

SPECIFICATION

BIPHENYLAMIDINE DERIVATIVES

Technical Field

5 The present invention relates to novel, and selective, activated blood coagulation factor Xa (hereafter, "FXa") inhibitors of the general formula (I).

Background Art

10 A therapy for anticoagulation plays an important part in the medical treatment and prophylaxis of thromboembolisms such as myocardial infarction, cerebral thrombosis, thrombosis of peripheral arteries, and thrombosis of deep veins.

15 In particular, for the prophylaxis of chronic thrombosis, harmless and appropriate oral anticoagulants which can be administrated over a long period of time are desired. However, to date, warfarin potassium agent which are difficult to control the extent of the anti-coagulation are the only above-mentioned
20 anticoagulants, and thus a need for anticoagulants which are easy to use is left.

 Though antithrombin agents have been developed as anticoagulants in the past, it is known that these agents, for example hirudin, have a risk of a tendency
25 toward bleeding as a side effect. The fact that inhibition of FXa, located upstream of thrombin in the blood coagulation cascade is systematically more effective than inhibition of thrombin and that the FXa inhibitors do not cause the above significant side effect
30 and is clinically preferable, has begun to be understood.

 Biphenylamidine compounds, which exhibit FXa inhibition activity, were disclosed in The 17th Symposium on Medicinal Chemistry, The 6th Annual Meeting of Division of Medicinal Chemistry, Abstracts, 184 - 185,
35 1997. However, compounds of the present invention are novel compounds which differ distinctly in the use of a heteroatom in a linkage between the biphenylamidine

structure which may interact with an S1 pocket and the cyclic structure which may interact with an aryl binding site, and in the presence of a substituent such as a carboxyl group on a linker benzene ring.

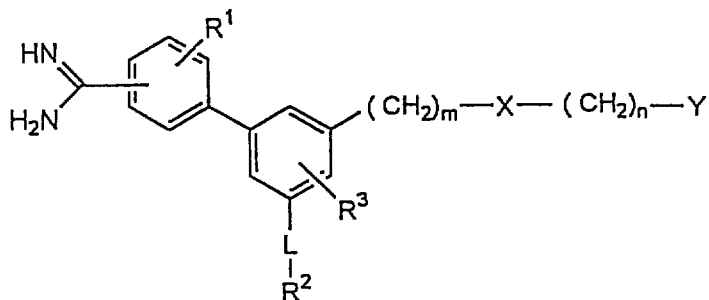
Further, Japanese Unexamined Patent Publication (Kokai) No. 4-264068 discloses biphenylamidine derivatives as cyclic imino-derivatives. However, compounds of the present invention differ in the presence of a bond, through a heteroatom, at a benzyl-position.

Therefore, an object of the present invention is to provide a novel compound which may be a FXa inhibitor having a clinical applicability.

Disclosure of the invention

The inventors have made every effort to achieve the above purpose and, as a result, devised the following 1 - 10 inventions.

1. A biphenylamidine derivative of general formula (1):



. . . (1)

wherein

R¹ is a hydrogen atom, a fluorine atom, a chlorine atom, a bromine atom, a hydroxyl group, an amino group, a nitro group, a C₁₋₈ alkyl group, or a C₁₋₈ alkoxy group;

L is a direct bond or a C₁₋₄ alkylene group;

R² is a fluorine atom; a chlorine atom; a bromine atom; a hydroxyl group; an amino group; a C₁₋₈ alkoxy group; a carboxyl group; a C₁₋₈ alkoxycarbonyl group; an aryloxy carbonyl group; an aralkoxycarbonyl group; a carbamoyl group wherein a nitrogen atom constituting the

carbamoyl may be substituted with a mono- or di-C₁₋₈ alkyl group or may be a nitrogen atom in an amino acid; a C₁₋₈ alkylcarbonyl group; a C₁₋₈ alkylsulfenyl group; a C₁₋₈ alkylsulfinyl group; a C₁₋₈ alkylsulfonyl group; a mono- or di-C₁₋₈ alkylamino group; a mono- or di-C₁₋₈ alkylaminosulfonyl group; a sulfo group; a phosphono group; a bis(hydroxycarbonyl)methyl group; a bis(alkoxycarbonyl)methyl group; or a 5-tetrazolyl group;

R³ is a hydrogen atom, a fluorine atom, a chlorine atom, a bromine atom, a hydroxyl group, an amino group, a nitro group, a C₁₋₈ alkyl group, a C₁₋₈ alkoxy group, a carboxyl group, or a C₁₋₈ alkoxycarbonyl group;

X is any of the formulae:

