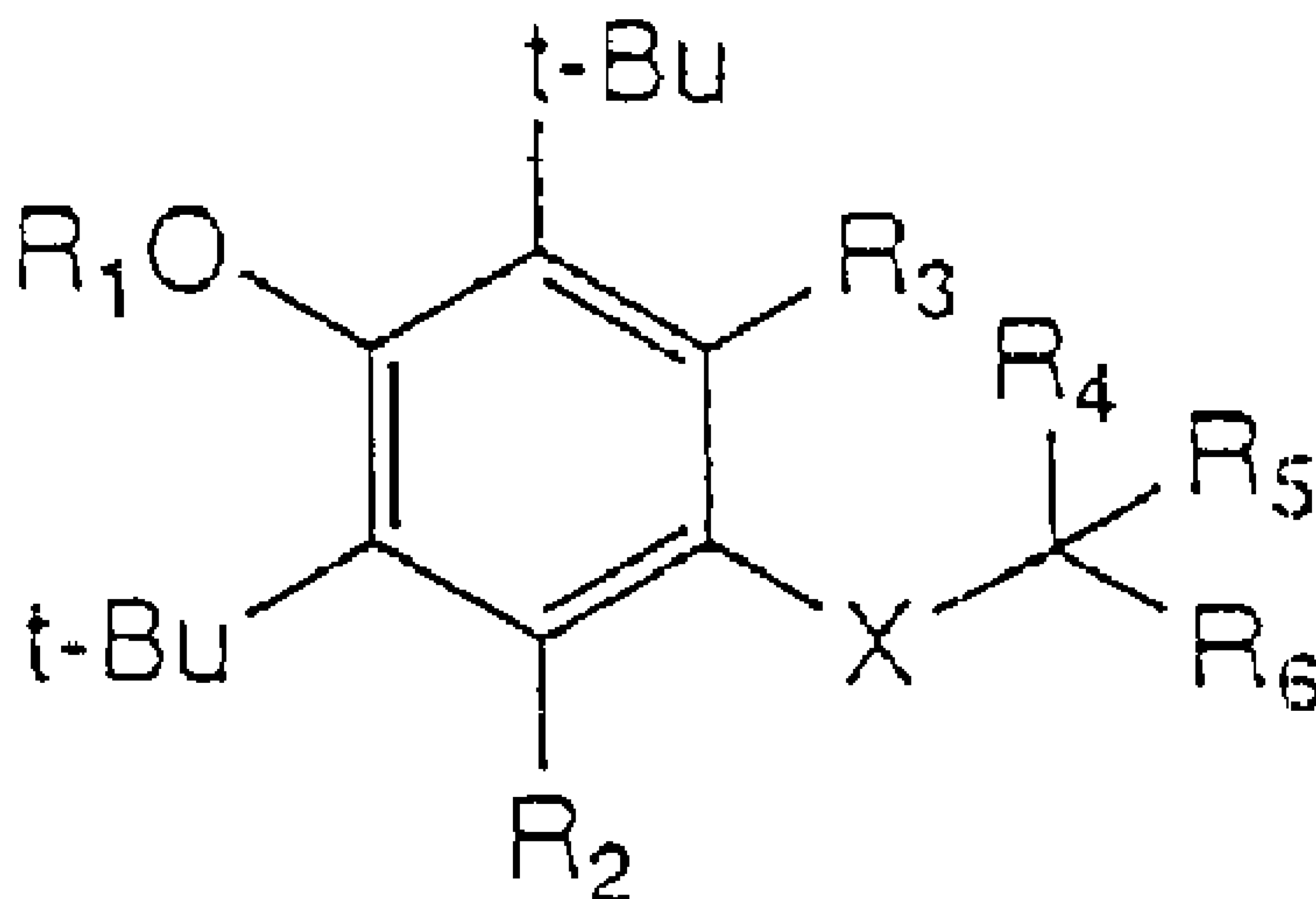




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(54) Title: INTIMAL THICKENING INHIBITORY AGENT



(1)



(2)

(57) **Abrégé/Abstract:**

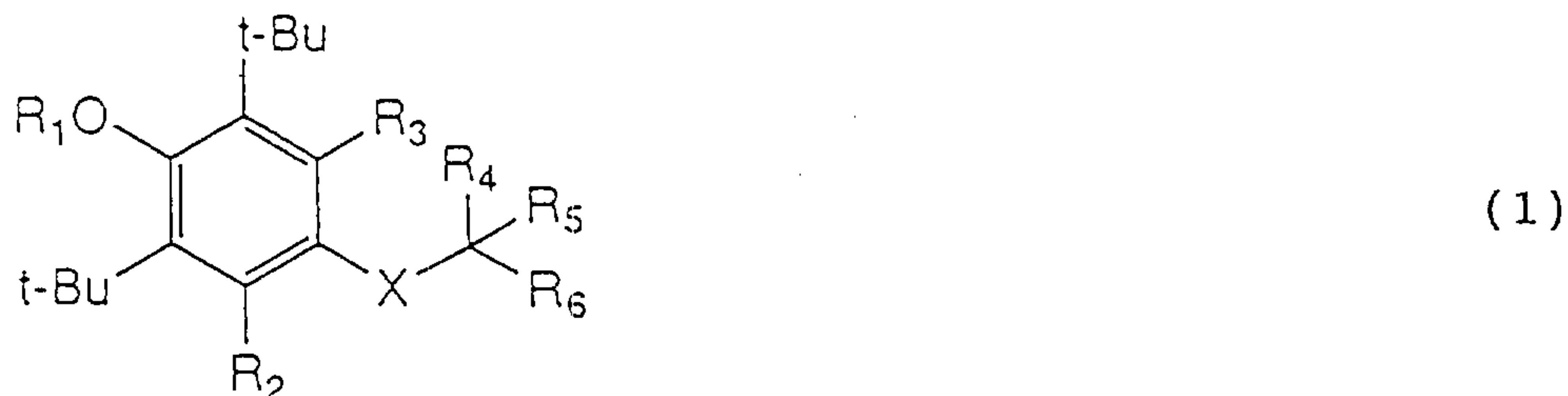
An intimal thickening inhibitory agent comprising, as an active ingredient, a compound represented by formula (1): (see formula 1) wherein X represents an oxygen atom or a group of formula (2): (see formula 2) wherein n represents an integer of from 0 to 2, R₁ represents a hydrogen atom or an acyl group; R₂ represents a hydrogen atom, a lower alkyl group or a lower alkenyl group; R₃ represents a lower alkyl group; and R₄, R₅, and R₆, which may be the same or different, each represent a hydrogen atom or a substituted or unsubstituted alkyl group; or R₃ and R₄ may be taken together to form a 5-membered ring; or R₅ and R₆ may be taken together to form a cycloalkyl group; provided that R₆ is nil when R₃ and R₄ are taken together to form benzofuran or benzo[b]thiophene.



ABSTRACT

An intimal thickening inhibitory agent comprising,
as an active ingredient, a compound represented by formula
(1):

5



10 wherein X represents an oxygen atom or a group of formula
(2):



15 wherein n represents an integer of from 0 to 2,

R_1 represents a hydrogen atom or an acyl group; R_2 represents a hydrogen atom, a lower alkyl group or a lower alkenyl group; R_3 represents a lower alkyl group; and R_4 , R_5 , and R_6 , which may be the same or different, each represent a hydrogen atom or a substituted or unsubstituted alkyl group; or R_3 and R_4 may be taken together to form a 5-membered ring; or R_5 and R_6 may be taken together to form a cycloalkyl group; provided that R_6 is nil when R_3 and R_4 are taken together to form benzofuran or benzo[b]thiophene.

20

SPECIFICATION

INTIMAL THICKENING INHIBITORY AGENT

Field of the Invention

This invention relates to an intimal thickening
5 inhibitory agent and more particularly an intimal thickening
inhibitory agent comprising a 2,6-di-t-butylphenol derivative
as an active ingredient.

Background of the Invention

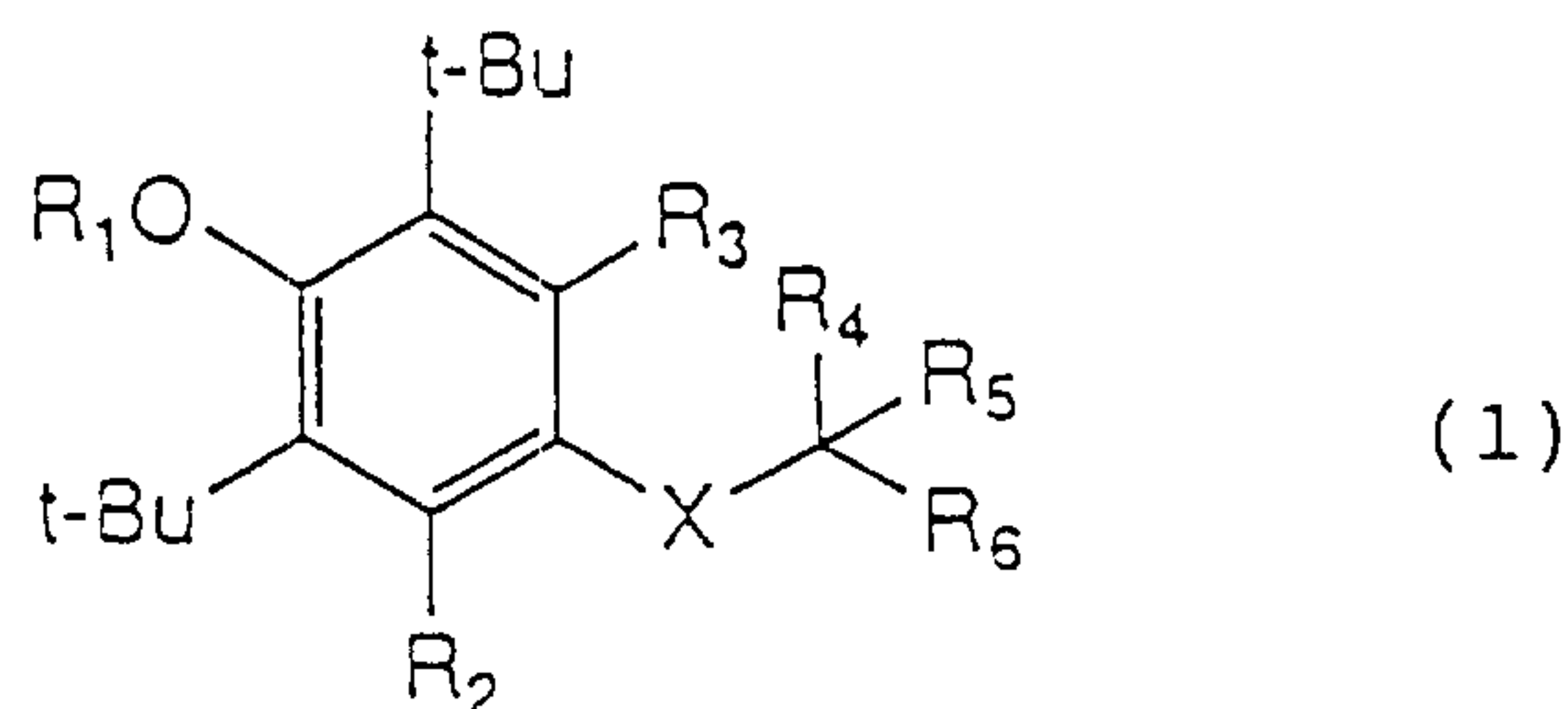
It is known that coronary sclerosis is a primary
10 cause of ischemic heart diseases such as angina pectoris and
cardiac infarction. Narrowing of the vascular lumen
resulting from arteriosclerotic thickening of the intima
brings about nutrition and oxygen deficiencies in the
myocardial tissues to induce the above diseases.
15 Percutaneous transluminal coronary angioplasty (hereinafter
abbreviated as "PTCA") that has recently been developed as a
treatment for the ischemic heart diseases such as angina
pectoris and cardiac infarction is to physically dilate a
blood vessel by inflating a balloon at the stenosis region of
20 the coronary artery. However, the problem which has been
recognized from the beginning of development of this
treatment is that restenosis appears at the treated region
within 3 to 6 months after the angioplasty at a frequency of
about 40% (see Circulation, 77, pp. 361-371 (1988)).

