yl group, 2-pentene-1-yl group, 3-pentene-1-yl group, 4-pentene-1-yl group, 1-pentene-2-yl group, 2-pentene-2-yl group, 3-pentene-2-yl group, 4-pentene-2-yl group, 1-pentene-3-yl group, 2-pentene-3-yl group, 1-pentene-1-yl group, 2-pentene-1-yl group, 3-pentene-1-yl group, 4-pentene-1-yl group, 1-pentene-2-yl group, 2-pentene-2-yl group, 3-pentene-2-yl group, 4-pentene-2-yl group, 1-pentene-3-yl group, 2-pentene-3-yl group, 1-methyl-1-pentene-1-yl group, 2-methyl-1-pentene-1-yl group, 3-methyl-1-pentene-1-yl group, 4-methyl-1-pentene-1-yl group, 1-methyl-2-pentene-1-yl group, 2-methyl-2-pentene-1-yl group, 3-methyl-2-pentene-1-yl group, 4-methyl-2-pentene-1-yl group, 1-methyl-3-pentene-1-yl group, 2-methyl-3-pentene-1-yl group, 3-methyl-3-pentene-1-yl group, 4-methyl-3-pentene-1-yl group, 1-methyl-4-pentene-1-yl group, 2-methyl-4-pentene-1-yl group, 3-methyl-4-pentene-1-yl group, 4-methyl-4-pentene-1-yl group, 1-methyl-1-pentene-2-yl group, 2-methyl-1-pentene-2-yl group, 3-methyl-1-pentene-2-yl group, 4-methyl-1-pentene-2-yl group, 1-methyl-2-pentene-2-yl group, 2-methyl-2-pentene-2-yl group, 3-methyl-2-pentene-2-yl group, 4-methyl-2-pentene-2-yl group, 1-methyl-3-pentene-2-yl group, 2-methyl-3-pentene-2-yl group, 3-methyl-3-pentene-2-yl group, 4-methyl-3-pentene-2-yl group, 1-methyl-4-pentene-2-yl group, 2-methyl-4-pentene-2-yl group, 3-methyl-4-pentene-2-yl group, 4-methyl-4-pentene-2-yl group, 1-methyl-1-pentene-3-yl group, 2-methyl-1-pentene-3-yl group, 3-methyl-1-pentene-3-yl group,

4-methyl-1-pentene-3-yl group, 1-methyl-2-pentene-3-yl group,
 2-methyl-2-pentene-3-yl group, 3-methyl-2-pentene-3-yl group,
 4-methyl-2-pentene-3-yl group, 1-hexene-1-yl group,
 1-hexene-2-yl group, 1-hexene-3-yl group, 1-hexene-4-yl group,
 1-hexene-5-yl group, 1-hexene-6-yl group, 2-hexene-1-yl group,
 2-hexene-2-yl group, 2-hexene-3-yl group, 2-hexene-4-yl group,
 2-hexene-5-yl group, 2-hexene-6-yl group, 3-hexene-1-yl group,
 3-hexene-2-yl group and 3-hexene-3-yl group; preferably ethenyl
 group, 1-propene-1-yl group, 2-propene-1-yl group,
 3-propene-1-yl group, 1-butene-1-yl group, 1-butene-2-yl group,
 1-butene-3-yl group, 1-butene-4-yl group, 2-butene-1-yl group,
 2-butene-2-yl group, 1-methyl-1-propene-1-yl group,
 2-methyl-1-propene-1-yl group, 1-methyl-2-propene-1-yl group,
 2-methyl-2-propene-1-yl group, 1-methyl-1-butene-1-yl group,
 2-methyl-1-butene-1-yl group, 3-methyl-1-butene-1-yl group,
 1-methyl-2-butene-1-yl group, 2-methyl-2-butene-1-yl group,
 3-methyl-2-butene-1-yl group, 1-methyl-3-butene-1-yl group,
 2-methyl-3-butene-1-yl group, 3-methyl-3-butene-1-yl group,
 1-ethyl-1-butene-1-yl group, 2-ethyl-1-butene-1-yl group,
 3-ethyl-1-butene-1-yl group, 1-ethyl-2-butene-1-yl group,
 2-ethyl-2-butene-1-yl group, 3-ethyl-2-butene-1-yl group,
 1-ethyl-3-butene-1-yl group, 2-ethyl-3-butene-1-yl group,
 3-ethyl-3-butene-1-yl group, 1,1-dimethyl-1-butene-1-yl group,
 1,2-dimethyl-1-butene-1-yl group, 1,3-dimethyl-1-butene-1-yl
 group, 2,2-dimethyl-1-butene-1-yl group,
 3,3-dimethyl-1-butene-1-yl group, 1,1-dimethyl-2-butene-1-yl

group, 1,2-dimethyl-2-butene-1-yl group,
 1,3-dimethyl-2-butene-1-yl group, 2,2-dimethyl-2-butene-1-yl
 group, 3,3-dimethyl-2-butene-1-yl group,
 1,1-dimethyl-3-butene-1-yl group, 1,2-dimethyl-3-butene-1-yl
 group, 1,3-dimethyl-3-butene-1-yl group,
 2,2-dimethyl-3-butene-1-yl group and
 3,3-dimethyl-3-butene-1-yl group; more preferably ethenyl
 group, 1-propene-1-yl group, 2-propene-1-yl group,
 3-propene-1-yl group, 1-butene-1-yl group, 1-butene-2-yl group,
 1-butene-3-yl group, 1-butene-4-yl group, 2-butene-1-yl group,
 2-butene-2-yl group, 1-methyl-1-propene-1-yl group,
 2-methyl-1-propene-1-yl group, 1-methyl-2-propene-1-yl group,
 2-methyl-2-propene-1-yl group, 1-methyl-1-butene-1-yl group,
 2-methyl-1-butene-1-yl group, 3-methyl-1-butene-1-yl group,
 1-methyl-2-butene-1-yl group, 2-methyl-2-butene-1-yl group,
 3-methyl-2-butene-1-yl group, 1-methyl-3-butene-1-yl group,
 2-methyl-3-butene-1-yl group, and 3-methyl-3-butene-1-yl
 group; and most preferably ethenyl group, 1-propene-1-yl group,
 2-propene-1-yl group, 3-propene-1-yl group, 1-butene-1-yl
 group, 1-butene-2-yl group, 1-butene-3-yl group, 1-butene-4-yl
 group, 2-butene-1-yl group and 2-butene-2-yl group.

Similarly, when R^1 , R^{x2} , R^{x3} , R^{x4} , R^{x5} , R^{x6} , R^{x7} , R^{x8} and R^{x9} represent a C_{2-6} alkenyloxy group which may have one or more substituents, the alkenyloxy group refers to a group having an oxygen atom bound to the end of the C_{2-6} linear or branched alkenyl group. Specific examples thereof include ethenyloxy group,

1-propene-1-yloxy group, 2-propene-1-yloxy group,
3-propene-1-yloxy group, 1-butene-1-yloxy group,
1-butene-2-yloxy group, 1-butene-3-yloxy group,
1-butene-4-yloxy group, 2-butene-1-yloxy group,
2-butene-2-yloxy group, 1-methyl-1-propene-1-yloxy group,
2-methyl-1-propene-1-yloxy group, 1-methyl-2-propene-1-yloxy
group, 2-methyl-2-propene-1-yloxy group,
1-methyl-1-butene-1-yloxy group, 2-methyl-1-butene-1-yloxy
group, 3-methyl-1-butene-1-yloxy group,
1-methyl-2-butene-1-yloxy group, 2-methyl-2-butene-1-yloxy
group, 3-methyl-2-butene-1-yloxy group,
1-methyl-3-butene-1-yloxy group, 2-methyl-3-butene-1-yloxy
group, 3-methyl-3-butene-1-yloxy group,
1-ethyl-1-butene-1-yloxy group, 2-ethyl-1-butene-1-yloxy
group, 3-ethyl-1-butene-1-yloxy group,
1-ethyl-2-butene-1-yloxy group, 2-ethyl-2-butene-1-yloxy
group, 3-ethyl-2-butene-1-yloxy group,
1-ethyl-3-butene-1-yloxy group, 2-ethyl-3-butene-1-yloxy
group, 3-ethyl-3-butene-1-yloxy group,
1,1-dimethyl-1-butene-1-yloxy group,
1,2-dimethyl-1-butene-1-yloxy group,
1,3-dimethyl-1-butene-1-yloxy group,
2,2-dimethyl-1-butene-1-yloxy group,
3,3-dimethyl-1-butene-1-yloxy group,
1,1-dimethyl-2-butene-1-yloxy group,
1,2-dimethyl-2-butene-1-yloxy group,

1,3-dimethyl-2-butene-1-yloxy group,
2,2-dimethyl-2-butene-1-yloxy group,
3,3-dimethyl-2-butene-1-yloxy group,
1,1-dimethyl-3-butene-1-yloxy group,
1,2-dimethyl-3-butene-1-yloxy group,
1,3-dimethyl-3-butene-1-yloxy group,
2,2-dimethyl-3-butene-1-yloxy group,
3,3-dimethyl-3-butene-1-yloxy group, 1-pentene-1-yloxy group,
2-pentene-1-yloxy group, 3-pentene-1-yloxy group,
4-pentene-1-yloxy group, 1-pentene-2-yloxy group,
2-pentene-2-yloxy group, 3-pentene-2-yloxy group,
4-pentene-2-yloxy group, 1-pentene-3-yloxy group,
2-pentene-3-yloxy group, 1-pentene-1-yloxy group,
2-pentene-1-yloxy group, 3-pentene-1-yloxy group,
4-pentene-1-yloxy group, 1-pentene-2-yloxy group,
2-pentene-2-yloxy group, 3-pentene-2-yloxy group,
4-pentene-2-yloxy group, 1-pentene-3-yloxy group,
2-pentene-3-yloxy group, 1-methyl-1-pentene-1-yloxy group,
2-methyl-1-pentene-1-yloxy group, 3-methyl-1-pentene-1-yloxy
group, 4-methyl-1-pentene-1-yloxy group,
1-methyl-2-pentene-1-yloxy group, 2-methyl-2-pentene-1-yloxy
group, 3-methyl-2-pentene-1-yloxy group,
4-methyl-2-pentene-1-yloxy group, 1-methyl-3-pentene-1-yloxy
group, 2-methyl-3-pentene-1-yloxy group,
3-methyl-3-pentene-1-yloxy group, 4-methyl-3-pentene-1-yloxy
group, 1-methyl-4-pentene-1-yloxy group,

2-methyl-4-pentene-1-yloxy group, 3-methyl-4-pentene-1-yloxy group, 4-methyl-4-pentene-1-yloxy group, 1-methyl-1-pentene-2-yloxy group, 2-methyl-1-pentene-2-yloxy group, 3-methyl-1-pentene-2-yloxy group, 4-methyl-1-pentene-2-yloxy group, 1-methyl-2-pentene-2-yloxy group, 2-methyl-2-pentene-2-yloxy group, 3-methyl-2-pentene-2-yloxy group, 4-methyl-2-pentene-2-yloxy group, 1-methyl-3-pentene-2-yloxy group, 2-methyl-3-pentene-2-yloxy group, 3-methyl-3-pentene-2-yloxy group, 4-methyl-3-pentene-2-yloxy group, 1-methyl-4-pentene-2-yloxy group, 2-methyl-4-pentene-2-yloxy group, 3-methyl-4-pentene-2-yloxy group, 4-methyl-4-pentene-2-yloxy group, 1-methyl-1-pentene-3-yloxy group, 2-methyl-1-pentene-3-yloxy group, 3-methyl-1-pentene-3-yloxy group, 4-methyl-1-pentene-3-yloxy group, 1-methyl-2-pentene-3-yloxy group, 2-methyl-2-pentene-3-yloxy group, 3-methyl-2-pentene-3-yloxy group, 4-methyl-2-pentene-3-yloxy group, 1-hexene-1-yloxy group, 1-hexene-2-yloxy group, 1-hexene-3-yloxy group, 1-hexene-4-yloxy group, 1-hexene-5-yloxy group, 1-hexene-6-yloxy group, 2-hexene-1-yloxy group, 2-hexene-2-yloxy group, 2-hexene-3-yloxy group, 2-hexene-4-yloxy group, 2-hexene-5-yloxy group, 2-hexene-6-yloxy group, 3-hexene-1-yloxy group, 3-hexene-2-yloxy group and 3-hexene-3-yloxy group; preferably ethenyloxy group, 1-propene-1-yloxy group, 2-propene-1-yloxy

group, 3-propene-1-yloxy group, 1-butene-1-yloxy group,
1-butene-2-yloxy group, 1-butene-3-yloxy group,
1-butene-4-yloxy group, 2-butene-1-yloxy group,
2-butene-2-yloxy group, 1-methyl-1-propene-1-yloxy group,
2-methyl-1-propene-1-yloxy group, 1-methyl-2-propene-1-yloxy
group, 2-methyl-2-propene-1-yloxy group,
1-methyl-1-butene-1-yloxy group, 2-methyl-1-butene-1-yloxy
group, 3-methyl-1-butene-1-yloxy group,
1-methyl-2-butene-1-yloxy group, 2-methyl-2-butene-1-yloxy
group, 3-methyl-2-butene-1-yloxy group,
1-methyl-3-butene-1-yloxy group, 2-methyl-3-butene-1-yloxy
group, 3-methyl-3-butene-1-yloxy group,
1-ethyl-1-butene-1-yloxy group, 2-ethyl-1-butene-1-yloxy
group, 3-ethyl-1-butene-1-yloxy group,
1-ethyl-2-butene-1-yloxy group, 2-ethyl-2-butene-1-yloxy
group, 3-ethyl-2-butene-1-yloxy group,
1-ethyl-3-butene-1-yloxy group, 2-ethyl-3-butene-1-yloxy
group, 3-ethyl-3-butene-1-yloxy group,
1,1-dimethyl-1-butene-1-yloxy group,
1,2-dimethyl-1-butene-1-yloxy group,
1,3-dimethyl-1-butene-1-yloxy group,
2,2-dimethyl-1-butene-1-yloxy group,
3,3-dimethyl-1-butene-1-yloxy group,
1,1-dimethyl-2-butene-1-yloxy group,
1,2-dimethyl-2-butene-1-yloxy group,
1,3-dimethyl-2-butene-1-yloxy group,

2,2-dimethyl-2-butene-1-yloxy group,
 3,3-dimethyl-2-butene-1-yloxy group,
 1,1-dimethyl-3-butene-1-yloxy group,
 1,2-dimethyl-3-butene-1-yloxy group,
 1,3-dimethyl-3-butene-1-yloxy group,
 2,2-dimethyl-3-butene-1-yloxy group and
 3,3-dimethyl-3-butene-1-yloxy group; more preferably
 ethenyloxy group, 1-propene-1-yloxy group, 2-propene-1-yloxy
 group, 3-propene-1-yloxy group, 1-butene-1-yloxy group,
 1-butene-2-yloxy group, 1-butene-3-yloxy group,
 1-butene-4-yloxy group, 2-butene-1-yloxy group,
 2-butene-2-yloxy group, 1-methyl-1-propene-1-yloxy group,
 2-methyl-1-propene-1-yloxy group, 1-methyl-2-propene-1-yloxy
 group, 2-methyl-2-propene-1-yloxy group,
 1-methyl-1-butene-1-yloxy group, 2-methyl-1-butene-1-yloxy
 group, 3-methyl-1-butene-1-yloxy group,
 1-methyl-2-butene-1-yloxy group, 2-methyl-2-butene-1-yloxy
 group, 3-methyl-2-butene-1-yloxy group,
 1-methyl-3-butene-1-yloxy group, 2-methyl-3-butene-1-yloxy
 group and 3-methyl-3-butene-1-yloxy group; further preferably
 ethenyloxy group, 1-propene-1-yloxy group, 2-propene-1-yloxy
 group, 3-propene-1-yloxy group, 1-butene-1-yloxy group,
 1-butene-2-yloxy group, 1-butene-3-yloxy group,
 1-butene-4-yloxy group, 2-butene-1-yloxy group and
 2-butene-2-yloxy group; and most preferably ethenyloxy group,
 1-propene-1-yloxy group, 2-propene-1-yloxy group and

3-propene-1-ylthio group.

Similarly when R^1 , R^{X2} , R^{X3} , R^{X4} , R^{X5} , R^{X6} , R^{X7} , R^{X8} and R^{X9} represent a C_{2-6} alkenylthio group which may have one or more substituents, the alkenylthio group refers to a group having sulfur atom bound to the end of the C_{2-6} linear or branched alkenyl group, and specific examples thereof include ethenylthio group, 1-propene-1-ylthio group, 2-propene-1-ylthio group, 3-propene-1-ylthio group, 1-butene-1-ylthio group, 1-butene-2-ylthio group, 1-butene-3-ylthio group, 1-butene-4-ylthio group, 2-butene-1-ylthio group, 2-butene-2-ylthio group, 1-methyl-1-propene-1-ylthio group, 2-methyl-1-propene-1-ylthio group, 1-methyl-2-propene-1-ylthio group, 2-methyl-2-propene-1-ylthio group, 1-methyl-1-butene-1-ylthio group, 2-methyl-1-butene-1-ylthio group, 3-methyl-1-butene-1-ylthio group, 1-methyl-2-butene-1-ylthio group, 2-methyl-2-butene-1-ylthio group, 3-methyl-2-butene-1-ylthio group, 1-methyl-3-butene-1-ylthio group, 2-methyl-3-butene-1-ylthio group, 3-methyl-3-butene-1-ylthio group, 1-ethyl-1-butene-1-ylthio group, 2-ethyl-1-butene-1-ylthio group, 3-ethyl-1-butene-1-ylthio group, 1-ethyl-2-butene-1-ylthio group, 2-ethyl-2-butene-1-ylthio group, 3-ethyl-2-butene-1-ylthio group, 1-ethyl-3-butene-1-ylthio group, 2-ethyl-3-butene-1-ylthio group, 3-ethyl-3-butene-1-ylthio group,

1,1-dimethyl-1-butene-1-ylthio group,
 1,2-dimethyl-1-butene-1-ylthio group,
 1,3-dimethyl-1-butene-1-ylthio group,
 2,2-dimethyl-2-butene-1-ylthio group,
 3,3-dimethyl-1-butene-1-ylthio group,
 1,1-dimethyl-2-butene-1-ylthio group,
 1,2-dimethyl-2-butene-1-ylthio group,
 1,3-dimethyl-2-butene-1-ylthio group,
 2,2-dimethyl-2-butene-1-ylthio group,
 3,3-dimethyl-2-butene-1-ylthio group,
 1,1-dimethyl-3-butene-1-ylthio group,
 1,2-dimethyl-3-butene-1-ylthio group,
 1,3-dimethyl-3-butene-1-ylthio group,
 2,2-dimethyl-3-butene-1-ylthio group,
 3,3-dimethyl-3-butene-1-ylthio group, 1-pentene-1-ylthio
 group, 2-pentene-1-ylthio group, 3-pentene-1-ylthio group,
 4-pentene-1-ylthio group, 1-pentene-2-ylthio group,
 2-pentene-2-ylthio group, 3-pentene-2-ylthio group,
 4-pentene-2-ylthio group, 1-pentene-3-ylthio group,
 2-pentene-3-ylthio group, 1-pentene-1-ylthio group,
 2-pentene-1-ylthio group, 3-pentene-1-ylthio group,
 4-pentene-1-ylthio group, 1-pentene-2-ylthio group,
 2-pentene-2-ylthio group, 3-pentene-2-ylthio group,
 4-pentene-2-ylthio group, 1-pentene-3-ylthio group,
 2-pentene-3-ylthio group, 1-methyl-1-pentene-1-ylthio group,
 2-methyl-1-pentene-1-ylthio group,

3-methyl-1-pentene-1-ylthio group,
4-methyl-1-pentene-1-ylthio group,
1-methyl-2-pentene-1-ylthio group,
2-methyl-2-pentene-1-ylthio group,
3-methyl-2-pentene-1-ylthio group,
4-methyl-2-pentene-1-ylthio group,
1-methyl-3-pentene-1-ylthio group,
2-methyl-3-pentene-1-ylthio group,
3-methyl-3-pentene-1-ylthio group,
4-methyl-3-pentene-1-ylthio group,
1-methyl-4-pentene-1-ylthio group,
2-methyl-4-pentene-1-ylthio group,
3-methyl-4-pentene-1-ylthio group,
4-methyl-4-pentene-1-ylthio group,
1-methyl-1-pentene-2-ylthio group,
2-methyl-1-pentene-2-ylthio group,
3-methyl-1-pentene-2-ylthio group,
4-methyl-1-pentene-2-ylthio group,
1-methyl-2-pentene-2-ylthio group,
2-methyl-2-pentene-2-ylthio group,
3-methyl-2-pentene-2-ylthio group,
4-methyl-2-pentene-2-ylthio group,
1-methyl-3-pentene-2-ylthio group,
2-methyl-3-pentene-2-ylthio group,
3-methyl-3-pentene-2-ylthio group,
4-methyl-3-pentene-2-ylthio group,

1-methyl-4-pentene-2-ylthio group,
 2-methyl-4-pentene-2-ylthio group,
 3-methyl-4-pentene-2-ylthio group,
 4-methyl-4-pentene-2-ylthio group,
 1-methyl-1-pentene-3-ylthio group,
 2-methyl-1-pentene-3-ylthio group,
 3-methyl-1-pentene-3-ylthio group,
 4-methyl-1-pentene-3-ylthio group,
 1-methyl-2-pentene-3-ylthio group,
 2-methyl-2-pentene-3-ylthio group,
 3-methyl-2-pentene-3-ylthio group,
 4-methyl-2-pentene-3-ylthio group, 1-hexene-1-ylthio group,
 1-hexene-2-ylthio group, 1-hexene-3-ylthio group,
 1-hexene-4-ylthio group, 1-hexene-5-ylthio group,
 1-hexene-6-ylthio group, 2-hexene-1-ylthio group,
 2-hexene-2-ylthio group, 2-hexene-3-ylthio group,
 2-hexene-4-ylthio group, 2-hexene-5-ylthio group,
 2-hexene-6-ylthio group, 3-hexene-1-ylthio group,
 3-hexene-2-ylthio group and 3-hexene-3-ylthio group;
 preferably ethenylthio group, 1-propene-1-ylthio group,
 2-propene-1-ylthio group, 3-propene-1-ylthio group,
 1-butene-1-ylthio group, 1-butene-2-ylthio group,
 1-butene-3-ylthio group, 1-butene-4-ylthio group,
 2-butene-1-ylthio group, 2-butene-2-ylthio group,
 1-methyl-1-propene-1-ylthio group,
 2-methyl-1-propene-1-ylthio group,

1-methyl-2-propene-1-ylthio group,
2-methyl-2-propene-1-ylthio group,
1-methyl-1-butene-1-ylthio group, 2-methyl-1-butene-1-ylthio
group, 3-methyl-1-butene-1-ylthio group,
1-methyl-2-butene-1-ylthio group, 2-methyl-2-butene-1-ylthio
group, 3-methyl-2-butene-1-ylthio group,
1-methyl-3-butene-1-ylthio group, 2-methyl-3-butene-1-ylthio
group, 3-methyl-3-butene-1-ylthio group,
1-ethyl-1-butene-1-ylthio group, 2-ethyl-1-butene-1-ylthio
group, 3-ethyl-1-butene-1-ylthio group,
1-ethyl-2-butene-1-ylthio group, 2-ethyl-2-butene-1-ylthio
group, 3-ethyl-2-butene-1-ylthio group,
1-ethyl-3-butene-1-ylthio group, 2-ethyl-3-butene-1-ylthio
group, 3-ethyl-3-butene-1-ylthio group,
1,1-dimethyl-1-butene-1-ylthio group,
1,2-dimethyl-1-butene-1-ylthio group,
1,3-dimethyl-1-butene-1-ylthio group,
2,2-dimethyl-1-butene-1-ylthio group,
3,3-dimethyl-1-butene-1-ylthio group,
1,1-dimethyl-2-butene-1-ylthio group,
1,2-dimethyl-2-butene-1-ylthio group,
1,3-dimethyl-2-butene-1-ylthio group,
2,2-dimethyl-2-butene-1-ylthio group,
3,3-dimethyl-2-butene-1-ylthio group,
1,1-dimethyl-3-butene-1-ylthio group,
1,2-dimethyl-3-butene-1-ylthio group,

1,3-dimethyl-3-butene-1-ylthio group,
 2,2-dimethyl-3-butene-1-ylthio group and
 3,3-dimethyl-3-butene-1-ylthio group; more preferably
 ethenylthio group, 1-propene-1-ylthio group,
 2-propene-1-ylthio group, 3-propene-1-ylthio group,
 1-butene-1-ylthio group, 1-butene-2-ylthio group,
 1-butene-3-ylthio group, 1-butene-4-ylthio group,
 2-butene-1-ylthio group, 2-butene-2-ylthio group,
 1-methyl-1-propene-1-ylthio group,
 2-methyl-1-propene-1-ylthio group,
 1-methyl-2-propene-1-ylthio group,
 2-methyl-2-propene-1-ylthio group,
 1-methyl-1-butene-1-ylthio group, 2-methyl-1-butene-1-ylthio
 group, 3-methyl-1-butene-1-ylthio group,
 1-methyl-2-butene-1-ylthio group, 2-methyl-2-butene-1-ylthio
 group, 3-methyl-2-butene-1-ylthio group,
 1-methyl-3-butene-1-ylthio group, 2-methyl-3-butene-1-ylthio
 group and 3-methyl-3-butene-1-ylthio group; further preferably
 ethenylthio group, 1-propene-1-ylthio group,
 2-propene-1-ylthio group, 3-propene-1-ylthio group,
 1-butene-1-ylthio group, 1-butene-2-ylthio group,
 1-butene-3-ylthio group, 1-butene-4-ylthio group,
 2-butene-1-ylthio group and 2-butene-2-ylthio group; and most
 preferably ethenylthio group, 1-propene-1-ylthio group,
 2-propene-1-ylthio group and 3-propene-1-ylthio group.

When R^1 , R^{x1} , R^{x2} , R^{x3} , R^{x4} , R^{x5} , R^{x6} , R^{x7} , R^{x8} , R^{x9} and R^{x10} represent

a C₂₋₆ alkynyl group which may have one or more substituents, the alkynyl group is a C₂₋₆ linear or branched alkynyl group and refers to a compound residue having a triple bond in the alkyl group containing 2 or more carbon atoms. Specific examples thereof include ethynyl group, 1-propyn-1-yl group, 2-propyn-1-yl group, 3-propyn-1-yl group, 1-butyn-1-yl group, 1-butyn-2-yl group, 1-butyn-3-yl group, 1-butyn-4-yl group, 2-butyn-1-yl group, 2-butyn-2-yl group, 1-methyl-1-propyn-1-yl group, 2-methyl-1-propyn-1-yl group, 1-methyl-2-propyn-1-yl group, 2-methyl-2-propyn-1-yl group, 1-methyl-1-butyn-1-yl group, 2-methyl-1-butyn-1-yl group, 3-methyl-1-butyn-1-yl group, 1-methyl-2-butyn-1-yl group, 2-methyl-2-butyn-1-yl group, 3-methyl-2-butyn-1-yl group, 1-methyl-3-butyn-1-yl group, 2-methyl-3-butyn-1-yl group, 3-methyl-3-butyn-1-yl group, 1-ethyl-1-butyn-1-yl group, 2-ethyl-1-butyn-1-yl group, 3-ethyl-1-butyn-1-yl group, 1-ethyl-2-butyn-1-yl group, 2-ethyl-2-butyn-1-yl group, 3-ethyl-2-butyn-1-yl group, 1-ethyl-3-butyn-1-yl group, 2-ethyl-3-butyn-1-yl group, 3-ethyl-3-butyn-1-yl group, 1,1-dimethyl-1-butyn-1-yl group, 1,2-dimethyl-1-butyn-1-yl group, 1,3-dimethyl-1-butyn-1-yl group, 2,2-dimethyl-1-butyn-1-yl group, 3,3-dimethyl-1-butyn-1-yl group, 1,1-dimethyl-2-butyn-1-yl group, 1,2-dimethyl-2-butyn-1-yl group, 1,3-dimethyl-2-butyn-1-yl group, 2,2-dimethyl-2-butyn-1-yl group, 3,3-dimethyl-2-butyn-1-yl group, 1,1-dimethyl-3-butyn-1-yl group, 1,2-dimethyl-3-butyn-1-yl

group, 1,3-dimethyl-3-butyne-1-yl group,
 2,2-dimethyl-3-butyne-1-yl group, 3,3-dimethyl-3-butyne-1-yl
 group, 1-pentyne-1-yl group, 2-pentyne-1-yl group, 3-pentyne-1-yl
 group, 4-pentyne-1-yl group, 1-pentyne-2-yl group, 2-pentyne-2-yl
 group, 3-pentyne-2-yl group, 4-pentyne-2-yl group, 1-pentyne-3-yl
 group, 2-pentyne-3-yl group, 1-pentyne-1-yl group, 2-pentyne-1-yl
 group, 3-pentyne-1-yl group, 4-pentyne-1-yl group, 1-pentyne-2-yl
 group, 2-pentyne-2-yl group, 3-pentyne-2-yl group, 4-pentyne-2-yl
 group, 1-pentyne-3-yl group, 2-pentyne-3-yl group,
 1-methyl-1-pentyne-1-yl group, 2-methyl-1-pentyne-1-yl group,
 3-methyl-1-pentyne-1-yl group, 4-methyl-1-pentyne-1-yl group,
 1-methyl-2-pentyne-1-yl group, 2-methyl-2-pentyne-1-yl group,
 3-methyl-2-pentyne-1-yl group, 4-methyl-2-pentyne-1-yl group,
 1-methyl-3-pentyne-1-yl group, 2-methyl-3-pentyne-1-yl group,
 3-methyl-3-pentyne-1-yl group, 4-methyl-3-pentyne-1-yl group,
 1-methyl-4-pentyne-1-yl group, 2-methyl-4-pentyne-1-yl group,
 3-methyl-4-pentyne-1-yl group, 4-methyl-4-pentyne-1-yl group,
 1-methyl-1-pentyne-2-yl group, 2-methyl-1-pentyne-2-yl group,
 3-methyl-1-pentyne-2-yl group, 4-methyl-1-pentyne-2-yl group,
 1-methyl-2-pentyne-2-yl group, 2-methyl-2-pentyne-2-yl group,
 3-methyl-2-pentyne-2-yl group, 4-methyl-2-pentyne-2-yl group,
 1-methyl-3-pentyne-2-yl group, 2-methyl-3-pentyne-2-yl group,
 3-methyl-3-pentyne-2-yl group, 4-methyl-3-pentyne-2-yl group,
 1-methyl-4-pentyne-2-yl group, 2-methyl-4-pentyne-2-yl group,
 3-methyl-4-pentyne-2-yl group, 4-methyl-4-pentyne-2-yl group,
 1-methyl-1-pentyne-3-yl group, 2-methyl-1-pentyne-3-yl group,

3-methyl-1-pentyn-3-yl group, 4-methyl-1-pentyn-3-yl group, 1-methyl-2-pentyn-3-yl group, 2-methyl-2-pentyn-3-yl group, 3-methyl-2-pentyn-3-yl group, 4-methyl-2-pentyn-3-yl group, 1-hexyn-1-yl group, 1-hexyn-2-yl group, 1-hexyn-3-yl group, 1-hexyn-4-yl group, 1-hexyn-5-yl group, 1-hexyn-6-yl group, 2-hexyn-1-yl group, 2-hexyn-2-yl group, 2-hexyn-3-yl group, 2-hexyn-4-yl group, 2-hexyn-5-yl group, 2-hexyn-6-yl group, 3-hexyn-1-yl group, 3-hexyn-2-yl group and 3-hexyn-3-yl group; preferably ethynyl group, 1-propyn-1-yl group, 2-propyn-1-yl group, 3-propyn-1-yl group, 1-butyn-1-yl group, 1-butyn-2-yl group, 1-butyn-3-yl group, 1-butyn-4-yl group, 2-butyn-1-yl group, 2-butyn-2-yl group, 1-methyl-1-propyn-1-yl group, 2-methyl-1-propyn-1-yl group, 1-methyl-2-propyn-1-yl group, 2-methyl-2-propyn-1-yl group, 1-methyl-1-butyn-1-yl group, 2-methyl-1-butyn-1-yl group, 3-methyl-1-butyn-1-yl group, 1-methyl-2-butyn-1-yl group, 2-methyl-2-butyn-1-yl group, 3-methyl-2-butyn-1-yl group, 1-methyl-3-butyn-1-yl group, 2-methyl-3-butyn-1-yl group, 3-methyl-3-butyn-1-yl group, 1-ethyl-1-butyn-1-yl group, 2-ethyl-1-butyn-1-yl group, 3-ethyl-1-butyn-1-yl group, 1-ethyl-2-butyn-1-yl group, 2-ethyl-2-butyn-1-yl group, 3-ethyl-2-butyn-1-yl group, 1-ethyl-3-butyn-1-yl group, 2-ethyl-3-butyn-1-yl group, 3-ethyl-3-butyn-1-yl group, 1,1-dimethyl-1-butyn-1-yl group, 1,2-dimethyl-1-butyn-1-yl group, 1,3-dimethyl-1-butyn-1-yl group, 2,2-dimethyl-1-butyn-1-yl group, 3,3-dimethyl-1-butyn-1-yl group, 1,1-dimethyl-2-butyn-1-yl

group, 1,2-dimethyl-2-butyne-1-yl group,
 1,3-dimethyl-2-butyne-1-yl group, 2,2-dimethyl-2-butyne-1-yl
 group, 3,3-dimethyl-2-butyne-1-yl group,
 1,1-dimethyl-3-butyne-1-yl group, 1,2-dimethyl-3-butyne-1-yl
 group, 1,3-dimethyl-3-butyne-1-yl group,
 2,2-dimethyl-3-butyne-1-yl group and 3,3-dimethyl-3-butyne-1-yl
 group; more preferably ethynyl group, 1-propyne-1-yl group,
 2-propyne-1-yl group, 3-propyne-1-yl group, 1-butyne-1-yl group,
 1-butyne-2-yl group, 1-butyne-3-yl group, 1-butyne-4-yl group,
 2-butyne-1-yl group, 2-butyne-2-yl group, 1-methyl-1-propyne-1-yl
 group, 2-methyl-1-propyne-1-yl group, 1-methyl-2-propyne-1-yl
 group, 2-methyl-2-propyne-1-yl group, 1-methyl-1-butyne-1-yl
 group, 2-methyl-1-butyne-1-yl group, 3-methyl-1-butyne-1-yl
 group, 1-methyl-2-butyne-1-yl group, 2-methyl-2-butyne-1-yl
 group, 3-methyl-2-butyne-1-yl group, 1-methyl-3-butyne-1-yl
 group, 2-methyl-3-butyne-1-yl group and 3-methyl-3-butyne-1-yl
 group; further preferably ethynyl group, 1-propyne-1-yl group,
 2-propyne-1-yl group, 3-propyne-1-yl group, 1-butyne-1-yl group,
 1-butyne-2-yl group, 1-butyne-3-yl group, 1-butyne-4-yl group,
 2-butyne-1-yl group and 2-butyne-2-yl group; and most preferably
 ethynyl group, 1-propyne-1-yl group, 2-propyne-1-yl group and
 3-propyne-1-yl group.