-O-, -S-, -SO-, -SO₂-, -NH-CO-NH-, -N(R⁴)-, -CO-N(R⁵)-, -N(R⁵)-CO-, -N(R⁵)-SO₂-, -SO₂-N(R⁵)-,

wherein

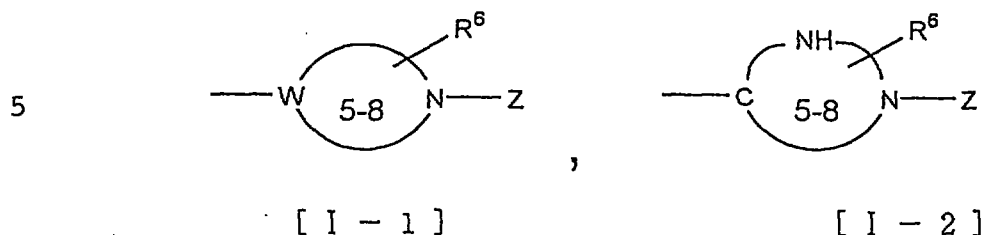
R⁴ is a hydrogen atom, a C₁₋₁₀ alkyl group, a C₁₋₁₀ alkylcarbonyl group, a C₁₋₁₀ alkylsulfonyl group, a C₃₋₈ cycloalkyl group, or an aryl group,

R⁵ is a hydrogen atom, a C₁₋₁₀ alkyl group, a C₃₋₈ cycloalkyl group, or an aryl group,

wherein an alkyl group in the R⁴ and R⁵ may be substituted with an aryl group, a hydroxyl group, an amino group, a fluorine atom, a chlorine atom, a bromine atom, a C₁₋₈ alkoxy group, a carboxyl group, a C₁₋₈ alkoxycarbonyl group, an aryloxycarbonyl group, an aralkoxycarbonyl group, a carbamoyl group, or a 5-tetrazolyl group;

Y is a C₄₋₈ cycloalkyl group wherein a methylene group in the C₄₋₈ cycloalkyl may be replaced with a carbonyl group, or may be substituted with a fluorine atom, a chlorine atom, a bromine atom, a hydroxyl group, an amino group, a C₁₋₈ alkyl group, a C₁₋₈ alkoxy group, a carbamoyl group, a C₁₋₈ alkoxycarbonyl group, a carboxyl group, an aminoalkyl group, a mono- or di-alkylamino group, or a mono- or di-alkylaminoalkyl

group; or the following 5 - 8-membered ring of the formulae I-1 or I-2:



10 wherein, in the formulae I-1 and I-2,

in each cyclic system, the methylene group may be replaced with a carbonyl group, and the cycle may have unsaturated bonds,

15 R^6 is a hydrogen atom, a fluorine atom, a chlorine atom, a bromine atom, a hydroxyl group, an amino group, a nitro group, a C_{1-8} alkyl group, or a C_{1-8} alkoxy group,

W is C-H, or a nitrogen atom, with the proviso that W is not a nitrogen atom when the cycle is 5-membered ring,

20 Z is a hydrogen atom; a C_{1-10} alkyl group wherein the alkyl group may be substituted with a hydroxyl group except when Z is a C_1 alkyl, an amino group, a C_{1-8} alkoxy group except when Z is a C_1 alkyl, a carboxyl group, a C_{1-8} alkoxycarbonyl group, an aryloxycarbonyl group or an aralkoxycarbonyl group; a C_{1-8} alkylcarbonyl group; an arylcarbonyl group; an aralkylcarbonyl group; an amidino group; or the following group of the formula I-3:



wherein, in the formula I-3,

35 R^7 is a C_{1-8} alkyl group wherein the alkyl group may be substituted with a hydroxyl group or a C_{1-8} alkoxy group; an aralkyl group; or an aryl group;

m is an integer of 1 - 3;

n is an integer of 0 - 3, with the proviso that W is not a nitrogen atom when n is 0 - 1;
or a pharmaceutically acceptable salt thereof.