25 Up to the present time, use of anticoagulants,
antiplatelet agents or drugs having an inhibitory effect on
proliferation of vascular smooth muscle cells has been
attempted to prevent stenosis due to arteriosclerotic intimal

thickening or restenosis after PTCA. Thus, an extensive research for such drug has been conducted (see, for example, JP 2-121922 A/90, JP 3-83923 A/91, JP 3-118383 A/91, JP 4-99775 A/92, JP 4-154720 A/92, JP 6-135829 A/94, JP 6-206842 A/94, JP 7-25768 A/95, JP 7-149641 A/95 and JP 7-223958 A/95). However, there has been found no drug having clinically sufficient inhibitory effect on vascular stenosis due to arteriosclerotic intimal thickening or restenosis due to intimal thickening after PTCA (see, Nihon Rinsyo, 52 (extra ed.), pp. 869-872 (1994)).

Disclosure of the Invention

As a result of an extensive research in an attempt to solve the foregoing problem, it has been found that a compound represented by formula (1):



wherein X represents an oxygen atom or a group of formula (2);



wherein n represents an integer of from 0 to 2;

R₁ represents a hydrogen atom or an acyl group;

R₂ represents a hydrogen atom, a lower alkyl group or a lower alkenyl group;

R₃ represents a lower alkyl group; and

R₄, R₅, and R₆, which may be the same or different, each represent a hydrogen atom, a substituted or unsubstituted alkyl group, a substituted or unsubstituted alkenyl group, a substituted or unsubstituted alkynyl group, or a substituted or unsubstituted aryl group; or

R₃ and R₄ may be taken together to form a 5-membered ring; or

R₅ and R₆ may be taken together to form a cycloalkyl group or a heterocyclic ring derived from a cycloalkyl group by substituting any one or more methylene groups on the ring with oxygen atoms, sulfur atoms or alkyl-substituted nitrogen atoms;

provided that R₆ is nil when R₃ and R₄ are taken together to form a benzofuran ring, a benzo[b]thiophene ring, a benzo[b]thiophene-1-oxide ring or a benzo[b]thiophene-1,1-dioxide ring,

exhibits an excellent inhibitory effect on proliferation of vascular smooth muscle cells as well as on intimal thickening in balloon injury models.

The fact that the compound represented by formula (1) is effective in the treatment and prevention of ischemic organopathy such as arteriosclerosis, cardiac infarction and apoplexy has already been revealed (see JP 6-206842 A/94, WO 94-08930, and WO 95-27710).

Best Mode for Carrying Out the Invention

In the above formula (1), the acyl groups include an acetyl group, a formyl group, a propionyl group, a benzoyl group, a benzyloxycarbonyl group, an aminoacetyl group, an N-

methylaminoacetyl group, and an N,N-dimethylaminoacetyl group. The term "lower alkyl group" means a straight- or branched-chain alkyl group having 1 to 6 carbon atoms, for example, a methyl group, an ethyl group, a n-propyl group, an i-propyl group, a n-butyl group, a sec-butyl group, and a tert-butyl group. The term "lower alkenyl group" means a straight- or branched-chain alkenyl group having 2 to 6 carbon atoms, for example, a vinyl group, an allyl group, a butenyl group, and a pentenyl group.

10 The alkyl group represented by R_4 , R_5 , or R_6 is a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, for example, a methyl group, an ethyl group, a n-propyl group, an i-propyl group, a n-butyl group, a sec-butyl group, a tert-butyl group, a pentyl group, a hexyl group, a
15 heptyl group, an octyl group, a nonyl group, and a decyl group. The alkenyl group is a straight- or branched-chain alkenyl group having 2 to 20 carbon atoms, for example, a vinyl group, an allyl group, a butenyl group, a pentenyl group, a geranyl group, and a farnesyl group. The alkynyl
20 group is a straight- or branched-chain alkynyl group having 2 to 20 carbon atoms, for example, an ethynyl group, a propynyl group, and a butynyl group. The aryl group is a monovalent substituent derived from an aromatic hydrocarbon by removing one hydrogen atom, for example, a phenyl group, a tolyl group,
25 a xylyl group, a biphenyl group, a naphthyl group, an anthryl group, and a phenanthryl group. Substituents in the substituted alkyl, alkenyl, alkynyl or aryl group include a halogen atom, a lower alkyl group, a hydroxyl group, an amino

group, an alkoxy group, an aryloxy group, a nitro group, and a trifluoromethyl group.

The 5-membered rings formed by R_3 and R_4 include a furan ring, a dihydrofuran ring, a thiophene ring, and a dihydrothiophene ring, which are taken together with the benzene ring to form a benzofuran ring, a dihydrobenzofuran ring, a benzo[b]thiophene ring, and a dihydrobenzothiophene ring, respectively.

The cycloalkyl group is a cycloalkyl group having 3 to 8 carbon atoms, for example, a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group, a cycloheptyl group, and a cyclooctyl group. The heterocyclic rings derived from the cycloalkyl group by substituting any one or more methylene groups on the ring with oxygen atoms, sulfur atoms or alkyl-substituted nitrogen atoms include, for example, a tetrahydropyranyl group.

Where X in formula (1) is an oxygen atom,

R_1 is preferably a hydrogen atom, an acetyl group, a benzyloxycarbonyl group, an aminoacetyl group, an N-methylaminoacetyl group or an N,N-dimethylaminoacetyl group, particularly a hydrogen atom, an acetyl group or an N,N-dimethylaminoacetyl group;

R_2 is preferably a hydrogen atom, a methyl group or a n-propyl group, particularly a hydrogen atom;

R_3 and R_4 are preferably taken together to form a furan ring or a dihydrofuran ring, particularly a dihydrofuran ring;

R_5 is preferably a hydrogen atom, a methyl group, a

n-butyl group, a n-pentyl group, a n-hexyl group or an i-amyl group, particularly a n-pentyl group; and

R₆ is preferably a hydrogen atom, a methyl group, a n-butyl group, a n-pentyl group, a n-hexyl group or an i-amyl group, particularly a n-pentyl group; or

R₅ and R₆ are preferably taken together to form a cyclopentyl group, a cyclohexyl group, a cycloheptyl group, a cyclooctyl group, or a tetrahydropyranyl group, particularly a cyclohexyl group, a cycloheptyl group, or a cyclooctyl group.

Where X in formula (1) is a group represented by formula (2):



wherein n is an integer of from 0 to 2,

R₁ is preferably a hydrogen atom, an acetyl group, a benzyloxycarbonyl group, an aminoacetyl group, an N-methyl-aminoacetyl group or an N,N-dimethylaminoacetyl group, particularly a hydrogen atom, an acetyl group or an N,N-dimethylaminoacetyl group;

R₂ is preferably a hydrogen atom, a methyl group or an n-propyl group, particularly a hydrogen atom;

R₃ and R₄ are preferably taken together to form a thiophene ring or a dihydrothiophene ring, particularly a dihydrothiophene ring;

R₅ is preferably a hydrogen atom, a methyl group, a n-butyl group, a n-pentyl group, a n-hexyl group or an i-amyl group, particularly a n-pentyl group; and

R₆ is preferably a hydrogen atom, a methyl group, a n-butyl group, a n-pentyl group, a n-hexyl group or an i-amyl group, particularly a n-pentyl group; or

R₅ and R₆ are preferably taken together to form a
 5 cyclopentyl group, a cyclohexyl group, a cycloheptyl group, a cyclooctyl group, or a tetrahydropyranyl group, particularly a cyclohexyl group, a cycloheptyl group, or a cyclooctyl group; and

n is preferably 0 or 1, particularly 0.