Similarly, when R^1 , R^{x2} , R^{x3} , R^{x4} , R^{x5} , R^{x6} , R^{x7} , R^{x8} and R^{x9}
 represent a C_{2-6} alkynyloxy group which may have one or more
 substituents, the alkynyloxy group refers to a group having
 oxygen atom bound to the end of the C_{2-6} linear or branched alkynyl

group, and specific examples thereof include ethynyloxy group,
1-propyn-1-yloxy group, 2-propyn-1-yloxy group,
3-propyn-1-yloxy group, 1-butyne-1-yloxy group, 1-butyne-2-yloxy
group, 1-butyne-3-yloxy group, 1-butyne-4-yloxy group,
2-butyne-1-yloxy group, 2-butyne-2-yloxy group,
1-methyl-1-propyn-1-yloxy group, 2-methyl-1-propyn-1-yloxy
group, 1-methyl-2-propyn-1-yloxy group,
2-methyl-2-propyn-1-yloxy group, 1-methyl-1-butyne-1-yloxy
group, 2-methyl-1-butyne-1-yloxy group,
3-methyl-1-butyne-1-yloxy group, 1-methyl-2-butyne-1-yloxy
group, 2-methyl-2-butyne-1-yloxy group,
3-methyl-2-butyne-1-yloxy group, 1-methyl-3-butyne-1-yloxy
group, 2-methyl-3-butyne-1-yloxy group,
3-methyl-3-butyne-1-yloxy group, 1-ethyl-1-butyne-1-yloxy group,
2-ethyl-1-butyne-1-yloxy group, 3-ethyl-1-butyne-1-yloxy group,
1-ethyl-2-butyne-1-yloxy group, 2-ethyl-2-butyne-1-yloxy group,
3-ethyl-2-butyne-1-yloxy group, 1-ethyl-3-butyne-1-yloxy group,
2-ethyl-3-butyne-1-yloxy group, 3-ethyl-3-butyne-1-yloxy group,
1,1-dimethyl-1-butyne-1-yloxy group,
1,2-diethyl-1-butyne-1-yloxy group,
1,3-dimethyl-1-butyne-1-yloxy group,
2,2-dimethyl-1-butyne-1-yloxy group,
3,3-dimethyl-1-butyne-1-yloxy group,
1,1-dimethyl-2-butyne-1-yloxy group,
1,2-dimethyl-2-butyne-1-yloxy group,
1,3-dimethyl-2-butyne-1-yloxy group,

2,2-dimethyl-2-butyne-1-yloxy group,
 3,3-dimethyl-2-butyne-1-yloxy group,
 1,1-dimethyl-3-butyne-1-yloxy group,
 1,2-dimethyl-3-butyne-1-yloxy group,
 1,3-dimethyl-3-butyne-1-yloxy group,
 2,2-dimethyl-3-butyne-1-yloxy group,
 3,3-dimethyl-3-butyne-1-yloxy group, 1-pentyne-1-yloxy group,
 2-pentyne-1-yloxy group, 3-pentyne-1-yloxy group,
 4-pentyne-1-yloxy group, 1-pentyne-2-yloxy group,
 2-pentyne-2-yloxy group, 3-pentyne-2-yloxy group,
 4-pentyne-2-yloxy group, 1-pentyne-3-yloxy group,
 2-pentyne-3-yloxy group, 1-pentyne-1-yloxy group,
 2-pentyne-1-yloxy group, 3-pentyne-1-yloxy group,
 4-pentyne-1-yloxy group, 1-pentyne-2-yloxy group,
 2-pentyne-2-yloxy group, 3-pentyne-2-yloxy group,
 4-pentyne-2-yloxy group, 1-pentyne-3-yloxy group,
 2-pentyne-3-yloxy group, 1-methyl-1-pentyne-1-yloxy group,
 2-methyl-1-pentyne-1-yloxy group, 3-methyl-1-pentyne-1-yloxy
 group, 4-methyl-1-pentyne-1-yloxy group,
 1-methyl-2-pentyne-1-yloxy group, 2-methyl-2-pentyne-1-yloxy
 group, 3-methyl-2-pentyne-1-yloxy group,
 4-methyl-2-pentyne-1-yloxy group, 1-methyl-3-pentyne-1-yloxy
 group, 2-methyl-3-pentyne-1-yloxy group,
 3-methyl-3-pentyne-1-yloxy group, 4-methyl-3-pentyne-1-yloxy
 group, 1-methyl-4-pentyne-1-yloxy group,
 2-methyl-4-pentyne-1-yloxy group, 3-methyl-4-pentyne-1-yloxy

group, 4-methyl-4-pentyn-1-yloxy group,
 1-methyl-1-pentyn-2-yloxy group, 2-methyl-1-pentyn-2-yloxy
 group, 3-methyl-1-pentyn-2-yloxy group,
 4-methyl-1-pentyn-2-yloxy group, 1-methyl-2-pentyn-2-yloxy
 group, 2-methyl-2-pentyn-2-yloxy group,
 3-methyl-2-pentyn-2-yloxy group, 4-methyl-2-pentyn-2-yloxy
 group, 1-methyl-3-pentyn-2-yloxy group,
 2-methyl-3-pentyn-2-yloxy group, 3-methyl-3-pentyn-2-yloxy
 group, 4-methyl-3-pentyn-2-yloxy group,
 1-methyl-4-pentyn-2-yloxy group, 2-methyl-4-pentyn-2-yloxy
 group, 3-methyl-4-pentyn-2-yloxy group,
 4-methyl-4-pentyn-2-yloxy group, 1-methyl-1-pentyn-3-yloxy
 group, 2-methyl-1-pentyn-3-yloxy group,
 3-methyl-1-pentyn-3-yloxy group, 4-methyl-1-pentyn-3-yloxy
 group, 1-methyl-2-pentyn-3-yloxy group,
 2-methyl-2-pentyn-3-yloxy group, 3-methyl-2-pentyn-3-yloxy
 group, 4-methyl-2-pentyn-3-yloxy group, 1-hexyn-1-yloxy group,
 1-hexyn-2-yloxy group, 1-hexyn-3-yloxy group, 1-hexyn-4-yloxy
 group, 1-hexyn-5-yloxy group, 1-hexyn-6-yloxy group,
 2-hexyn-1-yloxy group, 2-hexyn-2-yloxy group, 2-hexyn-3-yloxy
 group, 2-hexyn-4-yloxy group, 2-hexyn-5-yloxy group,
 2-hexyn-6-yloxy group, 3-hexyn-1-yloxy group, 3-hexyn-2-yloxy
 group and 3-hexyn-3-yloxy group; preferably ethynyloxy group,
 1-propyn-1-yloxy group, 2-propyn-1-yloxy group,
 3-propyn-1-yloxy group, 1-butyn-1-yloxy group, 1-butyn-2-yloxy
 group, 1-butyn-3-yloxy group, 1-butyn-4-yloxy group,

2-butyn-1-yloxy group, 2-butyn-2-yloxy group,
 1-methyl-1-propyn-1-yloxy group, 2-methyl-1-propyn-1-yloxy
 group, 1-methyl-2-propyn-1-yloxy group,
 2-methyl-2-propyn-1-yloxy group, 1-methyl-1-butyn-1-yloxy
 group, 2-methyl-1-butyn-1-yloxy group,
 3-methyl-1-butyn-1-yloxy group, 1-methyl-2-butyn-1-yloxy
 group, 2-methyl-2-butyn-1-yloxy group,
 3-methyl-2-butyn-1-yloxy group, 1-methyl-3-butyn-1-yloxy
 group, 2-methyl-3-butyn-1-yloxy group,
 3-methyl-3-butyn-1-yloxy group, 1-ethyl-1-butyn-1-yloxy group,
 2-ethyl-1-butyn-1-yloxy group, 3-ethyl-1-butyn-1-yloxy group,
 1-ethyl-2-butyn-1-yloxy group, 2-ethyl-2-butyn-1-yloxy group,
 3-ethyl-2-butyn-1-yloxy group, 1-ethyl-3-butyn-1-yloxy group,
 2-ethyl-3-butyn-1-yloxy group, 3-ethyl-3-butyn-1-yloxy group,
 1,1-dimethyl-1-butyn-1-yloxy group,
 1,2-dimethyl-1-butyn-1-yloxy group,
 1,3-dimethyl-1-butyn-1-yloxy group,
 2,2-dimethyl-1-butyn-1-yloxy group,
 3,3-dimethyl-1-butyn-1-yloxy group,
 1,1-dimethyl-2-butyn-1-yloxy group,
 1,2-dimethyl-2-butyn-1-yloxy group,
 1,3-dimethyl-2-butyn-1-yloxy group,
 2,2-dimethyl-2-butyn-1-yloxy group,
 3,3-dimethyl-2-butyn-1-yloxy group,
 1,1-dimethyl-3-butyn-1-yloxy group,
 1,2-dimethyl-3-butyn-1-yloxy group,

1,3-dimethyl-3-butyn-1-yloxy group,
 2,2-dimethyl-3-butyn-1-yloxy group and
 3,3-dimethyl-3-butyn-1-yloxy group; more preferably ethynyloxy
 group, 1-propyn-1-yloxy group, 2-propyn-1-yloxy group,
 3-propyn-1-yloxy group, 1-butyn-1-yloxy group, 1-butyn-2-yloxy
 group, 1-butyn-3-yloxy group, 1-butyn-4-yloxy group,
 2-butyn-1-yloxy group, 2-butyn-2-yloxy group,
 1-methyl-1-propyn-1-yloxy group, 2-methyl-1-propyn-1-yloxy
 group, 1-methyl-2-propyn-1-yloxy group,
 2-methyl-2-propyn-1-yloxy group, 1-methyl-1-butyn-1-yloxy
 group, 2-methyl-1-butyn-1-yloxy group,
 3-methyl-1-butyn-1-yloxy group, 1-methyl-2-butyn-1-yloxy
 group, 2-methyl-2-butyn-1-yloxy group,
 3-methyl-2-butyn-1-yloxy group, 1-methyl-3-butyn-1-yloxy
 group, 2-methyl-3-butyn-1-yloxy group and
 3-methyl-3-butyn-1-yloxy group; further preferably ethynyloxy
 group, 1-propyn-1-yloxy group, 2-propyn-1-yloxy group,
 3-propyn-1-yloxy group, 1-butyn-1-yloxy group, 1-butyn-2-yloxy
 group, 1-butyn-3-yloxy group, 1-butyn-4-yloxy group,
 2-butyn-1-yloxy group and 2-butyn-2-yloxy group; and most
 preferably ethynyloxy group, 1-propyn-1-yloxy group,
 2-propyn-1-yloxy group and 3-propyn-1-yloxy group.

Similarly, when R^1 , R^{x2} , R^{x3} , R^{x4} , R^{x5} , R^{x6} , R^{x7} , R^{x8} and R^{x9}
 represent a C_{2-6} alkynylthio group which may have one or more
 substituents, the alkynylthio group refers to a group having
 sulfur atom bound to the end of the C_{2-6} linear or branched alkynyl

group, and specific examples thereof include ethynylthio group,
1-propyn-1-ylthio group, 2-propyn-1-ylthio group,
3-propyn-1-ylthio group, 1-butyn-1-ylthio group,
1-butyn-2-ylthio group, 1-butyn-3-ylthio group,
1-butyn-4-ylthio group, 2-butyn-1-ylthio group,
2-butyn-2-ylthio group, 1-methyl-1-propyn-1-ylthio group,
2-methyl-1-propyn-1-ylthio group, 1-methyl-2-propyn-1-ylthio
group, 2-methyl-2-propyn-1-ylthio group,
1-methyl-1-butyn-1-ylthio group, 2-methyl-1-butyn-1-ylthio
group, 3-methyl-1-butyn-1-ylthio group,
1-methyl-2-butyn-1-ylthio group, 2-methyl-2-butyn-1-ylthio
group, 3-methyl-2-butyn-1-ylthio group,
1-methyl-3-butyn-1-ylthio group, 2-methyl-3-butyn-1-ylthio
group, 3-methyl-3-butyn-1-ylthio group,
1-ethyl-1-butyn-1-ylthio group, 2-ethyl-1-butyn-1-ylthio
group, 3-ethyl-1-butyn-1-ylthio group,
1-ethyl-2-butyn-1-ylthio group, 2-ethyl-2-butyn-1-ylthio
group, 3-ethyl-2-butyn-1-ylthio group,
1-ethyl-3-butyn-1-ylthio group, 2-ethyl-3-butyn-1-ylthio
group, 3-ethyl-3-butyn-1-ylthio group,
1,1-dimethyl-1-butyn-1-ylthio group,
1,2-dimethyl-1-butyn-1-ylthio group,
1,3-dimethyl-1-butyn-1-ylthio group,
2,2-dimethyl-1-butyn-1-ylthio group,
3,3-dimethyl-1-butyn-1-ylthio group,
1,1-dimethyl-2-butyn-1-ylthio group,

1,2-dimethyl-2-butyne-1-ylthio group,
 1,3-dimethyl-2-butyne-1-ylthio group,
 2,2-dimethyl-2-butyne-1-ylthio group,
 3,3-dimethyl-2-butyne-1-ylthio group,
 1,1-dimethyl-3-butyne-1-ylthio group,
 1,2-dimethyl-3-butyne-1-ylthio group,
 1,3-dimethyl-3-butyne-1-ylthio group,
 2,2-dimethyl-3-butyne-1-ylthio group,
 3,3-dimethyl-3-butyne-1-ylthio group, 1-pentyne-1-ylthio group,
 2-pentyne-1-ylthio group, 3-pentyne-1-ylthio group,
 4-pentyne-1-ylthio group, 1-pentyne-2-ylthio group,
 2-pentyne-2-ylthio group, 3-pentyne-2-ylthio group,
 4-pentyne-2-ylthio group, 1-pentyne-3-ylthio group,
 2-pentyne-3-ylthio group, 1-pentyne-1-ylthio group,
 2-pentyne-1-ylthio group, 3-pentyne-1-ylthio group,
 4-pentyne-1-ylthio group, 1-pentyne-2-ylthio group,
 2-pentyne-2-ylthio group, 3-pentyne-2-ylthio group,
 4-pentyne-2-ylthio group, 1-pentyne-3-ylthio group,
 2-pentyne-3-ylthio group, 1-methyl-1-pentyne-1-ylthio group,
 2-methyl-1-pentyne-1-ylthio group, 3-methyl-1-pentyne-1-ylthio
 group, 4-methyl-1-pentyne-1-ylthio group,
 1-methyl-2-pentyne-1-ylthio group, 2-methyl-2-pentyne-1-ylthio
 group, 3-methyl-2-pentyne-1-ylthio group,
 4-methyl-2-pentyne-1-ylthio group, 1-methyl-3-pentyne-1-ylthio
 group, 2-methyl-3-pentyne-1-ylthio group,
 3-methyl-3-pentyne-1-ylthio group, 4-methyl-3-pentyne-1-ylthio

group, 1-methyl-4-pentyn-1-ylthio group,
 2-methyl-4-pentyn-1-ylthio group, 3-methyl-4-pentyn-1-ylthio
 group, 4-methyl-4-pentyn-1-ylthio group,
 1-methyl-1-pentyn-2-ylthio group, 2-methyl-1-pentyn-2-ylthio
 group, 3-methyl-1-pentyn-2-ylthio group,
 4-methyl-1-pentyn-2-ylthio group, 1-methyl-2-pentyn-2-ylthio
 group, 2-methyl-2-pentyn-2-ylthio group,
 3-methyl-2-pentyn-2-ylthio group, 4-methyl-2-pentyn-2-ylthio
 group, 1-methyl-3-pentyn-2-ylthio group,
 2-methyl-3-pentyn-2-ylthio group, 3-methyl-3-pentyn-2-ylthio
 group, 4-methyl-3-pentyn-2-ylthio group,
 1-methyl-4-pentyn-2-ylthio group, 2-methyl-4-pentyn-2-ylthio
 group, 3-methyl-4-pentyn-2-ylthio group,
 4-methyl-4-pentyn-2-ylthio group, 1-methyl-1-pentyn-3-ylthio
 group, 2-methyl-1-pentyn-3-ylthio group,
 3-methyl-1-pentyn-3-ylthio group, 4-methyl-1-pentyn-3-ylthio
 group, 1-methyl-2-pentyn-3-ylthio group,
 2-methyl-2-pentyn-3-ylthio group, 3-methyl-2-pentyn-3-ylthio
 group, 4-methyl-2-pentyn-3-ylthio group, 1-hexyn-1-ylthio
 group, 1-hexyn-2-ylthio group, 1-hexyn-3-ylthio group,
 1-hexyn-4-ylthio group, 1-hexyn-5-ylthio group,
 1-hexyn-6-ylthio group, 2-hexyn-1-ylthio group,
 2-hexyn-2-ylthio group, 2-hexyn-3-ylthio group,
 2-hexyn-4-ylthio group, 2-hexyn-5-ylthio group,
 2-hexyn-6-ylthio group, 3-hexyn-1-ylthio group,
 3-hexyn-2-ylthio group and 3-hexyn-3-ylthio group; preferably

ethynylthio group, 1-propyn-1-ylthio group, 2-propyn-1-ylthio group, 3-propyn-1-ylthio group, 1-butyne-1-ylthio group, 1-butyne-2-ylthio group, 1-butyne-3-ylthio group, 1-butyne-4-ylthio group, 2-butyne-1-ylthio group, 2-butyne-2-ylthio group, 1-methyl-1-propyn-1-ylthio group, 2-methyl-1-propyn-1-ylthio group, 1-methyl-2-propyn-1-ylthio group, 2-methyl-2-propyn-1-ylthio group, 1-methyl-1-butyne-1-ylthio group, 2-methyl-1-butyne-1-ylthio group, 3-methyl-1-butyne-1-ylthio group, 1-methyl-2-butyne-1-ylthio group, 2-methyl-2-butyne-1-ylthio group, 3-methyl-2-butyne-1-ylthio group, 1-methyl-3-butyne-1-ylthio group, 2-methyl-3-butyne-1-ylthio group, 3-methyl-3-butyne-1-ylthio group, 1-ethyl-1-butyne-1-ylthio group, 2-ethyl-1-butyne-1-ylthio group, 3-ethyl-1-butyne-1-ylthio group, 1-ethyl-2-butyne-1-ylthio group, 2-ethyl-2-butyne-1-ylthio group, 3-ethyl-2-butyne-1-ylthio group, 1-ethyl-3-butyne-1-ylthio group, 2-ethyl-3-butyne-1-ylthio group, 3-ethyl-3-butyne-1-ylthio group, 1,1-dimethyl-1-butyne-1-ylthio group, 1,2-dimethyl-1-butyne-1-ylthio group, 1,3-dimethyl-1-butyne-1-ylthio group, 2,2-dimethyl-1-butyne-1-ylthio group, 3,3-dimethyl-1-butyne-1-ylthio group, 1,1-dimethyl-2-butyne-1-ylthio group, 1,2-dimethyl-2-butyne-1-ylthio group,

1,3-dimethyl-2-butyne-1-ylthio group,
 2,2-dimethyl-2-butyne-1-ylthio group,
 3,3-dimethyl-2-butyne-1-ylthio group,
 1,1-dimethyl-3-butyne-1-ylthio group,
 1,2-dimethyl-3-butyne-1-ylthio group,
 1,3-dimethyl-3-butyne-1-ylthio group,
 2,2-dimethyl-3-butyne-1-ylthio group and
 3,3-dimethyl-3-butyne-1-ylthio group; more preferably
 ethynylthio group, 1-propyne-1-ylthio group, 2-propyne-1-ylthio
 group, 3-propyne-1-ylthio group, 1-butyne-1-ylthio group,
 1-butyne-2-ylthio group, 1-butyne-3-ylthio group,
 1-butyne-4-ylthio group, 2-butyne-1-ylthio group,
 2-butyne-2-ylthio group, 1-methyl-1-propyne-1-ylthio group,
 2-methyl-1-propyne-1-ylthio group, 1-methyl-2-propyne-1-ylthio
 group, 2-methyl-2-propyne-1-ylthio group,
 1-methyl-1-butyne-1-ylthio group, 2-methyl-1-butyne-1-ylthio
 group, 3-methyl-1-butyne-1-ylthio group,
 1-methyl-2-butyne-1-ylthio group, 2-methyl-2-butyne-1-ylthio
 group, 3-methyl-2-butyne-1-ylthio group,
 1-methyl-3-butyne-1-ylthio group, 2-methyl-3-butyne-1-ylthio
 group and 3-methyl-3-butyne-1-ylthio group; further preferably
 ethynylthio group, 1-propyne-1-ylthio group, 2-propyne-1-ylthio
 group, 3-propyne-1-ylthio group, 1-butyne-1-ylthio group,
 1-butyne-2-ylthio group, 1-butyne-3-ylthio group,
 1-butyne-4-ylthio group, 2-butyne-1-ylthio group and
 2-butyne-2-ylthio group; and most preferably ethynylthio group,

1-propyn-1-ylthio group, 2-propyn-1-ylthio group and 3-propyn-1-ylthio group.

When $R^1, R^{x1}, R^{x2}, R^{x3}, R^{x4}, R^{x5}, R^{x6}, R^{x7}, R^{x8}, R^{x9}$ and R^{x10} represent a C_{6-12} aryl group which may have one or more substituents, the aryl group refers to an aromatic cyclic group, and specific examples thereof include phenyl group, 1-naphthyl group, 2-naphthyl group, as-indacenyl group, s-indacenyl group and acenaphthylenyl group; preferably phenyl group, 1-naphthyl group and 2-naphthyl group; more preferably phenyl group.

Similarly, when $R^1, R^{x2}, R^{x3}, R^{x4}, R^{x5}, R^{x6}, R^{x7}, R^{x8}$ and R^{x9} represent a C_{6-12} aryloxy group which may have one or more substituents, the aryloxy group refers to a group having an oxygen atom bound to the end of the C_{6-12} aryl group, and specific examples thereof include phenyloxy group, 1-naphthyloxy group, 2-naphthyloxy group, as-indacenyloxy group, s-indacenyloxy group and acenaphthylenyloxy group; preferably phenyloxy group, 1-naphthyloxy group and 2-naphthyloxy group; more preferably phenyloxy group.

Similarly, $R^1, R^{x2}, R^{x3}, R^{x4}, R^{x5}, R^{x6}, R^{x7}, R^{x8}$ and R^{x9} represent a C_{6-12} arylthio group which may have one or more substituents, the arylthio group refers to a group having a sulfur atom bound to the end of the C_{6-12} aryl group, and specific examples thereof include phenylthio group, 1-naphthylthio group, 2-naphthylthio group, as-indacenylthio group, s-indacenylthio group and acenaphthylenylthio group; preferably phenylthio group, 1-naphthylthio group and 2-naphthylthio group; more preferably

phenylthio group.

When R^1 , R^{x1} , R^{x2} , R^{x3} , R^{x4} , R^{x5} , R^{x6} , R^{x7} , R^{x8} , R^{x9} and R^{x10} represent a C_{7-18} alkylaryl group which may have one or more substituents, the alkylaryl group refers to a group having the C_{6-12} aryl group substituted at a substitutable site with the C_{1-6} alkyl group. Specific examples thereof include tolyl group, xylyl group, cumenyl group, mesityl group, cymenyl group and styryl group; preferably tolyl group, xylyl group, cumenyl group, mesityl group, cymenyl group and styryl group; more preferably tolyl group, xylyl group, cumenyl group and mesityl group; and further preferably tolyl group, xylyl group and cumenyl group.

Similarly, when R^1 , R^{x2} , R^{x3} , R^{x4} , R^{x5} , R^{x6} , R^{x7} , R^{x8} and R^{x9} represent a C_{7-18} alkylaryloxy group which may have one or more substituents, the alkylaryloxy group refers to a group having an oxygen atom bound to the end of the C_{7-18} alkylaryl group. Specific examples thereof include o-tolyloxy group, m-tolyloxy group, p-tolyloxy group, 2,3-xylyl-1-oxy group, 2,4-xylyl-1-oxy group, 2,5-xylyl-1-oxy group, o-cumenyloxy group, m-cumenyloxy group, p-cumenyloxy group, mesityloxy group, 2,3-cymenyl-1-oxy group, 2,4-cymenyl-1-oxy group, 2,5-cymenyl-1-oxy group, o-styryloxy group, m-styryloxy group and p-styryloxy group; preferably o-tolyloxy group, m-tolyloxy group, p-tolyloxy group, 2,3-xylyl-1-oxy group, 2,4-xylyl-1-oxy group, 2,5-xylyl-1-oxy group, o-cumenyloxy group, m-cumenyloxy group, p-cumenyloxy group, mesityloxy group, 2,3-cymenyl-1-oxy group, 2,4-cymenyl-1-oxy group,

2,5-cymenyl-1-oxy group, o-styryloxy group, m-styryloxy group and p-styryloxy group; more preferably o-tolyloxy group, m-tolyloxy group, p-tolyloxy group, 2,3-xylyl-1-oxy group, 2,4-xylyl-1-oxy group, 2,5-xylyl-1-oxy group, o-cumenyloxy group, m-cumenyloxy group, p-cumenyloxy group, mesityloxy group, o-styryloxy group, m-styryloxy group and p-styryloxy group; more preferably o-tolyloxy group, m-tolyloxy group, p-tolyloxy group, 2,3-xylyl-1-oxy group, 2,4-xylyl-1-oxy group, 2,5-xylyl-1-oxy group and mesityloxy group; and most preferably o-tolyloxy group, m-tolyloxy group and p-tolyloxy group.

Similarly, when R^1 , R^{x2} , R^{x3} , R^{x4} , R^{x5} , R^{x6} , R^{x7} , R^{x8} and R^{x9} represent a C_{7-18} alkylarylthio group which may have one or more substituents, the alkylarylthio group refers to a group having a sulfur atom bound to the end of the C_{7-18} alkylaryl group. Specific examples thereof include o-tolylthio group, m-tolylthio group, p-tolylthio group, 2,3-xylyl-1-thio group, 2,4-xylyl-1-thio group, 2,5-xylyl-1-thio group, o-cumenylthio group, m-cumenylthio group, p-cumenylthio group, mesitylthio group, 2,3-cymenyl-1-thio group, 2,4-cymenyl-1-thio group, 2,5-cymenyl-1-thio group, o-styrylthio group, m-styrylthio group and p-styrylthio group; preferably o-tolylthio group, m-tolylthio group, p-tolylthio group, 2,3-xylyl-1-thio group, 2,4-xylyl-1-thio group, 2,5-xylyl-1-thio group, o-cumenylthio group, m-cumenylthio group, p-cumenylthio group, mesitylthio group, 2,3-cymenyl-1-thio group, 2,4-cymenyl-1-thio group, 2,5-cymenyl-1-thio group, o-styrylthio group, m-styrylthio

group and p-styrylthio group; more preferably o-tolylthio group, m-tolylthio group, p-tolylthio group, 2,3-xylyl-1-thio group, 2,4-xylyl-1-thio group, 2,5-xylyl-1-thio group, o-cumenylthio group, m-cumenylthio group, p-cumenylthio group, mesitylthio group, o-styrylthio group, m-styrylthio group and p-styrylthio group; further preferably o-tolylthio group, m-tolylthio group, p-tolylthio group, 2,3-xylyl-1-thio group, 2,4-xylyl-1-thio group, 2,5-xylyl-1-thio group and mesitylthio group; and most preferably o-tolylthio group, m-tolylthio group and p-tolylthio group.

When R^1 , R^{x1} , R^{x2} , R^{x3} , R^{x4} , R^{x5} , R^{x6} , R^{x7} , R^{x8} , R^{x9} and R^{x10} represent a C_{7-18} aralkyl group which may have one or more substituents, the aralkyl group refers to a group having the C_{1-6} alkyl group substituted at a substitutable site with the C_{6-12} aryl group. Specific examples thereof include benzyl group, phenetyl group, 3-phenylpropyl group, 4-phenylbutyl group, 5-phenylpentyl group, 6-phenylhexyl group, 1-naphthylmethyl group, 2-naphthylmethyl group, 1-naphthylethyl group, 2-naphthylethyl group, 1-naphthylpropyl group and 2-naphthylpropyl group; preferably benzyl group, phenetyl group, 3-phenylpropyl group, 4-phenylbutyl group, 5-phenylpentyl group, 6-phenylhexyl group, 1-naphthylmethyl group, 2-naphthylmethyl group, 1-naphthylethyl group, 2-naphthylethyl group, 1-naphthylpropyl group and 2-naphthylpropyl group; more preferably benzyl group, phenetyl group, 3-phenylpropyl group, 4-phenylbutyl group, 5-phenylpentyl group, 6-phenylhexyl group, 1-naphthylmethyl

group and 2-naphthylmethyl group; further preferably benzyl group, phenethyl group, 3-phenylpropyl group and 4-phenylbutyl group; and most preferably benzyl group and phenethyl group.

Similarly, when R^1 , R^{X2} , R^{X3} , R^{X4} , R^{X5} , R^{X6} , R^{X7} , R^{X8} and R^{X9} represent a C_{7-18} aralkyloxy group which may have one or more substituents, the aralkyloxy group refers to a group having an oxygen atom bound to the C_{7-18} aralkyl group. Specific examples thereof include benzyloxy group, phenetyloxy group, 3-phenylpropyloxy group, 4-phenylbutyloxy group, 5-phenylpentyloxy group, 6-phenylhexyloxy group, 1-naphthylmethyloxy group, 2-naphthylmethyloxy group, 1-naphthylethyloxy group, 2-naphthylethyloxy group, 1-naphthylpropyloxy group and 2-naphthylpropyloxy group; preferably benzyloxy group, phenetyloxy group, 3-phenylpropyloxy group, 4-phenylbutyloxy group, 5-phenylpentyloxy group, 6-phenylhexyloxy group, 1-naphthylmethyloxy group, 2-naphthylmethyloxy group, 1-naphthylethyloxy group, 2-naphthylethyloxy group, 1-naphthylpropyloxy group and 2-naphthylpropyloxy group; more preferably benzyloxy group, phenetyloxy group, 3-phenylpropyloxy group, 4-phenylbutyloxy group, 5-phenylpentyloxy group, 6-phenylhexyloxy group, 1-naphthylmethyloxy group and 2-naphthylmethyloxy group; further preferably benzyloxy group, phenetyloxy group, 3-phenylpropyloxy group and 4-phenylbutyloxy group; and most preferably benzyloxy group and phenetyloxy group.

Similarly, when R^1 , R^{X2} , R^{X3} , R^{X4} , R^{X5} , R^{X6} , R^{X7} , R^{X8} and R^{X9} represent a C_{7-18} aralkylthio group which may have one or more substituents, the aralkylthio group refers to a group having a sulfur atom bound to the end of the C_{7-18} aralkyl group. Specific examples thereof include benzylthio group, phenethylthio group, 3-phenylpropylthio group, 4-phenylbutylthio group, 5-phenylpentylthio group, 6-phenylhexylthio group, 1-naphthylmethylthio group, 2-naphthylmethylthio group, 1-naphthylethylthio group, 2-naphthylethylthio group, 1-naphthylpropylthio group and 2-naphthylpropylthio group; preferably benzylthio group, phenethylthio group, 3-phenylpropylthio group, 4-phenylbutylthio group, 5-phenylpentylthio group, 6-phenylhexylthio group, 1-naphthylmethylthio group, 2-naphthylmethylthio group, 1-naphthylethylthio group, 2-naphthylethylthio group, 1-naphthylpropylthio group and 2-naphthylpropylthio group; more preferably benzylthio group, phenethylthio group, 3-phenylpropylthio group, 4-phenylbutylthio group, 5-phenylpentylthio group, 6-phenylhexylthio group, 1-naphthylmethylthio group and 2-naphthylmethylthio group; further preferably benzylthio group, phenethylthio group, 3-phenylpropylthio group and 4-phenylbutylthio group; and most preferably benzylthio group and phenethylthio group.

Similarly, when R^1 , R^{X1} , R^{X2} , R^{X3} , R^{X4} , R^{X5} , R^{X6} , R^{X7} , R^{X8} and R^{X9} represent a C_{4-13} cycloalkylalkyloxy group which may have one or more substituents, the cycloalkylalkyloxy group refers to

a group having the linear or branched C₁₋₆ alkoxy group wherein a substitutable site is substituted with the C₃₋₇ cyclic alkyl group, and specific examples thereof include cyclopropylmethoxy group, cyclobutylmethoxy group, cyclopentylmethoxy group, cyclohexylmethoxy group, cycloheptylmethoxy group, 1-cyclopropylethoxy group, 2-cyclopropylethoxy group, 1-cyclopropyl-n-propoxy group, 2-cyclopropyl-n-propoxy group, 3-cyclopropyl-n-propoxy group, cyclopropyl-i-propoxy group, cyclopropyl-n-butoxy group, cyclopropyl-i-butoxy group, cyclopropyl-sec-butoxy group, cyclopropyl-t-butoxy group, cyclopropyl-n-pentyloxy group, cyclopropyl-i-pentyloxy group, cyclopropyl-sec-pentyloxy group, cyclopropyl-t-pentyloxy group and cyclopropyl-neopentyloxy group; more preferably cyclopropyl-methoxy group, cyclopropyl-ethoxy group, cyclopropyl-n-propoxy group, cyclopropyl-i-propoxy group, cyclopropyl-n-butoxy group, cyclopropyl-i-butoxy group, cyclopropyl-sec-butoxy group, cyclopropyl-t-butoxy group, cyclopropyl-n-pentyloxy group, cyclopropyl-i-pentyloxy group, cyclopropyl-sec-pentyloxy group, cyclopropyl-t-pentyloxy group, cyclopropyl-neopentyloxy group; and most preferably cyclopropyl-methoxy group, cyclopropyl-ethoxy group, cyclopropyl-n-propoxy group, cyclopropyl-i-propoxy group and the like.

Herein, specific examples of "hetero atom" include oxygen atom, sulfur atom, nitrogen atom, phosphorus, arsenic, antimony, silicon, germanium, tin, lead, boron, mercury and the like,

oxygen atom, sulfur atom, nitrogen atom and phosphorus are preferred, and oxygen atom, sulfur atom and nitrogen atom are more preferred.

Hereinafter, when expressed as "which may have a hetero atom", the hetero atom is as defined above.