2. A biphenylamidine derivative wherein, in said
5 formula (1),

R¹ is a hydrogen atom, a fluorine atom, a chlorine atom, a bromine atom, a hydroxyl group, an amino group, a C₁₋₄ alkyl group, or a C₁₋₄ alkoxy group;

L is a direct bond or a C₁₋₄ alkylene group;

10 R² is a fluorine atom; a chlorine atom; a bromine atom; a hydroxyl group; an amino group; a C₁₋₈ alkoxy group; a carboxyl group; a C₁₋₈ alkoxy carbonyl group; an aryloxy carbonyl group; an aralkoxy carbonyl group; a carbamoyl group wherein a nitrogen atom in the carbamoyl
15 group may be substituted with a mono- or di-C₁₋₈ alkyl group or may be a nitrogen atom in an amino acid; a C₁₋₈ alkyl carbonyl group; a C₁₋₈ alkyl sulfenyl group; a C₁₋₈ alkyl sulfinyl group; a C₁₋₈ alkyl sulfonyl group; a mono- or di-C₁₋₈ alkyl amino group; a mono- or di-C₁₋₈
20 alkyl aminosulfonyl group; a sulfo group; a phosphono group; a bis(hydroxy carbonyl)methyl group; a bis(alkoxy carbonyl)methyl group; or a 5-tetrazolyl group;

R³ is a hydrogen atom;

X is any of the formulae:

25 -O-, -S-, -N(R⁴)-, -CO-N(R⁵)-, -N(R⁵)-CO-, -N(R⁵)SO₂-,
or -SO₂-N(R⁵)-;

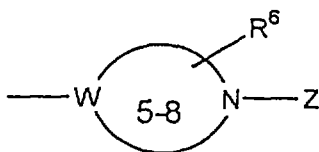
wherein

R⁴ is a hydrogen atom, a C₁₋₁₀ alkyl group, a C₁₋₁₀ alkyl carbonyl group, or a C₁₋₁₀ alkyl sulfonyl group,

30 R⁵ is a hydrogen atom, or a C₁₋₁₀ alkyl group,

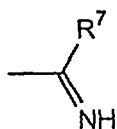
wherein an alkyl group in the R⁴ and R⁵ may be substituted with an aryl group, a hydroxy group, an amino group, a fluorine atom, a chlorine atom, a bromine atom, a C₁₋₈ alkoxy group, a carboxyl group, a C₁₋₈
35 alkoxy carbonyl group, an aryloxy carbonyl group, an aralkoxy carbonyl group, a carbamoyl group, or a 5-tetrazoyl group;

Y is a C₄₋₈ cycloalkyl group wherein a methylene group constituting the C₄₋₈ cycloalkyl may be replaced with a carbonyl group, or may be substituted with a fluorine atom, a chlorine atom, a bromine atom, a hydroxyl group, an amino group, a C₁₋₈ alkyl group, a C₁₋₈ alkoxy group, a carbamoyl group, a C₁₋₈ alkoxycarbonyl group, a carboxyl group, an aminoalkyl group, a mono- or di-alkylamino group, or a mono- or di-alkylaminoalkyl group; or the following 5 - 8-membered ring of the formula II-1:



[I I - 1]

wherein, in formulae II-1,
in the cyclic system, the methylene may be replaced with a carbonyl group,
R⁶ is a hydrogen atom, a fluorine atom, a chlorine atom, a bromine atom, a hydroxyl group, an amino group, a C₁₋₄ alkyl group, or a C₁₋₄ alkoxy group;
W is C-H, or a nitrogen atom, with the proviso that W is not a nitrogen atom when the cycle is 5-membered ring,
Z is a hydrogen atom; a C₁₋₁₀ alkyl group wherein the alkyl group may be substituted with a hydroxyl group except when Z is a C₁ alkyl, an amino group, a C₁₋₈ alkoxy group except when Z is a C₁ alkyl, a carboxyl group, a C₁₋₈ alkoxycarbonyl group, an aryloxycarbonyl group, or an aralkoxycarbonyl group; a C₁₋₈ alkylcarbonyl group; an arylcarbonyl group; an aralkylcarbonyl group; an amidino group; or the following group of the formula II-2:



[I I - 2]

5 wherein, in formula II-2,

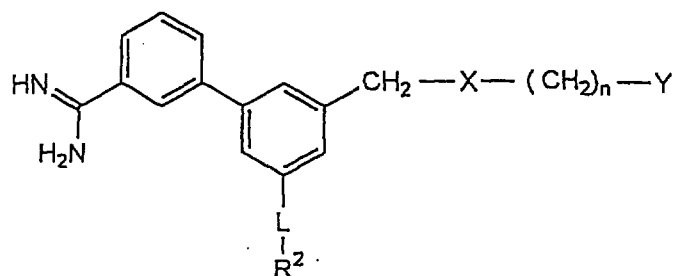
R⁷ is a C₁₋₈ alkyl group wherein the alkyl group may be substituted with a hydroxyl group or a C₁₋₄ alkoxy group; an aralkyl group; or an aryl group;

m is an integer of 1 - 3;

10 n is an integer of 0 - 3, with the proviso that W is not a nitrogen atom when n is 0 - 1;
or a pharmaceutically acceptable salt thereof.