10 Examples of the specific compounds used for the inhibitory agent of the present invention include 4,6-di-t-butyl-5-hydroxy-2,3-dihydrobenzofuran, 4,6-di-t-butyl-5-hydroxy-2-methyl-2,3-dihydrobenzofuran, 4,6-di-t-butyl-5-hydroxy-2,2-dimethyl-2,3-dihydrobenzofuran, 4,6-di-t-butyl-
 15 2,2-diethyl-5-hydroxy-2,3-dihydrobenzofuran, 4,6-di-t-butyl-2,2-di-n-propyl-5-hydroxy-2,3-dihydrobenzofuran, 4,6-di-t-butyl-2,2-di-n-butyl-5-hydroxy-2,3-dihydrobenzofuran, 4,6-di-t-butyl-5-hydroxy-2-octylbenzofuran, 4,6-di-t-butyl-5-hydroxy-2-octyl-2,3-dihydrobenzofuran, 2,4,6-tri-t-butyl-5-hydroxy-2,3-dihydrobenzofuran, 4,6-di-t-butyl-2,2-di-i-propyl-5-hydroxy-2,3-dihydrobenzofuran, 4,6-di-t-butyl-2,2-diphenyl-5-hydroxy-2,3-dihydrobenzofuran, 4,6-di-t-butyl-2,2-dibenzyl-5-hydroxy-2,3-dihydrobenzofuran, 4,6-di-t-butyl-2-chloromethyl-5-hydroxy-2,3-dihydrobenzofuran, 4,6-di-t-butyl-
 20 5-hydroxy-2,3-dihydrobenzofuran-2-spiro-1'-cyclopentane, 4,6-di-t-butyl-5-hydroxy-2,3-dihydrobenzofuran-2-spiro-1'-cyclohexane, 4,6-di-t-butyl-5-hydroxy-2,3-dihydrobenzofuran-2-spiro-1'-cycloheptane, 4,6-di-t-butyl-5-hydroxy-2,3-

dihydrobenzofuran-2-spiro-1'-cyclooctane, 4,6-di-t-butyl-5-hydroxy-2,3-dihydrobenzofuran-2-spiro-4'-tetrahydropyran, 5-hydroxy-4,6-di-t-butyl-2,2-dimethyl-7-propyl-2,3-dihydrobenzofuran, 4,6-di-t-butyl-5-hydroxybenzofuran, 4,6-di-t-butyl-5-hydroxy-2-methylbenzofuran, 2,4,6-tri-t-butyl-5-hydroxybenzofuran, 2,6-di-t-butyl-3-methyl-4-propyloxyphenol, 4-allyloxy-2,6-di-t-butyl-3-methylphenol, 1,3-bis(3,5-di-t-butyl-4-hydroxy-2-methylphenoxy)propane, 4,6-di-t-butyl-2,2-di-n-pentyl-5-hydroxy-2,3-dihydrobenzofuran, 4,6-di-t-butyl-2,2-di-n-octyl-5-hydroxy-2,3-dihydrobenzofuran, 4,6-di-t-butyl-2,2-di-n-heptyl-5-hydroxy-2,3-dihydrobenzofuran, 4,6-di-t-butyl-2,2-di-n-hexyl-5-hydroxy-2,3-dihydrobenzofuran, 2,2-di-i-amyl-4,6-di-t-butyl-5-hydroxy-2,3-dihydrobenzofuran, 4,6-di-t-butyl-5-hydroxy-2-methyl-2-(4,8,12-trimethyltrideca-3(E),7(E),11-trienyl)-2,3-dihydrobenzofuran, 4,6-di-t-butyl-5-hydroxy-2-methyl-2-(4',8',12'-trimethyltridecyl)-2,3-dihydrobenzofuran, 4,6-di-t-butyl-5-hydroxy-2-(5-hydroxy-4-methyl-3(E)-pentenyl)-2-methyl-2,3-dihydrobenzofuran, 4,6-di-t-butyl-5-hydroxy-2-hydroxymethyl-2-methyl-2,3-dihydrobenzofuran, 4,6-di-t-butyl-5-hydroxy-2,2-di-n-pentyl-2,3-dihydrobenzothiophene, 4,6-di-t-butyl-5-hydroxy-2-methyl-2,3-dihydrobenzothiophene, 4,6-di-t-butyl-5-hydroxy-2,2-dimethyl-2,3-dihydrobenzothiophene, 4,6-di-t-butyl-5-hydroxybenzo[b]thiophene, 4,6-di-t-butyl-5-hydroxy-2,3-dihydrobenzothiophene, 4,6-di-t-butyl-5-hydroxy-2,2-diethyl-2,3-dihydrobenzothiophene, 4,6-di-t-butyl-5-hydroxy-2,2-di-n-propyl-2,3-dihydrobenzothiophene, 4,6-di-t-butyl-5-hydroxy-2,2-di-i-propyl-2,3-dihydrobenzothiophene, 4,6-di-t-butyl-5-

- hydroxy-2,2-di-n-butyl-2,3-dihydrobenzothiophene, 4,6-di-t-butyl-5-hydroxy-2,2-di-i-amyl-2,3-dihydrobenzothiophene, 4,6-di-t-butyl-5-hydroxy-2,2-di-n-hexyl-2,3-dihydrobenzothiophene, 4,6-di-t-butyl-5-hydroxy-2,2-di-n-heptyl-2,3-
- 5 dihydrobenzothiophene, 4,6-di-t-butyl-5-hydroxy-2,2-di-n-octyl-2,3-dihydrobenzothiophene, 4,6-di-t-butyl-5-hydroxy-2,2-diphenyl-2,3-dihydrobenzothiophene, 4,6-di-t-butyl-5-hydroxy-2,2-dibenzyl-2,3-dihydrobenzothiophene, 4,6-di-t-butyl-5-hydroxy-2-methyl-2-(4,8,12-trimethyltrideca-
- 10 3(E),7(E),11-trienyl)-2,3-dihydrobenzothiophene, 4,6-di-t-butyl-5-hydroxy-2-methyl-2-(4,8,12-trimethyltridecyl)-2,3-dihydrobenzothiophene, 4,6-di-t-butyl-5-hydroxy-2-n-octyl-2,3-dihydrobenzothiophene, 2,4,6-tri-t-butyl-5-hydroxy-2,3-dihydrobenzothiophene, 4,6-di-t-butyl-5-hydroxy-2,2-dimethyl-
- 15 7-n-propyl-2,3-dihydrobenzothiophene, 4,6-di-t-butyl-5-hydroxy-2,3-dihydrobenzothiophene-2-spiro-1'-cyclopentane, 4,6-di-t-butyl-5-hydroxy-2,3-dihydrobenzothiophene-2-spiro-1'-cyclohexane, 4,6-di-t-butyl-5-hydroxy-2,3-dihydrobenzothiophene-2-spiro-1'-cycloheptane, 4,6-di-t-
- 20 butyl-5-hydroxy-2,3-dihydrobenzothiophene-2-spiro-1'-cyclooctane, 4,6-di-t-butyl-2-methyl-5-hydroxybenzo[b]thiophene, 2,4,6-tri-t-butyl-5-hydroxybenzo[b]thiophene, 4,6-di-t-butyl-2-octyl-5-hydroxybenzo[b]thiophene, 4,6-di-t-butyl-5-hydroxy-2-(N,N-
- 25 dimethylaminomethyl)-2-methyl-2,3-dihydrobenzothiophene, 4,6-di-t-butyl-5-hydroxy-2-hydroxymethyl-2-methyl-2,3-dihydrobenzothiophene, 4,6-di-t-butyl-5-hydroxy-2-methyl-2-(4,8-dimethylnona-3(E),7-dienyl)-2,3-dihydrobenzothiophene,

and 4,6-di-t-butyl-5-hydroxy-2-methyl-2-(4,8-dimethylnonyl)-
2,3-dihydrobenzothiophene.

The compound represented by formula (1) used in the
present invention is synthesized in accordance with, for
5 example, the process described in JP 6-206842 A/94 or WO 95-
27710.

The vascular intimal thickening inhibitory agent of
the present invention can be used in the form of a
pharmaceutical composition comprising a compound of formula
10 (1) together with physiologically non-toxic solid or liquid
pharmaceutical carrier. The pharmaceutical composition may be
in a variety of dosage forms depending on the administration
route. Suitable dosage forms include tablets, granules,
pills, capsules, solutions, syrups, suspensions, emulsions,
15 and injection solutions. Usual pharmaceutical carriers, such
as excipient, binder, disintegrant, lubricant, coating agent,
solubilizer, emulsifier, suspending agent, stabilizer, and
solvents, may be used.

The compound represented by formula (1) and the above
20 pharmaceutical composition according to the present invention
can be administered by an oral or parenteral route such as
intravenous injection or as a sustained release formulation
or by a topical route, such as through a catheter.

The actual dosage of the compound of formula (1) to
25 be required for inhibiting restenosis after PTCA depends on
the age of the patient, the severity of the condition to be
treated, the administration route, and the like. However,
the effective dosage which is generally accepted will be in

the range of, for example, 1 to 1000 mg, preferably 100 to 300 mg per day in the treatment of adult human. The dosage is preferably given in 1 to 3 dose administrations daily to the patient in need of such treatment.

5 Examples

The present invention will now be illustrated with reference to the following Examples, but it should be understood that the present invention is not construed as being limited thereto.

10 The compounds of Examples 1 to 46 were synthesized in accordance with the process described in JP 6-206842 A/94.

Example 1: 4,6-Di-t-butyl-5-hydroxy-2,3-dihydrobenzofuran

Example 2: 4,6-Di-t-butyl-5-hydroxy-2-methyl-2,3-dihydrobenzofuran

15 Example 3: 5-Acetoxy-4,6-di-t-butyl-2,2-dimethyl-2,3-dihydrobenzofuran

Example 4: 4,6-Di-t-butyl-5-hydroxy-2,2-dimethyl-2,3-dihydrobenzofuran

20 Example 5: 5-Acetoxy-4,6-di-t-butyl-2,2-diethyl-2,3-dihydrobenzofuran

Example 6: 4,6-Di-t-butyl-2,2-diethyl-5-hydroxy-2,3-dihydrobenzofuran

Example 7: 4,6-Di-t-butyl-2,2-di-n-propyl-5-hydroxy-2,3-dihydrobenzofuran

25 Example 8: 4,6-Di-t-butyl-2,2-di-n-butyl-5-hydroxy-2,3-dihydrobenzofuran

Example 9: 5-Acetoxy-4,6-di-t-butyl-2-(1-octenyl)benzofuran

Example 10: 5-Acetoxy-4,6-di-t-butyl-2-octylbenzofuran

- Example 11: 4,6-Di-t-butyl-5-hydroxy-2-octylbenzofuran
- Example 12: 4,6-Di-t-butyl-5-hydroxy-2-octyl-2,3-dihydrobenzofuran
- Example 13: 2,4,6-Tri-t-butyl-5-hydroxy-2,3-dihydrobenzofuran
- 5 Example 14: 4,6-Di-t-butyl-2,2-di-i-propyl-5-hydroxy-2,3-dihydrobenzofuran
- Example 15: 4,6-Di-t-butyl-2,2-diphenyl-5-hydroxy-2,3-dihydrobenzofuran
- 10 Example 16: 4,6-Di-t-butyl-2,2-dibenzyl-5-hydroxy-2,3-dihydrobenzofuran
- Example 17: 4,6-Di-t-butyl-2-chloromethyl-5-hydroxy-2,3-dihydrobenzofuran
- Example 18: 4,6-Di-t-butyl-5-hydroxy-2,3-dihydrobenzofuran-2-spiro-1'-cyclopentane
- 15 Example 19: 4,6-Di-t-butyl-5-hydroxy-2,3-dihydrobenzofuran-2-spiro-1'-cyclohexane
- Example 20: 4,6-Di-t-butyl-5-hydroxy-2,3-dihydrobenzofuran-2-spiro-1'-cycloheptane
- 20 Example 21: 4,6-Di-t-butyl-5-hydroxy-2,3-dihydrobenzofuran-2-spiro-1'-cyclooctane
- Example 22: 4,6-Di-t-butyl-5-hydroxy-2,3-dihydrobenzofuran-2-spiro-4'-tetrahydropyran
- Example 23: 4-Acetoxy-3,5-di-t-butyl-1-(2-methyl-2-propenyloxy)-2-propylbenzene
- 25 Example 24: 5-Acetoxy-4,6-di-t-butyl-2,2-dimethyl-7-propyl-2,3-dihydrobenzofuran
- Example 25: 5-Hydroxy-4,6-di-t-butyl-2,2-dimethyl-7-propyl-