In the expression "Y and the ring Z is a 5- to 14-membered aromatic group which may have one or more hetero atoms", the aromatic group means the C₆₋₁₂ aryl group, or the C₆₋₁₂ aryl groups wherein a substitutable site is substituted with the C₁₋₆ aliphatic hydrocarbon group, and specific examples of which include phenyl group, o-tolyl group, m-tolyl group, p-tolyl group, 2,3-xylyl group, 2,4-xylyl group, 2,5-xylyl group, mesityl group, cymenyl group, o-cumenyl group, m-cumenyl group, p-cumenyl group, benzyl group, phenethyl group, α -methylbenzyl group, benzhydryl group, trityl group, benzylidene group, styryl group, cinnamyl group, cinnamylidene group, 3-phenylpropyl group, 4-phenylbutyl group, 5-phenylpentyl group, 6-phenylhexyl group, 1-naphthyl group, 2-naphthyl group, 1-naphthylmethyl group, 2-naphthylmethyl group, 1-naphthylethyl group, 2-naphthylethyl group, as-indacenyl group, s-indacenyl group, acenaphthylenyl group and the like. Phenyl group, o-tolyl group, m-tolyl group, p-tolyl group, 2,3-xylyl group, 2,4-xylyl group, 2,5-xylyl group, mesityl group, cymenyl group, o-cumenyl group, m-cumenyl group, p-cumenyl group, benzyl group, phenethyl group, α -methylbenzyl group, benzhydryl group, trityl group, benzylidene group, styryl group, cinnamyl group, cinnamylidene group, 3-phenylpropyl

group, 4-phenylbutyl group, 5-phenylpentyl group, 6-phenylhexyl group, 1-naphthyl group, 2-naphthyl group, 1-naphthylmethyl group, 2-naphthylmethyl group, 1-naphthylethyl group, 2-naphthylethyl group, as-indacenyl group, s-indacenyl group and acenaphthylenyl group are preferred; phenyl group, o-tolyl group, m-tolyl group, p-tolyl group, 2,3-xylyl group, 2,4-xylyl group, 2,5-xylyl group, mesityl group, cymenyl group, o-cumenyl group, m-cumenyl group, p-cumenyl group, benzyl group, phenethyl group, α -methylbenzyl group, benzhydryl group, trityl group, benzylidene group, styryl group, cinnamyl group, cinnamylidene group, 3-phenylpropyl group, 4-phenylbutyl group, 5-phenylpentyl group, 6-phenylhexyl group, 1-naphthyl group, 2-naphthyl group, 1-naphthylmethyl group and 2-naphthylmethyl group are more preferred; phenyl group, o-tolyl group, m-tolyl group, p-tolyl group, 2,3-xylyl group, 2,4-xylyl group, 2,5-xylyl group, mesityl group, cymenyl group, o-cumenyl group, m-cumenyl group, p-cumenyl group, benzyl group, phenethyl group, α -methylbenzyl group, benzhydryl group, trityl group, benzylidene group, styryl group, cinnamyl group and cinnamylidene group are still preferred; phenyl group, o-tolyl group, m-tolyl group, p-tolyl group, 2,3-xylyl group, 2,4-xylyl group, 2,5-xylyl group, mesityl group, cymenyl group, o-cumenyl group, m-cumenyl group, p-cumenyl group, benzyl group and phenethyl group are further preferred; and phenyl group, o-tolyl group, m-tolyl group, p-tolyl group, 2,3-xylyl group, 2,4-xylyl group, 2,5-xylyl group

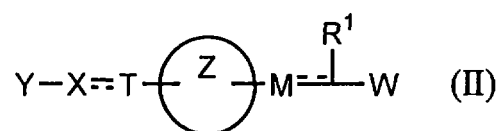
and benzyl group are most preferred. Therefore, specific examples of the aromatic group having a hetero atom include furyl group, thienyl group, pyrrolyl group, pyridyl group, quinolyl group, isoquinolyl group, cinnolyl group, quinazolyl group, quinoxalyl group, indolyl group, indazolyl group, oxazolyl group, isoxazolyl group, thiazolyl group, isothiazolyl group, imidazolyl group, pyrazolyl group, furazanyl group, pyridazinyl group, pyrimidyl group, pyrazyl group and the like.

When expressed as "the ring Z is a 5- to 14-membered aromatic group whose ring may be partially saturated", the aromatic group means 9- to 14-membered aromatic group wherein two or three rings are condensed, with 1 or 2 rings being nonaromatic, and specific examples of which include dihydrobenzofuranyl group, phthalanyl group, chromanyl group, chromanonyl group, isochromanyl group, tetrahydronaphthalenyl group, dihydrobenzothiophenyl group, indolinyl group, isatinylyl group, indanyl group, indanonyl group, tetranonyl group, coumarinyl group, naphthoquinonyl group and anthraquinonyl group; preferably dihydrobenzofuranyl group, phthalanyl group, chromanyl group, chromanonyl group, tetrahydronaphthalenyl group and indanyl group; and more preferably dihydrobenzofuranyl group and chromanyl group.

The expression "Y represents a C₃₋₇ alicyclic hydrocarbon" refers to that the alicyclic hydrocarbon group means a C₃₋₇ cyclic aliphatic hydrocarbon group, and specific examples of which include cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, cyclopropenyl group,

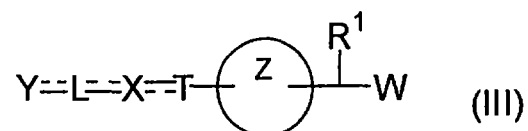
cyclobutenyl group, cyclopentenyl group, cyclohexenyl group, cycloheptenyl group and the like. Cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, cyclopropenyl group, cyclobutenyl group, cyclopentenyl group, cyclohexenyl group and cycloheptenyl group are preferred; cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group and cycloheptyl group are more preferred; cyclopropyl group, cyclobutyl group, cyclopentyl group and cyclohexyl group are still preferred; and cyclopropyl group, cyclobutyl group and cyclopentyl group are most preferred. Therefore, specific examples of the alicyclic hydrocarbon having a hetero atom include pyrrolynyl group, pyrrolidinyl group, imidazolinyl group, imidazolidinyl group, pyrazolinyl group, pyrazolidinyl group, piperidinyl group, piperazinyl group, morpholinyl group, dihydrofuranyl group and tetrahydrofuranyl group, with dihydrofuranyl group and tetrahydrofuranyl group being preferred.

When L represents a single bond, the compounds of the invention are exemplified by carboxylic acid derivatives having group X bound via a single bond to the group Y, represented by the following formula:



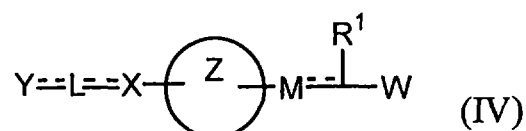
(wherein each symbol has the same meaning as defined above), a salts thereof, an ester thereof or a hydrate of them.

When M represents a single bond, the compounds of the invention are exemplified by carboxylic acid derivatives represented by the following formula:



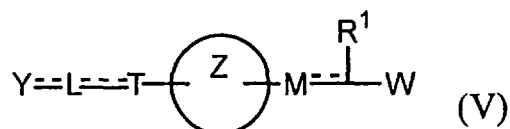
(wherein each symbol has the same meaning as defined above), a salt thereof, an ester thereof or a hydrate of them.

When T represents a single bond, the compounds of the invention are exemplified by carboxylic acid derivatives represented by the following formula:



(wherein each symbol has the same meaning as defined above), a salt thereof, an ester thereof or a hydrate of them.

When X represents a single bond, the compounds of the invention are exemplified by carboxylic acid derivatives represented by the following formula:



(wherein each symbol has the same meaning as defined above), a salt thereof, an ester thereof or a hydrate of them.

When L, T and M represent a C₁₋₆ alkylene group which may have one or more substituents, the alkylene group means a bivalent

group derived by removing one hydrogen atom from the C₁₋₆ alkyl group, and specific examples of which include methylene group, ethylene group, methylethylene group, propylene group, ethylethylene group, 1,1-dimethylethylene group, 1,2-dimethylethylene group, trimethylene group, 1-methyltrimethylene group, 1-ethyltrimethylene group, 2-methyltrimethylene group, 1,1-dimethyltrimethylene group, tetramethylene group, pentamethylene group, hexamethylene group and the like. Methylene group, ethylene group, methylethylene group, propylene group, ethylethylene group, 1,1-dimethylethylene group, 1,2-dimethylethylene group, trimethylene group, 1-methyltrimethylene group, 1-ethyltrimethylene group, 2-methyltrimethylene group, 1,1-dimethyltrimethylene group, tetramethylene group, pentamethylene group and hexamethylene group are preferred; methylene group, ethylene group, methylethylene group, propylene group, ethylethylene group, 1,1-dimethylethylene group, 1,2-dimethylethylene group, trimethylene group, 1-methyltrimethylene group, 1-ethyltrimethylene group, 2-methyltrimethylene group and 1,1-dimethyltrimethylene group are more preferred; methylene group, ethylene group, methylethylene group, propylene group, ethylethylene group, 1,1-dimethylethylene group, 1,2-dimethylethylene group and trimethylene group are still preferred; and methylene group, ethylene group, methylethylene group and propylene group are most preferred.

Similarly, when T represents a C₁₋₃ alkylene group which may have one or more substituents, the alkylene group means a bivalent group derived by removing one hydrogen atom from the C₁₋₃ alkyl group, and specific examples of which include the C₁₋₃ alkylene group as recited above. Methylene group, ethylene group and propylene group are preferred; methylene group and ethylene group are more preferred; and methylene group is most preferred.

When L, T and M represent a C₂₋₆ alkenylene group which may have one or more substituents, the alkenylene group means a bivalent group derived by removing one hydrogen atom from the alkenyl group of 2 to 6 carbons, and specific examples of which include vinylene group, propenylene group, butenylene group, pentenylene group, hexenylene group and the like. Vinylene group, propenylene group, butenylene group and pentenylene group are preferred; vinylene group, propenylene group and butenylene group are more preferred; vinylene group and propenylene group are still preferred; and vinylene group is most preferred.

When L and T represent a C₂₋₆ alkynylene group which may have one or more substituents, the alkynylene group means a bivalent group derived by removing one hydrogen atom from the C₂₋₆ alkynyl group, and specific examples of which include ethynylene group, propynylene group, butynylene group, pentynylene group, hexynylene group and the like. Ethynylene group, propynylene group, butynylene group and pentynylene group are preferred; ethynylene group, propynylene group and

butynylene group are more preferred; butynylene group and propynylene group are still preferred; and propynylene group is most preferred.

Similarly, when M represents a C₂₋₆ alkynylene group which may have one or more substituents, the alkynylene group means a bivalent group derived by removing one hydrogen atom from the C₂₋₆ alkynyl group, and specific examples of which include the C₂₋₆ alkynylene group as recited above. Ethynylene group and propynylene group are preferred, and ethynylene group is more preferred.

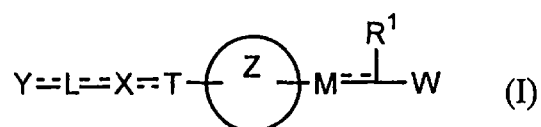
When R^{X1}, R^{X10}, R^{X11} and R^{X12} represent a C₂₋₇ aliphatic acyl group which may have one or more substituents, the aliphatic acyl group represents the C₁₋₆ alkyl group, the C₂₋₆ alkenyl group or the C₂₋₆ alkynyl group wherein a carbonyl group is bound to their terminal end, and specific examples of which include acetyl group, propionyl group, butyryl group, isobutyryl group, valeryl group, isovaleryl group, pivaloyl group, hexanoyl group, octanoyl group, acryloyl group, methacryloyl group, crotonoyl group and the like. Acetyl group, propionyl group, butyryl group, isobutyryl group, valeryl group, isovaleryl group, pivaloyl group, hexanoyl group, octanoyl group, acryloyl group, methacryloyl group and crotonoyl group are preferred; acetyl group, propionyl group, butyryl group, isobutyryl group, valeryl group, isovaleryl group, pivaloyl group, hexanoyl group and octanoyl group are more preferred; acetyl group, propionyl group, butyryl group and isobutyryl group are still preferred; and

acetyl group and propionyl group are most preferred.

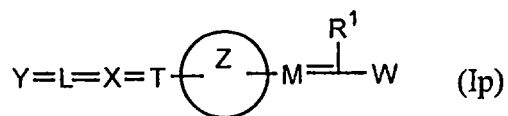
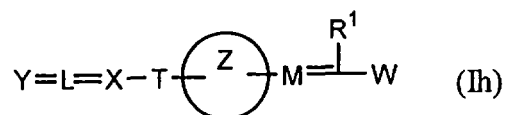
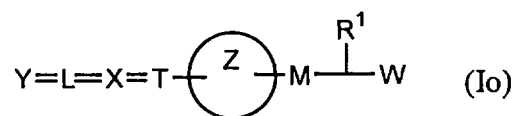
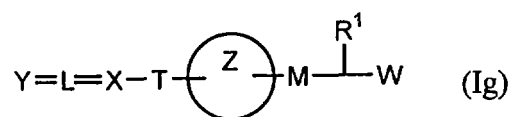
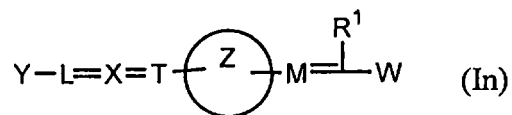
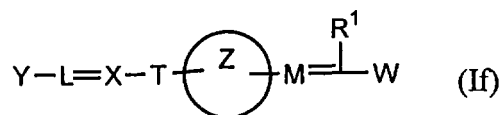
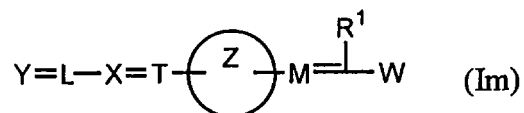
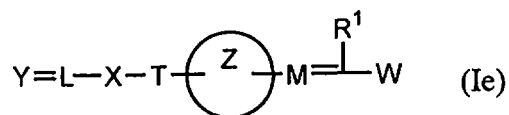
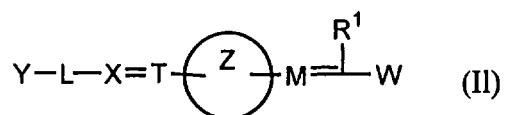
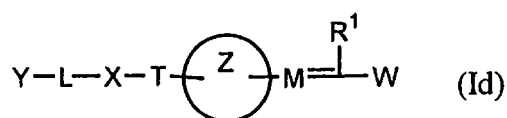
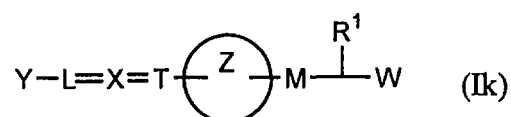
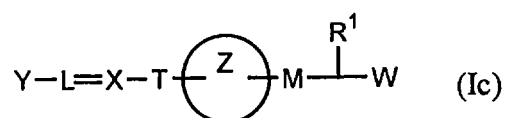
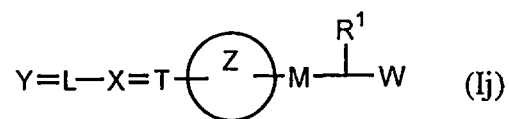
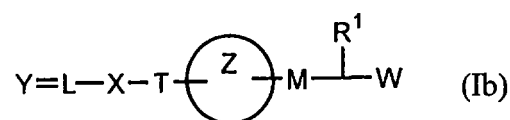
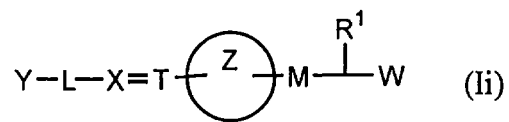
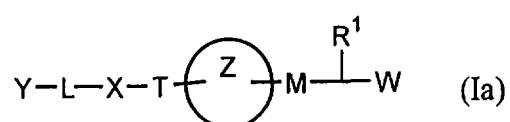
When R^{X1} , R^{X10} , R^{X11} and R^{X1} represent a C_{7-19} aromatic acyl group which may have one or more substituents, the C_{5-12} aromatic acyl group means the C_{5-12} aryl group wherein a carbonyl group or a group derived by removing one hydrogen atom from the C_{2-7} aliphatic acyl group is bound to their terminal end, and specific examples of which include benzoyl group, o-toluoyl group, m-toluoyl group, p-toluoyl group, cinnamoyl group, 1-naphthoyl group, 2-naphthoyl group and the like. Benzoyl group, o-toluoyl group, m-toluoyl group, p-toluoyl group, cinnamoyl group, 1-naphthoyl group and 2-naphthoyl group are preferred; benzoyl group, o-toluoyl group, m-toluoyl group, p-toluoyl group and cinnamoyl group are more preferred; benzoyl group and cinnamoyl group are still preferred; and benzoyl group is most preferred.

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represents a single bond or a double bond. Therefore, compounds of the present invention represented by the following formula (I):

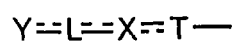


(wherein each symbol represents a group as defined above)
comprehend carboxylic acid compound represented by the following formulae:

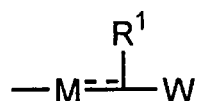


(wherein symbols are as described above), a salt thereof, an ester thereof or a hydrate of them.

The group represented by the formula:

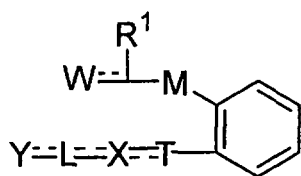


(wherein each symbol represents a group as defined above) and the group represented by the formula:



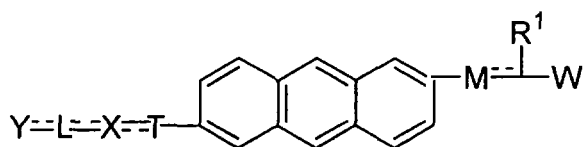
(wherein each symbol represents a group as defined above) are bound with each other on the ring Z via from 2 to 8 atoms. In the case where such wording is used, "bound with each other on the ring Z via from 2 to 8 atoms" represents the following cases.

For example, when the ring Z is benzene, and 2 atoms are involved in binding, the formula is as follows:

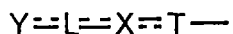


wherein each symbol represents a group as defined above.

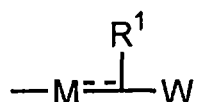
When the ring Z is anthracene and 8 atoms are involved in binding, the formula is as follows:



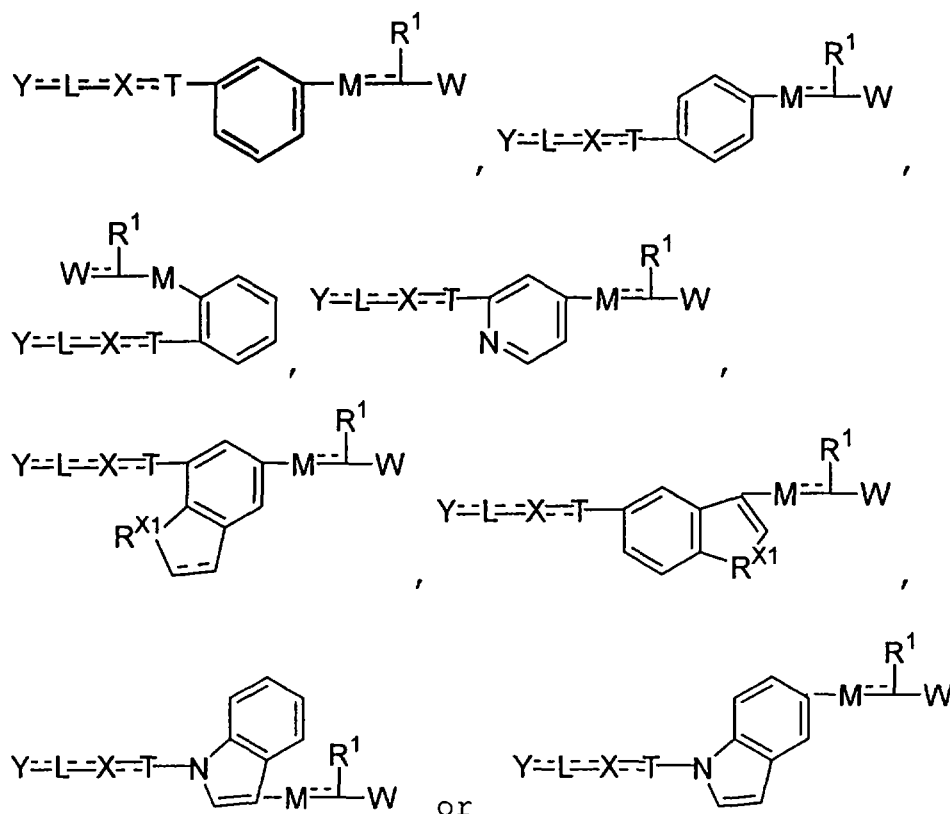
(wherein each symbol represents a group as defined above). Therefore, those defined by the ring Z, and the group represented by the formula:



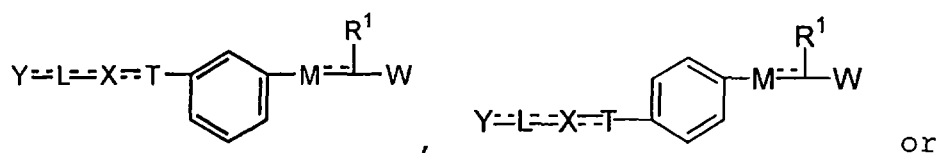
(wherein each symbol represents a group as defined above), and the group represented by the formula:

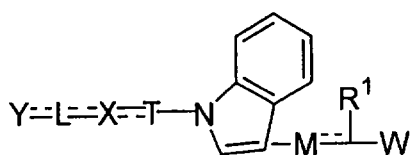


(wherein each symbol represents a group as defined above) may be bound in any positions. Preferably the compound represented by the formula:



(wherein each symbol represents a group as defined above, and the aromatic group may further have 1 to 4 substituents), and more preferably the formula:





(wherein each symbol represents a group as defined above, and the aromatic group may further have 1 to 4 substituents).

"Salts" used herein are not particularly limited with regard to the kind, and specific examples include additive salts of inorganic acid such as hydrofluoride, hydrochloride, sulfate, nitrate, perchlorate, phosphate, carbonate, bicarbonate, hydrobromide or hydroiodide; additive salts of organic carboxylic acid such as acetate, maleate, fumarate, oxalate, lactate, tartrate or trifluoroacetate; additive salts of organic sulfonic acid such as methanesulfonate, trifluoromethanesulfonate, ethanesulfonate, hydroxymethanesulfonate, hydroxyethanesulfonate, benzensulfonate, toluenesulfonate or taurine salt and the like; additive salts of amine such as trimethylamine salt, triethylamine salt, pyridine salt, procaine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzyl diaminoethane salt, N-methylglucamine salt, diethanolamine salt, triethanolamine salt, tris(hydroxymethylamino)methane salt or phenethyl benzyl amine salt; additive salts of alkaline metal such as sodium salt or potassium salt; additive salts of alkaline earth metal such as magnesium salt or calcium salt; and additive salts of amino acid such as arginine salt, lysine salt, serine salt, glycine salt, aspartate or glutamate and the like. Pharmaceutically

acceptable salt is preferred.

Pharmaceutically acceptable salts are not particularly limited with regard to the kind, and specific examples include additive salts of inorganic acid such as hydrochloride, sulfate, carbonate, bicarbonate, hydrobromide or hydroiodide; additive salts of organic carboxylic acid such as acetate, maleate, lactate, tartrate or trifluoroacetate; additive salts of organic sulfonic acid such as methanesulfonate, hydroxymethanesulfonate, hydroxyethanesulfonate, benzensulfonate, toluenesulfonate or taurine salt; additive salts of amine such as trimethylamine salt, triethylamine salt, pyridine salt, procaine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzyl diaminoethane salt, N-methylglucamine salt, diethanolamine salt, triethanolamine salt, tris(hydroxymethylamino)methane salt or phenethyl benzyl amine; additive salts of alkaline metal such as sodium salt or potassium salt; additive salts of amino acid such as arginine salt, lysine salt, serine salt, glycine salt, aspartate or glutamate.

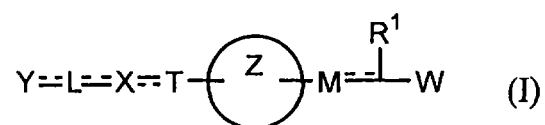
"Ester" used in the present invention refers to esters of carboxyl group of W in the general formula (I). These are not particularly limited insofar as they are commonly used in organic synthesis, and physiologically acceptable ester groups which are hydrolyzed under physiological conditions are comprehended. Specific examples include C₁₋₆ alkyl groups, C₆₋₁₂ aryl groups, C₇₋₂₀ aralkyl groups such as benzyl group, C₇₋₂₀ heteroarylalkyl

groups, 4-methoxybenzyl group, alkanoyloxyalkyl groups such as acetoxymethyl group, propionyloxymethyl group or pivaloxymethyl group, alkoxycarbonyloxyalkyl groups such as methoxycarbonyloxymethyl group, ethoxycarbonyloxymethyl group or 2-methoxycarbonyloxyethyl group, (5-methyl-2-oxo-1,3-dioxo-4-yl)methyl group and the like.

It is to be noted that if the carboxylic acid derivative having the above general formula (I), a salt pharmacologically acceptable salt thereof or a pharmacologically acceptable ester thereof form solvates, all such solvates are comprehended in the present invention.

Salts, hydrates or esters of compounds of the present invention are preferably those pharmaceutically acceptable.

The compound of the present invention represented by the formula (I):



(wherein each symbol represents a group as defined above) can be synthesized in a conventional method, and can be synthesized, for example, in the manner as described below.

General production example A



wherein each symbol represents a group as defined above, and "Hal" represents a halogen.

The compound represented by the formula (3a) is obtained by treating the compound represented by the formula (2a) with the compound represented by the formula (1a).

The reaction condition is not particularly limited, and for example, the reaction is conducted in a solvent such as methanol, ethanol, propanol, dimethylsulfoxide, N,N-dimethylformamide, N-methylpyrrolidone, dioxane, tetrahydrofuran or toluene, in the presence of a base such as lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium carbonate, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride or potassium hydride at a temperature from 0°C to 150°C.

The compound represented by the formula (4a) can be obtained by halogenation of the compound represented by the formula (3a).

The reaction condition is not particularly limited, and for example, it can be obtained by making phosphorus oxychloride, thionyl chloride, phosphorus trichloride or phosphorus tribromide in a solvent such as dioxane, tetrahydrofuran or dimethoxyethane. The reaction temperature is from 0°C to 150°C. Conditions which combine triphenyl phosphine, carbon tetrachloride, carbon tetrabromide, N-bromo succinimide and the like may be used as well.

The compound represented by the formula (7a) can be obtained by treating the compound represented by the formula (6a) with

the compound represented by the formula (5a).

The reaction condition is not particularly limited, and the reaction may be conducted in a solvent such as methanol, ethanol, propanol, dimethylsulfoxide, N,N-dimethylformamide, N-methylpyrrolidone, dioxane, tetrahydrofuran or toluene, in the presence of from 0.0001 to 0.5 mole equivalent of copper halide, from 0.0001 to 0.5 mole equivalent of palladium catalyst such as tetrakis(triphenylphosphine)palladium or dichlorobis(triphenylphosphine)palladium, and an organic base such as triethylamine, N,N-diisopropylethylamine, butylamine or tributylamine at a temperature from 0°C to 150°C.

The compound represented by the formula (8a) can be obtained by halogenation of the compound represented by the formula (7a).

The reaction condition corresponds to that of production example of the formula (4a) in Production example A.

The compound represented by the formula (10a) is obtained by aldol reaction between the compound represented by the formula (9a) and aliphatic esters, alkoxyacetic acid esters (these alkyl or alkoxy groups correspond to R¹ of the formula, and ester groups correspond to W of the formula) and the like, or Wittig-Horner-Emmons reaction of alkylphosphonic acid esters, alkoxyphosphonic acid esters (these alkyl or alkoxy groups correspond to R¹ of the formula, and ester groups correspond to W of the formula) and the like followed by reduction of alcohol or double bond.

The reaction condition for aldol reaction and

Wittig-Horner-Emmons reaction is not particularly limited, and for example, the reaction may be conducted in a solvent such as methanol, ethanol, propanol, dimethylsulfoxide, N,N-dimethylformamide, N-methylpyrrolidone, dioxane, tetrahydrofuran or toluene, in a presence of a base such as lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium carbonate, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride, potassium hydride, butyllithium, methyl lithium, lithium bistrimethylsilylamide, sodium bistrimethylsilylamide or potassium bistrimethylsilylamide and the like at a temperature from 0°C to 150°C.

As to the condition of reduction reaction and the like, the reaction may be conducted in a solvent such as methanol, ethanol, propanol, dimethylsulfoxide, N,N-dimethylformamide, N-methylpyrrolidone, dioxane, tetrahydrofuran or toluene, in the presence of a metal catalyst such as palladium carbon, platinum oxide or Raney's nickel, in hydrogen atmosphere, at temperature between 0°C and 150°C. Optionally, the reduction may be conducted after acylation or sulfonylation of an alcohol group on an aldol adduct.

The compound represented by the formula (11a) can be obtained by hydrolyzing an ester in the molecule after alkylation between the compound represented by the formula (10a) and the compound represented by the formula (4a) or the compound represented by the formula (8a).

The condition for alkylation corresponds to that of the

production example of the formula (4a) in Production example A.

The condition for hydrolysis reaction is not particularly limited, and the reaction may be conducted by treating an aqueous solution of lithium hydroxide, sodium hydroxide, potassium hydroxide and the like, for example, in a solvent such as methanol, ethanol, propanol, dimethylsulfoxide, N,N-dimethylformamide, N-methylpyrrolidone, dioxane or tetrahydrofuran, at a temperature from 0°C to 150°C.

The compound represented by the formula (13a) can be obtained by hydrolyzing the ester in the molecule after alkylation of the compound represented by the formula (10a) and the compound represented by the formula (8a), or by hydrolyzing the ester in the molecule after reaction between the compound represented by the formula (10a) and propargyl bromide followed by a coupling reaction using palladium catalyst.

The conditions for the alkylation reaction and hydrolysis reaction correspond to those of the production example of the formula (11a) of Production example A.

The reaction condition for the coupling reaction corresponds to that of the production example of the formula (7a) in Production example A.

The compound represented by the formula (15a) can be obtained by treating the compound represented by the formula (1a) after alkylation of the compound represented by the formula (10a) with the compound represented by the formula (14a).

The reaction condition for alkylation of the formula (14a) follows the production example of the formula (3a) in Production example A.

The reaction condition for the treatment of the formula (1a) is not particularly limited, and it can be achieved by reacting in a solvent such as methanol, ethanol, propanol, dimethylsulfoxide, N,N-dimethylformamide, N-methylpyrrolidone, dioxane or tetrahydrofuran, in the presence of 0.0001 to 1.0 mole equivalent of catalyst such as potassium carbonate, triethylamine or cesium fluoride at a temperature from 0°C to 150°C.

The compound represented by the formula (16a) can be obtained by hydrolyzing the ester in the molecule after fluorination of the compound represented by the formula (15a).

The reaction condition of fluorination is not particularly limited, and the reaction can be achieved, for example, by treating a reagent such as (diethylamino)sulfur trifluoride in a solvent such as dichloromethane or chloroform at a temperature from 0°C to 150°C.

The condition for hydrolysis reaction corresponds to that of the production example of the formula (11a) in Production example A.

The compound represented by the formula (17a) can be obtained by hydrolyzing the ester in the molecule after alkylation of the compound represented by the formula (15a) with an alkyl halide.

The reaction condition corresponds to that of the production example of the formula (3a) in Production example A.

The compound represented by the formula (19a) can be obtained by hydrolyzing the ester of the molecule after modifying the compound represented by the formula (10a) into a sulfonates using sulfonyl chloride.

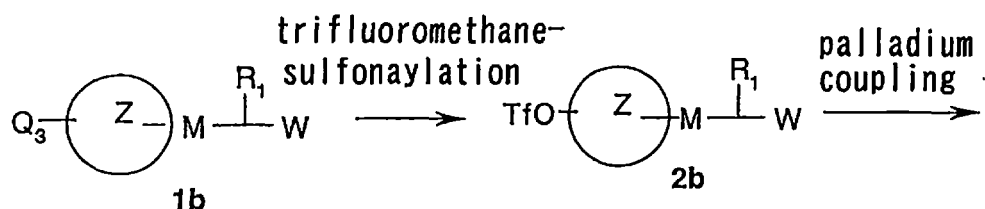
The reaction condition for sulfonylation is not particularly limited, and the reaction can be conducted in a solvent such as pyridine, dichloromethane or chloroform, in the presence of an organic base such as triethylamine, N,N-diisopropylethylamine or tributylamine at a temperature from 0°C to 150°C.

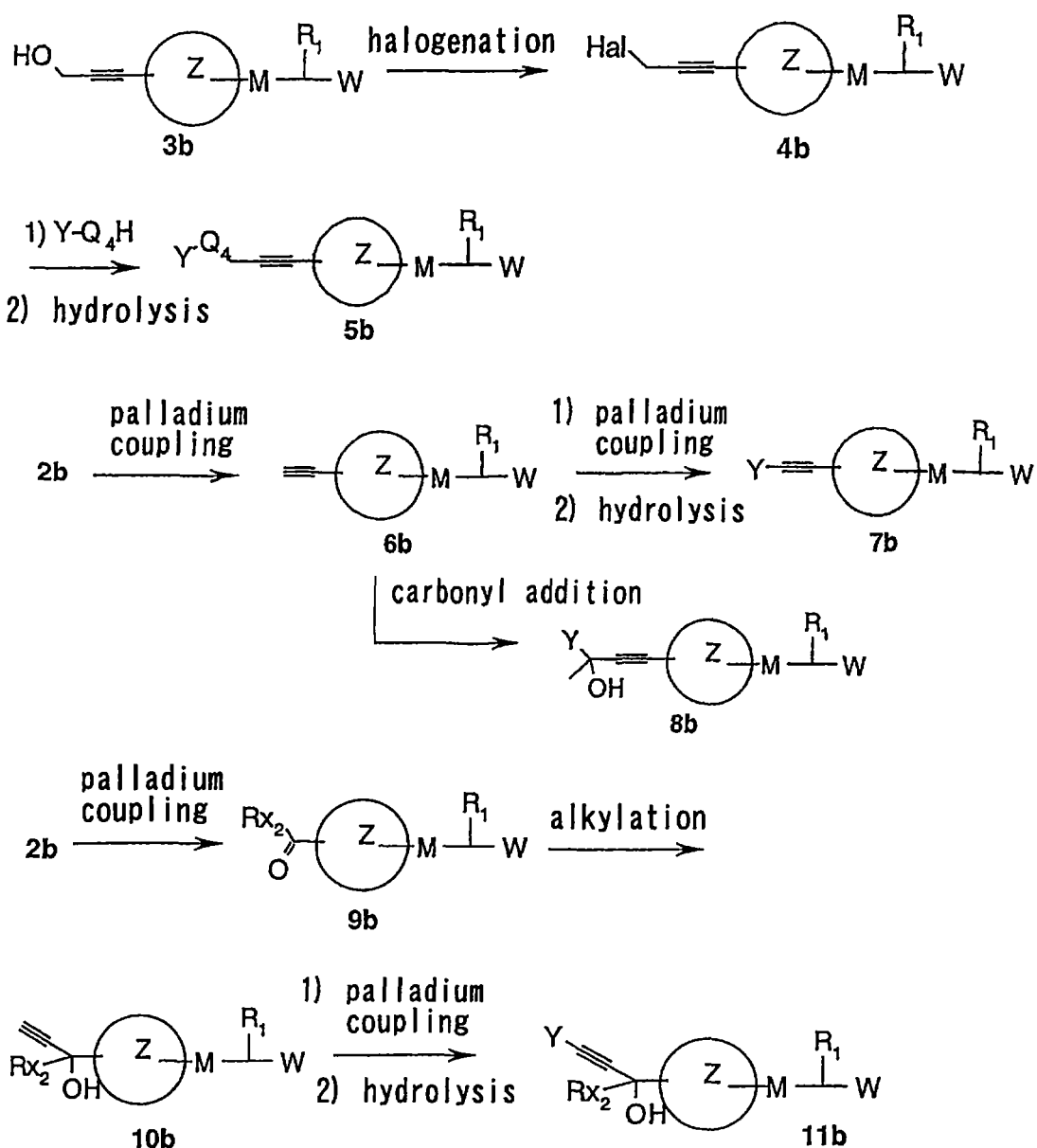
The condition for hydrolysis reaction corresponds to that of the production example of the formula (11a) in Production example A.

The compound represented by the formula (20a) can be obtained by hydrolyzing the compound represented by the formula (15a).

The condition for hydrolysis reaction corresponds to that of the production example of the formula (11a) in Production example A.

General production example B





wherein each symbol represents a group as defined above; and Tf represents a trifluoromethanesulfonyl group.

The compound represented by the formula (2b) can be obtained by trifluoromethanesulfonylation of the compound represented by the formula (1b).