3. A biphenylamidine derivative of general formula (2):

15



20

. . . (2)

wherein

25 L is a bond or a C₁₋₄ alkylene group;

R² is a carboxyl group; a C₁₋₄ alkoxycarbonyl group; an aralkoxycarbonyl group; a carbamoyl group wherein a nitrogen atom constituting the carbamoyl group may be substituted with a mono- or di-C₁₋₄ alkyl group or may be
30 a nitrogen atom in an amino acid; or a C₁₋₄ alkylcarbonyl group;

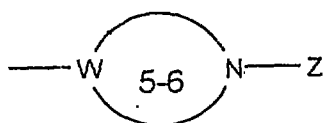
X is -O-, -N(R⁴)-, or -NH-CO-,

wherein

35 R⁴ is a hydrogen atom, a C₁₋₁₀ alkyl group, a C₁₋₁₀ alkylcarbonyl group or a C₁₋₁₀ alkylsulfonyl group, the alkyl group being optionally substituted with a hydroxyl group, an amino group, a fluorine group, a carboxyl group

or a C₁₋₈ alkoxy carbonyl group;

Y is a C₅₋₆ cycloalkyl group wherein a methylene group constituting the C₅₋₆ cycloalkyl group may be substituted with a carbamoyl group, a C₁₋₄ alkoxy group or a carboxyl group; or the following 5 - 6-membered ring of the formula III-1:

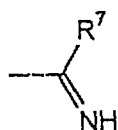


[III - 1]

wherein, in formula III-1,

W is C-H, or a nitrogen atom, with the proviso that W is not a nitrogen atom when the cycle is 5-membered ring,

Z is a hydrogen atom; a C₁₋₄ alkyl group wherein the alkyl group may be substituted with a hydroxyl group except when Z is a C₁ alkyl, an amino group, a carboxyl group or a C₁₋₄ alkoxy carbonyl group; a C₁₋₄ alkyl carbonyl group; an amidino group; or the following group of the formula III-2:



[III - 2]

wherein, in formula III-2,

R⁷ is a C₁₋₄ alkyl group wherein the alkyl group may be substituted with a hydroxyl group;

n is an integer of 0 - 2; with the proviso that W is not a nitrogen atom when n is 0 - 1; or a pharmaceutically acceptable salt thereof.

4. A biphenylamidine derivative wherein, in said formula (2),

X is -O-, or -N(R⁴)-,

wherein

R⁴ is a hydrogen atom, a C₁₋₁₀ alkyl group, a C₁₋₁₀

alkylcarbonyl group or a C_{1-10} alkylsulfonyl group,
wherein the alkyl being optionally substituted with a
hydroxyl group, an amino group, a fluorine atom, a
carboxyl group or a C_{1-8} alkoxy carbonyl group;
5 or a pharmaceutically acceptable salt thereof.

5. A biphenylamidine derivative wherein, in said
formula (2),

X is $-NH-CO-$,

or a pharmaceutically acceptable salt thereof.

10 6. A biphenylamidine derivative wherein, in
general formula (2),

L is a bond;

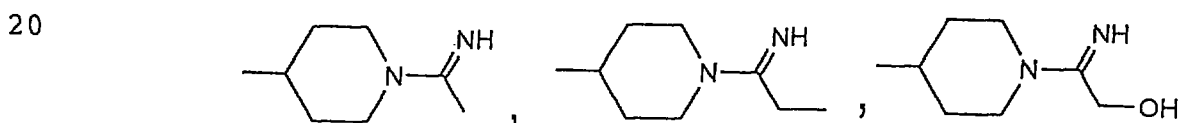
R^2 is a carboxyl group or a methoxycarbonyl group;

X is $-O-$, or $-N(R^4)-$,

15 wherein

R^4 is a hydrogen atom, a methyl group or a 2-
hydroxyethyl group;

Y is any of the formulae:



n is 1;

25 or a pharmaceutically acceptable salt thereof.

7. A prodrug which generates a biphenylamidine
derivative or a pharmaceutically acceptable salt thereof
according to any one of said 1 - 6, in vivo.

8. A blood coagulation inhibitor comprising at
30 least a biphenylamidine derivative or a pharmaceutically
acceptable salt thereof according to any one of said
1 - 7, and a pharmaceutically acceptable carrier.

9. A prophylactic agent for thrombosis or embolus,
comprising at least a biphenylamidine derivative or a
35 pharmaceutically acceptable salt thereof according to any
one of said 1 - 7, and a pharmaceutically acceptable
carrier.