2,3-dihydrobenzofuran

Example 26: 5-Acetoxy-4,6-di-t-butylbenzofuran

Example 27: 4,6-Di-t-butyl-5-hydroxybenzofuran

Example 28: 4,6-Di-t-butyl-5-hydroxy-2-methylbenzofuran

5 Example 29: 2,4,6-Tri-t-butyl-5-hydroxybenzofuran

Example 30: 1-Acetoxy-2,6-di-t-butyl-3-methyl-4-propyloxybenzene

Example 31: 2,6-Di-t-butyl-3-methyl-4-propyloxyphenol

10 Example 32: 1-Acetoxy-4-allyloxy-2,6-di-t-butyl-3-methylbenzene

Example 33: 4-Allyloxy-2,6-di-t-butyl-3-methylphenol

Example 34: 1,3-Bis(4-acetoxy-3,5-di-t-butyl-2-methylphenoxy)propane

15 Example 35: 1,3-Bis(3,5-di-t-butyl-4-hydroxy-2-methylphenoxy)propane

Example 36: 4,6-Di-t-butyl-2,2-di-n-pentyl-5-hydroxy-2,3-dihydrobenzofuran

Example 37: 4,6-Di-t-butyl-2,2-di-n-octyl-5-hydroxy-2,3-dihydrobenzofuran

20 Example 38: 4,6-Di-t-butyl-2,2-di-n-heptyl-5-hydroxy-2,3-dihydrobenzofuran

Example 39: 4,6-Di-t-butyl-2,2-di-n-hexyl-5-hydroxy-2,3-dihydrobenzofuran

25 Example 40: 5-Acetoxy-2,2-di-i-amyl-4,6-di-t-butyl-2,3-dihydrobenzofuran

Example 41: 2,2-Di-i-amyl-4,6-di-t-butyl-5-hydroxy-2,3-dihydrobenzofuran

Example 42: 5-Acetoxy-4,6-di-t-butyl-2-methyl-2-(4,8,12-

trimethyltrideca-3(E),7(E),11-trienyl)-2,3-dihydrobenzofuran

Example 43: 4,6-Di-t-butyl-5-hydroxy-2-methyl-2-(4,8,12-trimethyltrideca-3(E),7(E),11-trienyl)-2,3-dihydrobenzofuran

Example 44: 4,6-Di-t-butyl-5-hydroxy-2-methyl-2-(4',8',12'-trimethyltridecyl)-2,3-dihydrobenzofuran

Example 45: 5-Acetoxy-4,6-di-t-butyl-2-(5-hydroxy-4-methyl-3(E)-pentenyl)-2-methyl-2,3-dihydrobenzofuran

Example 46: 4,6-Di-t-butyl-5-hydroxy-2-(5-hydroxy-4-methyl-3(E)-pentenyl)-2-methyl-2,3-dihydrobenzofuran

Example 47: 5-Acetoxy-4,6-di-t-butyl-2-hydroxymethyl-2-methyl-2,3-dihydrobenzofuran

In 200 ml of chloroform was dissolved 10.0 g of 4-acetoxy-3,5-di-t-butyl-2-(2-methyl-2-propenyl)phenol synthesized in accordance with JP 6-206842 A/94, and 11.0 g of m-chloroperbenzoic acid was added thereto, followed by heating under reflux for one day. After cooling, a saturated aqueous solution of sodium thiosulfate was added to the reaction mixture, and the mixture was extracted with chloroform. The organic layer was washed with a saturated sodium chloride aqueous solution, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography (25% ethyl acetate in n-hexane) to give 7.3 g (yield: 70%) of 5-acetoxy-4,6-di-t-butyl-2-hydroxymethyl-2-methyl-2,3-dihydrobenzofuran (rotational isomer mixture) as a colorless oil.

¹H-NMR (270 MHz, CDCl₃) δ ppm:

1.30 (s, 9H), 1.37 (s, 9H), 1.38 (s, 1.5H), 1.45
 (s, 1.5H), 2.30 (s, 3H), 3.06 (d, 0.5H, J=15.5Hz),
 3.16 (d, 0.5H, J=15.5Hz), 3.38 (d, 0.5H, J=15.5Hz),
 3.52 (d, 0.5H, J=15.5Hz), 3.58-3.72 (m, 2H), 6.75
 5 (s, 0.5H), 6.76 (s, 0.5H).

Mass: 334 (M⁺)

Example 48: 4,6-Di-t-butyl-5-hydroxy-2-hydroxymethyl-2-
 methyl-2,3-dihydrobenzofuran

A solution of 500 mg of 5-acetoxy-4,6-di-t-butyl-
 10 2-hydroxymethyl-2-methyl-2,3-dihydrobenzofuran in 7 ml of
 tetrahydrofuran was added dropwise to a suspension of 114 mg
 of lithium aluminum hydride in 3 ml of tetrahydrofuran under
 nitrogen atmosphere. The reaction mixture was heated under
 reflux for 2 hours. After allowing the mixture to attain
 15 room temperature, ethyl acetate was added dropwise, 10%
 hydrochloric acid was added thereto, and the mixture was
 extracted with ethyl acetate. The organic layer was dried
 over anhydrous magnesium sulfate and concentrated. The
 residue was purified by silica gel column chromatography (20%
 20 ethyl acetate in n-hexane) to yield 320 mg (73%) of 4,6-di-t-
 butyl-5-hydroxy-2-hydroxymethyl-2-methyl-2,3-
 dihydrobenzofuran as a white solid.

Melting point: 126-128°C

¹H-NMR (270 MHz, CDCl₃) δ ppm:

25 1.38 (s, 3H), 1.40 (s, 9H), 1.49 (s, 9H), 2.04 (bs,
 1H), 3.14 (d, 1H, J=15.5Hz), 3.45 (d, 1H,
 J=15.5Hz), 3.59 (d, 2H, J=1.65Hz), 4.74 (s, 1H),
 6.65 (s, 1H).

IR (cm⁻¹): 3648, 3448, 2960

Mass: 292 (M⁺)

The compounds of Examples 49 to 67 were synthesized according to the process described in WO 95-27710.

- 5 Example 49: 5-Acetoxy-4,6-di-t-butyl-2,2-di-n-pentyl-2,3-dihydrobenzothiophene
- Example 50: 4,6-Di-t-butyl-5-hydroxy-2,2-di-n-pentyl-2,3-dihydrobenzothiophene
- Example 51: 4,6-Di-t-butyl-5-hydroxy-2-methyl-2,3-dihydrobenzothiophene
- 10 Example 52: 4,6-Di-t-butyl-5-hydroxy-2,2-dimethyl-2,3-dihydrobenzothiophene
- Example 53: 5-Acetoxy-4,6-di-t-butylbenzo[b]thiophene
- Example 54: 4,6-Di-t-butyl-5-hydroxybenzo[b]thiophene
- 15 Example 55: 5-Acetoxy-4,6-di-t-butylbenzo[b]thiophene-1,1-dioxide
- Example 56: 5-Acetoxy-4,6-di-t-butyl-2,3-dihydrobenzothiophene-1,1-dioxide
- Example 57: 4,6-Di-t-butyl-5-hydroxy-2,3-dihydrobenzothiophene
- 20 Example 58: 4,6-Di-t-butyl-5-hydroxy-2,3-dihydrobenzothiophene-2-spiro-1'-cyclohexane
- Example 59: 5-Acetoxy-4,6-di-t-butyl-2-iodomethyl-2-methyl-2,3-dihydrobenzothiophene
- 25 Example 60: 5-Acetoxy-4,6-di-t-butyl-2-(N,N-dimethylaminomethyl)-2-methyl-2,3-dihydrobenzothiophene
- Example 61: 4,6-Di-t-butyl-5-hydroxy-2-(N,N-

dimethylaminomethyl)-2-methyl-2,3-
dihydrobenzothiophene

Example 62: 5-Acetoxy-2-acetoxymethyl-4,6-di-t-butyl-2-methyl-2,3-dihydrobenzothiophene

5 Example 63: 4,6-Di-t-butyl-5-hydroxy-2-hydroxymethyl-2-methyl-2,3-dihydrobenzothiophene

Example 64: 4,6-Di-t-butyl-5-hydroxy-2-methyl-2-(4,8-dimethylnona-3(E),7-dienyl)-2,3-dihydrobenzothiophene

10 Example 65: 4,6-Di-t-butyl-5-hydroxy-2-methyl-2-(4,8-dimethylnonyl)-2,3-dihydrobenzothiophene

Example 66: 4,6-Di-t-butyl-5-hydroxy-2-methyl-2-(4,8,12-trimethyltrideca-3(E),7(E),11-trienyl)-2,3-dihydrobenzothiophene

15 Example 67: 4,6-Di-t-butyl-5-hydroxy-2-methyl-2-(4,8,12-trimethyltridecyl)-2,3-dihydrobenzothiophene

Test Example 1: Inhibitory Effect on Proliferation of
Vascular Smooth Muscle Cells (in vitro)

In order to assess the inhibitory effect of a
20 compound of the present invention on serum-stimulated proliferation of vascular smooth muscle cells in vitro, the compound obtained in Example 36 was tested using A7r5 cells derived from the aorta of a rat (ATCC-CRL-1444).