The reaction condition is not particularly limited, and it can be synthesized by treating N,N-bistrifluoromethylaniline,

trifluoromethanesulfonic anhydride, trifluoromethanesulfonyl chloride and the like in a solvent such as pyridine, dichloromethane or chloroform, in the presence of an organic base such as triethylamine, N,N-diisopropylethylamine or tributylamine at a temperature from 0°C to 150°.

The compound represented by the formula (3b) can be obtained by palladium coupling of the compound represented by the formula (2b).

The reaction condition corresponds to that of the production example of the formula (7a) in Production example A.

The compound represented by the formula (4b) can be obtained by halogenation of the compound represented by the formula (3b).

The reaction condition corresponds to that of the production example of the formula (4a) in Production example A.

The compound represented by the formula (5b) can be obtained by alkylation of the compound represented by the formula (4b).

The reaction condition corresponds to that of the production example of the formula (3a) in Production example A.

The compound represented by the formula (6b) can be obtained by palladium coupling of the compound represented by the formula (2b).

The reaction condition corresponds to that of the production example of the formula (7a) in Production example A.

The compound represented by the formula (7b) can be obtained by hydrolyzing the ester in the molecule after palladium coupling of the compound represented by the formula (6b).

The reaction conditions for palladium coupling and hydrolysis correspond to those of the production example of the formula (7a) in Production example A, and the production example of the formula (11a) in Production example A, respectively.

The compound represented by the formula (8b) can be obtained by treating a carbonyl compound such as ketone or aldehyde with the compound represented by the formula (6b).

The reaction condition is not particularly limited, and the reaction can be conducted, for example, in a solvent such as dioxane, tetrahydrofuran or dimethoxyethane, in the presence of a base such as lithium bistrimethylsilylamide, sodium bistrimethylsilylamide or potassium bistrimethylsilyl amide at a temperature from 0°C to room temperature.

The compound represented by the formula (9b) can be obtained by palladium coupling of the compound represented by the formula (2b).

The reaction condition is not particularly limited, and it can be synthesized, for example, in a solvent such as dioxane, tetrahydrofuran, dimethoxyethane or toluene, by reacting 1,1-ethoxyvinyltributyltin, butylvinyl ether and the like in the presence of from 0.0001 to 0.5 mole equivalent of palladium catalyst such as tetrakis(triphenylphosphine)palladium or dichlorobis(triphenylphosphine)palladium, and lithium chloride, at a temperature from 0°C to 150°C.

The compound represented by the formula (10b) can be obtained by adding acetylene to the compound represented by the formula

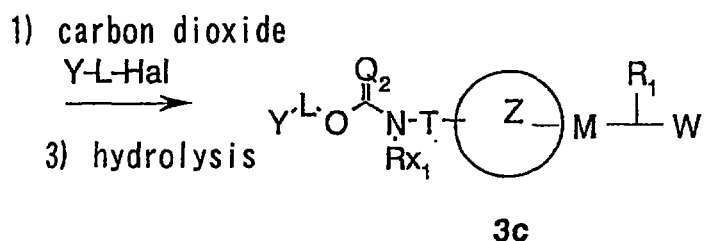
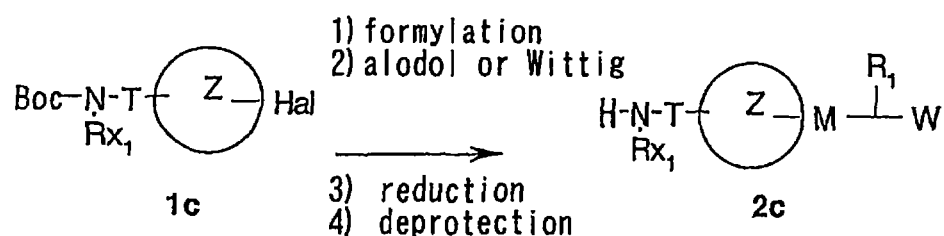
(9b).

The reaction condition is not particularly limited, and the reaction can be conducted, for example in a solvent such as dioxane, tetrahydrofuran or dimethoxyethane, in the presence of a base such as butyl lithium, methyl lithium, ethyl magnesium hydride, lithium bistrimethylsilylamide, sodium bistrimethylsilylamide or potassium bistrimethylsilylamide, and a Lewis acid such as boron trifluoride ether complex, at a temperature from 0°C to room temperature.

The compound represented by the formula (11b) can be obtained by hydrolysis after palladium coupling to the compound represented by the formula (10b).

The reaction condition corresponds to that of the production example of the formula (7b) in Production example B.

General production example C



wherein each symbol represents a group as defined above; Boc represents a t-butoxycarbonyl group; and Hal represents a

halogen.

The compound represented by the formula (2c) can be obtained by formylation of the compound represented by the formula (1c), followed by aldol reaction or Wittig- Horner-Emmons reaction, reduction and deprotection.

The reaction condition for formylation is not particularly limited, and it may be achieved by acting butyl lithium in a solvent such as dioxane, tetrahydrofuran or dimethoxyethane, followed by acting N,N-dimethylformamide, N,N-dimethylformamide and the like at a temperature from -78°C to 0°C.

The reaction conditions for aldol reaction or Wittig-Horner-Emmons reaction corresponds to that of the production example of the formula (10a) in Production example A.

The reaction condition for reduction reaction corresponds to that of the production example of the formula (10a) in Production example A.

The reaction condition for deprotection is not particularly limited, and it can be achieved by causing an acid such as hydrogen chloride or trifluoroacetic acid in an organic solvent such as dichloromethane, chloroform, tetrahydrofuran or dioxane, at a temperature from 0°C to 150°C.

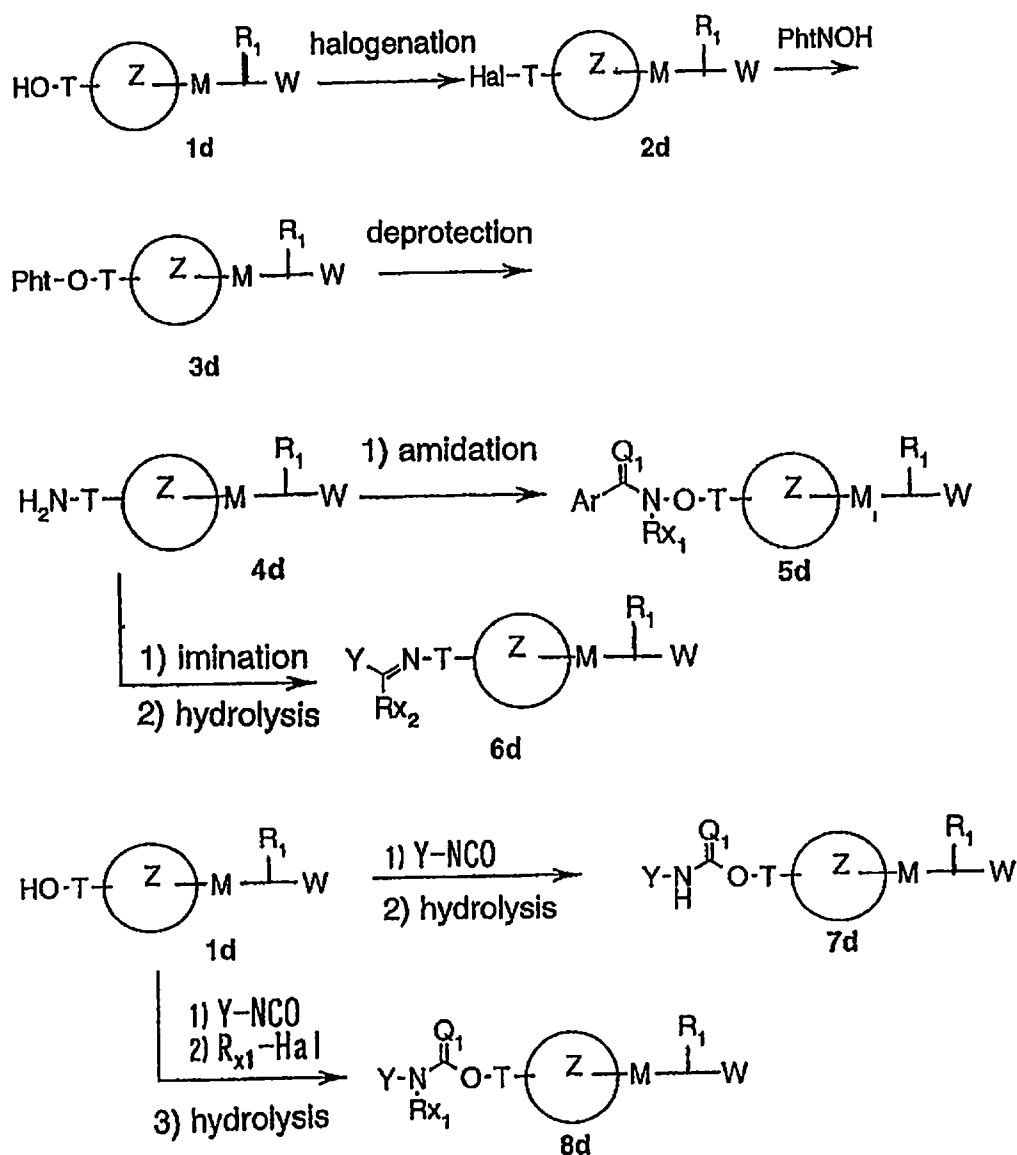
The compound represented by the formula (3c) can be obtained by causing carbon dioxide and Y-L-Hal to act on the compound represented by the formula (2c), to form carbamate, and

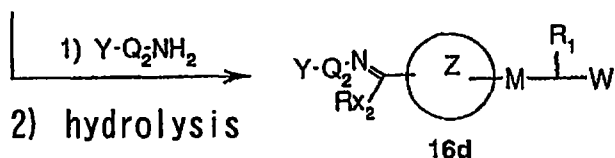
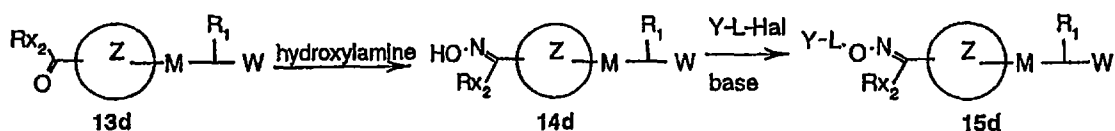
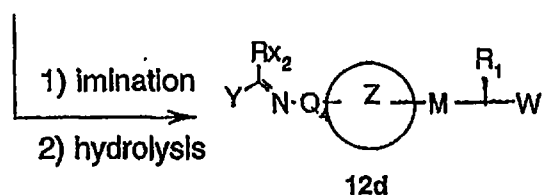
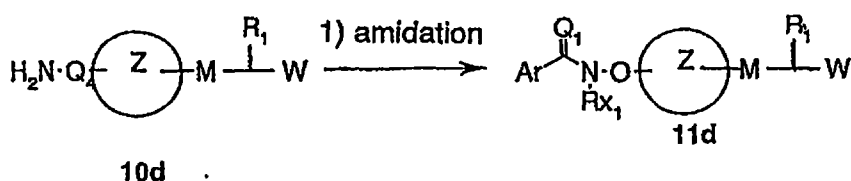
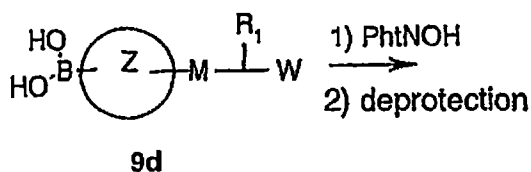
hydrolyzing the ester in the molecule.

As to reaction condition for synthesis of carbamate follows, but not particularly limited thereto, the document (*J. Org. Chem.* 2000, 66, 1035.).

The reaction condition for hydrolysis follows the production example of the formula (11a) in Production example A.

General production example D





wherein each symbol represents a group as described above; Hal represents a halogen; PhtNOH represents N-hydroxyphthalimide; and -NCO represents an isocyanate group.

The compound represented by the formula (2d) can be obtained by halogenation of the compound represented by the formula (1d).

The reaction condition follows the production example of the formula (4a) in Production example A.

The compound represented by the formula (3d) can be obtained by causing N-hydroxyphthalimide to act on the compound represented by the formula (2d).

The reaction condition is not particularly limited, and

the reaction can be conducted, for example, in a solvent such as methanol, ethanol, propanol, dimethylsulfoxide, N,N-dimethylformamide, N-methylpyrrolidone, dioxane, tetrahydrofuran or toluene in the presence of a base such as lithium carbonate, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride, potassium hydride, triethylamine, N,N-diisopropylethylamine or tributylamine at a temperature from 0°C to 150°C.

The compound represented by the formula (4d) can be obtained by deprotection of the phthalimide group of the compound represented by the formula (3d).

The reaction condition is not particularly limited, and for example, hydrazine, N-methyl hydrazine and the like may be caused to act in a solvent such as methanol, ethanol, propanol, dimethylsulfoxide, N,N-dimethylformamide, N-methylpyrrolidone, dioxane, tetrahydrofuran or toluene at a temperatures from 0°C to 150°C.

The compound represented by the formula (5d) can be obtained by amidation of the compound represented by the formula (4d), and hydrolysis of the ester in the molecule.

The reaction condition for amidation is not particularly limited, and it can be achieved by causing an appropriate carboxylic acid to act in a solvent such as N,N-dimethylformamide, N-methylpyrrolidone, dioxane, tetrahydrofuran, toluene, dichloromethane or chloroform, in the presence of a condensing agent such as diphenylphosphoryl azide,

diethylphosphorylcyanide or dicyclohexylcarbodiimide, and a base such as triethylamine, N,N-diisopropylethylamine, tributylamine, sodium hydrogencarbonate or potassium hydrogen carbonate at a temperature from 0°C to 150°C.

The reaction condition of hydrolysis reaction follows the production example of the formula (11a) in Production example A.

The compound represented by the formula (6d) can be obtained by imitation of the compound represented by the formula (4d) followed by hydrolysis of the ester in the molecule.

The reaction condition for the imination is not particularly limited, and it can be synthesized, for example, by causing an appropriate carbonyl compound such as ketone or aldehyde in a solvent such as methanol, ethanol, propanol, dimethylsulfoxide, N,N-dimethylformamide, N-methylpyrrolidone, dioxane, tetrahydrofuran or toluene at a temperature from 0°C to 150°C. An acid such as acetic acid, trifluoroacetic acid or hydrogen chloride may also exist.

The reaction condition for hydrolysis corresponds to that of the production example of the formula (11a) in Production example A.

The compound represented by the formula (7d) can be obtained by treating Y-NCO with the compound represented by the formula (1d) to form a carbamate, and hydrolyzing the ester in the molecule.

The reaction condition for synthesis of the carbamate is

not particularly limited, and it can be achieved by causing an organic base such as pyridine or triethylamine to act in a solvent such as tetrahydrofuran, toluene, ether or dioxane at a temperature from 0°C to 150°C.

The reaction condition for hydrolysis reaction corresponds to that of the production example of the formula (11a) in Production example A.

The compound represented by the formula (8d) can be obtained by causing Y-NCO to act on the compound represented by the formula (1d), thereby forming a carbamate, followed by alkylation by causing R_{X1}-Hal to act thereon, and hydrolysis of the ester in the molecule.

The reaction condition for synthesis of the carbamate corresponds to that of the production example of the formula (7d) in Production example D.

The reaction condition for alkylation corresponds to that of the production example of the formula (4a) in Production example A.

The reaction condition for hydrolysis reaction corresponds to that of the production example of the formula (11a) in Production example A.

The compound represented by the formula (10d) can be obtained by treating N-hydroxyphthalimide with the compound represented by the formula (9d), followed by deprotection of the phthalimide group.

The hydroxyphthalimidation can be conducted in accordance

with the document (*Org. Lett.* 2001, 3, 139).

The reaction condition for hydrolysis corresponds to that of the production example of the formula (4d) in Production example D.

The compound represented by the formula (11d) can be obtained by amidation of the compound represented by the formula (10d) followed by hydrolysis of the ester in the molecule.

The reaction condition corresponds to that of the production example of the formula (5d) in Production example D.

The compound represented by the formula (12d) can be obtained by the imination of the compound represented by the formula (10d) followed by hydrolysis of the ester in the molecule.

The reaction condition corresponds to that of the production example of the formula (6d) in Production example D.

The compound represented by the formula (14d) can be obtained by imination of the compound represented by the formula (13d).

The reaction condition corresponds to that of the production example of the formula (6d) in Production example D.

The compound represented by the formula (15d) can be obtained by alkylation of the compound represented by the formula (14d) with Y-L-Hal.

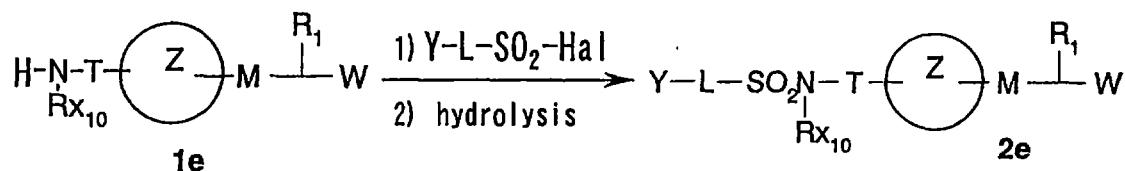
The reaction condition corresponds to that of the production example of the formula (3a) in Production example A.

The compound represented by the formula (16d) can be obtained by imination of the compound represented by the formula (13d) with Y-Q₂-NH₂, and followed by hydrolysis of the ester in the

molecule.

The reaction condition corresponds to that of the production example of the formula (6d) in Production example D.

General production example E



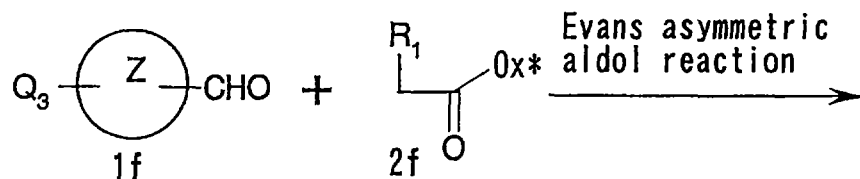
wherein each symbol represents a group as defined above; and Hal represents a halogen.

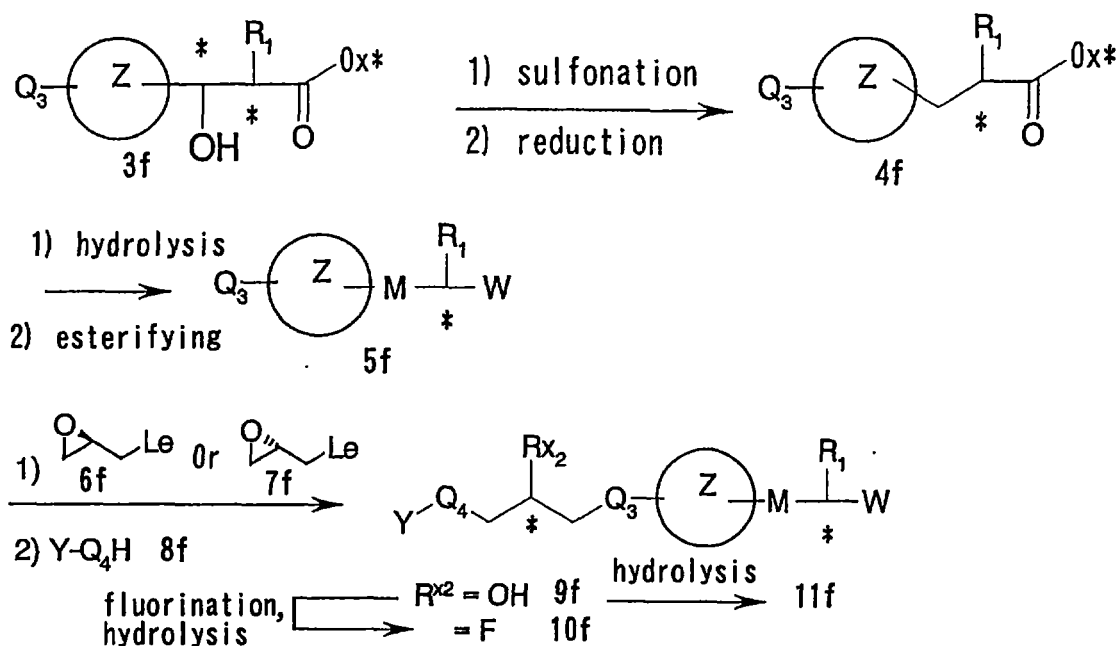
The compound represented by the formula (2e) can be obtained by sulfonamidation by causing Y-L-SO₂-Hal to act on the compound represented by the formula (1e), and hydrolyzing the ester in the molecule.

The reaction condition for synthesis of sulfonamide is not particularly limited, and it can be achieved, for example, by causing an organic base such as pyridine or triethylamine to act in an organic solvent such as dichloromethane or chloroform at a temperature from 0°C to 150°C.

The reaction condition for hydrolysis reaction corresponds to that of the production example of the formula (11a) in Production example A.

General production example F





wherein each symbol represents a group as defined above; and t Ox* represents an Evans aldol asymmetric auxiliary group (chiral oxazolidinone), Le represents a leaving group such as halogen or sulfonate; and symbol * represents an asymmetric carbon.

The compound represented by the formula (3f) can be obtained by treating the compound represented by the formula (2f) with the compound represented by the formula (1f) in an Evans asymmetrical aldol condition.

The reaction condition is not particularly limited, but for example, the reaction is conducted in a solvent such as dichloromethane, chloroform, dioxane, tetrahydrofuran or toluene, in the presence of a base such as triethylamine or diisopropylethylamine, at a temperature from 0°C to 150°C.

The compound represented by the formula (4f) can be obtained by sulfonylation of the compound represented by the formula (3f),

followed by reduction of the sulfonate group.

The reaction condition for sulfonylation is not particularly limited, and for example, it can be achieved by treating methanesulfonyl chloride, tosyl chloride, 4-nitrobenzenesulfonyl chloride and the like in a solvent such as dichloromethane, chloroform, dioxane, tetrahydrofuran, toluene or pyridine, in the presence of a base such as trimethylamine, diisopropylethylamine, pyridine or N,N-dimethylaminopyridine, at a temperature from 0°C to 150°C.

The condition for reduction is conducted in a solvent such as methanol, ethanol, propanol, dimethylsulfoxide, N,N-dimethylformamide, N-methylpyrrolidone, dioxane, tetrahydrofuran or toluene, in the presence of a metal catalyst such as palladium carbon, platinum oxide or Raney's nickel, in hydrogen atmosphere, at a temperature from 0°C to 150°. A base such as sodium acetate, potassium acetate or pyridine may exist as the case requires.

The compound represented by the formula (5f) can be obtained by hydrolysis of the compound represented by the formula (4f), followed by esterification of the carboxyl group.

The condition for hydrolysis reaction is not particularly limited, and for example, it can be achieved by causing an aqueous solution of lithium hydroxide, sodium hydroxide, potassium hydroxide and the like to act in a solvent such as methanol, ethanol, propanol, dimethylsulfoxide, N,N-dimethylformamide, N-methylpyrrolidone, dioxane or tetrahydrofuran, in the

presence of hydrogen peroxide solution at a temperature from 0°C to 150°C.

The reaction condition for esterification is not particularly limited, and for example, it can be achieved, for example, by treating an alkyl halide such as iodomethane, iodoethane, iodopropane or benzyl bromide in a solvent such as methanol, ethanol, propanol, dimethylsulfoxide, N,N-dimethylformamide, N-methylpyrrolidone, dioxane, tetrahydrofuran or toluene, in the presence of a base such as lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium carbonate, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride, potassium hydride, butyl lithium, methyl lithium, lithium bistrimethylsilylamide, sodium bistrimethylsilyl amide or potassium bistrimethylsilylamide at a temperature from 0°C to 150°C.

The compound of the formula (9f) can be obtained by treating an alkylation agent containing epoxy represented by the formula (6f) or the formula (7f) or the like with the compound represented by the formula (5f), and opening the epoxy group with phenol represented by (8f) and the like.

The reaction condition for alkylation of the formula (6f), the formula (7f) or the like is not particularly limited, and for example, it can be achieved by conducting the reaction in a solvent such as methanol, ethanol, propanol, dimethylsulfoxide, N,N-dimethylformamide, N-methylpyrrolidone, dioxane,

tetrahydrofuran or toluene, in the presence of a base such as lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium carbonate, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride, potassium hydride, butyl lithium, methyl lithium, lithium bistrimethylsilylamide, sodium bistrimethylsilylamide, potassium bistrimethylsilylamide or cesium fluoride at a temperature from 0°C to 150°C.

The reaction condition for the treatment of the formula (8a) is not particularly limited, and for example, it can be achieved by conducting the reaction in a solvent such as methanol, ethanol, propanol, dimethylsulfoxide, N,N-dimethylformamide, N-methylpyrrolidone, dioxane or tetrahydrofuran, in the presence of 0.0001 to 1.0 mole equivalent of a catalyst such as potassium carbonate, triethylamine or cesium fluoride at a temperature from 0°C to 150°C.

The compound represented by the formula (10f) can be obtained by fluorination of the compound represented by the formula (9f), followed by hydrolysis of the ester in the molecule.

The reaction condition for fluorination is not particularly limited, and for example, it can be achieved by treating a reagent such as diethylaminosulfate trifluoride in a solvent such as dichloromethane or chloroform, at a temperature from 0°C to 150°C.

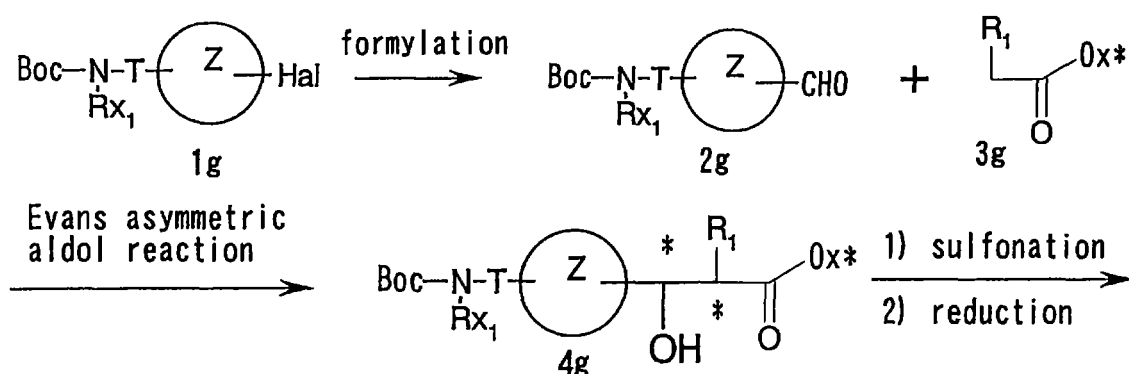
The condition for hydrolysis reaction is not particularly limited, and for example, it can be achieved by treating an aqueous

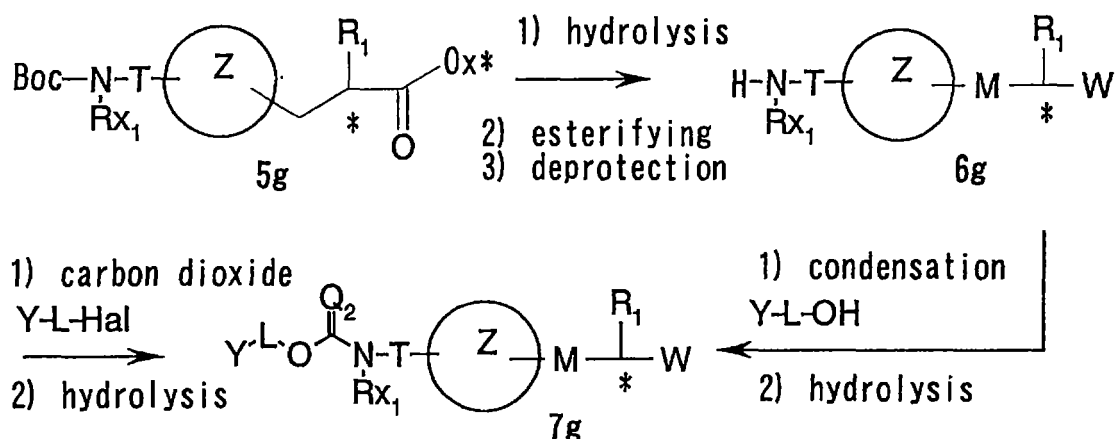
solution of lithium hydroxide, sodium hydroxide, potassium hydroxide and the like in a solvent such as methanol, ethanol, propanol, dimethylsulfoxide, N,N-dimethylformamide, N-methylpyrrolidone, dioxane or tetrahydrofuran, in the presence of hydrogen peroxide solution at a temperature from 0°C to 150°C.

The compound represented by the formula (11f) can be obtained by hydrolyzing the ester in the compound represented by the formula (9f).

The condition for hydrolysis reaction is not particularly limited, and for example, it can be achieved by treating an aqueous solution of lithium hydroxide, sodium hydroxide, potassium hydroxide and the like in a solvent such as methanol, ethanol, propanol, dimethylsulfoxide, N,N-dimethylformamide, N-methylpyrrolidone, dioxane or tetrahydrofuran, in the presence of hydrogen peroxide solution at a temperature from 0°C to 150°C.

General production example G





wherein each symbol represents a group as defined above; Ox* represents an Evans aldol asymmetric auxiliary group (chiral oxazolidinone); Le represents a leaving group such as halogen or sulfonate; and symbol * represents an asymmetric carbon.

The compound represented by the formula (2g) can be obtained by formylation of the compound represented by the formula (1g).

The reaction condition for formylation is not particularly limited, and for example, it can be achieved by treating butyl lithium in a solvent such as dioxane, tetrahydrofuran or dimethoxyethane, followed by reacting N,N-dimethylformamide, N-formylmorpholine and the like at a temperature from -78°C to 0°C.

The compound represented by the formula (4g) can be obtained by causing the compound represented by the formula (3g) to act on the compound represented by the formula (2g) in Evans asymmetric aldol condition.

The Evans asymmetric aldol condition corresponds to that of the production example of the compound represented by the formula (3f) in General production example F.

The compound represented by the formula (5g) can be obtained by sulfonylation of the compound represented by the formula (4g), followed by reduction of the sulfonate group.

The reaction condition for sulfonylation corresponds to that of the production example of the formula (4f) in General production example F.

The reaction condition for reduction corresponds to that of the production example of the formula (4f) in General production example F.

The compound represented by the formula (5f) can be obtained by hydrolyzing the compound represented by the formula (4f), and esterifying the carboxyl group, followed by deprotection of the amino group.

The reaction condition for hydrolysis corresponds to that of the production example of the formula (5f) in General production example F.

The reaction condition for esterification corresponds to that of the production example of the formula (5f) in General production example F.

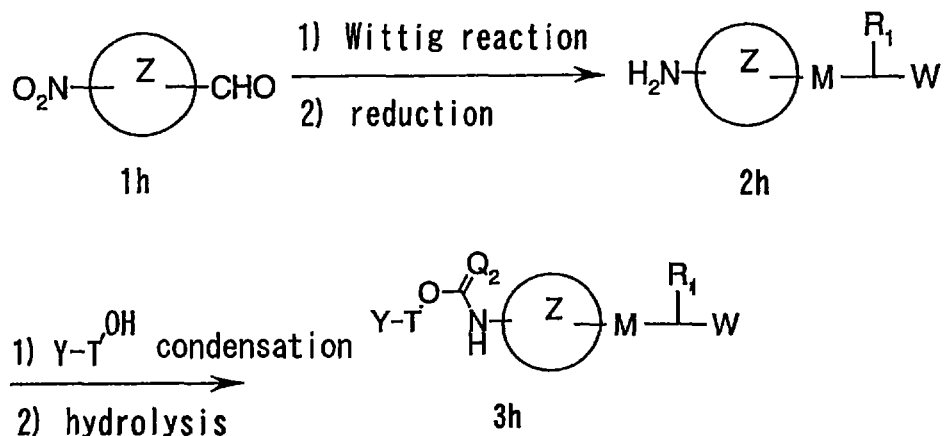
As to deprotection of amino group, though the method differs depending on the employed protecting group, for example, deprotection of t-butylcarbonyl group can be achieved by using a solution of anhydrous hydrochloric acid in methanol, a solution of anhydrous hydrochloric acid in ethanol, a solution of anhydrous hydrochloric acid in dioxane, trifluoroacetic acid, formic acid and the like.

The compound represented by the formula (7g) can be obtained by treating carbon dioxide and Y-L-Hal with the compound represented by the formula (6g) or treating phosgene, diphosgene, triphosgene and the like with the compound represented by the formula (6g), to give a corresponding isocyanate, acting a benzyl alcohol such as Y-L-OH so as to form a carbamate, and hydrolyzing the ester in the molecule.

The reaction condition for synthesis of the carbamate is not particularly limited, and it can be achieved in accordance with the document (*J. Org. Chem.* 2000, 66, 1035.), or can be achieved by causing phosgene, diphosgene, triphosgene and the like to act in a solvent such as dichloromethane, chloroform, dioxane, tetrahydrofuran or toluene, in the presence of a base such as triethylamine, diisopropylethylamine, pyridine or N,N-dimethylaminopyridine at a temperature from 0°C to 150°C, and thereafter causing a benzyl alcohol such as Y-L-OH to act at a temperature from 0°C to 150°C. Alternatively, it may be obtained by treating a carbonyldiimidazole with Y-L-OH in a solvent such as dichloromethane, chloroform, tetrahydrofuran, toluene or acetonitrile at a temperature from 0°C to 50°C, and then causing the compound represented by the formula (6g) to act at a temperature from 0°C to 50°C.

The reaction condition for hydrolysis corresponds to that of the production example of the formula (10f) in Production example F.