10. A therapeutic agent for thrombosis or embolus, comprising at least a biphenylamidine derivative or a pharmaceutically acceptable salt thereof according to any one of said 1 - 7, and a pharmaceutically acceptable carrier.

Best Mode for Carrying Out the Invention

The present invention is detailed in the following description.

In the definition regarding the substituents in a compound of formula (1) of the present invention:

The term " C_{1-8} alkyl" means a branched or straight carbon chain having 1 to 8 carbons, and includes for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neo-pentyl, isopentyl, 1,2-dimethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, isoheptyl, octyl, or isooctyl, etc. Among them, one having 1 to 4 carbons is preferable and methyl or ethyl is particularly preferable.

The term " C_{1-8} alkoxy" means an alkoxy group having 1 to 8 carbons, and includes for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, neo-pentyloxy, tert-pentyloxy, 2-methylbutoxy, hexyloxy, isohexyloxy, heptyloxy, isoheptyloxy, octyloxy, or isooctyloxy, etc.. Among them, one having 1 to 4 carbons is preferable and methoxy or ethoxy is particularly preferable.

The term " C_{1-4} alkylene" means a straight alkylene having 1 to 4 carbons, and includes methylene, ethylene, propylene, or butylene.

The term " C_{1-8} alkoxy carbonyl" means methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, isopentyloxycarbonyl, neopentyloxycarbonyl, hexyloxycarbonyl, heptyloxycarbonyl, or octyloxycarbonyl, etc.; preferably,

it is methoxycarbonyl, ethoxycarbonyl or tert-butoxycarbonyl; and more preferably, it is methoxycarbonyl.

5 The term "aryloxycarbonyl" means phenoxycarbonyl, naphthyloxycarbonyl, 4-methylphenoxycarbonyl, 3-chlorophenoxycarbonyl, or 4-methoxyphenoxycarbonyl, etc.; and preferably, it is phenoxycarbonyl.

10 The term "aralkoxycarbonyl" means benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, or 3-trifluoromethylbenzyloxycarbonyl, etc.; and preferably, it is benzyloxycarbonyl.

15 The term "amino acid" means a natural or non-natural commercially available amino acid; preferably, is glycine, alanine or β -alanine; and more preferably, it is glycine.

20 The term " C_{1-8} alkylcarbonyl" means a carbonyl group having a straight or branched carbon chain having 1 to 8 carbons, and includes for example, hormyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl, or octanoyl, etc.; preferably, it is the one having 1 to 4 carbons; and more preferably, it is acetyl or propionyl.

25 The term " C_{1-8} alkylsulfenyl" means an alkylsulfenyl group having 1 to 8 carbons, and includes for example, methylthio, ethylthio, butylthio, isobutythio, pentylthio, hexylthio, heptylthio, or octylthio, etc., and preferably, it is methylthio.

30 The term " C_{1-8} alkylsulfinyl" means an alkylsulfinyl group having 1 to 8 carbons, and includes for example, methylsulfinyl, ethylsulfinyl, butylsulfinyl, hexylsulfinyl, or octylsulfinyl, etc., and preferably, it is methylsulfinyl.

35 The term " C_{1-8} alkylsulfonyl" means an alkylsulfonyl group having 1 to 8 carbons, and includes for example, methylsulfonyl, ethylsulfonyl, butylsulfonyl, hexylsulfonyl, or octylsulfonyl, etc., and preferably, it is methylsulfonyl.

The term "mono- or di-C₁₋₈ alkylamino" means methylamino, dimethylamino, ethylamino, propylamino, diethylamino, isopropylamino, diisopropylamino, dibutylamino, butylamino, isobutylamino, sec-butylamino, 5 tert-butylamino, pentylamino, hexylamino, heptylamino, or octylamino, etc.; preferably, it is methylamino, dimethylamino, ethylamino, diethylamino or propylamino; and more preferably, it is methylamino or dimethylamino.

The term "mono- or di-C₁₋₈ alkylaminosulfonyl" means 10 for example methylaminosulfonyl, dimethylaminosulfonyl, ethylaminosulfonyl, propylaminosulfonyl, diethylaminosulfonyl, isopropylaminosulfonyl, diisopropylaminosulfonyl, dibutylaminosulfonyl, butylaminosulfonyl, isobutylaminosulfonyl, 15 sec-butylaminosulfonyl, tert-butylaminosulfonyl, pentylaminosulfonyl, hexylaminosulfonyl, heptylamino-sulfonyl, or octylaminosulfonyl, etc.; preferably, it is methylaminosulfonyl, dimethylaminosulfonyl, ethylaminosulfonyl, 20 diethylaminosulfonyl or propylaminosulfonyl; and more preferably, it is methylaminosulfonyl or dimethylaminosulfonyl.