Using DMEM medium containing 10% FBS, the cells
25 were placed on 96-well microtiter plates with 5×10^3 cells/0.2 ml/well and then incubated. The medium was exchanged for 2% FBS-containing DMEM medium on the third day and then for 0.2% FBS-containing DMEM medium on the fourth

day from the start of the incubation. After 48-hour incubation in the 0.2% FBS-containing DMEM medium, the medium was removed, 0.1 ml of DMEM medium and the test compound were added, and the cells were stimulated with serum (2% FBS) to proliferate. The test compound was added to the wells in the form of a solution or suspension in ethanol in an amount of 0.5 μ l/well to final compound concentrations indicated in Table 1 below and the resultant ethanol concentration of 0.5% in each well. BrdU was pulsed to the wells from the 16th to 38th hours or from the 38th to 64th hours after the stimulation to a final concentration of 10 μ M, and the uptake of BrdU into DNA was evaluated as an indication of cell proliferation. The BrdU uptake was measured by means of an EIA kit containing an anti-BrdU antibody (5-Bromo-2'-deoxy-uridine Labeling and Detection Kit III, available from Bohringer Mannheim Biochemica). The results obtained are shown in Table 1 below.

TABLE 1

Inhibitory Effect on Proliferation
of Vascular Smooth Muscle Cells (1)

	Concn. (μ M)	Absorbance (difference between 405 nm and 492 nm)	
		16-38 hrs.	38-64 hrs.
Control		0.433 $\pm$ 0.008	0.436 $\pm$ 0.060
Example 36	10	0.397 $\pm$ 0.054	0.195 $\pm$ 0.017
Example 36	30	0.362 $\pm$ 0.026	0.085 $\pm$ 0.006
Example 36	100	0.290 $\pm$ 0.031	0.049 $\pm$ 0.006

5

n=3; Mean $\pm$ Standard Deviation

As is shown in Table 1, the compound of Example 36 inhibits the serum-stimulated proliferation of vascular smooth muscle cells dose-dependently.

Test Example 2: Inhibitory Effect on Proliferation of

10

Vascular Smooth Muscle Cells (in vitro)

In order to assess the inhibitory effect of a compound of the present invention on serum- or PDGF-stimulated proliferation of vascular smooth muscle cells in vitro, the compound obtained in Example 36 was tested using A7r5 cells derived from the aorta of a rat (ATCC-CRL-1444). Further, the effect was compared with that of α -tocopherol which was reported to have an inhibitory effect on proliferation of vascular smooth muscle cells (see J. Biol. Chem., 266, pp. 6188-6194 (1991)).

20

Using DMEM medium containing 10%FBS, the cells

were placed on 96-well microtiter plates with 5×10^3 cells/0.2 ml/well and then incubated. The medium was exchanged for 2% FBS-containing DMEM medium on the third day and then for 0.2% FBS-containing DMEM medium on the fourth
5 day from the start of the incubation. After 48-hour incubation in the 0.2% FBS-containing DMEM medium, the medium was removed, 0.2 ml of DMEM medium and the test compound were added, and the cells were stimulated with serum (2% FBS) or PDGF (PDGF-BB: human origin, available from Becton Dickinson
10 Labware) (4 ng/ml) to proliferate. The test compound was added to the wells in the form of a solution or suspension in ethanol in amount of $1 \mu\text{l}$ /well to final compound concentrations indicated in Table 2 below and the resultant ethanol concentration of 0.5% in each well. Eight hours
15 after the stimulation, hydroxyurea was added to a final concentration of 1.5 mM to synchronize the cell cycle strictly. After additional 14-hour incubation, the medium containing hydroxyurea was removed and the cells were washed, and DMEM medium, the test compound and the proliferation
20 stimulator were added thereto again. Further, [^3H]-thymidine (1 μCi /well; 20 μCi /mmol; available from NEN Research) was added. The [^3H]-thymidine uptake in 5 hours was measured as an indication of cell proliferation. The results obtained are shown in Table 2 below.

TABLE 2

Inhibitory Effect on Proliferation
of Vascular Smooth Muscle Cells (2)

	Concn. (μ M)	Count by Liquid Scintillation Counter	
		FBS Stimulation (CPM)	PDGF Stimulation (CPM)
Control		42789 $\pm$ 1063	24517 $\pm$ 2370
α -Tocopherol	30	28058 $\pm$ 3912	12493 $\pm$ 2978
α -Tocopherol	100	25706 $\pm$ 4160	12159 $\pm$ 2362
Example 36	100	14147 $\pm$ 1372	7881 $\pm$ 356

5

n=3; Mean $\pm$ Standard Deviation

As shown in Table 2 above, the compound of Example 36 inhibits serum- or PDGF-stimulated proliferation of vascular smooth muscle cells. The inhibitory effect of the compound is higher than that of α -tocopherol.

10 Test Example 3: Inhibitory Effect on Proliferation of
Vascular Smooth Muscle Cells (in vitro)

In order to assess the inhibitory effect of the compounds of the present invention on serum-stimulated proliferation of vascular smooth muscle cells in vitro, the
15 compounds of Examples 1, 4, 20, 22, 27, 31, 36, 50, 52, and 58 were tested using A7r5 cells derived from the aorta of a rat (ATCC-CRL-1444).

Using DMEM medium containing 10% FBS, the cells were placed on 96-well microtiter plates with 5×10^3
20 cells/0.2 ml/ well and then incubated. The medium was exchanged for 2% FBS-containing DMEM medium on the third day

and then for 0.2% FBS-containing DMEM medium on the fourth day from the start of the incubation. After 24-hour incubation in the 0.2% FBS-containing DMEM medium, the test compound was added. Each of the test compounds were added to
5 the wells in the form of a solution or suspension in ethanol in an amount of 1 µl/well to final compound concentrations indicated in Table 3 below and the resultant ethanol concentration of 0.5% in each well. After additional 24-hour incubation, the medium was removed, and 0.2 ml of DMEM medium
10 and the test compound were added thereto again, and the cells were stimulated by serum (2% FBS). Forty-eight hours after the stimulation, the acid phosphatase activity in the wells was measured by means of a kit (ABACUS CELL PROLIFERATION KIT*, available from Clontech Lab. Inc. CA, U.S.A.) and evaluated
15 as an indication of cell proliferation. The results obtained are shown in Table 3 below.

* Trade-mark

TABLE 3

Inhibitory Effect on Proliferation
of Vascular Smooth Muscle Cells (3)

Test Compound	Concn. (μ M)	Acid Phosphatase Activity	
		Absorbance (OD405)	% Control (%)
Control		0.867 $\pm$ 0.089	100 $\pm$ 10
Example 1	10	0.727 $\pm$ 0.032	84 $\pm$ 4
	100	0.288 $\pm$ 0.073	33 $\pm$ 8
Example 22	10	0.875 $\pm$ 0.013	101 $\pm$ 1
	100	0.777 $\pm$ 0.062	90 $\pm$ 7
Example 31	10	0.756 $\pm$ 0.025	87 $\pm$ 3
	100	0.600 $\pm$ 0.102	69 $\pm$ 12
Example 36	10	0.733 $\pm$ 0.060	84 $\pm$ 7
	100	0.539 $\pm$ 0.055	62 $\pm$ 6
Example 4	10	0.606 $\pm$ 0.020	70 $\pm$ 2
	30	0.062 $\pm$ 0.026	7 $\pm$ 3
Example 20	10	0.472 $\pm$ 0.031	54 $\pm$ 4
	30	0.105 $\pm$ 0.027	12 $\pm$ 3
Example 27	10	0.553 $\pm$ 0.033	64 $\pm$ 4
	30	0.225 $\pm$ 0.064	26 $\pm$ 7
Example 50	10	0.699 $\pm$ 0.131	81 $\pm$ 15
	30	0.146 $\pm$ 0.026	17 $\pm$ 3
Example 52	10	0.690 $\pm$ 0.071	80 $\pm$ 8
	30	0.043 $\pm$ 0.008	5 $\pm$ 1
Example 58	10	0.417 $\pm$ 0.125	48 $\pm$ 14
	30	0.045 $\pm$ 0.006	5 $\pm$ 1

5

n=3, Mean $\pm$ Standard Deviation

As is shown in Table 3, all the compounds tested inhibit the serum-stimulated proliferation of vascular smooth muscle cells.

Test Example 4: In Vivo Effect in Intimal Thickening Model

5 (1)

In order to assess the inhibitory effect of the compound of the present invention on intimal thickening in vivo, the compound of Example 36 was tested using rabbit balloon injury models.

10 Cholesterol-fed rabbits in groups of eight (JW: CSK male, 11-week-old) were used to prepare rabbit balloon injury models. Briefly, rabbits were fed with a high cholesterol diet (cholesterol content: 1%) for 2 weeks before balloon treatment. The animals were balloon-treated with a
15 balloon catheter (3 French, available from Baxter) under anesthesia to peel the aortic intima 5 times. The animals were orally administered with the compound which was suspended in a 1% carboxymethyl cellulose (CMC) solution (200 mg/kg). On the other hand, control animals were orally
20 administered with a 1% CMC solution without the compound. The administrations were performed once a day from 1 week before the balloon treatment until the day before the dissection for evaluation.

After four weeks from the balloon treatment,
25 specimens were taken from the aorta, stained with Elastica van Gelson, and analyzed under an optical microscope. The image was processed to measure the thickness and area of the thickened intima. Averages of the thickness and area were

obtained for each individual animal. The animals which died due to the operation and those having a serum cholesterol level of 3500 mg/dl or higher were excluded from the measurement. The number of animals used for the evaluation was 5 or 6 per group. The results obtained are shown in Table 4.

TABLE 4

Inhibitory Effect on Intimal
Thickening in Balloon Injury Models (1)

	Control	Compound of Example 36
Thickness of Intima (μm)	103 $\pm$ 12	45 $\pm$ 31**
Area of Intima (mm^2)	0.26 $\pm$ 0.03	0.11 $\pm$ 0.08**

Means $\pm$ Standard Deviation; **: P<0.01

As shown in Table 4, the compound of Example 36 exhibits significant inhibitory effect on intimal thickening in the rabbit balloon injury intimal thickening models on both parameters of intimal thickness and intimal area.

Test Example 5: In Vivo Effect in Intimal Thickening Model
(2)

In order to assess the inhibitory effect of the compound of the present invention on intimal thickening in vivo, the compound of Example 36 was tested using rabbit balloon injury models that were different from those used in Test Example 4 in week-age. Further, the effect was compared with that of Probucol which was reported to have an inhibitory effect on intimal thickening in balloon injury

models (see Proc. Natl. Acad. Sci., U.S.A., 89, pp 11312-11316 (1992)).