General production example H



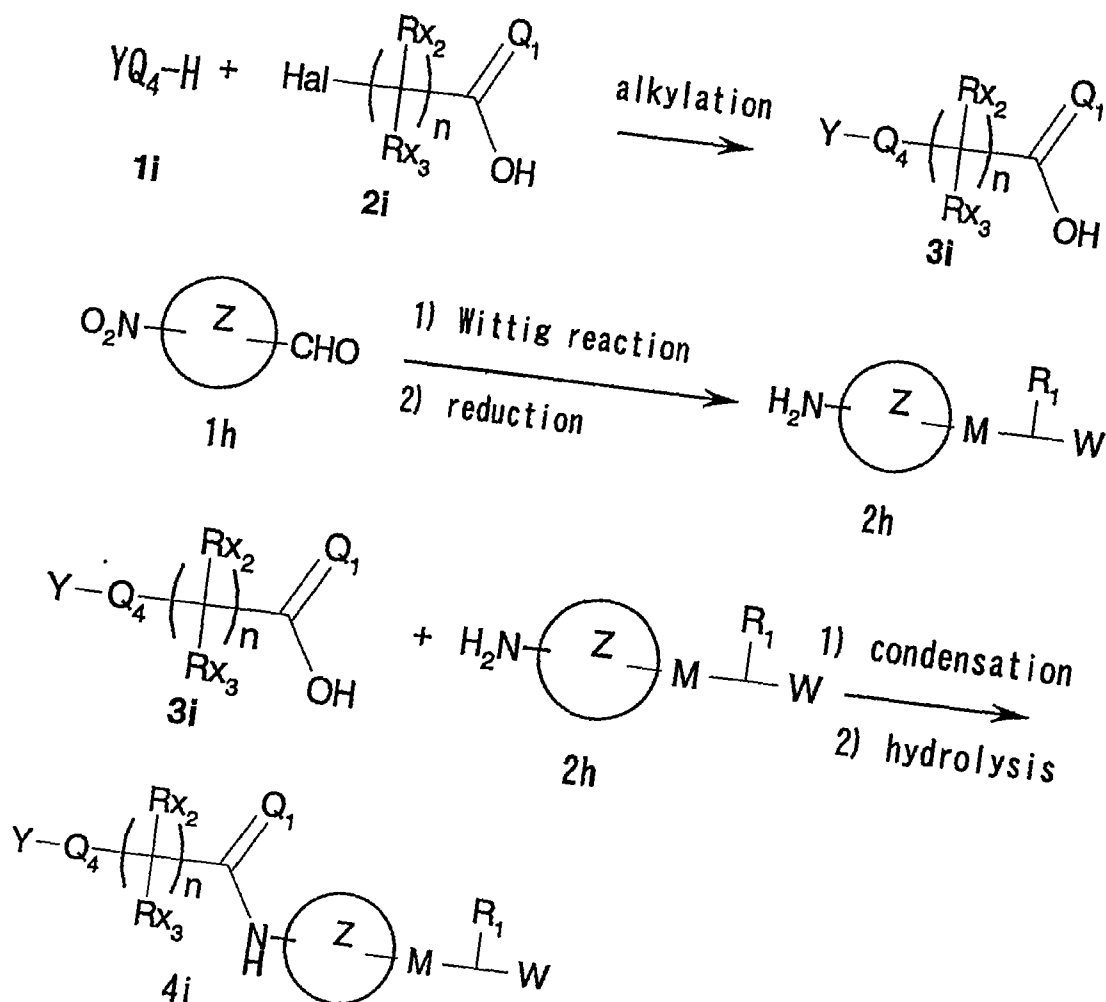
The compound represented by the formula (2h) can be obtained by conducting Wittig-Horner-Emmons reaction on the compound represented by the formula (1h) and reducing the resultant compound. The condition for Wittig-Horner-Emmons reaction corresponds to that of the production example of the formula (10a) in Production example A.

The reaction condition for reduction corresponds to that of the production example of the formula (10a) in Production example A.

The compound represented by the formula (3h) can be obtained by treating phosgene, diphosgene, triphosgene, di-tert-butylidicarbonate and the like with the compound represented by the formula (2h) in a solvent such as dichloromethane, tetrahydrofuran or acetonitrile, in the presence of a base such as pyridine, triethylamine or 4-dimethylaminopyridine, thereby generating an isocyanate, and by treating Y-T-OH with the isocyanate, to give a carbamate, and followed by the subsequent alkaline hydrolysis of the

carbamate. The reaction temperature at the time of generating isocyanate is from 0°C to 50°C.

General production example I

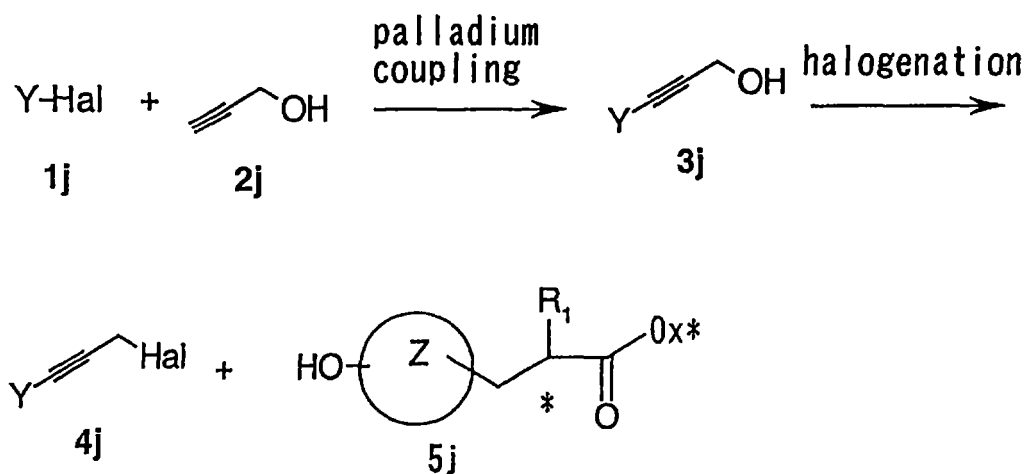


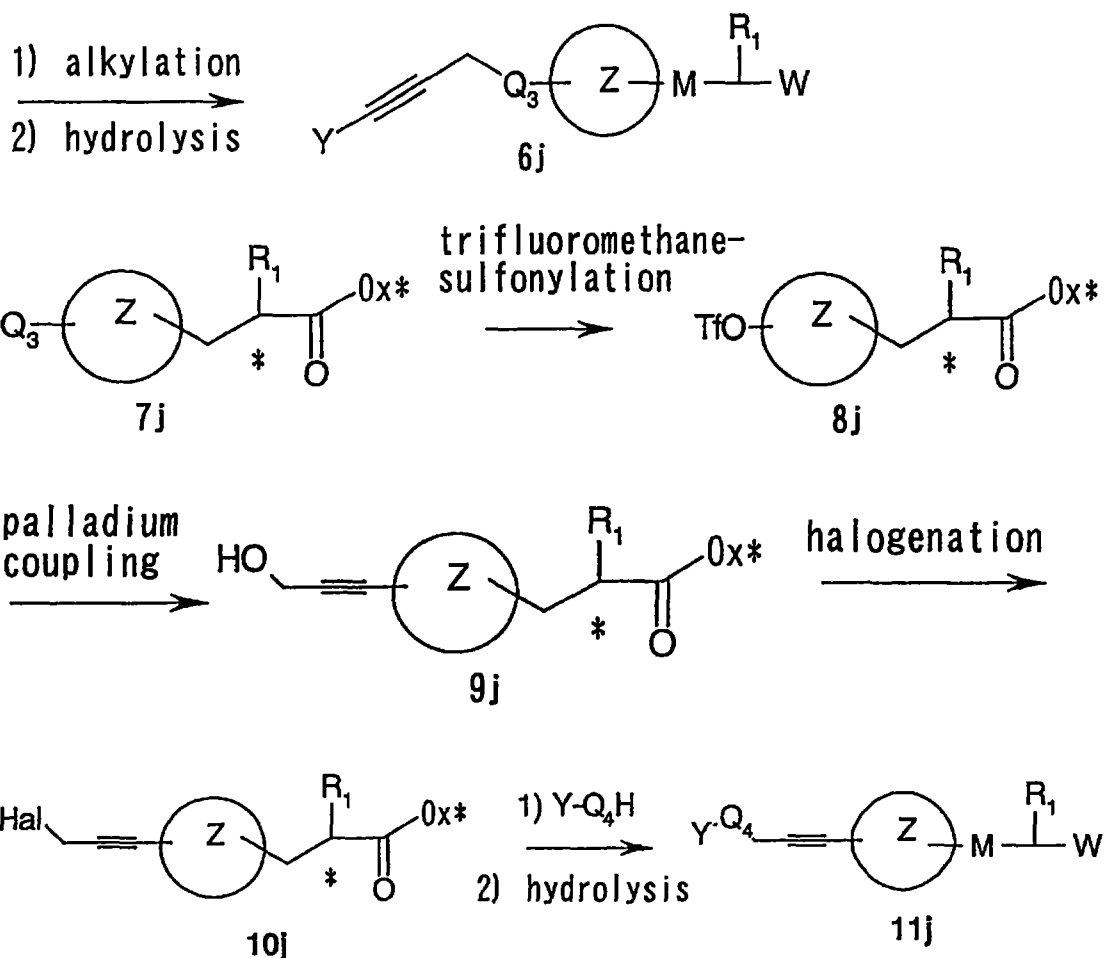
The compound represented by the formula (3i) can be obtained by reacting the compound represented by the formula (1i) and the compound represented by the formula (2i). The reaction condition is not particularly limited, and for example, it can be achieved by treating a base such as potassium carbonate or sodium hydride with the compound represented by the formula (1i) in a solvent such as tetrahydrofuran, N,N-dimethylformamide or

dioxane and the like, and further treating the compound represented by the formula (2i). The reaction temperature is from 0°C to 100°C.

The compound represented by the formula (4i) can be obtained by reacting the compound represented by the formula (3i) and the compound represented by the formula (2h), followed by hydrolyzing. The reaction condition is not particularly limited, and the condensing reaction can be achieved by treating the compound represented by the formula (3i) with the compound represented by the formula (2h) in a solvent such as tetrahydrofuran or N,N-dimethylformamide, in the presence of a base such as triethylamine or pyridine, and in the presence of a condensing agent such as 1,1-carbonyldiimidazole, diethylcyanophosphonate or carbodiimide. The reaction temperature is from 0°C to 100°C. The reaction condition for hydrolysis corresponds to that of the production example of the formula (11a) in Production example A.

General production example J





wherein each symbol represents a group as defined above; Ox* represents an Evans aldol asymmetric auxiliary group (chiral oxazolidinone); Tf represents a trifluoromethanesulfonyl group; Hal represents a leaving group such as halogen or sulfonate; and symbol * represents an asymmetric carbon.

The compound represented by the formula (3j) can be obtained by treating the compound represented by the formula (2j) with the compound represented by the formula (1j).

The reaction condition is not particularly limited, and for example, the reaction can be conducted in a solvent such as methanol, ethanol, propanol, dimethylsulfoxide,

N,N-dimethylformamide, N-methylpyrrolidone, dioxane, tetrahydrofuran or toluene, in the presence of from 0.0001 to 0.5 mole equivalent of copper halide, from 0.0001 to 0.5 mole equivalent of a palladium catalyst such as tetrakis(triphenylphosphine)palladium or dichlorobis(triphenylphosphine)palladium in the presence of an organic base such as triethylamine, N,N-diisopropylethylamine, butylamine or tributylamine at a temperature from 0°C to 150°C.

The compound represented by the formula (4j) can be obtained by halogenation of the compound represented by the formula (3j).

The compound represented by the formula (6j) can be obtained by causing the compound represented by the formula (5j) to act on the compound represented by the formula (4j), followed by hydrolysis.

The reaction condition for alkylation corresponds to that of the production example of the formula (4a) in Production example A.

The reaction condition for hydrolysis corresponds to that of the production example of the formula (5f) in Production example F.

The compound represented by the formula (8j) can be obtained by trifluoromethanesulfonylation of the compound represented by the formula (7j).

The reaction condition corresponds to that of the production example of the formula (2b) in Production example B.

The compound represented by the formula (9j) can be obtained

by palladium coupling of the compound represented by the formula (8j).

The reaction condition corresponds to that of the production example of the formula (7a) in Production example A.

The compound represented by the formula (10j) can be obtained by halogenation of the compound represented by the formula (9j).

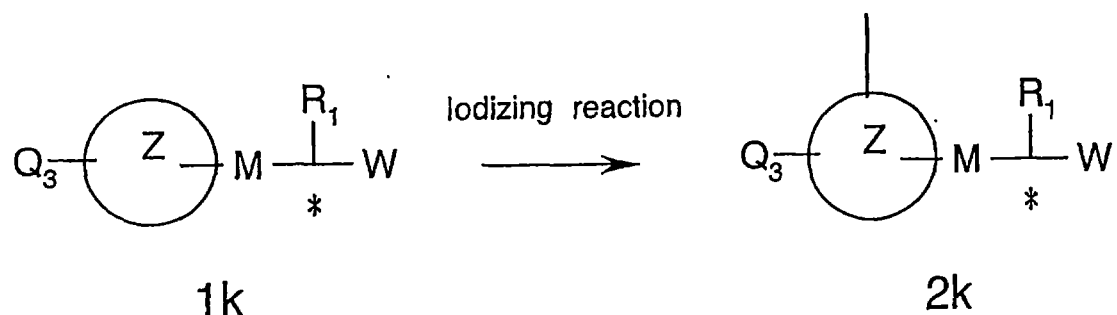
The reaction condition corresponds to that of the production example of the formula (4a) in Production example A.

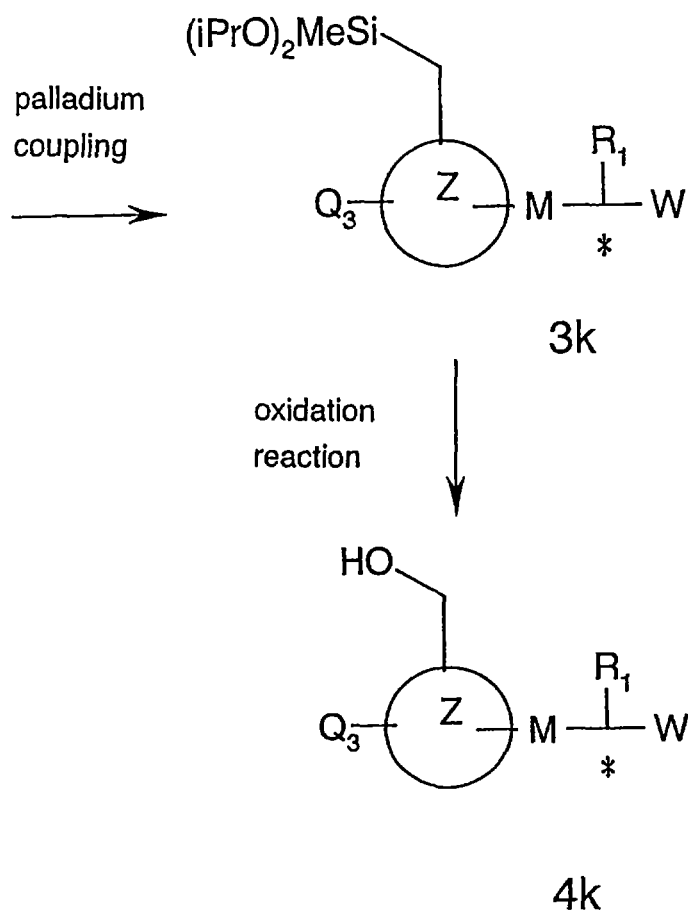
The compound represented by the formula (11j) can be obtained by alkylation of the compound represented by the formula (10j) with the compound of Y-QH, followed by hydrolysis.

The condition for alkylation reaction corresponds to that of the production example of the formula (4a) in Production example A.

The reaction condition for hydrolysis corresponds to the production example of the formula (5f) in Production example F.

General production example K





wherein each symbol represents a group as defined above.

The compound represented by the formula (2k) can be obtained by treating an iodizing agent with the compound represented by the formula (1k).

The reaction condition is not particularly limited, and for example, it can be achieved by treating iodine or an iodizing agent such as N-iodosuccinimide in a solvent such as methanol, ethanol, propanol, dimethylsulfoxide, N,N-dimethylformamide, N-methylpyrrolidone, dioxane, tetrahydrofuran or toluene, or a mixed solvent thereof, in the presence of a silver salt such as silver sulfate, at a temperature from 0°C to 100°C.

The compound represented by the formula (3k) can be obtained

by causing an organic zinc compound to react with the compound represented by the formula (2k) in the presence of a palladium catalyst.

The reaction condition is not particularly limited, and for example, it can be achieved by causing an organic zinc reagent such as dialkoxymethylsilylmethylzinc to react in an ether solvent such as tetrahydrofuran, in the presence of a palladium catalyst such as palladium acetate or dichlorophosphinoferrocene palladium, at a temperature from 0°C to 100°C.

The compound represented by the formula (4k) can be obtained by oxidizing the compound represented by the formula (3k).

The reaction condition is not particularly limited, and for example, hydrogen peroxide may be caused to react in a mixed solvent of an alcohol solvent such as methanol, ethanol or propanol and an ether solvent such as tetrahydrofuran, or in a solvent of N,N-dimethylformamide at a temperature from 0°C to 80°C.

Although compounds of the present invention can be synthesized in the above methods, they may be also synthesized in commonly used general organic synthesizing methods. As for protecting groups for a hydroxyl group which may be used herein, any hydroxyl groups are possible without limitation insofar as they are protected by groups which are generally known as a protecting group for a hydroxyl group in organic synthesis, and specific examples of protecting groups for a hydroxyl group

include lower alkylsilyl groups such as trimethylsilyl group or t-butyldimethylsilyl; lower alkoxymethyl groups such as methoxymethyl group or 2-methoxyethoxymethyl group; tetrahydropyranyl group; aralkyl groups such as benzyl group, p-methoxybenzyl group, 2,4-dimethoxybenzyl group, o-nitrobenzyl group, p-nitrobenzyl group or trityl group; acyl groups such as formyl group or acetyl group; lower alkoxycarbonyl groups such as t-butoxycarbonyl group, 2-iodoethoxycarbonyl group or 2,2,2-trichloroethoxycarbonyl group; alkenyloxycarbonyl groups such as 2-propenyloxycarbonyl group, 2-chloro-2-propenyloxycarbonyl group, 3-methoxycarbonyl-2-propenyloxycarbonyl group, 2-methyl-2-propenyloxycarbonyl group, 2-butenyloxycarbonyl group or cinnamyloxycarbonyl group; aralkyloxycarbonyl groups such as benzyloxycarbonyl group, p-methoxybenzyloxycarbonyl group, o-nitrobenzyloxycarbonyl group or p-nitrobenzyloxycarbonyl group and the like.

These protecting groups may be eliminated by conventional methods such as hydrolysis and reduction depending on the kind of the employed protecting group.

Although compounds of the present invention can be synthesized by the methods as described above, they may be also synthesized in commonly used general organic synthesizing methods. Specific examples of protecting groups for an amino group which may be used herein include, but not limited to, any groups which are generally known as a protecting group for an

amino group in organic synthesis. For example, substituted or unsubstituted lower alkanoyl groups such as formyl group, acetyl group, chloroacetyl group, dichloroacetyl group, propionyl group, phenylacetyl group, phenoxyacetyl group or thienylacetyl group; substituted or unsubstituted lower alkoxycarbonyl groups such as benzyloxycarbonyl group, t-butoxycarbonyl group or p-nitrobenzyloxycarbonyl group; substituted lower alkyl groups such as methyl group, t-butyl group, 2,2,2-trichloroethyl group, trityl group, p-methoxybenzyl group, p-nitrobenzyl group, diphenylmethyl group or pivaloyloxymethyl group; substituted silyl groups such as trimethylsilyl group or t-butyldimethylsilyl group; substituted silylalkoxyalkyl groups such as trimethylsilylmethoxymethyl group, trimethylsilylethoxymethyl group, t-butyldimethylsilylmethoxymethyl group or t-butyldimethylsilylethoxymethyl group; substituted or unsubstituted benzylidene groups such as benzylidene group, salicylidene group, p-nitrobenzylidene group, m-chlorobenzylidene group, 3,5-di(t-butyl)-4-hydroxybenzylidene group or 3,5-di(t-butyl)benzylidene group may be proposed.

These protecting groups may be eliminated by conventional methods such as hydrolysis and reduction depending on the kind of the employed protecting group.

Although compounds of the present invention can be synthesized in the above methods, they may be also synthesized

in commonly used general organic synthesizing methods. As for protecting groups for a carboxyl group which may be used herein, any carboxyl groups are possible without limitation insofar as they are protected by groups which are generally known as a protecting group for a carboxyl group in organic synthesis, and specific examples of a protecting group for a carboxyl group include linear or branched lower alkyl groups of from 1 to 4 carbon atoms such as methyl group, ethyl group, isopropyl group or t-butyl group; halogeno lower alkyl groups such as 2-iodoethyl group or 2,2,2-trichloroethyl group; lower alkoxymethyl groups such as methoxymethyl group, ethoxymethyl group or isobutoxymethyl group; lower aliphatic acyloxymethyl groups such as butyryloxymethyl group or pivaloyloxymethyl group; 1-lower alkoxycarbonyloxyethyl groups such as 1-methoxycarbonyloxyethyl group or 1-ethoxycarbonyloxyethyl group; aralkyl groups such as benzyl, p-methoxybenzyl group, o-nitrobenzyl group or p-nitrobenzyl group; benzhydryl group; phthalidyl group, etc.

Elimination of such a protective group can be carried out in a conventional method such as hydrolysis and reduction etc, depending on the type of the protective group used.

Although compounds of the present invention can be synthesized by the methods as described above, they may be synthesized in commonly used general organic synthesizing methods. Specific examples of solvents which may be used herein include, but not limited to, any solvents which do not inhibit

the reaction and are generally used in organic synthesis, for example, lower alcohols such as methanol, ethanol, propanol or butanol; polyalcohols such as ethylene glycol or glycerin; ketones such as acetone, methyl ethyl ketone, diethyl ketone or cyclohexanone; ethers such as diethyl ether, isopropyl ether, tetrahydrofuran, dioxane, 2-methoxyethanol or 1,2-dimethoxyethane; nitriles such as acetonitrile or propionitrile; esters such as methyl acetate, ethyl acetate, isopropyl acetate, butyl acetate or diethyl phthalate; hydrocarbon halides such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, trichloroethylene or tetrachloroethylene; aromatic compounds such as benzene, toluene, xylene, monochlorobenzene, nitrobenzene, indene, pyridine, quinoline, collidine or phenol; hydrocarbons such as pentane, cyclohexane, hexane, heptane, octane, isooctane, petroleum benzene or petroleum ether; amines such as ethanolamine, diethylamine, triethylamine, pyrrolidine, piperidine, piperazine, morpholine, aniline, dimethylaniline, benzylamine or toluidine; amides such as formamide, N-methylpyrrolidone, N,N-dimethylimidazolone, N,N-dimethylacetamide or N,N-dimethylformamide; phosphate amides such as hexamethylphosphate triamide or hexamethylphosphite triamide; water; and mixed solvents of one or more kinds of commonly used solvents. The mixing ratio is not particularly limited.

Although compounds of the present invention can be synthesized by the methods as described above, they may be

synthesized in commonly used general organic synthesizing methods. Specific examples of bases which may be used herein include, but not limited to, any bases which do not inhibit the reaction and are generally used in organic synthesis, for example, sodium carbonate, sodium hydrogencarbonate, potassium carbonate, sodium hydride, potassium hydride, potassium t-butoxide, pyridine, dimethylaminopyridine, trimethylamine, triethylamine, N, N-diisopropylethylamine, N-methylmorpholine, N-methylpyrrolidine, N-methylpiperidine, N,N-dimethylaniline, 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU), pyridine, 4-dimethylaminopyridine, picoline, lutidine, quinoline, isoquinoline, sodium hydroxide, potassium hydroxide, lithium hydroxide, butyl lithium, sodium or potassium alcoholates such as sodium methylate, potassium methylate or sodium ethylate, and the like.

Although compounds of the present invention can be synthesized by the methods as described above, they may be synthesized in commonly used general organic synthesizing methods. Specific examples of reducing agents which may be used herein include, but not limited to, any reducing agents which do not inhibit the reaction and are generally used in organic synthesis, for example, NaBH_4 , LiBH_4 , $\text{Zn}(\text{BH}_4)_2$, $\text{Me}_4\text{NBH}(\text{OAc})_3$, NaBH_3CN , Selectride, Super Hydride (LiBHEt_3), LiAlH_4 , DIBAL, $\text{LiAlH}(\text{t-BuO})_3$, Red-al, binap, as well as catalysts such as platinum, palladium, rhodium, ruthenium, nickel and the like.

After the reaction is completed, the product can be purified

if necessary by usual methods such as column chromatography on silica gel or adsorption resin, or by re-crystallization from a suitable solvent.

The medicament according to the present invention improves insulin resistance by the agonism of PPAR as described above, and the present invention can be applied not only as an insulin sensitizer but also as various medicaments based on PPAR (α , β , γ) agonism (based on e.g. PPAR α and γ dual agonism or on PPAR α , β and γ triple agonism).

For example, the relationship of PPAR not only with insulin resistance but also with blood lipid or inflammatory diseases is known (Current Opinion in Lipidol. 10:245-257, 1999; Jiang, C., et al., PPAR-gamma agonists inhibit production of monocyte inflammatory cytokines, Nature 391:82-86 (1998); Jackson, S.M., et al., Peroxisome proliferator-activated receptor activators target human endothelial cells to inhibit leukocyte-endothelial cell interaction., Arterioscler. Thromb. Vasc. Biol. 19: 2094-2104 (1999); Su, C.G., et al., A novel therapy for colitis utilizing PPAR-gamma ligands to inhibit the epithelial inflammatory response., J Clin Invest 1999 Aug;104(4):383-9; Ricote, M., et al., The peroxisome proliferator-activated receptor-gamma is a negative regulator of macrophage activation., Nature 1998 Jan 1;391(6662):79-82), and the medicament of the present invention can be applied to diseases against which it is reported to be effective in these literatures.

The dose of the pharmaceutical preparation of the present

invention, though being varied depending on the severeness of symptom, age, sex, body weight, administration form and the type of disease, is usually 100 μ g to 10 g/day/adult, and this dose is administered in one or divided portions.

The administration form of the medicament of the present invention is not particularly limited, and it can be administered orally or parenterally by an ordinarily used method.

For manufacturing of the medicament, ordinarily used fillers, binders, lubricants, coloring agents, flavoring agents and if necessary stabilizers, emulsifiers, absorption promoters, surfactants etc. can be used, and ingredients used generally as starting materials for medicament are compounded in a usual manner.

These ingredients include e.g. animal and vegetable oils (such as soybean oil, tallow and synthetic glyceride), hydrocarbons (such as liquid paraffin, squalene and solid paraffin), ester oils (such as octyldodecyl myristate and isopropyl myristate), higher alcohols (such as cetostearyl alcohol and behenyl alcohol), silicon resin, silicon oil, surfactants (polyoxyethylene fatty ester, sorbitan fatty ester, glycerin fatty ester, polyoxyethylene sorbitan fatty ester, polyoxyethylene hardened castor oil and polyoxyethylene-polyoxypropylene block copolymer), water-soluble polymers (such as hydroethyl cellulose, polyacrylic acid, carboxyvinyl polymer, polyethylene glycol, polyvinyl pyrrolidone and methyl cellulose), alcohols (such as

ethanol and isopropanol), polyvalent alcohols (such as glycerin, propylene glycol, dipropylene glycol and sorbitol), sugars (such as glucose and sucrose), inorganic powder (such as silicic anhydride, aluminum magnesium silicate and aluminum silicate), and pure water. For pH adjustment, it is possible to use inorganic acids (such as hydrochloric acid and phosphoric acid), alkali metal salt of inorganic acid (such as sodium phosphate), inorganic bases (such as sodium hydroxide), organic acids (such as lower fatty acids, citric acid and lactic acid), alkali metal salts of organic acid (such as sodium citrate and sodium lactate) and organic bases (such as arginine and ethanolamine). If necessary, preservatives, antioxidants etc. can be added.

Hereinafter, pharmacological experiment examples are shown to show the usefulness of this invention.

Experiment Example 1: Measurement of blood glucose reduction, blood triglyceride reduction and blood non-esterified fatty acids reduction (evaluation of sugar and lipid metabolism improving effect in mouse)

A chemical suspended in 0.5 % methyl cellulose was orally administered via a sonde into male db/db mice (Nippon Charles River, Yokohama, JP) once a day (0.3 to 30 mg/kg/day). Before treatment and after 4 and 9 days treatment, blood was collected through a tail vein after the mice were fasted for 1 hour, respectively. On Day 10, an oral glucose loading test was conducted; in this test, the mice were fasted overnight from the previous day, and in the next morning, 2 g/kg glucose was

given to the mice. Plasma glucose, triglycerides (TG), non-esterified fatty acid (NEFA) were measured by using commercial kits, that is, Glucose C-II Test Wako (trade name) (Wako Pure Chemical Industries, Ltd., Tokyo), Deteminer L TG II (trade name) (Kyowa Medex, Tokyo) and NEFA C-Test Wako (Wako Pure Chemical Industries, Ltd., Tokyo), respectively.

The determined blood glucose reduction, blood triglyceride reduction and blood non-esterified fatty acid reduction at day 9 after administration are shown in Table 1.

Table 1

in vivo db/db mice day 9 after administration

	Dose (mg/kg)	Blood sugar	Blood trigly	Blood free
Ex 100	6	65.1	79.3	60.7
Ex 132	6	50.4	75.5	72.5
Ex 113	6	70.0	81.8	39.5
Ex 320	3	56.3	80.3	35.4
Ex 335	3	57.2	81.4	40.0
Ex 282	3	17.9	59.7	18.4
Ex 344	3	45.8	61.8	58.1
Ex 329	3	37.7	36.8	47.5

Compounds of the present invention showed excellent blood glucose reduction, blood triglyceride reduction and blood non-esterified fatty acid reduction.

Experiment Example 2: Measurement of blood triglyceride reduction and blood cholesterol reduction (evaluation of lipid metabolism improving effect in dog)

A chemical suspended in 0.5 % methyl cellulose was orally administered via a sonde into male beagle (Nosan Corporation,

YOKOHAMA) once a day. The dosage of drug was increased every week. Blood was collected from forefoot vein prior to administration of drug and every time the dosage was increased, and levels of triglyceride and cholesterol in non-HDL and HDL fractions were measured by ultracentrifugation. At the day of collecting blood, the animal was fasted and blood was collected. Compounds of the present invention showed excellent blood triglyceride reduction and cholesterol reduction.

Experiment Example 3: Measurement of transcriptional activity

A GAL4-PPAR LBD chimera expression vector was constructed by ligating human PPAR 167-468 (PPAR), 138-440 (NUC-1) and 174-475 (PPAR) amino acid regions (LBD: Ligand Binding Domain) to a yeast transcriptional factor GAL4 1-147 amino acid region. As the reporter gene, PLAP (Placental Alkaline Phosphatase) was used, and this was ligated downstream of a TK promoter containing a 5-copy GAL4 DNA binding element to construct a vector. As host cells, CV-1 (ATCC CCL-70) was used. That is, CV-1 cells were spread at a density of 5×10^5 cells on a 35-mm dish and cultured in 10 % FCS/DMEM for 24 hours, and using FuGENE 6 transfection reagent, the cells were co-transfected with the GAL4-PPAR LBD expression vector and GAL4 DBD-TK-PLAP expression vector. 24 hours after this transfection, the cells were spread again on a 96-well plate at a density of 1×10^4 /well and further cultured for 24 hours. After 24 hours, the medium was exchanged with DMEM containing 10 % FCS, which was previously treated at 65 °C for inactivating intrinsic alkaline phosphatase, and a test

compound was added at an arbitrary concentration. The transcriptional activity was determined in terms of PLAP activity secreted 24 hours after addition of the compound, to calculate EC₅₀. The PLAP activity was determined after adding 50 µl assay buffer and 50 µl chemoluminescence substrate to 10 µl culture supernatant and incubating the mixture at room temperature for 1 hour. In this way, transcription activities with respect to PPAR α , PPAR β and PPAR γ could be determined. Transcription activities with respect to PPAR α , PPAR β and PPAR γ are shown in Table 2.

Table 2

Transcription activity EC₅₀ (nM)

	PPAR α	PPAR β	PPAR γ
Ex 100	0.008	1.249	0.008
Ex 132	0.604	1.544	0.001
Ex 113	0.027	0.954	0.115
Ex 320	0.064	0.686	0.024
Ex 335	0.119	>30	0.031
Ex 282	0.062	1.521	0.114
Ex 344	0.020	1.742	0.038
Ex 329	0.117	1.290	0.053

The Compounds of the present invention showed an excellent transcription activity.

As described above, the compounds of the present invention have an excellent blood glucose- and blood lipid-ameliorating action and are very useful as anti-diabetes agents, anti-hyperlipemia agents and insulin sensitizers.

Experiment Example 4: Anti-inflammatory effect

Experimental colitis was induced to female ICR mice (10

mice/group, Charles River Japan, Yokohama) by giving 4% dextran sodium in drinking water for 5 days. After 8 days, the mice were grouped into sections from "0" (normal) to "4" (severe) based on change in diarrhea, hematochezia and weight loss as described by Cooper HS et al., (Laboratory Invest (69), pp.238-249, 1993) and the average of the values was used as the Disease Activity Index for colitis. Each test compound was suspended in a 0.5% methylcellulose solution and administered to the mice orally once a day via a sonde from the day when the induction of colitis was initiated. The compounds of the present invention had an excellent anti-inflammatory effect.

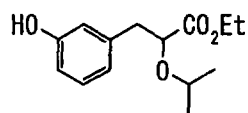
Examples

The present invention will be explained more specifically and more concretely by way of the following Examples which are not intended to limit the present invention.

Example 1. 3-(3-2-Hydroxy-3-[4-(trifluoromethyl)phenoxy]-propoxyphenyl)-2-isopropoxypropanoic acid

Production example 1a)

Ethyl 3-(3-hydroxyphenyl)-2-isopropoxypropanoate



9.5 g of Ethyl 2-isopropoxyacetate was dissolved in 200 ml of tetrahydrofuran anhydride, and the mixture was cooled to -78°C under nitrogen atmosphere. After adding 6.5 ml of lithium

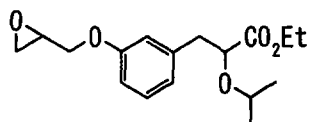
bis(trimethylsilyl)amide (1M solution in tetrahydrofuran), 15 g of 3-benzyloxybenzaldehyde in tetrahydrofuran (50 ml) was added via a cannula. The temperature of the solution was elevated to room temperature, and the mixture was stirred for 3 hours. The reaction solution was treated with saturated aqueous ammonium chloride, and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent was distilled off. The residue was purified by silica gel column chromatography, to give 10.8 g of ethyl 3-[3-(benzyloxy)phenyl]-3-hydroxy-2-isopropoxypropanoate as a mixture of erythro and threo in the 3:1 hexane-ethyl acetate fraction. This product was dissolved in 50 ml of pyridine and 3.5 ml of methanesulfonyl chloride was added under ice-cooling. After stirring overnight at room temperature, the reaction mixture was diluted with ethyl acetate, and washed with 1N hydrochloric acid. The organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent was distilled off, to give 13.7 g of ethyl 3-[3-(benzyloxy)phenyl]-2-isopropoxy-3-[(methanesulfonyl)oxy]propanoate. This product was dissolved in 450 ml of ethanol, 3.9 g of 10% palladium carbon was added, and the mixture was stirred overnight at room temperature under hydrogen atmosphere. The reaction mixture was filtered through Celite, and the filtrate was concentrated, to give 7.5 g of the title compound.

¹H NMR (CDCl₃)

δ: 0.98 (d, J=6.4 Hz, 3H) 1.16 (d, J=6.4 Hz, 3H) 1.24 (t, J=7.2 Hz, 3H) 2.89

(dd, J=8.8, 14.0Hz, 1H) 2.97 (dd, J=4.8, 13.6Hz, 1H) 3.52 (Sept, J=6.0Hz, 1H) 4.05 (dd, J=4.8, 8.8Hz, 1H) 4.12-4.19 (m, 2H) 5.01 (br, 1H) 6.09-6.72 (m, 1H) 6.81-6.83 (m, 1H) 6.75 (t, J=1.6Hz, 1H) 7.15 (t, J=7.6Hz, 1H)

Production example 1b) Ethyl 2-isopropoxy-3-[3-(2-oxilanylmethoxy)phenyl]propanoate

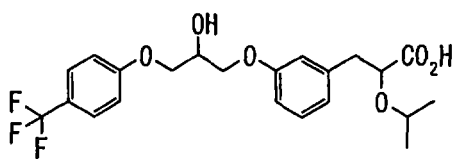


519 mg of Ethyl 3-(3-hydroxyphenyl)-2-isopropoxypropanoate was dissolved in 7 ml of N,N-dimethylformamide, and 250 mg of epichlorohydrin and 400 mg of potassium carbonate were successively added, and the mixture was stirred overnight at 50°C. The reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent was distilled off. Then, the residue was purified by silica gel column chromatography, to give 465 mg of the title compound in the 5:1 hexane-ethyl acetate fraction.