The term "bis(alkoxycarbonyl)methyl" means, particularly, bis(methoxycarbonyl)methyl, or 25 bis(ethoxycarbonyl)methyl, etc.; preferably it is bis(methoxycarbonyl)methyl.

The term "C₁₋₁₀ alkyl" means a straight or branched carbon chain having 1 to 10 carbons, and includes for 30 example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neo-pentyl, isopentyl, 1,2-dimethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, heptyl, isoheptyl, 1-methylhexyl, 2-methylhexyl, octyl, 2-ethylhexyl, nonyl, decyl, or 1-methylnonyl, etc. Among 35 them, the one having 1 to 4 carbons is preferable, and methyl or ethyl is particularly preferable.

The term "C₁₋₁₀ alkylcarbonyl" means a carbonyl

group having a straight or branched carbon chain having 1 to 10 carbons, and includes for example, hormyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, or
5 decanoyl, etc.; preferably, it is one having 1 to 4 carbons; and more preferably, it is acetyl or propionyl.

The term " C_{1-10} alkylsulfonyl" means an alkylsulfonyl group having 1 to 10 carbons, and includes
10 for example, methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, isobutylsulfonyl, pentylsulfonyl, isopentylsulfonyl, neopentylsulfonyl, hexylsulfonyl, heptylsulfonyl, octylsulfonyl, nonylsulfonyl, or decylsulfonyl, etc.;
15 preferably, it is one having 1 to 4 carbons; and more preferably, it is methylsulfonyl or ethylsulfonyl.

The term " C_{3-8} cycloalkyl" means a cycloalkyl group having 3 to 8 carbons, and includes particularly, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,
20 cycloheptyl, or cyclooctyl; and is preferably cyclopropyl.

The term "aryl" means particularly a carbocyclic aryl group such as phenyl or naphthyl, or heteroaryl such as pyridyl or furyl, and preferably, it is phenyl.

25 The term " C_{4-8} cycloalkyl" means a cycloalkyl group having 4 to 8 carbons, and includes particularly, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl, etc.; and it is preferably, cyclopentyl or cyclohexyl.

30 The term "aminoalkyl" means an straight alkyl having an amino group and 1 to 8 carbons, and includes particularly, 8-aminooctyl, 6-aminoethyl, 4-aminobutyl, 2-aminoethyl, or aminomethyl; preferably, it is 2-aminoethyl or aminomethyl.

35 The term "mono- or di-alkylamino" means methylamino, dimethylamino, ethylamino, propylamino, diethylamino, isopropylamino, diisopropylamino, dibutylamino,

butylamino, isobutylamino, sec-butylamino, tert-butylamino, etc.; preferably, it is methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, or diisopropylamino; and more preferably, it is
5 ethylamino, diethylamino, or isopropylamino.

The term "mono- or di-alkylaminoalkyl" means particularly, methylaminoethyl, dimethylaminoethyl, ethylaminoethyl, methylaminopropyl, dimethylaminopropyl, ethylaminopropyl, diethylaminopropyl, methylaminobutyl, or dimethylaminobutyl, etc.; preferably, it is
10 methylaminoethyl, dimethylaminoethyl, or ethylaminoethyl. "C₁₋₁₀ alkyl" which binds to a nitrogen atom as Z means a straight or branched carbon chain having 1 to 10 carbons, and is for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neo-pentyl,
15 isopentyl, 1,2-dimethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, heptyl, isoheptyl, 1-methylhexyl, 2-methylhexyl, octyl, 2-ethylhexyl, nonyl,
20 decyl, or 1-methylnonyl, etc. Among them, one having 1 to 4 carbons is preferable, and isopropyl or propyl is particularly preferable.

The term "arylcarbonyl" means benzoyl, 4-methoxybenzoyl, or 3-trifluoromethylbenzoyl, etc., and
25 preferably, it is benzoyl.

The term "aralkylcarbonyl" includes particularly, benzylcarbonyl, phenethylcarbonyl, phenylpropylcarbonyl, 1-naphthylmethylcarbonyl, or 2-naphthylmethylcarbonyl, etc.; and preferably, it is benzylcarbonyl.

30 The term "aralkyl" includes particularly, benzyl, phenethyl, phenylpropyl, 1-naphthylmethyl, or 2-naphthylmethyl, etc.; and preferably, it is benzyl.