Cholesterol-fed rabbits in groups of seven (JW: CSK male, 15-week-old) were used to prepare rabbit balloon injury models. Briefly, rabbits were fed with a high cholesterol diet (cholesterol content: 1%) for 2 weeks before balloon treatment. The animals were balloon-treated with a balloon catheter (4 French, available from Baxter) under anesthesia to peel the aortic intima 5 times. The animals were orally administered with the compound which was suspended in a 1% CMC solution (200 mg/kg). On the other hand, control animals were orally administered with a 1% CMC solution without the compound. The administrations were performed once a day from 1 week before the balloon treatment until the day before the dissection for evaluation. In order to evaluate the degree of balloon injury, a balloon-nontreated group (3 animals) was prepared.

After four weeks from the balloon treatment, specimens were taken from the aorta, stained with Elastica van Geison, and analyzed under an optical microscope. The image was processed to measure the thickness and area of the thickened intima. Averages of the thickness and area were obtained for each individual animal. The animals which died after the operation and those having a serum cholesterol level of 3500 mg/dl or higher were excluded from the measurement. The number of animals used for the evaluation was 4 or 5 per group. The results obtained are shown in Table 5.

TABLE 5

Inhibitory Effect on Intimal
Thickening in Balloon Injury Models (2)

	Control	Probucol	Compound of Example 36	Balloon- nontreated
Thickness of Intima (μm)	119 $\pm$ 19	92 $\pm$ 17	76 $\pm$ 16**	46 $\pm$ 20**
Area of Intima (mm^2)	1.32 $\pm$ 0.22	0.97 $\pm$ 0.28	0.81 $\pm$ 0.22*	0.45 $\pm$ 0.21**

5 Mean $\pm$ Standard Deviation; *: P<0.05; **: P<0.01

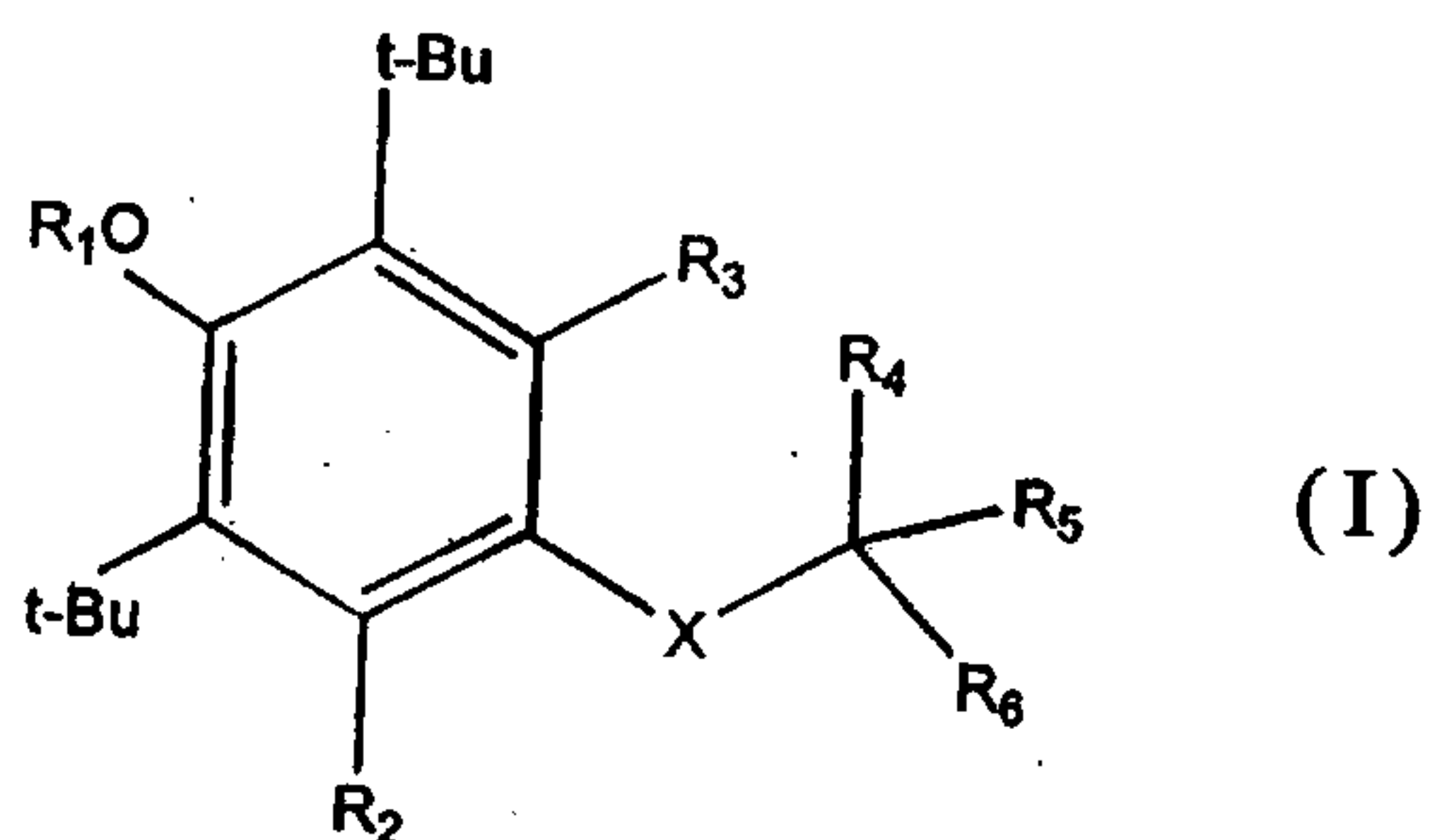
As can be seen from the results in Table 5, the compound of Example 36 exhibits significant inhibitory effect on intimal thickening in the rabbit balloon injury induced intimal thickening models on both parameters of intimal thickness and intimal area. The effect is higher than that of Probucol.

INDUSTRIAL APPLICABILITY

The vascular intimal thickening inhibitory agent according to the present invention which comprises a 2,6-di-
t-butylphenol derivative as an active ingredient shows a potent inhibitory action on cell proliferation caused by serum or PDGF in cultured vascular smooth muscle cells as well as a potent inhibitory effect on intimal thickening in balloon injury intimal thickening models. Therefore, the agent is useful for the treatment and prevention of restenosis due to vascular intimal thickening following PTCA.

The embodiments of the invention, in which an exclusive property or privilege is claimed are defined as follows:

1. Use of a 2,6-di-t-butylphenol derivative represented by formula (I):



wherein X represents an oxygen atom or a group of formula (II):



wherein n represents an integer of from 0 to 2;

R₁ represents a hydrogen atom or a acetyl, formyl, propionyl, benzoyl, benzyloxycarbonyl, aminoacetyl, N-methylaminoacetyl or N,N-dimethylaminoacetyl group;

R₂ represents a hydrogen atom, a straight- or branched-chain alkyl group having 1 to 6 carbon atoms or a straight- or branched-chain alkenyl group having 2 to 6 carbon atoms;

R₃ represents a straight- or branched-chain alkyl group having 1 to 6 carbon atoms; and

R_4 , R_5 and R_6 are the same or different and each represent:

a hydrogen atom,

a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, unsubstituted or substituted with a halogen atom or a lower alkyl, hydroxyl, amino, alkoxy, aryloxy, nitro or trifluoromethyl group, wherein the lower alkyl group is a straight- or branched-chain alkyl group having 1 to 6 carbon atoms, the alkoxy group is derived from a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, and the aryloxy group is derived from a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group,

a straight- or branched-chain alkenyl group having 2 to 20 carbon atoms, unsubstituted or substituted with a halogen atom or a lower alkyl, hydroxyl, amino, alkoxy, aryloxy, nitro or trifluoromethyl group, wherein the lower alkyl group is a straight- or branched-chain alkyl group having 1 to 6 carbon atoms, the alkoxy group is derived from a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, and the aryloxy group is derived from a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group,

a straight- or branched-chain alkynyl group having 2 to 20 carbon atoms, unsubstituted or substituted with a halogen atom or a lower alkyl, hydroxyl, amino, alkoxy, aryloxy, nitro or trifluoromethyl group, wherein the lower alkyl group is a straight- or branched-chain alkyl group having 1 to 6 carbon atoms, the alkoxy group is

derived from a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, and the aryloxy group is derived from a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group, or

a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group unsubstituted or substituted with a halogen atom or a lower alkyl, hydroxyl, amino, alkoxy, aryloxy, nitro or trifluoromethyl group, wherein the lower alkyl group is a straight- or branched-chain alkyl group having 1 to 6 carbon atoms, the alkoxy group is derived from a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, and the aryloxy group is derived from a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group;

R_3 and R_4 taken together from a 5-membered ring; or

R_5 and R_6 taken together form a C_3-C_8 cycloalkyl group or a heterocyclic ring derived from a C_3-C_8 cycloalkyl group by substituting any one or more methylene groups on the ring with oxygen atoms, sulfur atoms or alkyl-substituted nitrogen atoms;

with the proviso that R_6 is nil where R_3 and R_4 taken together form a benzofuran ring, a benzo[b]thiophene ring, a benzo[b]thiophene-1-oxide ring or a benzo[b]thiophene-1,1-dioxide ring, for the preparation of a medicament for inhibiting intimal thickening or for inhibiting restenosis in the coronary artery which occurs after percutaneous transluminal coronary angioplasty.

2. Use according to claim 1, wherein in formula (I)

X is an oxygen atom;

R₁ is a hydrogen atom or a acetyl, formyl, propionyl, benzoyl, benzyloxycarbonyl, aminoacetyl, N-methylaminoacetyl or N,N-dimethylaminoacetyl group;

R₂ is a hydrogen atom, a straight- or branched-chain alkyl group having 1 to 6 carbon atoms or a straight- or branched-chain alkenyl group having 2 to 6 carbon atoms;

R₃ and R₄ taken together form a 5-membered ring;

and

R₅ and R₆ are the same or different and each represent:

a hydrogen atom,

a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, unsubstituted or substituted with a halogen atom or a lower alkyl, hydroxyl, amino, alkoxy, aryloxy, nitro or trifluoromethyl group, wherein the lower alkyl group is a straight- or branched-chain alkyl group having 1 to 6 carbon atoms, the alkoxy group is derived from a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, and the aryloxy group is derived from a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group,

a straight- or branched-chain alkenyl group having 2 to 20 carbon atoms, unsubstituted or substituted with a halogen atom or a lower alkyl, hydroxyl, amino, alkoxy, aryloxy, nitro or trifluoromethyl group, wherein the lower alkyl group is a straight- or branched-chain alkyl group having 1 to 6 carbon atoms, the alkoxy group is derived from a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, and the aryloxy group is derived from a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group,

a straight- or branched-chain alkynyl group having 2 to 20 carbon atoms, unsubstituted or substituted with a halogen atom or a lower alkyl, hydroxyl, amino, alkoxy, aryloxy, nitro or trifluoromethyl group, wherein the lower alkyl group is a straight- or branched-chain alkyl group having 1 to 6 carbon atoms, the alkoxy group is derived from a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, and the aryloxy group is derived from a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group, or

a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group unsubstituted or substituted with a halogen atom, or a lower alkyl, hydroxyl, amino, alkoxy, aryloxy, nitro or trifluoromethyl group, wherein the lower alkyl group is a straight- or branched-chain alkyl group having 1 to 6 carbon atoms, the alkoxy group is derived from a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, and the

aryloxy group is derived from a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group; or

R_5 and R_6 taken together form a C_3-C_8 cycloalkyl group or a heterocyclic ring derived from a C_3-C_8 cycloalkyl group by substituting any one or more methylene groups on the ring with oxygen atoms, sulfur atoms or alkyl-substituted nitrogen atoms;

with the proviso that R_6 is nil when R_3 and R_4 taken together form a benzofuran ring.