¹H NMR (CDCl₃)

δ: 0.96 (d, J=6.4Hz, 3H) 1.15 (d, J=6.4Hz, 3H) 1.24 (t, J=7.2Hz, 3H) 2.75 (dd, J=2.8, 4.8Hz, 1H) 2.87-2.93 (m, 2H) 2.96 (dd, J=8.8, 13.6Hz, 1H) 3.34 (dt, J=2.8, 9.6Hz, 1H) 3.50 (Sept, J=6.0Hz, 1H) 3.94 (ddd, J=2.0, 5.6, 11.2Hz, 1H) 4.04 (dd, J=4.8, 8.8Hz, 1H) 4.15-4.22 (m, 2H) 6.78 (d, J=8.0Hz, 1H) 6.82 (s, 1H) 6.86 (d, J=7.6Hz, 1H) 7.19 (t, J=8.0Hz, 1H)

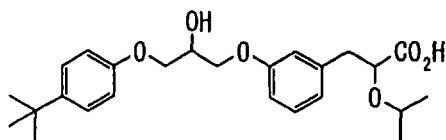
Example 1c) 3-(3-2-Hydroxy-3-[4-(trifluoromethyl)phenoxy]-propoxyphenyl)-2-isopropoxypropanoic acid



41 mg of Ethyl 2-isopropoxy-3-[3-(2-oxilanylmethoxy)phenyl]propanoate was dissolved in 2 ml of ethanol, 22 mg of 4-hydroxybenzotrifluoride and two drops of triethylamine were added, and the mixture was stirred overnight at 80°C. The reaction solution was evaporated, and the residue was purified by silica gel column chromatography, to give 6 mg of ethyl 3-(3-2-hydroxy-3-[4-(trifluoromethyl)phenoxy]-propoxyphenyl)-2-isopropoxypropanoate in the 4:1 hexane-ethyl acetate fraction. This product was dissolved in 0.4 ml of ethanol, and 0.1 ml of 5N-sodium hydroxide was added, and the mixture was kept still overnight at room temperature. The reaction solution was acidified by adding 1N-hydrochloric acid, and extracted with ethyl acetate. The residue was purified by reverse-phase high performance liquid chromatography, to give 3.15 mg of the title compound.

MS m/e (ESI) 443 (MH^+)

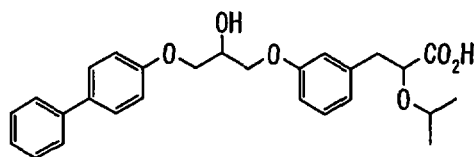
Example 2. 3-(3-3-[4-(t-Butyl)phenoxy]-2-hydroxypropoxyphenyl)-2-isopropoxypropanoic acid



Using 4-t-butylphenol, the title compound was obtained in the same manner as described in Example 1c).

MS m/e (ESI) 431 (MH^+)

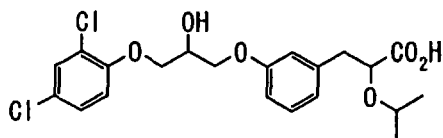
Example 3. 3-(3-3-[4-(Phenyl)phenoxy]-2-hydroxypropoxyphenyl)-2-isopropoxypropanoic acid



Using 4-hydroxybiphenyl, the title compound was obtained in the same manner as described in Example 1c).

MS m/e (ESI) 451 (MH^+)

Example 4. 3-(3-3-[4-(2,4-Dichlorophenyl)phenoxy]-2-hydroxypropoxyphenyl)-2-isopropoxypropanoic acid



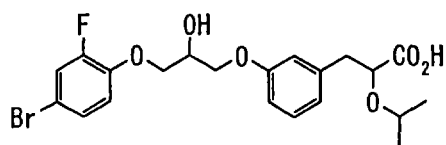
Using 2,4-dichlorophenol, the title compound was obtained in the same manner as described in Example 1c).

1H NMR ($CDCl_3$)

δ : 1.03 (d, $J=6.0$ Hz, 3H) 1.17 (d, $J=6.0$ Hz, 3H) 2.93 (dd, $J=8.0, 14.0$ Hz, 1H) 3.11 (dd, $J=4.0, 14.0$ Hz, 1H) 3.55 (Sept, $J=6.0$ Hz, 1H) 4.14 (dd, $J=4.0, 8.0$ Hz, 1H) 4.16-4.23 (m, 4H) 4.42 (Sept, $J=6.4$ Hz, 1H) 6.82-6.85 (m, 2H) 6.87 (d, $J=7.6$ Hz, 1H) 6.90 (d, $J=8.8$ Hz, 1H) 7.19 (dd, $J=2.8, 8.8$ Hz, 1H) 7.22 (dd, $J=7.6, 8.8$ Hz, 1H) 7.37 (d, $J=2.8$ Hz, 1H)

MS m/e (ESI) 443 (MH^+)

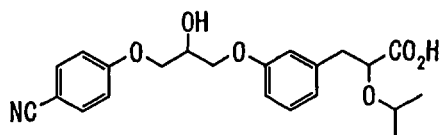
Example 5. 3-(3-3-[4-(4-Bromo-2-fluorophenyl)phenoxy]-2-hydroxypropoxyphenyl)-2-isopropoxypropanoic acid



Using 4-bromo-2-fluorophenol, the title compound was obtained in the same manner as described in Example 1c).

MS m/e (ESI) 471 (MH^+)

Example 6. 3-(3-3-[4-(4-Cyanophenyl)phenoxy]-2-hydroxypropoxyphenyl)-2-isopropoxypropanoic acid

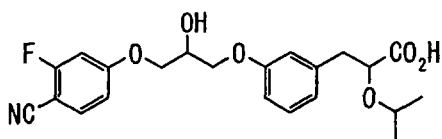


Using 4-hydroxybenzonitrile, the title compound was obtained in the same manner as described in Example 1c).

MS m/e (ESI) 400 (MH^+)

Example 7.

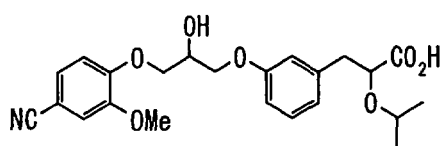
3-3-[3-(4-Cyano-3-fluorophenoxy)-2-hydroxypropoxy]phenyl-2-isopropoxypropanoic acid



Using 2-fluoro-4-hydroxybenzonitrile, the title compound was obtained in the same manner as described in Example 1c).

MS m/e (ESI) 418 (MH^+)

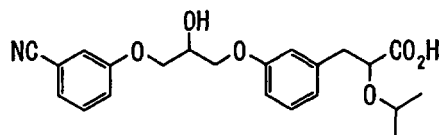
Example 8. 3-3-[3-(4-Cyano-2-methoxyphenoxy)-2-hydroxypropoxy]phenyl-2-isopropoxypropanoic acid



Using 3-methoxy-4-hydroxybenzonitrile, the title compound was obtained in the same manner as described in Example 1c).

MS m/e (ESI) 430 (MH^+)

Example 9. 3-3-[3-(3-Cyanophenoxy)-2-hydroxypropoxy]phenyl-2-isopropoxypropanoic acid

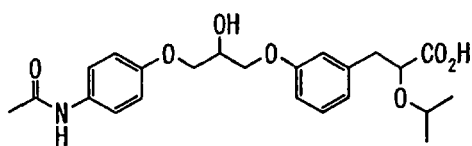


Using 3-hydroxybenzonitrile, the title compound was obtained in the same manner as described in Example 1c).

MS m/e (ESI) 400 (MH^+)

Example 10.

3-3-[3-(4-Acetoaminophenoxy)-2-hydroxypropoxy]phenyl-2-isopropoxypropanoic acid

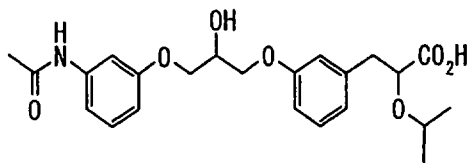


Using 4-acetamidophenol, the title compound was obtained in the same manner as described in Example 1c).

MS m/e (ESI) 432 (MH^+)

Example 11.

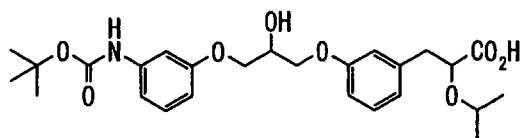
3-3-[3-(3-Acetaminophenoxy)-2-hydroxypropoxy]phenyl-2-isopropoxypropanoic acid



Using 3-acetamidophenol, the title compound was obtained in the same manner as described in Example 1c).

MS m/e (ESI) 432 (MH^+)

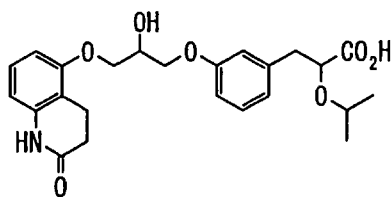
Example 12. 3-3-[3-(3-t-Butoxycarbonylaminoxy)-2-hydroxypropoxy]phenyl-2-isopropoxypropanoic acid



Using 3-t-butoxycarbonylaminoxyphenol, the title compound was obtained in the same manner as described in Example 1c).

MS m/e (ESI) 490 (MH^+)

Example 13. 3-(3-2-Hydroxy-3-[(2-oxo-1,2,3,4-tetrahydro-5-quinolinyl)oxy]propoxyphenyl)-2-isopropoxypropanoic acid



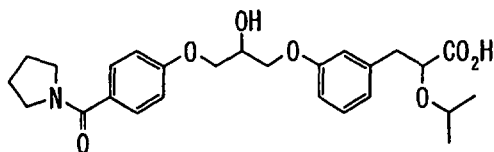
Using 5-hydroxy-1,2,3,4-tetrahydro-2-quinolinone, the title compound was obtained in the same manner as described in Example 1c).

MS m/e (ESI) 444 (MH^+)

Example 14.

3-(3-2-Hydroxy-3-[4-(tetrahydro-1H-1-pyrrolylcarbonyl)-

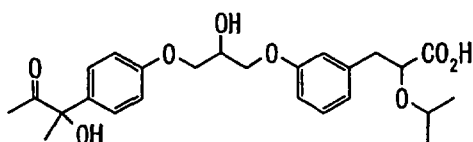
phenoxy]propoxyphenyl)-2-isopropoxypropanoic acid



Using (4-hydroxyphenyl) (tetrahydro-1*H*-1-pyrrolyl)methanone, the title compound was obtained in the same manner as described in Example 1c).

MS *m/e*(ESI) 472 (MH⁺)

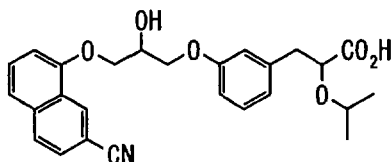
Example 15. 3-(3-2-Hydroxy-3-[4-(1-hydroxy-1-methyl-2-oxopropyl)phenoxy]propoxyphenyl)-2-isopropoxypropanoic acid



Using 3-hydroxy-3-(4-hydroxyphenyl)-2-butanone, the title compound was obtained in the same manner as described in Example 1c).

MS *m/e*(ESI) 461 (MH⁺)

Example 16. 3-(3-3-[(7-Cyano-1-naphthyl)oxy]-2-hydroxypropoxyphenyl)-2-isopropoxypropanoic acid

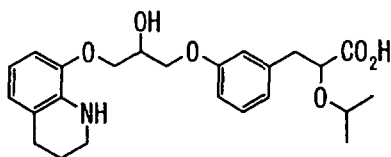


Using 8-hydroxy-2-naphthonitrile, the title compound was obtained in the same manner as described in Example 1c).

MS *m/e*(ESI) 450 (MH⁺)

Example 17. 3-3-[2-Hydroxy-3-(1,2,3,4-tetrahydro-8-

quinolinylloxy)propoxy]phenyl-2-isopropoxypropanoic acid

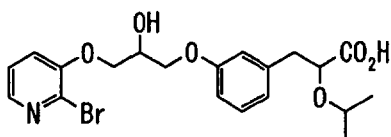


1,2,3,4-Tetrahydro-8-quinolinol, the title compound was obtained in the same manner as described in Example 1c).

MS m/e (ESI) 430 (MH^+)

Example 18.

3-3-[2-Hydroxy-3-(2-bromo-3-pyridyloxy)propoxy]phenyl-2-isopropoxypropanoic acid

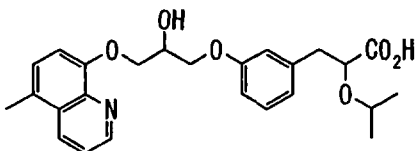


Using 2-bromo-3-pyridinol, the title compound was obtained in the same manner as described in Example 1c).

MS m/e (ESI) 454 (MH^+)

Example 19.

3-3-[2-Hydroxy-3-(5-methyl-8-quinolinylloxy)propoxy]phenyl-2-isopropoxypropanoic acid

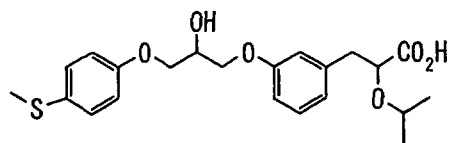


Using 5-methyl-8-quinolinol, the title compound was obtained in the same manner as described in Example 1c).

MS m/e (ESI) 440 (MH^+)

Example 20. 3-(3-2-Hydroxy-3-[4-(methylsulfonyl)phenoxy]-

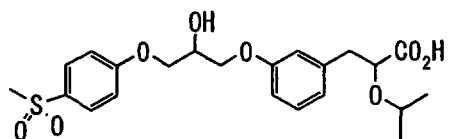
propoxyphenyl)-2-isopropoxypropanoic acid



Using 4-methylthiophenol, the title compound was obtained in the same manner as described in Example 1c).

MS m/e (ESI) 421 (MH^+)

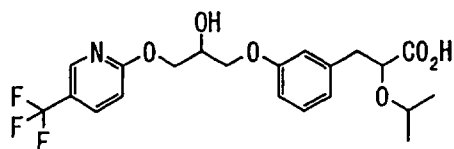
Example 21. 3-(3-(2-Hydroxy-3-[4-(methylsulfonyl)phenoxy]-propoxyphenyl)-2-isopropoxypropanoic acid



3-(3-(2-Hydroxy-3-[4-(methylsulfonyl)phenoxy]-propoxyphenyl)-2-isopropoxypropanoic acid was dissolved in 2 ml of methanol and 0.5 ml of water, and 100 mg of oxone was added. After stirring was continued at room temperature for 2 hours, the reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was evaporated, and the residue was purified by reverse-phase high performance liquid chromatography, to give 1.86 mg of the title compound.

MS m/e (ESI) 453 (MH^+)

Example 22. 3-[3-(2-Hydroxy-3-[5-(trifluoromethyl)-2-pyridyl]oxypropoxy)phenyl]-2-isopropoxypropanoic acid



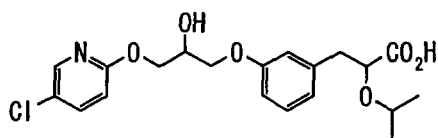
Using 2-hydroxy-5-trifluoromethyl pyridine, the title compound was obtained in the same manner as described in Example 1c).

¹H NMR (CDCl₃)

δ: 1.05 (d, J=6.0Hz, 3H) 1.16 (d, J=6.0Hz, 3H) 2.93 (dd, J=7.6, 14.0Hz, 1H) 3.11 (dd, J=3.6, 14.4Hz, 1H) 3.56 (Sept, J=6.0Hz, 1H) 4.11 (d, J=5.6Hz, 2H) 4.14 (dd, J=4.0, 8.0Hz, 1H) 4.36-4.43 (m, 1H) 4.57 (dd, J=6.0, 12.8Hz, 1H) 6.43 (dd, J=4.0, 11.6Hz, 1H) 6.80-6.83 (m, 2H) 6.86 (d, J=7.6Hz, 1H) 6.91 (d, J=8.4Hz, 1H) 7.19-7.26 (m, 1H) 7.82 (dd, J=2.8, 8.8Hz, 1H) 8.42 (s, 1H)

MS *m/e*(ESI) 444 (MH⁺)

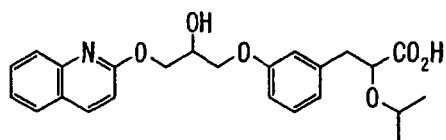
Example 23. 3-[3-(2-Hydroxy-3-[5-chloro-2-pyridyl]-oxypropoxy)phenyl]-2-isopropoxypropanoic acid



Using 2-hydroxy-5-chloropyridine, the title compound was obtained in the same manner as described in Example 1c).

MS *m/e*(ESI) 410 (MH⁺)

Example 24. 3-3-[2-Hydroxy-3-(2-quinolyloxy)propoxy]phenyl-2-isopropoxypropanoic acid



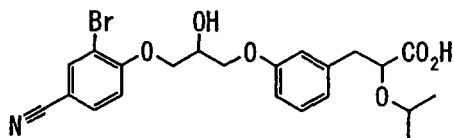
Using 2-hydroxyquinoline, the title compound was obtained in the same manner as described in Example 1c).

¹H NMR (CDCl₃)

δ: 1.03, 1.04 (each d, J=6.0Hz and 6.4Hz, 3H) 1.15 (d, J=6.0Hz, 3H) 2.91 (dd, J=8.0, 13.6Hz, 1H) 3.12 (dd, J=4.0, 14.0Hz, 1H) 3.53 (Sept, J=6.4Hz, 1H) 4.09-4.12 (m, 2H) 4.14 (dd, J=4.0, 8.4Hz, 1H) 4.37-4.44 (m, 1H) 4.72 (dd, J=5.6, 12.0Hz, 1H) 4.78 (ddd, J=1.2, 3.2, 12.8Hz, 2H) 6.83-6.87 (m, 3H) 6.98-7.01 (m, 1H) 7.22 (dd, J=7.2, 8.4Hz, 1H) 7.42 (ddd, J=1.2, 6.8, 8.0Hz, 1H) 7.65 (dt, J=1.6, 8.4Hz, 1H) 7.75 (d, J=6.8Hz, 1H) 7.82 (d, J=8.4Hz, 1H) 8.06 (d, J=8.8Hz, 1H)

MS *m/e*(ESI) 426 (MH⁺)

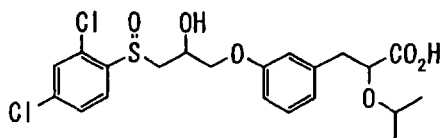
Example 25. 3-3-[3-(2-Bromo-4-cyanophenoxy)-2-hydroxypropoxy]phenyl-2-isopropoxypropanoic acid



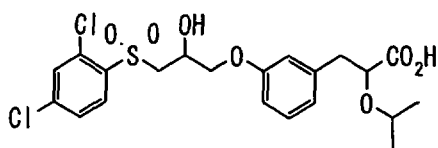
Using 3-bromo-4-hydroxybenzonitrile, the title compound was obtained in the same manner as described in Example 1c).

MS *m/e*(ESI) 478 (MH⁺)

Example 26. 3-(3-3-[(2,4-Dichlorophenyl)sulfinyl]-2-hydroxypropoxyphenyl)-2-isopropoxypropanoic acid



Example 27. 3-(3-3-[(2,4-Dichlorophenyl)sulfonyl]-2-hydroxypropoxyphenyl)-2-isopropoxypropanoic acid



15 mg of 2,4-Dichlorothiophenol and 10 mg of ethyl 2-isopropoxy-3-[3-(2-oxilanylmethoxy)phenyl]propanoate were dissolved in 0.4 ml of ethanol, and 2 drops of triethylamine were added, and the mixture was stirred at 80°C overnight. The reaction solution was evaporated, to give ethyl 3-(3-2-hydroxy-3-[2,4-dichlorophenoxy]propoxyphenyl)-2-isopropoxypropanoate. This product was dissolved in 2 ml of methanol and 0.5 ml of water, and 100 mg of oxone was added, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was concentrated, and the residue was treated with 0.4 ml of ethanol and 0.1 ml of 5N-sodium hydroxide, and the mixture was kept still overnight at room temperature. The reaction solution was acidified by adding 1N-hydrochloric, and then extracted with ethyl acetate. The residue was purified by reverse-phase high performance liquid chromatography, to give 5.81 mg of the title compound (Example 26) (MS m/e (ESI) 475 (MH⁺)), and 3.44 mg of the title compound (Example 27).

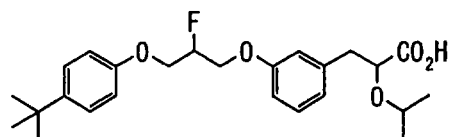
¹H NMR (CDCl₃)

δ: 1.04 (d, J=6.0Hz, 3H) 1.17 (d, J=6.0Hz, 3H) 2.92 (dd, J=8.0, 14.4Hz, 1H) 3.09 (dd, J=4.0, 13.6Hz, 1H) 3.56 (Sept, J=6.0Hz, 1H) 3.73 (dd, J=8.0, 14.8Hz, 1H) 3.79 (dd, H=3.2, 14.4Hz, 1H) 3.97-4.05 (m, 2H) 4.13 (dd, J=4.0, 7.6Hz, 1H) 4.52 (dt, J=2.8, 8.0Hz, 4H) 6.73 (d, J=6.8Hz, 1H) 6.74 (s, 1H)

6.86 (d, J=6.8Hz, 1H) 7.19 (dd, J=7.6, 8.8Hz, 1H) 7.46 (ddd, J=0.8, 2.0, 8.4Hz, 1H) 7.57 (d, J=2.0Hz, 1H) 8.07 (d, J=8.8Hz, 1H)

MS m/e (ESI) 491 (MH^+)

Example 28. 3-(3-3-[4-t-Butylphenoxy]-2-fluoropropoxyphenyl)-2-isopropoxypropanoic acid

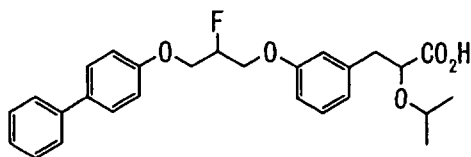


Using 4-t-butyl phenol, the process was conducted in the same manner as described in Example 1c), to give 32 mg of ethyl 3-(3-2-hydroxy-3-[4-t-butylphenoxy]propoxyphenyl)-2-isopropoxypropanoate. 16 mg of this compound was dissolved in 1 ml of dichloromethane and 10 mg of DAST was added. After stirring was continued overnight at room temperature, the reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was evaporated, to give ethyl 3-(3-3-[4-t-butylphenoxy]-2-fluoropropoxyphenyl)-2-isopropoxypropanoate. This product was dissolved in 0.4 ml of ethanol, and 0.1 ml of 5N-sodium hydroxide was added, and the mixture was kept still overnight at room temperature. The reaction solution was acidified by adding 1N-hydrochloric acid, and extracted with ethyl acetate. The residue was purified by reverse-phase high performance liquid chromatography, to give 2.22 mg of the title compound.

MS m/e (ESI) 433 (MH^+)

Example 29. 3-(3-3-[4-Phenylphenoxy]-2-fluoropropoxyphenyl)-

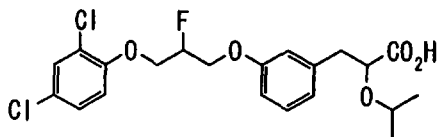
2-isopropoxypropanoic acid



Using 4-hydroxybiphenyl, the title compound was obtained in the same manner as described in Example 28.

MS m/e (ESI) 453 (MH^+)

Example 30. 3-(3-3-[4-(2,4-Dichlorophenyl)phenoxy]-2-fluoropropoxyphenyl)-2-isopropoxypropanoic acid



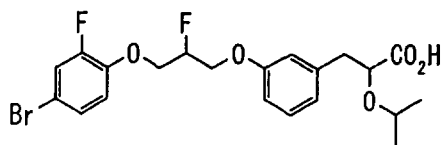
Using 2,4-dichlorophenol, the title compound was obtained in the same manner as described in Example 28.

1H NMR ($CDCl_3$)

δ : 1.03, 1.03 (each d, $J=6.0$ Hz, 3H) 1.16 (d, $J=6.0$ Hz, 3H) 2.93 (dd, $J=8.0$, 13.6Hz, 1H) 3.12 (dd, $J=4.0$, 14.0Hz, 1H) 3.55, 3.55 (each Sept, $J=6.0$ Hz, 1H) 4.11-4.16 (m, 1H) 4.29-4.41 (m, 4H) 5.18 (dSept, $J=4.8$, 46.8Hz, 1H) 6.81-6.85 (m, 2H) 6.98 (d, $J=7.6$ Hz, 1H) 6.91 (d, $J=9.2$ Hz, 1H) 7.20 (dd, $J=2.4$, 8.8Hz, 1H) 7.23 (dd, $J=7.6$, 9.2Hz, 1H) 7.38 (d, $J=2.4$ Hz, 1H)

MS m/e (ESI) 445 (MH^+)

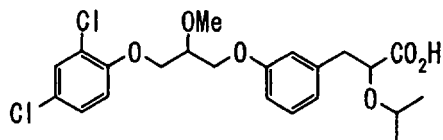
Example 31. 3-(3-3-[4-(4-Bromo-2-fluorophenyl)phenoxy]-2-fluoropropoxyphenyl)-2-isopropoxypropanoic acid



Using 4-bromo-2-fluorophenol, the title compound was obtained in the same manner as described in Example 28.

MS m/e (ESI) 473 (MH^+)

Example 32. 3-(3-3-[4-(2,4-Dichlorophenyl)phenoxy]-2-methoxypropoxyphenyl)-2-isopropoxypropanoic acid



15 mg of Ethyl 3-(3-3-[4-(2,4-dichlorophenyl)phenoxy]-2-hydroxypropoxyphenyl)-2-isopropoxypropanoate was dissolved in 0.4 ml of tetrahydrofuran, and 0.1 ml of methyl iodide and 10 mg of sodium hydride were added, and the mixture was stirred overnight at room temperature. To the reaction solution were added ethanol and 0.1 ml of 5N-sodium hydroxide, after stirring was continued at room temperature for 3 hours, the mixture was neutralized with 1N-hydrochloric acid, and extracted with ethyl acetate. The organic layer was evaporated, and the residue was purified by reverse-phase high performance liquid chromatography, to give 4.32 mg of the title compound.

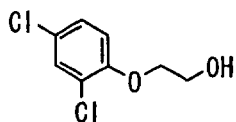
1H NMR ($CDCl_3$)

δ : 1.02 (d, $J=6.0$ Hz, 3H) 1.15 (d, $J=6.0$ Hz, 3H) 2.91 (dd, $J=7.6, 12.8$ Hz, 1H) 3.11 (dd, $J=3.2, 13.6$ Hz, 1H) 3.53 (dSept, $J=3.2, 6.6$ Hz, 1H) 3.61 (s, 3H) 3.99 (dd, $J=4.8, 10.0$ Hz, 1H) 4.09-4.26 (m, 5H) 6.80-6.85 (m, 2H) 6.85 (d, $J=8.0$ Hz, 1H) 6.89 (d, $J=8.8$ Hz, 1H) 7.18 (dd, $J=2.4, 8.8$ Hz, 1H) 7.21 (dd, $J=7.2, 9.2$ Hz, 1H) 7.36 (d, $J=2.4$ Hz, 1H)

MS m/e (ESI) 457 (MH^+)

Example 33. 3-3-[2-(2,4-Dichlorophenoxy)ethoxy]phenyl-2-isopropoxypropanoic acid

Production example 33a) 2-(2,4-Dichlorophenoxy)-1-ethanol

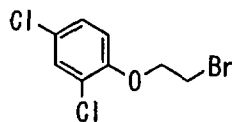


To a solution of 15.0g of 2,4-dichlorophenoxyacetic acid in tetrahydrofuran (300 ml) was added dropwise 96 ml of 1.0 M borane-tetrahydrofuran complex/tetrahydrofuran solution under ice-cooling over 1.5 hours. The reaction solution was stirred at room temperature for 22 hours. After the reaction solution was concentrated, the residue was diluted with saturated aqueous ammonium chloride and ethyl acetate. The organic layer was washed with saturated ammonium chloride, saturated aqueous sodium hydrogen carbonate ($\times 2$) and saturated ammonium chloride, then dried over anhydrous sodium sulfate and concentrated, to give 14 g the title compound as a colorless oil.

$^1\text{H-NMR}$ (CDCl_3)

δ : 2.21 (d, $J=6.4\text{Hz}$, 1H) 3.99 (dt, $J=4.4, 6.4\text{Hz}$, 2H) 4.12 (t, $J=4.4\text{Hz}$, 2H) 6.87 (d, $J=8.8\text{Hz}$, 1H) 7.20 (dd, $J=2.4, 8.8\text{Hz}$, 1H) 7.37 (d, $J=2.4\text{Hz}$, 1H)

Production example 33b) 1-(2-Bromoethoxy)-2,4-dichlorobenzene



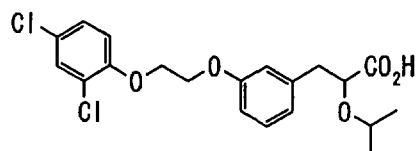
To a solution of 10.0 g of 2-(2,4-dichlorophenoxy)-1-ethanol in 1,2-dimethoxyethane (200 ml) was added dropwise a solution of 14g of phosphorus tribromide in 1,2-dimethoxyethane (20 ml) under ice-cooling. The reaction

solution was stirred at room temperature for 20 hours. After the reaction solution was concentrated, the residue was diluted with water and ethyl acetate. Saturated aqueous sodium hydrogencarbonate was added to the organic layer, and the resulting emulsion formed was subjected to Celite filtration. The filtrate was diluted with diethyl ether and saturated aqueous ammonium chloride. The organic layer was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography, to give 6.15 g of the title compound as a pale yellow oil.

$^1\text{H-NMR}$ (CDCl_3)

δ : 3.67 (t, $J=6.4\text{Hz}$, 2H) 4.32 (t, $J=6.4\text{Hz}$, 2H) 6.87 (d, $J=8.8\text{Hz}$, 1H) 7.19 (dd, $J=2.6, 8.8\text{Hz}$, 1H) 7.39 (d, $J=2.6\text{ Hz}$, 1H)

Example 33c) 3-3-[2-(2,4-Dichlorophenoxy)ethoxy]phenyl-2-isopropoxypropanoic acid



140 mg of 1-(2-Bromoethoxy)-2,4-dichlorobenzene, 100 mg of ethyl 3-(3-hydroxyphenyl)-2-isopropoxypropanoate and 110 mg of potassium carbonate were dissolved in N,N -dimethylformamide, and the mixture was stirred overnight at 60°C . The reaction solution was diluted with saturated aqueous ammonium chloride and ethyl acetate. The organic layer was washed with saturated ammonium chloride, saturated aqueous sodium hydrogen carbonate ($\times 2$) and saturated ammonium chloride, dried over anhydrous sodium

sulfate and concentrated. The residue was dissolved in 4 ml of methanol, and 1 ml of 5N-sodium hydroxide was added thereto, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was neutralized with 1N-hydrochloric acid and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography, to give 83.6 mg of the title compound in the 4:1 → 1:2 hexane-ethyl acetate fraction.

¹H-NMR(CDCl₃)

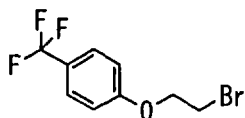
δ: 1.02 (d, J=6.0Hz, 3H) 1.16 (d, J=6.0Hz, 3H) 2.93 (dd, J=8.2, 13.8Hz, 1H) 3.12 (dd, J=3.8, 13.8Hz, 1H) 3.55 (sept, J=6.0Hz, 1H) 4.14 (dd, J=3.8, 8.2Hz, 1H) 4.33-4.38 (m, 4H) 6.81-6.89 (m, 3H) 6.95 (d, J=8.8Hz, 1H) 7.18-7.25 (m, 2H) 7.37 (d, J=2.8Hz, 1H)

MS *m/e*(ESI) 435 (MNa⁺)

Example 34. 3-3-[2-(4-Trifluoromethylphenoxy)ethoxy]phenyl-2-isopropoxypropanoic acid

Production example 34a)

1-(2-Bromoethoxy)-4-trifluoromethylbenzene



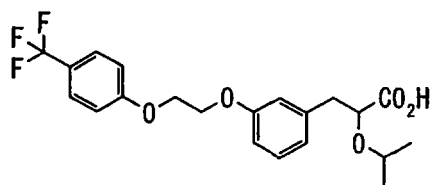
A suspension of 5.0 g of 4-hydroxybenzotrifluoride, 17.4 g of 1,2-dibromoethane and 2.6 g potassium carbonate in acetone (100 ml) was heated under reflux for 3 days. The reaction solution was diluted with water and ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogen carbonate

and saturated ammonium chloride ($\times 2$), dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography to give 1.78g of the title compound as a colorless oil.

$^1\text{H-NMR}$ (CDCl_3)

δ : 3.66 (t, $J=6.4\text{Hz}$, 2H) 4.34 (t, $J=6.4\text{Hz}$, 2H) 6.98 (d, $J=8.4\text{Hz}$, 2H) 7.56 (d, $J=8.4\text{Hz}$, 1H)

Example 34b) 3-3-[2-(4-Trifluoromethylphenoxy)ethoxy]phenyl-2-isopropoxypropanoic acid



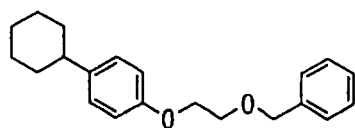
Using 1-(2-bromoethoxy)-4-trifluoromethylbenzene, the title compound was obtained in the same manner as described in Example 33c).

MS m/e (ESI) 435 (MNa^+)

Example 35. 3-3-[2-(4-Cyclohexylphenoxy)ethoxy]phenyl-2-isopropoxypropanoic acid

Production example 35a)

1-[2-(Benzyloxy)ethoxy]-4-cyclohexylbenzene



A suspension of 2.5g of 4-cyclohexylphenol, 3.0g of benzyl 2-bromoethyl ether and 2.4 g of potassium carbonate in

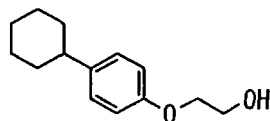
N,N-dimethylformamide (50 ml) was stirred at 60°C for 23 hours. The reaction solution was diluted with water and ethyl acetate. The organic layer was washed with saturated aqueous potassium carbonate and saturated ammonium chloride (×2), dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography, to give 3.9 g of the title compound as a colorless oil.

¹H-NMR(CDCl₃)

δ: 1.20-1.44 (m, 5H) 1.70-1.90 (m, 5H) 2.39-2.48 (m, 1H) 3.82 (t, J=4.8Hz, 2H) 4.13 (t, J=4.8Hz, 2H) 4.63 (s, 2H) 6.83-6.88 (m, 2H) 7.09-7.14 (m, 2H) 7.26-7.38 (m, 5H)

Production example 35b)

1-(2-Hydroxyethoxy)-4-cyclohexylbenzene



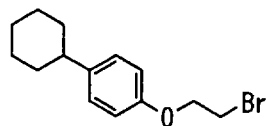
3.2 g of 1-[2-(Benzyloxy)ethoxy]-4-cyclohexylbenzene was dissolved in 100 ml of ethanol, and 300 mg of 20% palladium hydroxide was added, and the mixture was stirred at room temperature under hydrogen atmosphere for 25 hours. The catalyst was filtered off and washed with ethyl acetate. The filtrate was evaporated, and the residue was subjected to azeotropy with toluene (×2), to give 2.34 g of the title compound as a colorless solid.