Further, in the definition regarding the substituent in a compound of formula (2) of the present invention:

35 The term "C₁₋₄ alkoxy carbonyl" means methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl,

sec-butoxycarbonyl, or tert-butoxycarbonyl; preferably, it is methoxycarbonyl, ethoxycarbonyl, or tert-butoxycarbonyl; and more preferably, it is methoxycarbonyl.

5 The term "C₁₋₄ alkyl" means a straight or branched carbon chain having 1 to 4 carbons, and includes for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, or tert-butyl; and preferably, it is methyl or ethyl.

10 The term "C₁₋₄ alkylcarbonyl" means a carbonyl group having a straight or branched carbon chain having 1 to 4 carbons, and includes for example, formyl, acetyl, propionyl, butyryl, or isobutyryl, etc.; and preferably, it is acetyl or propionyl.

15 The term "C₅₋₆ cycloalkyl" means a cycloalkyl group having 5 to 6 carbons, and includes cyclopentyl or cyclohexyl; and it is preferably cyclohexyl.

 The term "C₁₋₄ alkoxy" means an alkoxy group having 1 to 4 carbons, and includes particularly, methoxy, 20 ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, or tert-butoxy, etc. Among them, methoxy or ethoxy is preferable.

 The compound (1) of the present invention may form acid addition salts. Further, it may form salts with 25 bases, depending on the species of the substituent. These salts are not restricted insofar as they are pharmaceutically acceptable, and include particularly, mineral salts such as hydrochloride, hydrobromide, hydroiodide, phosphate, nitrate or sulfate, etc.; organic 30 sulfonates such as methanesulfonate, 2-hydroxyethanesulfonate or p-toluenesulfonate, etc.; and organic carbonates such as acetate, trifluoroacetate, propionate, oxalate, citrate, malonate, succinate, glutarate, adipate, tartrate, maleate, malate, or 35 mandelate, etc. As salts with bases, salts with inorganic bases such as sodium salts, potassium salts, magnesium salts, calcium salts or aluminium salts, and

salts with organic bases such as methylamine salts, ethylamine salts, lysine salts or ornithine salts, etc. are included.

5 The preferred compounds of the invention are found in Table 1.

More preferred compounds of the invention are compounds specified by the following compound numbers, among compounds listed in Table 1.

10 Compound No.: 23, 29, 30, 31, 53, 54, 57, 58, 59, 60, 91, 92, 93, 115, 119, 120, 121, 156, 166, 168, 201, 205, 206, 207, 244, 245, and 246.

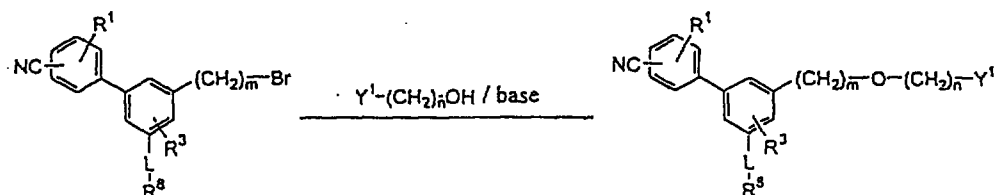
The representative strategies for synthesizing compounds of formula (1) of the present invention are detailed in the following description.

15 According to the present invention, in the case that starting compounds or intermediates have substituents which influence the reaction such as hydroxyl, amino or carboxyl, etc., it is preferred to adequately protect such functional groups to carry out the reaction of
20 etherification, and then detach the protecting group. The protecting group is not limited insofar as it is one which is usually employed on respective substituents and does not have an adverse effect on the other elements during processes of the protection and deprotection, and
25 includes for example, trialkylsilyl, $C_1 - 4$ alkoxymethyl, tetrahydropyranyl, acyl or $C_1 - 4$ alkoxycarbonyl as a protecting group on hydroxyl; $C_1 - 4$ alkoxycarbonyl, benzyloxycarbonyl or acyl as a protecting group on amino; and $C_1 - 4$ alkyl as a protecting group on carboxyl. The
30 deprotection reaction can be carried out according to processes which are usually practiced on respective protecting groups.