3. Use according to claim 1, wherein in formula (I)

X is an oxygen atom;

R_1 is a hydrogen atom or a acetyl, formyl, propionyl, benzoyl, benzyloxycarbonyl, aminoacetyl, N-methylaminoacetyl or N,N-dimethylaminoacetyl group;

R_2 is a hydrogen atom, a straight- or branched-chain alkyl group having 1 to 6 carbon atoms or a straight- or branched-chain alkenyl group having 2 to 6 carbon atoms;

R_3 and R_4 taken together form a 5-membered ring;

and

R_5 and R_6 are the same or different and each represent:

a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, unsubstituted or substituted with a halogen atom or a lower alkyl, hydroxyl, amino, alkoxy,

aryloxy, nitro or trifluoromethyl group, wherein the lower alkyl group is a straight- or branched-chain alkyl group having 1 to 6 carbon atoms, the alkoxy group is derived from a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, and the aryloxy group is derived from a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group,

a straight- or branched-chain alkenyl group having 2 to 20 carbon atoms, unsubstituted or substituted with a halogen atom or a lower alkyl, hydroxyl, amino, alkoxy, aryloxy, nitro or trifluoromethyl group, wherein the lower alkyl group is a straight- or branched-chain alkyl group having 1 to 6 carbon atoms, the alkoxy group is derived from a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, and the aryloxy group is derived from a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group,

a straight- or branched-chain alkynyl group having 2 to 20 carbon atoms, unsubstituted or substituted with a halogen atom or a lower alkyl, hydroxyl, amino, alkoxy, aryloxy, nitro or trifluoromethyl group, wherein the lower alkyl group is a straight- or branched-chain alkyl group having 1 to 6 carbon atoms, the alkoxy group is derived from a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, and the aryloxy group is derived from a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group, or

a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group unsubstituted or substituted with a halogen atom, or a lower alkyl, hydroxyl, amino, alkoxy, aryloxy, nitro or trifluoromethyl group, wherein the lower alkyl group is a straight- or branched-chain alkyl group having 1 to 6 carbon atoms, the alkoxy group is derived from a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, and the aryloxy group is derived from a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group; or

R_5 and R_6 taken together form a C_3 - C_8 cycloalkyl group or a heterocyclic ring derived from a C_3 - C_8 cycloalkyl group by substituting any one or more methylene groups on the ring with oxygen atoms, sulfur atoms or alkyl-substituted nitrogen atoms;

with the proviso that R_6 is nil when R_3 and R_4 taken together form a benzofuran ring.

4. Use according to claim 1, wherein in formula (I)

X is an oxygen atom;

R_1 is a hydrogen atom;

R_2 is a hydrogen atom;

R_3 and R_4 are taken together to form a 5-membered ring; and

R_5 and R_6 are the same or different and each represent:

a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, unsubstituted or substituted with a halogen atom or a lower alkyl, hydroxyl, amino, alkoxy, aryloxy, nitro or trifluoromethyl group, wherein the lower alkyl group is a straight- or branched-chain alkyl group having 1 to 6 carbon atoms, the alkoxy group is derived from a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, and the aryloxy group is derived from a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group,

a straight- or branched-chain alkenyl group having 2 to 20 carbon atoms, unsubstituted or substituted with a halogen atom or a lower alkyl, hydroxyl, amino, alkoxy, aryloxy, nitro or trifluoromethyl group, wherein the lower alkyl group is a straight- or branched-chain alkyl group having 1 to 6 carbon atoms, the alkoxy group is derived from a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, and the aryloxy group is derived from a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group,

a straight- or branched-chain alkynyl group having 2 to 20 carbon atoms, unsubstituted or substituted with a halogen atom or a lower alkyl, hydroxyl, amino, alkoxy, aryloxy, nitro or trifluoromethyl group, wherein the lower alkyl group is a straight- or branched-chain alkyl group having 1 to 6 carbon atoms, the alkoxy group is derived from a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, and the aryloxy group is

derived from a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group, or

a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group unsubstituted or substituted with a halogen atom, or a lower alkyl, hydroxyl, amino, alkoxy, aryloxy, nitro or trifluoromethyl group, wherein the lower alkyl group is a straight- or branched-chain alkyl group having 1 to 6 carbon atoms, the alkoxy group is derived from a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, and the aryloxy group is derived from a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group; or

R_5 and R_6 taken together form a C_3 - C_8 cycloalkyl group or a heterocyclic ring derived from a C_3 - C_8 cycloalkyl group by substituting any one or more methylene groups on the ring with oxygen atoms, sulfur atoms or alkylsubstituted nitrogen atoms;

with the proviso that R_6 is nil when R_3 and R_4 taken together form a benzofuran ring.

5. Use according to claim 1, wherein in formula (I)

X is an oxygen atom;

R_1 is a hydrogen atom;

R_2 is a hydrogen atom;

R_3 and R_4 taken together form a 5-membered ring;

and

R_5 and R_6 are the same or different and each represent:

a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, unsubstituted or substituted with a halogen atom or a lower alkyl, hydroxyl, amino, alkoxy, aryloxy, nitro or trifluoromethyl group, wherein the lower alkyl group is a straight- or branched-chain alkyl group having 1 to 6 carbon atoms, the alkoxy group is derived from a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, and the aryloxy group is derived from a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group, or

a straight- or branched-chain alkenyl group having 2 to 20 carbon atoms, unsubstituted or substituted with a halogen atom or a lower alkyl, hydroxyl, amino, alkoxy, aryloxy, nitro or trifluoromethyl group, wherein the lower alkyl group is a straight- or branched-chain alkyl group having 1 to 6 carbon atoms, the alkoxy group is derived from a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, and the aryloxy group is derived from a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group; or

R_5 and R_6 taken together form a C_3 - C_8 cycloalkyl group;

with the proviso that R_6 is nil when R_3 and R_4 taken together form a benzofuran ring.

6. Use according to claim 1, wherein in formula (I)

X is a group of formula (II)



wherein n represents an integer of from 0 to 2;

R₁ is a hydrogen atom or a acetyl, formyl, propionyl, benzoyl, benzyloxycarbonyl, aminoacetyl, N-methylaminoacetyl or N,N-dimethylaminoacetyl group;

R₂ is a hydrogen atom, a straight- or branched-chain alkyl group having 1 to 6 carbon atoms or a straight- or branched-chain alkenyl group having 2 to 6 carbon atoms;

R₃ and R₄ taken together form a 5-membered ring;

and

R₅ and R₆ are the same or different and each represent:

a hydrogen atom,

a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, unsubstituted or substituted with a halogen atom or a lower alkyl, hydroxyl, amino, alkoxy, aryloxy, nitro or trifluoromethyl group, wherein the lower alkyl group is a straight- or branched-chain alkyl group having 1 to 6 carbon atoms, the alkoxy group is derived from a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, and the aryloxy group is

derived from a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group,

a straight- or branched-chain alkenyl group having 2 to 20 carbon atoms, unsubstituted or substituted with a halogen atom or a lower alkyl, hydroxyl, amino, alkoxy, aryloxy, nitro or trifluoromethyl group, wherein the lower alkyl group is a straight- or branched-chain alkyl group having 1 to 6 carbon atoms, the alkoxy group is derived from a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, and the aryloxy group is derived from a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group,

a straight- or branched-chain alkynyl group having 2 to 20 carbon atoms, unsubstituted or substituted with a halogen atom or a lower alkyl, hydroxyl, amino, alkoxy, aryloxy, nitro or trifluoromethyl group, wherein the lower alkyl group is a straight- or branched-chain alkyl group having 1 to 6 carbon atoms, the alkoxy group is derived from a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, and the aryloxy group is derived from a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group, or

a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group unsubstituted or substituted with a halogen atom, or a lower alkyl, hydroxyl, amino, alkoxy, aryloxy, nitro or trifluoromethyl group, wherein the lower alkyl group is a straight- or branched-chain alkyl group having 1 to 6 carbon atoms, the alkoxy

group is derived from a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, and the aryloxy group is derived from a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group; or

R_5 and R_6 taken together form a C_3 - C_8 cycloalkyl group or a heterocyclic ring derived from a C_3 - C_8 cycloalkyl group by substituting any one or more methylene groups on the ring with oxygen atoms, sulfur atoms or alkylsubstituted nitrogen atoms;

with the proviso that R_6 is nil when R_3 and R_4 taken together form a benzo[b]thiophene ring, a benzo[b]thiophene-1-oxide ring or a benzo-[b]thiophene-1,1-dioxide ring.