¹H-NMR(CDCl₃)

δ: 1.17-1.44 (m, 5H) 1.70-1.90 (m, 5H) 2.40-2.50 (m, 1H) 3.62 (t, J=6.4Hz,

2H) 4.27 (t, J=6.4Hz, 2H) 6.82-6.87 (m, 2H) 7.11-7.15 (m, 2H)

Production example 35c) 1-(2-Bromoethoxy)-4-cyclohexylbenzene

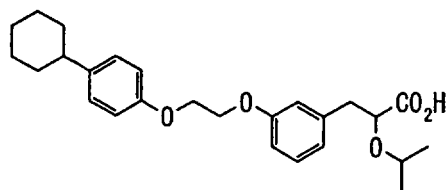


The compound of Production example 3c) was synthesized in the same manner as described in Production example 33b).

¹H-NMR(CDCl₃)

δ: 1.17-1.44 (m, 5H) 1.70-1.90 (m, 5H) 2.40-2.50 (m, 1H) 3.62 (t, J=6.4Hz, 2H) 4.27 (t, J=6.4Hz, 2H) 6.82-6.87 (m, 2H) 7.11-7.15 (m, 2H)

Example 35d) 3-3-[2-(4-Cyclohexylphenoxy)ethoxy]phenyl-2-isopropoxypropanoic acid



Using 1-(2-bromoethoxy)-4-cyclohexylbenzene, the title compound was obtained in the same manner as described in Example 33c).

¹H-NMR(CDCl₃)

δ: 1.02 (d, J=6.0Hz, 3H) 1.16 (d, J=6.0Hz, 3H) 1.19-1.45 (m, 5H) 1.70-1.90 (m, 5H) 2.41-2.50 (m, 1H) 2.92 (dd, J=8.4, 14.0Hz, 1H) 3.12 (dd, J=4.0, 14.0Hz, 1H) 3.54 (sept, J=6.0Hz, 1H) 4.13 (dd, J=4.0, 8.4Hz, 1H) 4.30 (brs, 4H) 6.82-6.91 (m, 4H) 7.11-7.16 (m, 2H) 7.19-7.24 (m, 2H)

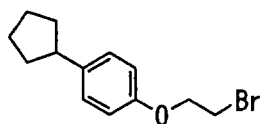
MS *m/e*(ESI) 449 (MNa⁺)

Example 36. 3-3-[2-(4-Cyclopentylphenoxy)ethoxy]phenyl-

2-isopropoxypropanoic acid

Production example 36a)

1-(2-Bromoethoxy)-4-cyclopentylbenzene

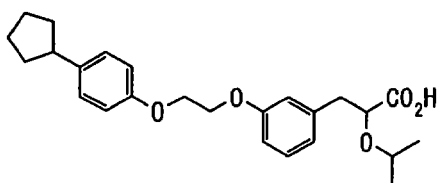


Using cyclopentylphenol, the title compound was obtained in the same manner as described in Production examples 35a), 35b) and 35c).

¹H-NMR(CDCl₃)

δ: 1.48-1.84 (m, 6H) 2.00-2.08 (m, 2H) 2.90-2.98 (m, 1H) 3.63 (t, J=6.4Hz, 2H) 4.27 (t, J=6.4Hz, 2H) 6.83-6.86 (m, 2H) 7.14-7.18 (m, 2H)

Example 36b) 3-3-[2-(4-Cyclohexylphenoxy)ethoxy]phenyl-2-isopropoxypropanoic acid

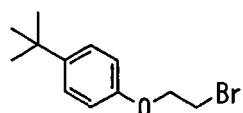


Using 1-(2-bromoethoxy)-4-cyclopentylbenzene, the title compound was obtained in the same manner as described in Example 33c).

MS *m/e*(ESI) 435 (MNa⁺)

Example 37. 3-3-[2-(4-t-Butylphenoxy)ethoxy]phenyl-2-isopropoxypropanoic acid

Production example 37a) 1-(2-Bromoethoxy)-4-t-butylbenzene

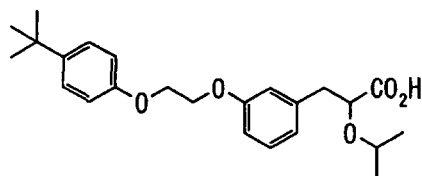


Using 4-*t*-butylphenol, the title compound was obtained in the same manner as described in Production examples 35a), 35b) and 35c).

$^1\text{H-NMR}$ (CDCl_3)

δ : 1.31 (s, 9H) 3.64 (t, $J=6.4\text{Hz}$, 2H) 4.29 (t, $J=6.4\text{Hz}$, 2H) 6.84-6.89 (m, 2H) 7.30-7.34 (m, 2H)

Example 37b) 3-3-[2-(4-*t*-Butylphenoxy)ethoxy]phenyl-2-isopropoxypropanoic acid

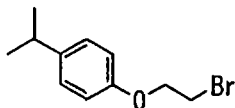


Using 1-(2-bromoethoxy)-4-*t*-butylbenzene, the title compound was obtained in the same manner as described in Example 33c).

MS m/e (ESI) 423 (MNa^+)

Example 38. 3-3-[2-(4-Isopropylphenoxy)ethoxy]phenyl-2-isopropoxypropanoic acid

Production example 38a) 1-(2-Bromoethoxy)-4-isopropylbenzene

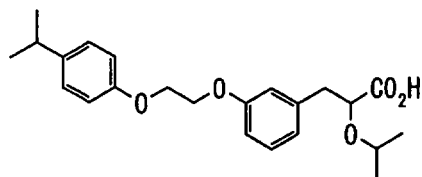


Using 4-isopropylphenol, the title compound was obtained in the same manner as described in Production examples 35a), 35b) and 35c).

$^1\text{H-NMR}$ (CDCl_3)

δ : 1.23 (d, $J=6.8\text{Hz}$, 6H) 2.87 (sept, $J=6.8\text{Hz}$, 1H) 3.63 (t, $J=6.4\text{Hz}$, 2H)
4.27 (t, $J=6.4\text{Hz}$, 2H) 6.83-6.88 (m, 2H) 7.13-7.17 (m, 2H)

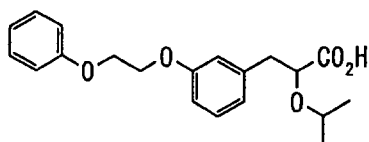
Example 38b) 3-3-[2-(4-Isopropylphenoxy)ethoxy]phenyl-2-isopropoxypropanoic acid



Using 1-(2-bromoethoxy)-4-isopropylbenzene, the title compound was obtained in the same manner as described in Example 33c).

MS m/e (ESI) 409 (MNa^+)

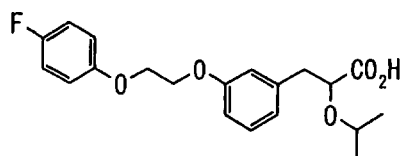
Example 39. 3-3-[2-(Phenoxy)ethoxy]phenyl-2-isopropoxypropanoic acid



Using 2-(bromoethoxy)benzene, the title compound was obtained in the same manner as described in Example 33c).

MS m/e (ESI) 367 (MNa^+)

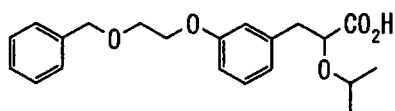
Example 40. 3-3-[2-(4-Fluorophenoxy)ethoxy]phenyl-2-isopropoxypropanoic acid



Using 1-(2-bromoethoxy)-4-fluorobenzene, the title compound was obtained in the same manner as described in Example 33c).

MS m/e (ESI) 385 (MNa^+)

Example 41. 3-3-[2-(4-Benzyloxy)ethoxy]phenyl-2-isopropoxypropanoic acid

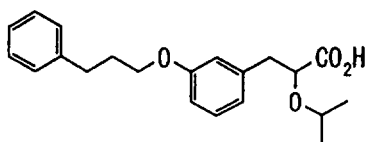


Using 1-[(2-bromoethoxy)methyl]benzene, the title compound was obtained in the same manner as described in Example 33c).

MS m/e (ESI) 381 (MNa^+)

Example 42.

2-Isopropoxy-3-[3-(3-phenylpropoxy)phenyl]propanoic acid

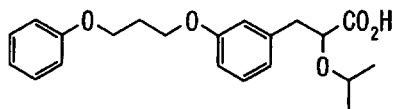


Using 3-phenylpropylbromide, the title compound was obtained in the same manner as described in Example 33c).

MS m/e (ESI) 365 (MNa^+)

Example 43.

2-Isopropoxy-3-[3-(3-phenoxypropoxy)phenyl]propanoic acid



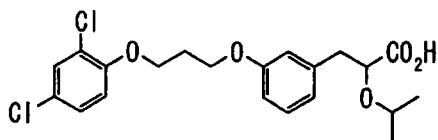
Using 1-(3-bromopropoxy)benzene, the title compound was obtained in the same manner as described in Example 33c).

$^1\text{H-NMR}$ (CDCl_3)

δ : 1.01 (d, $J=6.0\text{Hz}$, 3H) 1.15 (d, $J=6.0\text{Hz}$, 3H) 2.26 (quint, $J=6.0\text{Hz}$, 2H)
2.90 (dd, $J=8.8, 13.8\text{Hz}$, 1H) 3.10 (dd, $J=3.6, 13.8\text{Hz}$, 1H) 3.52 (sept,
 $J=6.0\text{Hz}$, 1H) 4.10-4.19 (m, 5H) 6.89-6.96 (m, 3H) 6.78-6.85 (m, 3H) 7.20
(t, $J=8.2\text{Hz}$, 1H) 7.25-7.31 (m, 2H)

MS m/e (ESI) 381 (MNa^+)

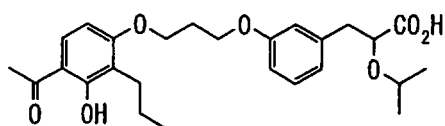
Example 44. 3-{3-[3-(2,4-Dichlorophenoxy)propoxy]phenyl}-
2-isopropoxypropanoic acid



Using 1-(3-bromopropoxy)-2,4-dichlorobenzene, the title compound was obtained in the same manner as described in Example 33c).

MS m/e (ESI) 449 (MNa^+)

Example 45. 3-{3-[3-(4-Acetyl-3-hydroxy-2-propoxyphenoxy)propoxy]phenyl}-2-isopropoxypropanoic acid



Using

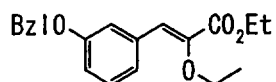
1-[4-(3-bromopropoxy)-2-hydroxy-3-propylphenyl]-1-ethanone, the title compound was obtained in the same manner as described in Example 33c).

MS m/e (ESI) 481 (MNa^+)

Example 46. 3-3-[2-(2,4-Dichlorophenoxy)ethoxy]phenyl-2-

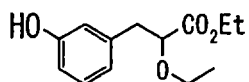
ethoxypropanoic acid

Production example 46a) Ethyl (E, Z)-3-[3-(benzyloxy)phenyl]-2-ethoxy-2-propenoate



3.6 g of Ethyl 2-(diethoxyphosphoryl)-2-ethoxyacetate was dissolved in tetrahydrofuran, and 520 mg of 60% sodium hydride was added, and the mixture was stirred for 10 minutes. A solution of 2.5 g of 3-benzyloxybenzaldehyde in 10 ml of N,N-dimethylformamide was added and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate. Saturated aqueous sodium hydrogencarbonate was added to the organic layer, and the resulting emulsion formed was subjected to Celite filtration. The filtrate was diluted with diethyl ether and saturated aqueous ammonium chloride. The organic layer was dried over anhydrous magnesium sulfate and concentrated, to give 4.5 g of the title compound.

Production example 46b) Ethyl 2-ethoxy-3-(3-hydroxyphenyl)propanoate

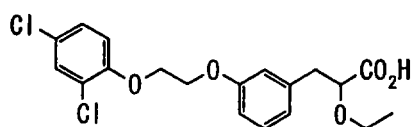


4.5 g of Ethyl (E, Z)-3-[3-(benzyloxy)phenyl]-2-ethoxy-2-propenoate was dissolved in ethyl acetate, and 450 mg of 10% palladium carbon was added thereto and the mixture was stirred overnight at room temperature under hydrogen atmosphere. The reaction solution was filtered through Celite and the filtrate

was evaporated. The residue was purified by silica gel column chromatography, to give 3.7 g of the title compound in the 5:1 hexane-ethyl acetate fraction.

δ : 1.16 (t, $J=7.2\text{Hz}$, 3H) 1.23 (t, $J=7.2\text{Hz}$, 3H) 2.95–2.98 (m, 2H) 3.37 (dq, $J=7.2$, 9.2Hz, 1H) 3.61 (dq, $J=7.2$, 9.2Hz, 1H) 4.02 (dd, $J=5.6$, 7.6Hz, 1H) 4.18 (q, $J=7.2\text{Hz}$, 2H) 5.14 (s, 1H) 6.69–6.73 (m, 1H) 6.74–6.76 (m, 1H) 6.79–6.82 (m, 1H) 7.15 (t, $J=8.0\text{Hz}$, 1H)

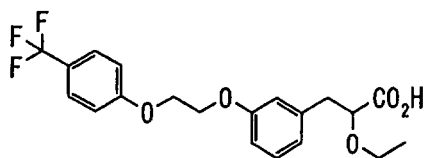
Example 46c) 3-3-[2-(2,4-Dichlorophenoxy)ethoxy]phenyl-2-ethoxypropanoic acid



Using 1-(2-bromoethoxy)-2,4-dichlorobenzene and ethyl 2-ethoxy-3-(3-hydroxyphenyl)propanoate, the title compound was obtained in the same manner as described in Example 33c).

MS m/e (ESI) 421 (MNa^+)

Example 47. 3-3-[2-(4-Trifluoromethylphenoxy)ethoxy]phenyl-2-ethoxypropanoic acid

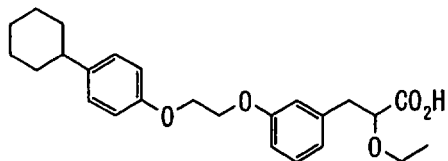


Using 1-(2-bromoethoxy)-4-trifluoromethylbenzene, the title compound was obtained in the same manner as described in Example 46c).

MS m/e (ESI) 421 (MNa^+)

Example 48. 3-3-[2-(4-Cyclohexylphenoxy)ethoxy]phenyl-2-

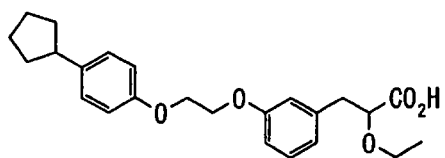
ethoxypropanoic acid



Using 1-(2-bromoethoxy)-4-cyclohexylbenzene, the title compound was obtained in the same manner as described in Example 46c) .

MS m/e (ESI) 435 (MNa^+)

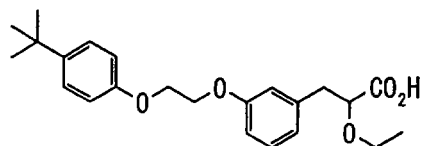
Example 49. 3-3-[2-(4-Cyclopentylphenoxy)ethoxy]phenyl-2-ethoxypropanoic acid



Using 1-(2-bromoethoxy)-4-cyclopentylbenzene, the title compound was obtained in the same manner as described in Example 46c) .

MS m/e (ESI) 421 (MNa^+)

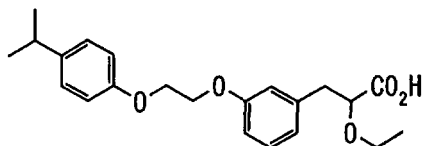
Example 50. 3-3-[2-(4-t-Butylphenoxy)ethoxy]phenyl-2-ethoxypropanoic acid



Using 1-(2-bromoethoxy)-4-t-butylbenzene, the title compound was obtained in the same manner as described in Example 46c) .

MS m/e (ESI) 409 (MNa^+)

Example 51. 3-3-[2-(4-Isopropylphenoxy)ethoxy]phenyl-2-ethoxypropanoic acid

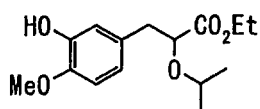


Using 1-(2-bromoethoxy)-4-isopropylbenzene, the title compound was obtained in the same manner as described in Example 46c).

MS m/e (ESI) 395 (MNa⁺)

Example 52. 3-{3-[2-(2,4-Dichlorophenoxy)ethoxy]-4-methoxyphenyl}-2-isopropoxypropanoic acid

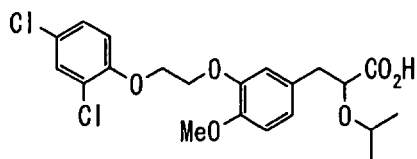
Production example 52a) Ethyl 3-(3-hydroxy-4-methoxyphenyl)-2-isopropoxypropanoate



Using 3-benzyloxy-4-methoxybenzaldehyde and ethyl 2-(diethoxyphosphoryl)-2-isopropoxyacetate, the title compound was obtained in the same manner as described in Example 46b).

δ : 0.99 (d, $J=6.0$ Hz, 3H) 1.16 (d, $J=6.0$ Hz, 3H) 1.23 (t, $J=7.2$ Hz, 3H) 2.85 (dd, $J=8.4, 14.0$ Hz, 1H) 2.91 (dd, $J=4.8, 14.0$ Hz, 1H) 3.45-3.55 (m, 1H) 3.87 (s, 3H) 4.01 (dd, $J=4.8, 8.4$ Hz, 1H) 4.14-4.20 (m, 2H) 5.55 (s, 1H) 6.70-6.78 (m, 2H) 6.84 (d, $J=2.0$ Hz, 1H)

Example 52b) 3-{3-[2-(2,4-Dichlorophenoxy)ethoxy]-4-methoxyphenyl}-2-isopropoxypropanoic acid



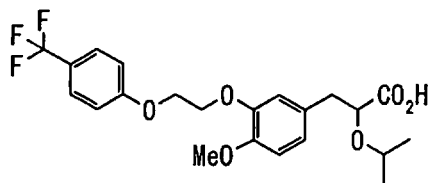
Using 1-(2-bromoethoxy)-2,4-dichlorobenzene and ethyl 3-(3-hydroxy-4-methoxyphenyl)-2-isopropoxypropanoate, the title compound was obtained in the same manner as described in Example 33c).

$^1\text{H-NMR}$ (CDCl_3)

δ : 1.04 (d, $J=6.0\text{Hz}$, 3H) 1.16 (d, $J=6.0\text{Hz}$, 3H) 2.89 (dd, $J=8.0$, 14.0Hz , 1H) 3.07 (dd, $J=4.0$, 14.0Hz , 1H) 3.56 (sept, $J=6.0\text{Hz}$, 1H) 3.84 (s, 3H) 4.13 (dd, $J=4.0$, 8.0Hz , 1H) 4.37-4.44 (m, 4H) 6.83 (s, 1H) 6.83 (d, $J=1.2\text{Hz}$, 1H) 6.91 (d, $J=1.2\text{Hz}$, 1H) 6.98 (d, $J=8.6\text{Hz}$, 1H) 7.18 (dd, $J=2.6$, 8.6Hz , 1H) 7.37[~] (d, $J=2.6\text{Hz}$, 1H)

MS m/e (ESI) 465 (MNa^+)

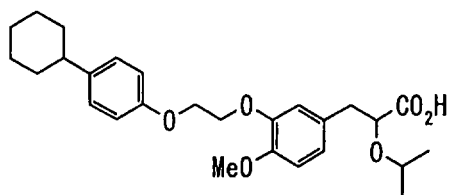
Example 53. 3-{3-[2-(4-Trifluoromethoxyphenyl)ethoxy]-4-methoxyphenyl}-2-isopropoxypropanoic acid



Using 1-(2-bromoethoxy)-4-trifluoromethylbenzene, the title compound was obtained in the same manner as described in Example 52b).

MS m/e (ESI) 465 (MNa^+)

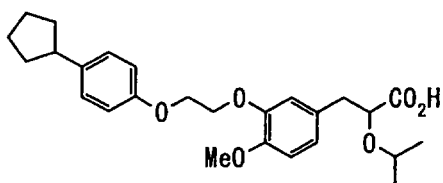
Example 54. 3-{3-[2-(4-Cyclohexylphenoxy)ethoxy]-4-methoxyphenyl}-2-isopropoxypropanoic acid



Using 1-(2-bromoethoxy)-4-cyclohexylbenzene, the title compound was obtained in the same manner as described in Example 52b) .

MS m/e (ESI) 479 (MNa^+)

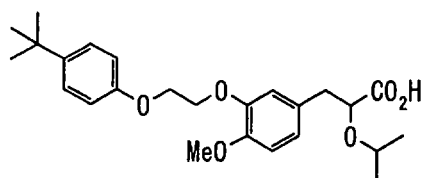
Example 55. 3-{3-[2-(4-Cyclopentylphenoxy)ethoxy]-4-methoxyphenyl}-2-isopropoxypropanoic acid



Using 1-(2-bromoethoxy)-4-cyclopentylbenzene, the title compound was obtained in the same manner as described in Example 52b) .

MS m/e (ESI) 465 (MNa^+)

Example 56. 3-{3-[2-(4-t-Butylphenoxy)ethoxy]-4-methoxyphenyl}-2-isopropoxypropanoic acid

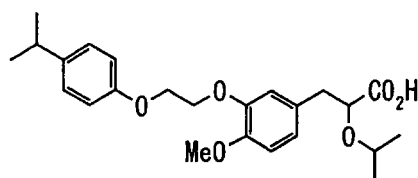


Using 1-(2-bromoethoxy)-4-t-butylbenzene, the title compound was obtained in the same manner as described in Example

52b).

MS m/e (ESI) 453 (MNa^+)

Example 57. 3-{3-[2-(4-Isopropylphenoxy)ethoxy]-4-methoxyphenyl}-2-isopropoxypropanoic acid

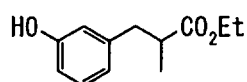


Using 1-(2-bromoethoxy)-4-isopropylbenzene, the title compound was obtained in the same manner as described in Example 52b).

MS m/e (ESI) 439 (MNa^+)

Example 58. 3-{3-[2-(2,4-Dichlorophenoxy)ethoxy]phenyl}-2-methylpropanoic acid

Production example 58a) Ethyl 3-(3-hydroxyphenyl)-2-methylpropanoate

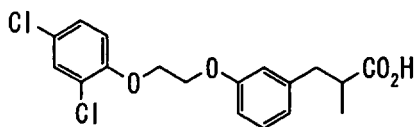


Using 3-benzyloxybenzaldehyde and ethyl 2-(diethoxyphosphoryl)-2-methylacetate, the title compound was obtained in the same manner as described in Production examples 46a) and 46b).

1H -NMR ($CDCl_3$)

δ : 1.15 (d, $J=6.8$ Hz, 3H) 1.20 (t, $J=7.2$ Hz, 3H) 2.62 (dd, $J=7.6, 13.2$ Hz, 1H) 2.67-2.76 (m, 1H) 2.96 (dd, $J=7.2, 13.2$ Hz, 1H) 4.10 (q, $J=7.2$ Hz, 2H) 5.28 (s, 1H) 6.66-6.70 (m, 2H) 6.72-6.75 (m, 1H) 7.14 (t, $J=6.8$ Hz, 1H)

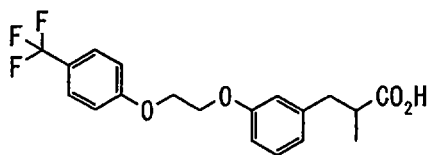
Example 58b) 3-{3-[2-(2,4-Dichlorophenoxy)ethoxy]phenyl}-2-methylpropanoic acid



Using 1-(2-bromoethoxy)-2,4-dichlorobenzene and ethyl 3-(3-hydroxy-4-methoxyphenyl)-2-methylpropanoate, the title compound was obtained in the same manner as described in Example 33c).

MS m/e (ESI) 391 (MNa^+)

Example 59. 3-{3-[2-(4-Trifluoromethylphenoxy)ethoxy]phenyl}-2-methylpropanoic acid



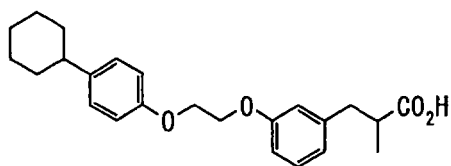
Using 1-(2-bromoethoxy)-4-trifluoromethylbenzene, the title compound was obtained in the same manner as described in Example 58b).

1H -NMR($CDCl_3$)

δ : 1.18 (d, $J=6.8$ Hz, 3H) 2.64 (dd, $J=8.0, 13.6$ Hz, 1H) 2.72-2.81 (m, 1H) 3.05 (dd, $J=6.8, 13.6$ Hz, 1H) 4.30-4.37 (m, 4H) 6.77-6.84 (m, 3H) 6.99-7.04 (m, 2H) 7.19-7.24 (m, 1H) 7.53-7.58 (m, 2H)

MS m/e (ESI) 391 (MNa^+)

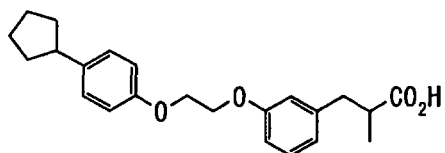
Example 60. 3-{3-[2-(4-Cyclohexylphenoxy)ethoxy]phenyl}-2-methylpropanoic acid



Using 1-(2-bromoethoxy)-4-cyclohexylbenzene, the title compound was obtained in the same manner as described in Example 58b).

MS m/e (ESI) 405 (MNa^+)

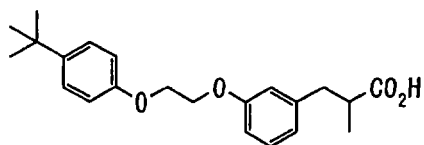
Example 61. 3-{3-[2-(4-Cyclopentylphenoxy)ethoxy]phenyl}-2-methylpropanoic acid



Using 1-(2-bromoethoxy)-4-cyclopentylbenzene, the title compound was obtained in the same manner as described in Example 58b).

MS m/e (ESI) 391 (MNa^+)

Example 62. 3-{3-[2-(4-t-Butylphenoxy)ethoxy]phenyl}-2-methylpropanoic acid

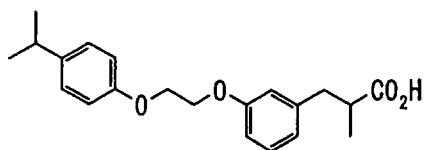


Using 1-(2-bromoethoxy)-4-*t*-butylbenzene, the title compound was obtained in the same manner as described in Example 58b).

MS m/e (ESI) 379 (MNa^+)

Example 63. 3-{3-[2-(4-Isopropylphenoxy)ethoxy]phenyl}-2-

methylpropanoic acid

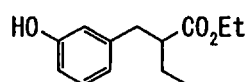


Using 1-(2-bromoethoxy)-4-isopropylbenzene, the title compound was obtained in the same manner as described in Example 58b).

MS m/e (ESI) 365 (MNa^+)

Example 64. 3-{3-[2-(2,4-Dichlorophenoxy)ethoxy]phenyl}-2-ethylpropanoic acid

Production example 64a) Ethyl 3-(3-hydroxyphenyl)-2-ethylpropanoate

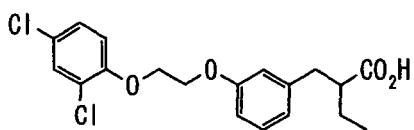


Using 3-benzyloxybenzaldehyde, ethyl 2-(diethoxyphosphoryl)-2-ethylacetate, the title compound was obtained in the same manner as described in Production examples 46a) and 46b).

1H -NMR ($CDCl_3$)

δ : 0.92 (t, $J=7.2$ Hz, 3H) 1.16 (t, $J=7.2$ Hz, 3H) 1.50-1.70 (m, 2H) 2.53-2.60 (m, 1H) 2.70 (dd, $J=6.4, 13.6$ Hz, 1H) 2.87 (dd, $J=8.6, 13.6$ Hz, 1H) 4.08 (q, $J=7.2$ Hz, 2H) 5.26 (s, 1H) 6.64-6.69 (m, 2H) 6.71-6.75 (m, 1H) 7.14 (t, $J=7.8$ Hz, 1H)

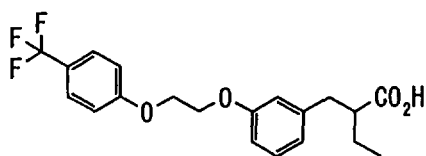
Example 64b) 3-{3-[2-(2,4-Dichlorophenoxy)ethoxy]phenyl}-2-ethylpropanoic acid



Using 1-(2-bromoethoxy)-2,4-dichlorobenzene and ethyl 3-(3-hydroxy-4-methoxyphenyl)-2-ethylpropanoate, the title compound was obtained in the same manner as described in Example 33c).

MS m/e (ESI) 405 (MNa^+)

Example 65. 3-{3-[2-(4-Trifluoromethylphenoxy)ethoxy]phenyl}-2-ethylpropanoic acid



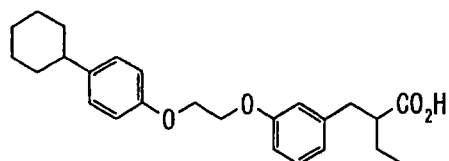
Using 1-(2-bromoethoxy)-4-trifluoromethylbenzene, the title compound was obtained in the same manner as described in Example 64b).

1H -NMR($CDCl_3$)

δ : 0.95 (t, $J=7.2$ Hz, 3H) 1.53-1.72 (m, 2H) 2.57-2.65 (m, 1H) 2.73 (dd, $J=6.8, 13.6$ Hz, 1H) 2.96 (dd, $J=8.0, 13.6$ Hz, 1H) 4.29-4.36 (m, 4H) 6.77-6.82 (m, 3H) 6.99-7.03 (m, 2H) 7.18-7.23 (m, 1H) 7.53-7.58 (m, 2H)

MS m/e (ESI) 405 (MNa^+)

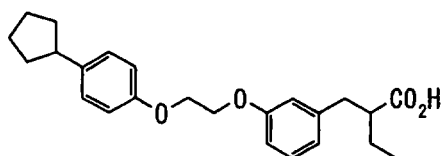
Example 66. 3-{3-[2-(4-Cyclohexylphenoxy)ethoxy]phenyl}-2-ethylpropanoic acid



Using 1-(2-bromoethoxy)-4-cyclohexylbenzene, the title compound was obtained in the same manner as described in Example 64b).

MS m/e (ESI) 419 (MNa^+)

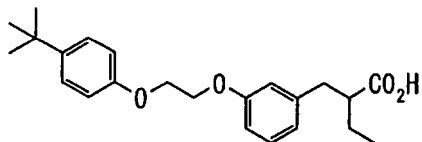
Example 67. 3-{3-[2-(4-Cyclopentylphenoxy)ethoxy]phenyl}-2-ethylpropanoic acid



Using 1-(2-bromoethoxy)-4-cyclopentylbenzene, the title compound was obtained in the same manner as described in Example 64b).

MS m/e (ESI) 405 (MNa^+)

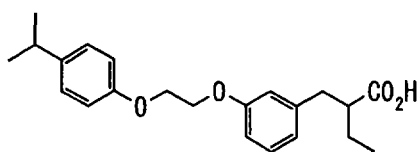
Example 68. 3-{3-[2-(4-t-Butylphenoxy)ethoxy]phenyl}-2-ethylpropanoic acid



Using 1-(2-bromoethoxy)-4-t-butylbenzene, the title compound was obtained in the same manner as described in Example 64b).

MS m/e (ESI) 393 (MNa^+)

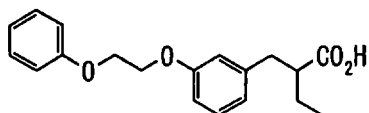
Example 69. 3-{3-[2-(4-Isopropylphenoxy)ethoxy]phenyl}-2-ethylpropanoic acid



Using 1-(2-bromoethoxy)-4-isopropylbenzene, the title compound was obtained in the same manner as described in Example 64b).

MS m/e (ESI) 379 (MNa^+)

Example 70. 3-3-[2-(Phenoxy)ethoxy]phenyl-2-ethylpropanoic acid

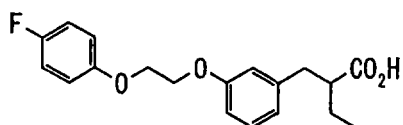


Using 1-(2-bromoethoxy)benzene, the title compound was obtained in the same manner as described in Example 64b).

MS m/e (ESI) 337 (MNa^+)

Example 71.

3-3-[2-(4-Fluorophenoxy)ethoxy]phenyl-2-ethylpropanoic acid

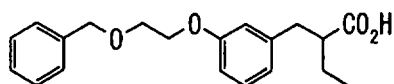


Using 1-(2-bromoethoxy)-4-fluorobenzene, the title compound was obtained in the same manner as described in Example 64b).

MS m/e (ESI) 355 (MNa^+)

Example 72.

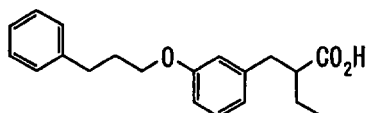
3-3-[2-(4-Benzyloxy)ethoxy]phenyl-2-ethylpropanoic acid



Using 1-[(2-bromoethoxy)methyl]benzene, the title compound was obtained in the same manner as described in Example 64b).

MS m/e (ESI) 351 (MNa^+)

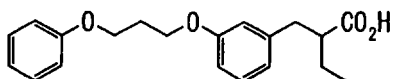
Example 73. 2-Ethyl-3-[3-(3-phenylpropoxy)phenyl]propanoic acid



Using 3-phenylpropyl bromide, the title compound was obtained in the same manner as described in Example 64b).

MS m/e (ESI) 335 (MNa^+)

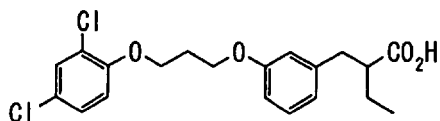
Example 74. 2-Ethyl-3-[3-(3-phenoxypropoxy)phenyl]propanoic acid



Using 1-(3-bromopropoxy)benzene, the title compound was obtained in the same manner as described in Example 64b).

MS m/e (ESI) 351 (MNa^+)

Example 75. 3-[3-[3-(2,4-Dichlorophenoxy)propoxy]phenyl]-2-ethylpropanoic acid

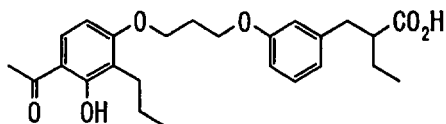


Using 1-(3-bromopropoxy)-2,4-dichlorobenzene, the title

compound was obtained in the same manner as described in Example 64b).

MS m/e (ESI) 419 (MNa^+)

Example 76. 3-{3-[3-(4-Acetyl-3-hydroxy-2-propoxyphenoxy)propoxy]phenyl}-2-ethylpropanoic acid

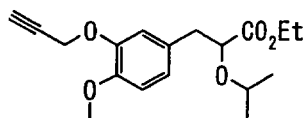


Using 1-[4-(3-bromopropoxy)-2-hydroxy-3-propylphenyl]-1-ethanone, the title compound was obtained in the same manner as described in Example 64b).

MS m/e (ESI) 451 (MNa^+)

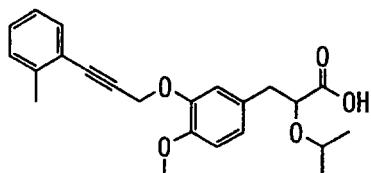
Example 77. 2-Isopropoxy-3-(4-methoxy-3-[3-(2-methylphenyl)-2-propynyloxy]oxyphenyl)propanoic acid

Production example 77a) Ethyl 2-isopropoxy-3-[3-(2-propynyloxy)-4-methoxyphenyl]propanoate



685 mg of Ethyl 3-(3-hydroxy-4-methoxyphenyl)-2-isopropanoate was dissolved in 10 ml of N,N-dimethylformamide, and 350 mg of propargyl bromide and 500 mg of potassium carbonate were added, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was diluted with ethyl acetate, and washed with water and 1N hydrochloric acid. The organic layer was dried over anhydrous magnesium sulfate, filtered and

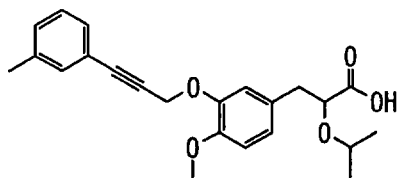
Example 77b) 2-Isopropoxy-3-(4-methoxy-3-[3-(2-methylphenyl)-2-propynyl]oxyphenyl)propanoic acid



2-isopropoxy-3-[3-(2-propynyloxy)phenyl]propanoate, 20 mg of 2-iodotoluene, 5 mg of copper iodide, 5 mg of tetrakis(triphenylphosphine)palladium and 50µl triethylamine were dissolved in 0.2 ml of N,N-dimethylformamide, and the mixture was stirred at room temperature for two days under nitrogen atmosphere. The reaction mixture was diluted with ethyl acetate, and washed with water and 1N hydrochloric acid. The organic layer was dried over anhydrous magnesium sulfate, filtered, and the solvent was distilled off, to give ethyl 2-isopropoxy-3-(3-[3-(2-methylphenyl)-2-propynyl]-oxyphenyl)propanoate. This product was dissolved in 0.4 ml of ethanol, and 0.1 ml of 5N-sodium hydroxide was added, and the mixture was kept still overnight at room temperature. The reaction solution was acidified by adding 1N-hydrochloric acid and extracted with ethyl acetate. The residue was purified by reverse-phase high performance liquid chromatography, to give 1.10 mg of the title compound.

180

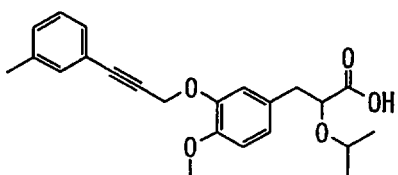
Example 78. 2-Isopropoxy-3-(4-methoxy-3-[3-(3-methylphenyl)-2-propynyl]oxyphenyl)propanoic acid



Using 3-iodotoluene, the title compound was obtained in the same manner as described in Example 77b).

MS m/e (ESI) 383 (MH^+)

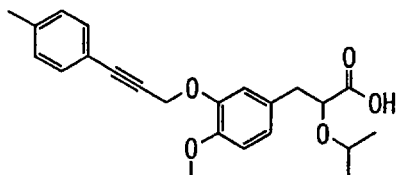
Example 79. 2-Isopropoxy-3-(4-methoxy-3-[3-(3-methylophenyl)-2-propynyl]oxyphenyl)propanoic acid



Using 3-iodotoluene, the title compound was obtained in the same manner as described in Example 77b).

MS m/e (ESI) 383 (MH^+)

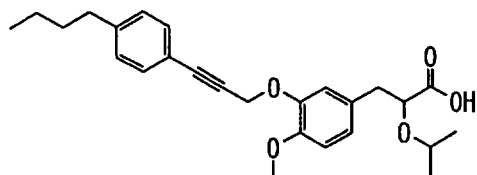
Example 80. 2-Isopropoxy-3-(4-methoxy-3-[3-(4-methylphenyl)-2-propynyl]oxyphenyl)propanoic acid



Using 4-iodotoluene, the title compound was obtained in the same manner as described in Example 77b).

MS m/e (ESI) 383 (MH^+)

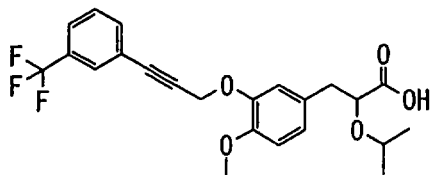
Example 81. 2-Isopropoxy-3-(4-methoxy-3-[3-(4-butylphenyl)-2-propynyl]oxyphenyl)propanoic acid



Using 4-butyliodobenzene, the title compound was obtained in the same manner as described in Example 77b).

MS m/e (ESI) 425 (MH^+)

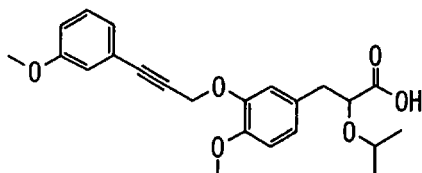
Example 82. 2-Isopropoxy-3-(4-methoxy-3-[3-(3-trifluoromethylphenyl)-2-propynyl]oxyphenyl)propanoic acid



Using 3-iodobenzene trifluoride, the title compound was obtained in the same manner as described in Example 77b).

MS m/e (ESI) 437 (MH^+)

Example 83. 2-Isopropoxy-3-(4-methoxy-3-[3-(3-methoxyphenyl)-2-propynyl]oxyphenyl)propanoic acid

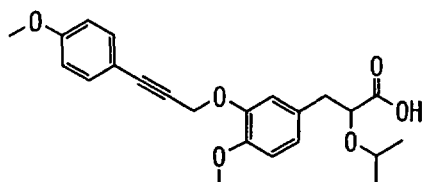


Using 3-methoxyiodobenzene, the title compound was

obtained in the same manner as described in Example 77b).

MS m/e (ESI) 399 (MH^+)

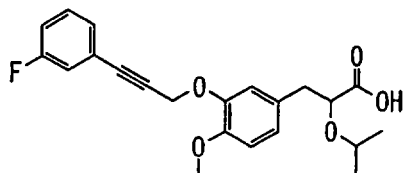
Example 84. 2-Isopropoxy-3-(4-methoxy-3-[3-(4-methoxyphenyl)-2-propynyl]oxyphenyl)propanoic acid



Using 4-methoxyiodobenzene, the title compound was obtained in the same manner as described in Example 77b).

MS m/e (ESI) 399 (MH^+)

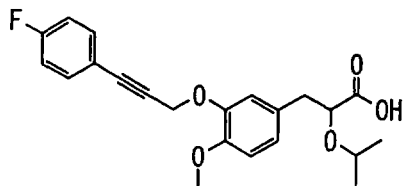
Example 85. 2-Isopropoxy-3-(4-methoxy-3-[3-(3-fluorophenyl)-2-propynyl]oxyphenyl)propanoic acid



Using 3-fluoriodobenzene, the title compound was obtained in the same manner as described in Example 77b).

MS m/e (ESI) 387 (MH^+)

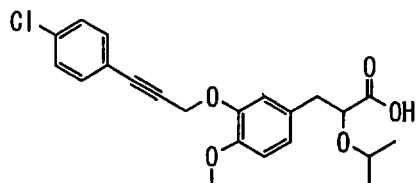
Example 86. 2-Isopropoxy-3-(4-methoxy-3-[3-(4-fluorophenyl)-2-propynyl]oxyphenyl)propanoic acid



Using 4-fluoriodobenzene, the title compound was obtained in the same manner as described in Example 77b).

MS m/e (ESI) 387 (MH^+)

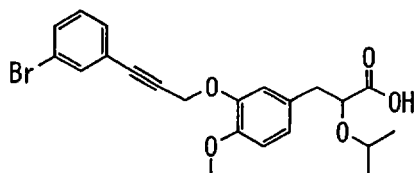
Example 87. 2-Isopropoxy-3-(4-methoxy-3-[3-(4-chlorophenyl)-2-propynyl]oxyphenyl)propanoic acid



Using 4-chloriodobenzene, the title compound was obtained in the same manner as described in Example 77b).

MS m/e (ESI) 403 (MH^+)

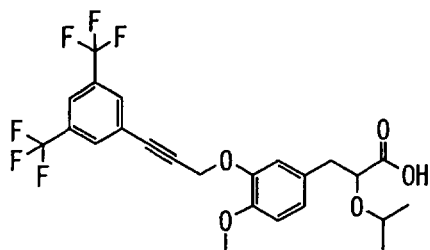
Example 88. 2-Isopropoxy-3-(4-methoxy-3-[3-(3-bromophenyl)-2-propynyl]oxyphenyl)propanoic acid



Using 3-bromiodobenzene, the title compound was obtained in the same manner as described in Example 77b).

MS m/e (ESI) 447 (MH^+)

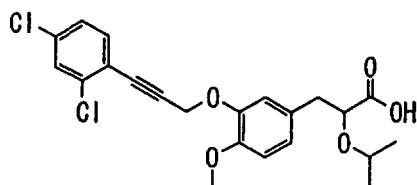
Example 89. 2-Isopropoxy-3-(4-methoxy-3-[3-(3,5-bistrifluoromethylphenyl)-2-propynyl]oxyphenyl)propanoic acid



Using 3,5-bis(trifluoromethyl)iodobenzene, the title compound was obtained in the same manner as described in Example 77b).

MS m/e (ESI) 505 (MH^+)

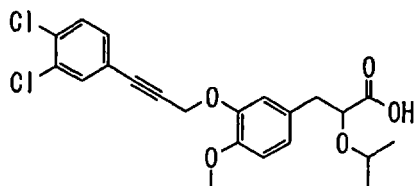
Example 90. 2-Isopropoxy-3-(4-methoxy-3-[3-(2,4-
dichlorophenyl)-2-propynyl]oxyphenyl)propanoic acid



Using 2,4-dichloriodobenzene, the title compound was obtained in the same manner as described in Example 77b).

MS m/e (ESI) 437 (MH^+)

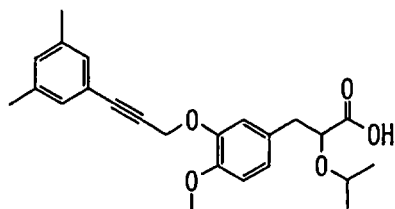
Example 91. 2-Isopropoxy-3-(4-methoxy-3-[3-(3,4-
dichlorophenyl)-2-propynyl]oxyphenyl)propanoic acid



Using 3,4-dichloriodobenzene, the title compound was obtained in the same manner as described in Example 77b).

MS m/e (ESI) 437 (MH^+)

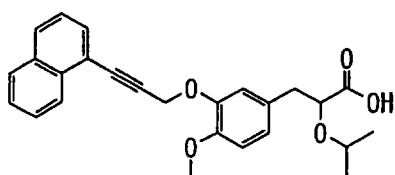
Example 92. 2-Isopropoxy-3-(4-methoxy-3-[3-(3,5-dimethylphenyl)-2-propynyl]oxyphenyl)propanoic acid



Using 3,5-dimethyliodobenzene, the title compound was obtained in the same manner as described in Example 77b).

MS m/e (ESI) 397 (MH^+)

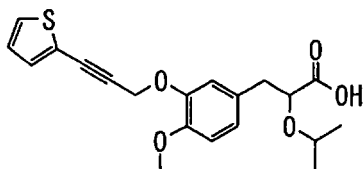
Example 93. 2-Isopropoxy-3-(4-methoxy-3-[3-(1-naphthyl)-2-propynyl]oxyphenyl)propanoic acid



Using 1-iodonaphthalene, the title compound was obtained in the same manner as described in Example 77b).

MS m/e (ESI) 419 (MH^+)

Example 94. 2-Isopropoxy-3-(4-methoxy-3-[3-(2-thienyl)-2-propynyl]oxyphenyl)propanoic acid

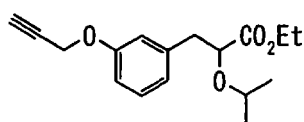


Using 2-iodothiophene, the title compound was obtained in the same manner as described in Example 77b).

MS m/e (ESI) 375 (MH^+)

Example 95. 2-Isopropoxy-3-(3-[3-(4-methylphenyl)-2-propynyl]oxyphenyl)propanoic acid

Production example 95a) Ethyl 2-isopropoxy-3-[3-(2-propynyloxy)phenyl]propanoate

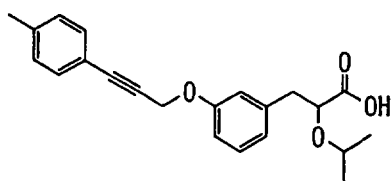


Using ethyl 3-(3-hydroxyphenyl)-2-isopropoxypropanoate, the title compound was obtained in the same manner as described in Example 77a).

¹H NMR (CDCl₃)

δ : 0.96 (d, J=6.4Hz, 3H) 1.16 (d, J=6.0Hz, 3H) 1.25 (t, J=7.2Hz, 3H) 2.51 (t, J=2.4Hz, 1H) 2.92 (dd, J=8.8, 14.0Hz, 1H) 2.99 (dd, J=4.8, 13.6Hz, 1H) 3.51 (Sept, J=6.4Hz, 1H) 4.05 (dd, J=4.4, 8.8Hz, 1H) 4.14-4.23 (m, 2H) 4.68 (d, J=2.4Hz, 2H) 6.83-6.86 (m, 1H) 6.88-6.90 (m, 1H) 6.90 (s, 1H) 7.21 (dt, J=0.8, 8.0Hz, 1H)

Example 95b) 2-Isopropoxy-3-(3-[3-(4-methylphenyl)-2-propynyl]oxyphenyl)propanoic acid

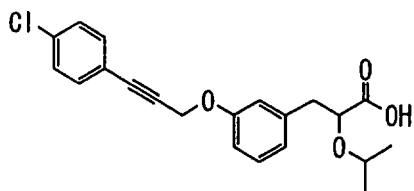


Using 4-iodotoluene, the title compound was obtained in the same manner as described in Example 77b).

MS *m/e*(ESI) 353 (MH⁺)

Example 96. 2-Isopropoxy-3-(3-[3-(4-chlorophenyl)-2-

propynyl]oxyphenyl)propanoic acid



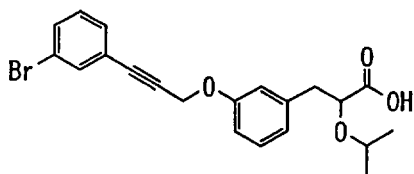
Using 4-iodochlorobenzene, the title compound was obtained in the same manner as described in Example 77b).

¹H NMR (CDCl₃)

δ : 0.99 (d, J=6.4Hz, 3H) 1.13 (d, J=6.0Hz, 3H) 2.93 (dd, J=8.4, 14.0Hz, 1H) 3.13 (dd, J=3.6, 13.6Hz, 1H) 3.52 (Sept, J=6.4Hz, 1H) 4.14 (dd, J=3.6, 8.4Hz, 1H) 4.89 (s, 2H) 6.87-6.93 (m, 3H) 7.22-7.30 (m, 3H) 7.36 (d, J=8.4Hz, 2H)

MS *m/e*(ESI) 373 (MH⁺)

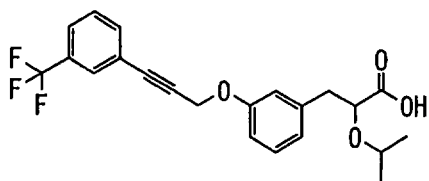
Example 97. 2-Isopropoxy-3-(3-[3-(3-bromophenyl)-2-propynyl]oxyphenyl)propanoic acid



Using 3-bromiodobenzene, the title compound was obtained in the same manner as described in Example 77b).

MS *m/e*(ESI) 417 (MH⁺)

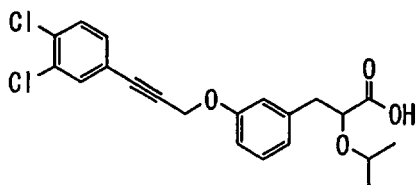
Example 98. 2-Isopropoxy-3-(3-[3-(3-trifluoromethylphenyl)-2-propynyl]oxyphenyl)propanoic acid



Using 3-iodobenzotrifluoride, the title compound was obtained in the same manner as described in Example 77b).

MS m/e (ESI) 407 (MH^+)

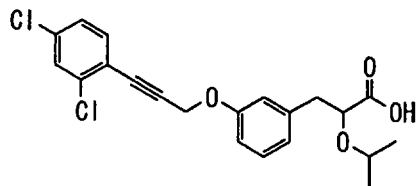
Example 99. 2-Isopropoxy-3-(3-[3-(3,4-dichlorophenyl)-2-propynyl]oxyphenyl)propanoic acid



Using 3,4-dichloriodobenzene, the title compound was obtained in the same manner as described in Example 77b).

MS m/e (ESI) 407 (MH^+)

Example 100. 2-Isopropoxy-3-(3-[3-(2,4-dichlorophenyl)-2-propynyl]oxyphenyl)propanoic acid



Using 2,4-dichloriodobenzene, the title compound was obtained in the same manner as described in Example 77b).

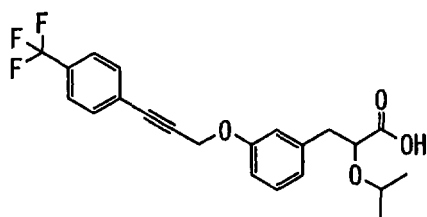
1H NMR ($CDCl_3$)

δ : 0.99 (d, $J=6.0$ Hz, 3H) 1.14 (d, $J=6.0$ Hz, 3H) 2.92 (dd, $J=8.4, 14.0$ Hz,

1H) 3.13 (dd, J=3.6, 14.0Hz, 1H) 3.52 (Sept, J=6.0Hz, 1H) 4.14 (dd, J=3.6, 8.0Hz, 1H) 4.94 (s, 2H) 6.89 (d, J=7.6Hz, 1H) 6.91-6.95 (m, 2H) 7.19 (dd, J=2.0, 8.4Hz, 1H) 7.24 (dd, J=7.2, 8.8Hz, 1H) 7.39 (d, J=8.4Hz, 1H) 7.40 (d, J=2.0Hz, 1H)

MS *m/e*(ESI) 407 (MH⁺)

Example 101. 2-Isopropoxy-3-(3-[3-(4-trifluoromethylphenyl)-2-propynyl]oxyphenyl)propanoic acid

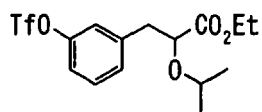


Using 4-iodobenzotrifluoride, the title compound was obtained in the same manner as described in Example 77b).

MS *m/e*(ESI) 407 (MH⁺)

Example 102. 2-Isopropoxy-3-(3-3-[4-(trifluoromethyl)phenoxy]-1-propynylphenyl)propanoic acid

Production example 102a) Ethyl 2-isopropoxy-3-(3-[(trifluoromethyl)sulfonyl]oxyphenyl)-propanoate

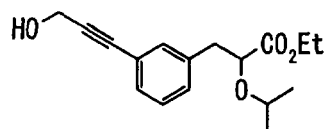


688 mg of Ethyl

3-(3-hydroxyphenyl)-2-isopropoxypropanoate was dissolved in dichloromethane, and 600μl of triethylamine, 15 mg of 4-dimethylaminopyridine and 1.045g of N,N-bistrifluoromethanesulfonyl aniline were added. The solution was stirred at room temperature overnight and the

solvent was evaporated. The residue was purified by silica gel column chromatography, to give 1.132 g of the title compound in the 10:1 hexane-ethyl acetate fraction.

Production example 102b) Ethyl 3-[3-(3-hydroxy-1-propynyl)phenyl]-2-isopropoxypropanoate

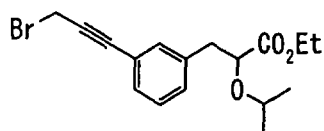


550 mg of Ethyl 2-isopropoxy-3-(3-[(trifluoromethyl)sulfonyl]oxyphenyl)propanoate was dissolved in 5 ml of N,N-dimethylformamide, and 160 mg of propargyl alcohol, 13 mg of copper iodide, 83 mg of tetrakis(triphenylphosphine)palladium and 1 ml of triethylamine were added. After stirring was continued at 50°C for 4 hours under nitrogen atmosphere, the reaction mixture was diluted with ethyl acetate and washed with water and 1N hydrochloric acid. The organic layer was dried over anhydrous magnesium sulfate, filtered, and the solvent was distilled off. Then, the residue was purified by silica gel column chromatography, to give 184 mg of the title compound in the 4:1 → 2:1 hexane-ethyl acetate fraction.

¹H NMR (CDCl₃)

δ : 0.94 (d, J=6.0Hz, 3H) 1.15 (d, J=6.4Hz, 3H) 1.24 (t, J=7.6Hz, 3H) 1.70 (t, J=6.0Hz, 1H) 2.90 (dd, J=8.8, 14.0Hz, 1H) 2.98 (dd, J=4.8, 14.0Hz, 1H) 3.49 (Sept, J=6.0Hz, 1H) 4.02 (dd, J=4.8, 8.4Hz, 1H) 4.14-4.22 (m, 2H) 4.50 (d, J=5.6Hz, 2H) 7.22-7.25 (m, 2H) 7.27-7.34 (m, 2H)

Production example 102c) Ethyl 3-[3-(3-bromo-1-propynyl)phenyl]-2-isopropoxypropanoate



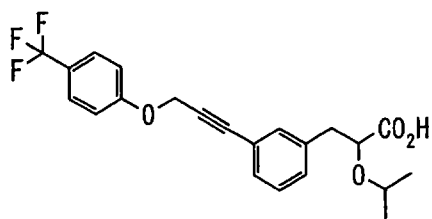
184 mg of Ethyl

3-[3-(3-hydroxy-1-propynyl)phenyl]-2-isopropoxypropanoate was dissolved in 4 ml of dimethoxyethane, and 50 μ l of phosphorous tribromide was added. After stirring was continued at room temperature overnight, the reaction mixture was diluted with ethyl acetate and washed with water and 1N hydrochloric acid. The organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent was distilled off. Then, the residue was purified by silica gel column chromatography, to give 209 mg of the title compound in the 20:1 hexane-ethyl acetate fraction.

^1H NMR (CDCl_3)

δ : 0.94 (d, $J=6.4\text{Hz}$, 3H) 1.15 (d, $J=6.4\text{Hz}$, 3H) 1.24 (t, $J=7.2\text{Hz}$, 3H) 2.90 (dd, $J=8.4$, 14.0Hz , 1H) 2.98 (dd, $J=4.8$, 13.6Hz , 1H) 3.47 (Sept, $J=6.0\text{Hz}$, 1H) 4.02 (dd, $J=4.8$, 8.8Hz , 1H) 4.14-4.22 (m, 2H) 4.16 (s, 2H) 7.23-7.25 (m, 2H) 7.30-7.35 (m, 2H)

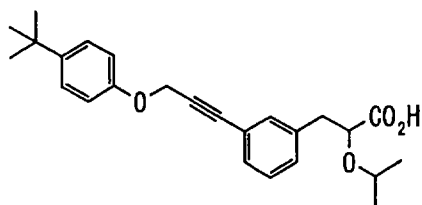
Example 102d) 2-Isopropoxy-3-(3-3-[4-(trifluoromethyl)phenoxy]-1-propynylphenyl)propanoic acid



10 mg of Ethyl 3-[3-(3-bromo-1-propynyl)phenyl]-2-isopropoxypropanoate was dissolved in 0.3 ml of N,N-dimethylformamide, and 10 mg of 4-hydroxybenzotrifluoride and 20 mg of potassium carbonate were added. After stirring was continued at room temperature overnight, the reaction mixture was diluted with ethyl acetate and washed with water. After distilling off the solvent from the organic layer, the residue was dissolved in 0.4 ml of ethanol, and 0.1 ml of 5N-sodium hydroxide was added, and the mixture was kept still at room temperature overnight. The reaction solution was acidified by adding 1N-hydrochloric acid, and extracted with ethyl acetate. The solvent was concentrated, and the residue was purified by reverse-phase high performance liquid chromatography, to give 3.55 mg of the title compound.

MS *m/e* (ESI) 407 (MH⁺)

Example 103. 2-Isopropoxy-3-(3-3-[4-t-butylphenoxy]-1-propynylphenyl)propanoic acid

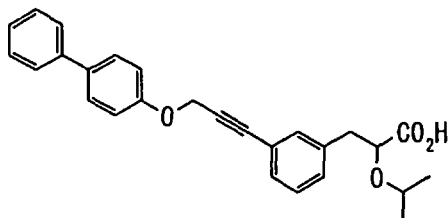


Using 4-t-butylphenol, the title compound was obtained in

the same manner as described in Example 102d).

MS m/e (ESI) 395 (MH^+)

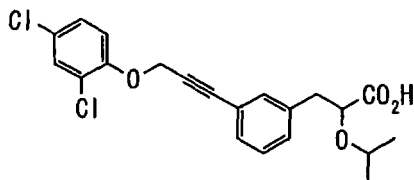
Example 104. 2-Isopropoxy-3-(3-3-[4-(phenyl)phenoxy]-1-propynylphenyl)propanoic acid



Using 4-hydroxybiphenyl, the title compound was obtained in the same manner as described in Example 102d).

MS m/e (ESI) 415 (MH^+)

Example 105. 2-Isopropoxy-3-(3-3-[4-(phenyl)phenoxy]-1-propynylphenyl)propanoic acid



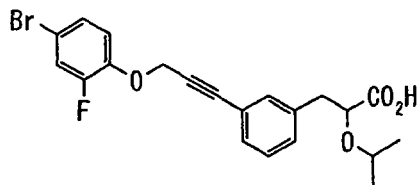
Using 2,4-dichlorophenol, the title compound was obtained in the same manner as described in Example 102d).

1H NMR ($CDCl_3$)

δ : 1.00 (d, $J=6.0$ Hz, 3H) 1.16 (d, $J=6.4$ Hz, 3H) 2.91 (dd, $J=8.0, 13.6$ Hz, 1H) 3.09 (dd, $J=2.8, 13.6$ Hz, 1H) 3.52 (Sept, $J=6.0$ Hz, 1H) 4.10 (dd, $J=3.6, 8.0$ Hz, 1H) 4.97 (s, 2H) 7.11 (d, $J=8.8$ Hz, 1H) 7.22 (dd, $J=2.8, 8.8$ Hz, 1H) 7.23 (t, $J=1.2$ Hz, 1H) 7.25 (t, $J=7.6$ Hz, 1H) 7.29–7.32 (m, 2H) 7.40 (d, $J=2.4$ Hz, 1H)

MS m/e (ESI) 407 (MH^+)

Example 106. 2-Isopropoxy-3-(3-[4-bromo-2-fluorophenoxy]-1-propynylphenyl)propanoic acid

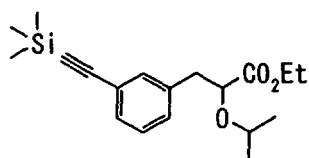


Using 4-bromo-2-fluorophenol, the title compound was obtained in the same manner as described in Example 102d).

MS m/e (ESI) 435 (MH^+)

Example 107. 2-Isopropoxy-3-3-[2-(4-methylphenyl)-1-ethynyl]phenylpropanoic acid

Production example 107a) Ethyl 3-[3-(2-trimethylsilyl-1-propynyl)phenyl]-2-isopropoxypropanoate



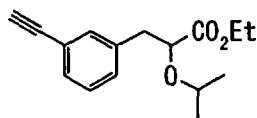
932 mg of Ethyl 2-isopropoxy 3-(3-[(trifluoromethyl)sulfonyl]oxyphenyl)propanoate was dissolved in 8 ml of N,N-dimethylformamide, and 480 mg of trimethylsilyl acetylene, 40 mg of copper iodide, 280 mg of tetrakis(triphenylphosphine)palladium and 1 ml of triethylamine were added. After stirring was continued at 50°C for 8 hours under nitrogen atmosphere, and the reaction mixture was diluted with ethyl acetate, and washed with water and 1N hydrochloric acid. The organic layer was dried over anhydrous magnesium sulfate, and after filtration and distilling off the

solvent. Then, the residue was purified by silica gel column chromatography, to give 442 mg of the title compound in the 30:1 hexane-ethyl acetate fraction.

^1H NMR (CDCl_3)

δ : 0.24 (s, 9H) 0.94 (d, $J=6.0\text{Hz}$, 3H) 1.15 (d, $J=6.0\text{Hz}$, 3H) 1.24 (t, $J=7.2\text{Hz}$, 3H) 2.89 (dd, $J=9.2, 14.0\text{Hz}$, 1H) 2.97 (dd, $J=4.8, 13.6\text{Hz}$, 1H) 3.49 (Sept, $J=6.0\text{Hz}$, 1H) 4.01 (dd, $J=6.4, 12.4\text{Hz}$, 1H) 4.14-4.22 (m, 2H) 7.21 (dd, $J=1.4, 4.0\text{Hz}$, 2H) 7.31-7.35 (m, 1H) 7.37 (s, 1H)

Production example 107b) Ethyl 3-[3-(propynyl)phenyl]-2-isopropoxypropanoate



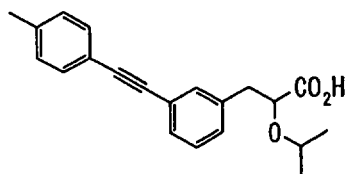
442 mg of Ethyl 3-[3-(2-trimethylsilyl-1-propynyl)phenyl]-2-isopropoxypropanoate was dissolved in 10 ml of tetrahydrofuran, and 0.5 ml of acetic acid and 2 ml of tetrabutylammonium fluoride (solution in 1M tetrahydrofuran) were added. The solution was stirred at 50°C for 3 hours, and the reaction mixture was diluted with ethyl acetate, and washed with water and saturated sodium bicarbonate. The organic layer was dried over anhydrous magnesium sulfate, filtered, and the solvent was distilled off. Then, the residue was purified by silica gel column chromatography, to give 233 mg of the title compound in the 30:1 hexane-ethyl acetate fraction.

^1H NMR (CDCl_3)

δ : 0.94 (d, $J=6.0\text{Hz}$, 3H) 1.15 (d, $J=6.0\text{Hz}$, 3H) 1.24 (t, $J=7.2\text{Hz}$, 3H) 2.91

(dd, J=8.8, 13.6Hz, 1H) 2.99 (dd, J=4.8, 13.6Hz, 1H) 3.05 (s, 1H) 3.50 (Sept, J=6.4Hz, 1H) 4.02 (dd, J=4.8, 8.8Hz, 1H) 4.14-4.22 (m, 2H) 7.22-7.26 (m, 2H) 7.35-7.37 (m, 1H) 7.40 (s, 1H)

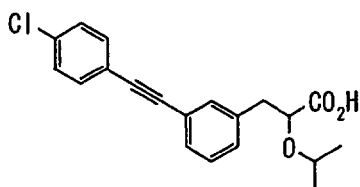
Example 107c) 2-Isopropoxy-3-3-[2-(4-methylphenyl)-1-ethynyl]phenylpropanoic acid



10 mg of Ethyl 3-[3-(2-trimethylsilyl-1-propynyl)phenyl]-2-isopropoxypropanoate, 20 mg of 4-iodotoluene, 5 mg of copper iodide, 5 mg of tetrakis(triphenylphosphine)palladium and 50 μ l of triethylamine were dissolved in 0.2 ml of N,N-dimethylformamide, and the mixture was stirred at 50°C overnight under nitrogen atmosphere. The reaction mixture was diluted with ethyl acetate, and washed with water and 1N hydrochloric acid. The organic layer was dried over anhydrous magnesium sulfate, filtered, and the solvent was distilled off, to give ethyl 2-isopropoxy-3-3-[2-(4-methylphenyl)-1-ethynyl]phenylpropanoate. This product was dissolved in 0.4 ml of ethanol, and 0.1 ml of 5N-sodium hydroxide was added, and the mixture was kept still at room temperature overnight. The reaction solution was acidified by adding 1N-hydrochloric acid and extracted with ethyl acetate. The residue was purified by reverse-phase high performance liquid chromatography, to give 1.90 mg of the title compound.

MS m/e (ESI) 323 (MH^+)

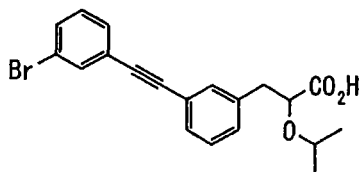
Example 108. 2-Isopropoxy-3-3-[2-(4-chlorophenyl)-1-ethynyl]phenylpropanoic acid



Using 4-chloriodobenzene, 3.70 mg of the title compound was obtained in the same manner as described in Example 107c).

MS m/e (ESI) 343 (MH^+)

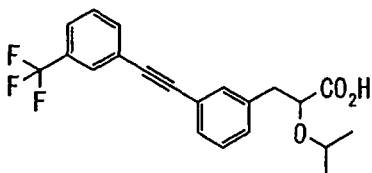
Example 109. 2-Isopropoxy-3-3-[2-(3-bromophenyl)-1-ethynyl]phenylpropanoic acid



Using 3-bromiodobenzene, the title compound was obtained in the same manner as described in Example 107c).

MS m/e (ESI) 387 (MH^+)

Example 110. 2-Isopropoxy-3-3-[2-(3-trifluoromethylphenyl)-1-ethynyl]phenylpropanoic acid

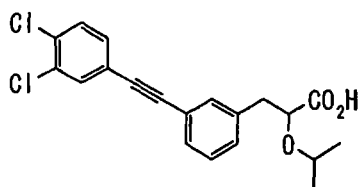


Using 3-iodobenzotrifluoride, the title compound was

obtained in the same manner as described in Example 107c).

MS m/e (ESI) 377 (MH^+)

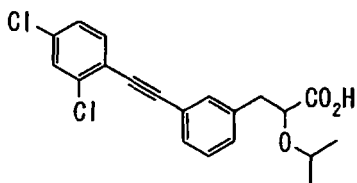
Example 111. 2-Isopropoxy-3-3-[2-(3,4-dichlorophenyl)-1-ethynyl]phenylpropanoic acid



Using 3,4-dichloriodobenzene, the title compound was obtained in the same manner as described in Example 107c).

MS m/e (ESI) 377 (MH^+)

Example 112. 2-Isopropoxy-3-3-[2-(2,4-dichlorophenyl)-1-ethynyl]phenylpropanoic acid

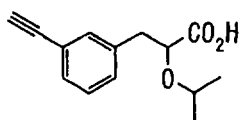


Using 2,4-dichloriodobenzene, the title compound was obtained in the same manner as described in Example 107c).

MS m/e (ESI) 377 (MH^+)

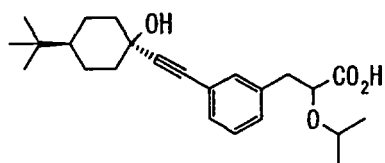
Example 113. 3-(3-2-[4-t-Butyl-1-hydroxycyclohexyl]-1-ethynylphenyl)-2-isopropoxypropanoic acid

Production example 113a) 3-[3-(1-Ethynyl)phenyl]-2-isopropoxypropanoic acid



156 mg of Ethyl 3-[3-(propynyl)phenyl]-2-isopropoxypropanoate was dissolved in 2 ml of ethanol, and 0.5 ml of 5N-sodium hydroxide was added. After the mixture was kept at room temperature for 1 hour, the solution was neutralized with 1N-hydrochloric acid and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent was distilled off, to give 138 mg of the title compound.

Example 113b) trans-3-(3-2-[4-t-Butyl-1-hydroxycyclohexyl]-1-ethynylphenyl)-2-isopropoxypropanoic acid



12 mg of 3-[3-(1-Ethynyl)phenyl]-2-isopropoxypropanoic acid was dissolved in 1 ml of tetrahydrofuran, and 130 μ l of 1M-lithium bistrimethylsilylamide and 40 mg of 4-t-butylcyclohexanone were added. The solution was stirred at room temperature for 1 hour, neutralized with 1N-hydrochloric acid and extracted with ethyl acetate. The organic layer was concentrated, and the residue was purified by reverse-phase high performance liquid chromatography, to give 4.70 mg of the title compound.

MS m/e (ESI) 409 (MNa^+)