7. Use according to claim 1, wherein in formula (I)

X is a sulfur atom;

R_1 is a hydrogen atom or a acetyl, formyl, propionyl, benzoyl, benzyloxycarbonyl, aminoacetyl, N-methylaminoacetyl or N,N-dimethylaminoacetyl group;

R_2 is a hydrogen atom, a straight- or branched-chain alkyl group having 1 to 6 carbon atoms or a straight- or branched-chain alkenyl group having 2 to 6 carbon atoms;

R_3 and R_4 taken together form a 5-membered ring;

and

R_5 and R_6 are the same or different and each represent:

a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, unsubstituted or substituted with a halogen atom or a lower alkyl, hydroxyl, amino, alkoxy, aryloxy, nitro or trifluoromethyl group, wherein the lower alkyl group is a straight- or branched-chain alkyl group having 1 to 6 carbon atoms, the alkoxy group is derived from a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, and the aryloxy group is derived from a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group,

a straight- or branched-chain alkenyl group having 2 to 20 carbon atoms, unsubstituted or substituted with a halogen atom or a lower alkyl, hydroxyl, amino, alkoxy, aryloxy, nitro or trifluoromethyl group, wherein the lower alkyl group is a straight- or branched-chain alkyl group having 1 to 6 carbon atoms, the alkoxy group is derived from a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, and the aryloxy group is derived from a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group,

a straight- or branched-chain alkynyl group having 2 to 20 carbon atoms, unsubstituted or substituted with a halogen atom or a lower alkyl, hydroxyl, amino, alkoxy, aryloxy, nitro or trifluoromethyl group, wherein the lower alkyl group is a straight- or branched-chain alkyl group having 1 to 6 carbon atoms, the alkoxy group is

derived from a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, and the aryloxy group is derived from a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group, or

a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group unsubstituted or substituted with a halogen atom, or a lower alkyl, hydroxyl, amino, alkoxy, aryloxy, nitro or trifluoromethyl group, wherein the lower alkyl group is a straight- or branched-chain alkyl group having 1 to 6 carbon atoms, the alkoxy group is derived from a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, and the aryloxy group is derived from a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group; or

R_5 and R_6 taken together form a C_3 – C_8 cycloalkyl group or a heterocyclic ring derived from a C_3 – C_8 cycloalkyl group by substituting any one or more methylene groups on the ring with oxygen atoms, sulfur atoms or alkylsubstituted nitrogen atoms;

with the proviso that R_6 is nil when R_3 and R_4 taken together form a benzo[b]thiophene ring.

8. Use according to claim 1, wherein in formula (I)

X is a sulfur atom;

R_1 is a hydrogen atom or a acetyl, formyl, propionyl, benzoyl, benzyloxycarbonyl, aminoacetyl, N-methylaminoacetyl or N,N-dimethylaminoacetyl group;

R_2 is a hydrogen atom, a straight- or branched-chain alkyl group having 1 to 6 carbon atoms or a straight- or branched-chain alkenyl group having 2 to 6 carbon atoms;

R_3 and R_4 taken together form a 5-membered ring;

and

R_5 and R_6 are the same or different and each represent:

a hydrogen atom,

a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, unsubstituted or substituted with a halogen atom or a lower alkyl, hydroxyl, amino, alkoxy, aryloxy, nitro or trifluoromethyl group, wherein the lower alkyl group is a straight- or branched-chain alkyl group having 1 to 6 carbon atoms, the alkoxy group is derived from a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, and the aryloxy group is derived from a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group, or

a straight- or branched-chain alkenyl group having 2 to 20 carbon atoms, unsubstituted or substituted with a halogen atom or a lower alkyl, hydroxyl, amino, alkoxy, aryloxy, nitro or trifluoromethyl group, wherein the lower alkyl group is a straight- or branched-chain alkyl group having 1 to 6 carbon atoms, the alkoxy group is derived from a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, and the aryloxy group is

derived from a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group; or

R_5 and R_6 taken together form a C_3 - C_8 cycloalkyl group;

with the proviso that R_6 is nil when R_3 and R_4 taken together form a benzo[b]thiophene ring.

9. Use according to claim 1, wherein in formula (I)

X is a sulfur atom;

R_1 is a hydrogen atom;

R_2 is a hydrogen atom;

R_3 and R_4 taken together form a 5-membered ring;

and

R_5 and R_6 are the same or different and each represent:

a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, unsubstituted or substituted with a halogen atom or a lower alkyl, hydroxyl, amino, alkoxy, aryloxy, nitro or trifluoromethyl group, wherein the lower alkyl group is a straight- or branched-chain alkyl group having 1 to 6 carbon atoms, the alkoxy group is derived from a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, and the aryloxy group is derived from a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group, or

a straight- or branched-chain alkenyl group having 2 to 20 carbon atoms, unsubstituted or substituted with a halogen atom or a lower alkyl, hydroxyl, amino, alkoxy, aryloxy, nitro or trifluoromethyl group, wherein the lower alkyl group is a straight- or branched-chain alkyl group having 1 to 6 carbon atoms, the alkoxy group is derived from a straight- or branched-chain alkyl group having 1 to 20 carbon atoms, and the aryloxy group is derived from a phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl or phenanthryl group; or

R_5 and R_6 taken together form a C_3 - C_8 cycloalkyl group;

with the proviso that R_6 is nil when R_3 and R_4 taken together form a benzo[b]thiophene ring.

10. Use according to claim 1, wherein the 2,6-di-t-butylphenol derivative of formula (I) is selected from the group consisting of:

4,6-di-t-butyl-2,2-di-n-butyl-5-hydroxy-2,3-dihydro-benzofuran,

4,6-di-t-butyl-5-hydroxy-2,3-dihydrobenzofuran-2-spiro-1'-cyclohexane,

4,6-di-t-butyl-5-hydroxy-2,3-dihydrobenzofuran-2-spiro-1'-cycloheptane,

4,6-di-t-butyl-5-hydroxy-2,3-dihydrobenzofuran-2-spiro-1'-cyclooctane,

4,6-di-t-butyl-2,2-di-n-pentyl-5-hydroxy-2,3-dihydrobenzofuran,

4,6-di-t-butyl-2,2-di-n-hexyl-5-hydroxy-2,3-dihydrobenzofuran,

2,2-di-i-amyl-4,6-t-butyl-5-hydroxy-2,3-dihydrobenzofuran,

4,6-di-t-butyl-5-hydroxy-2,2-di-n-pentyl-2,3-dihydrobenzothiophene,

4,6-di-t-butyl-5-hydroxy-2,2-di-n-butyl-2,3-dihydrobenzothiophene,

4,6-di-t-butyl-5-hydroxy-2,2-di-i-amyl-2,3-dihydrobenzothiophene,

4,6-di-t-butyl-5-hydroxy-2,2-di-n-hexyl-2,3-dihydrobenzothiophene,

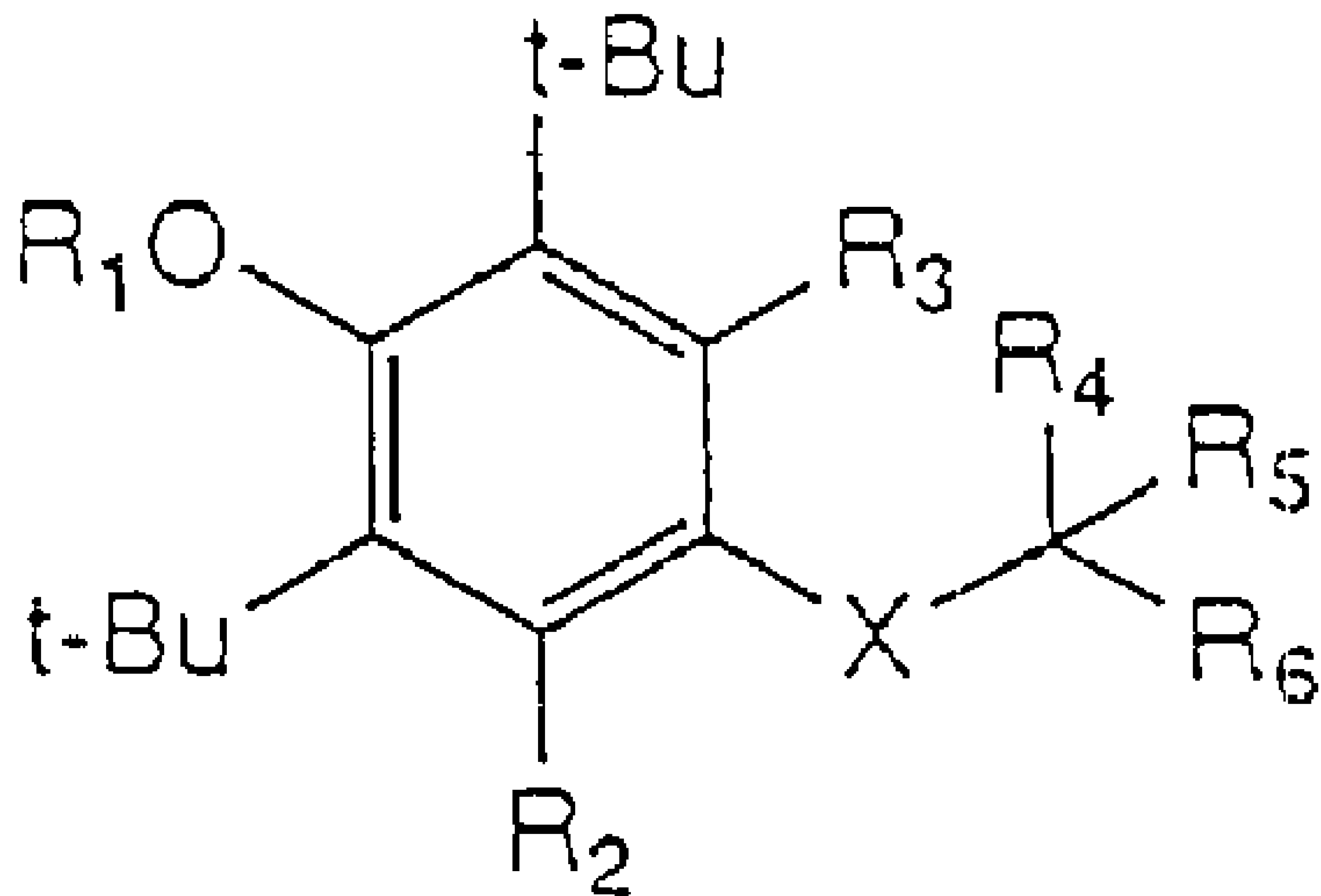
4,6-di-t-butyl-5-hydroxy-2,3-dihydrobenzothiophene-2-spiro-1'-cyclohexane,

4,6-di-t-butyl-5-hydroxy-2,3-dihydrobenzothiophene-2-spiro-1'-cycloheptane, and

4,6-di-t-butyl-5-hydroxy-2,3-dihydrobenzothiophene-2-spiro-1'-cyclooctane.

11. Use according to claim 10, wherein-the 2,6-di-t-butylphenol derivative of formula (I) is 4,6-di-t-butyl-2,2-di-n-pentyl-5-hydroxy-2,3-dihydrobenzofuran or 4,6di-t-butyl-5-hydroxy-2,2-di-n-pentyl-2,3dihydrobenzothiophene.

12. Use according to claim 11, wherein the 2,6-di-t-butylphenol derivative of formula (I) is 4,6-di-t-butyl-2,2-di-n-pentyl-5-hydroxy-2,3-dihydrobenzofuran.



(1)



(2)