Among nitriles which are precursors of the present compounds of formula (1), compounds having an oxygen as X
35 can be synthesized, for example, according to the following reaction:

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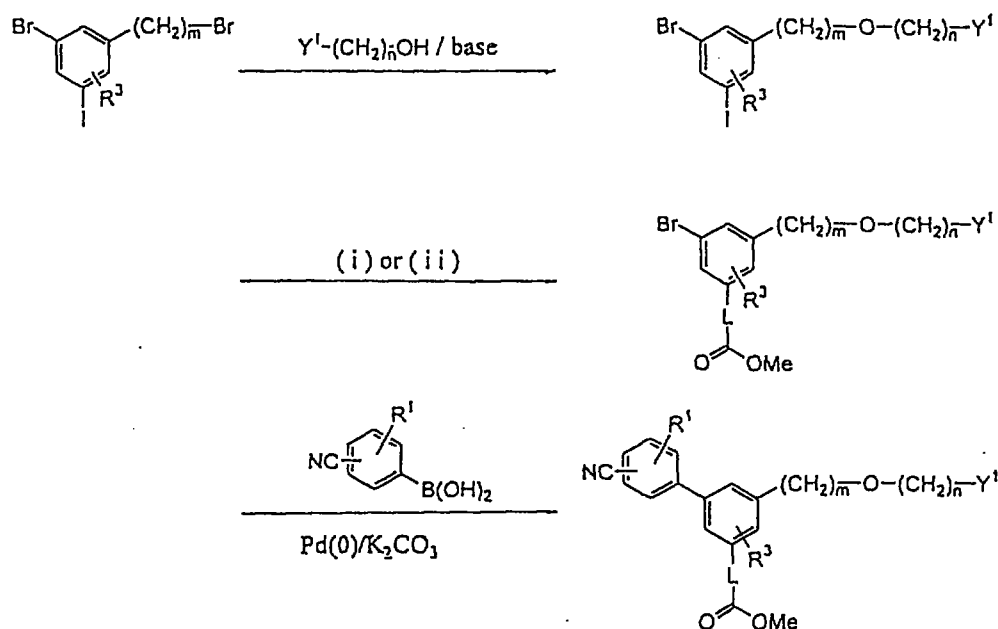


5 (a-1)

wherein R^1 , R^3 , L , m , and n are as defined in formula (1); Y^1 means a substituent Y defined in formula (1) except for the one having the structures defined in the formula I-3 as a substituent Z on Y ; R^8 means hydrogen, fluorine, chlorine, bromine, hydroxyl or protected hydroxyl, amino or protected amino, or C_{1-8} alkoxy.

That is, as seen in the above reaction (a-1), nitriles which are precursors of the compound of the invention can be produced by mixing alcohol represented by formula: $Y^1-(CH_2)_n-OH$ with a raw material, biphenylalkyl bromide in the presence of bases.

Moreover, among nitriles which are precursors of the present compounds of formula (1), compounds having an oxygen as X can be synthesized, for example, according to the following reaction:



25

30

35

(a-2)

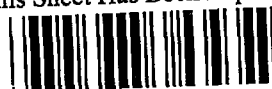
wherein R^1 , R^3 , L, m, and n are as defined in formula (1); Y^1 means a substituent Y defined in formula (1) except for the one having the structures defined in the formula I-3 as a substituent Z on Y.

5 That is, nitriles which are precursors of the present compound can be produced by mixing alcohol represented by formula $Y^1-(CH_2)_n-OH$ with a raw material, 3-bromo-3-iodophenylalkyl bromide in the presence of bases to produce 3-bromo-3-iodophenylalkyl ether, then
10 introducing substituent $-L-COOMe$ into the resulting ether by the monocarbonylation or monoalkylation to produce 3-bromophenylalkylether, and then carrying out the coupling reaction with a cyanophenyl-boronic acid derivative.

The etherification of the first step in reactions
15 (a-1) and (a-2) is carried out using aliphatic ether solvent, such as tetrahydrofuran or diethylether, aprotic hydrocarbons such as benzene or toluene, aprotic polar solvents such as DMF or HMPA, or a mixture thereof, etc., and as bases, a metal oxide such as barium oxide or zinc
20 oxide, metal hydroxide such as sodium hydroxide or potassium hydroxide, or a metal hydride such as sodium hydride, etc. are used. The reaction proceeds at $0 - 100^\circ C$ for 3 - 72 hours with stirring. Preferably, it is carried out at $20 - 80^\circ C$ for 8 - 36 hours, using
25 sodium hydride, in absolute aliphatic ethers such as THF or ether.

The reaction for introducing a substituent: $-L-COOMe$ to ethers, which is the second step of reaction (a-2), can be carried out according to the following
30 reactions (i) or (ii):

(i) Monocarbonylation by introduction of carbon monoxide (in the case that L is a bond): Iodine can be substituted with methoxycarbonyl group by dissolving the ethers obtained from the first step of reaction (a-1)
35 into methanol, adding bivalent palladium catalyst and bases such as tertiary amine such as triethylamine, and



optionally phosphine ligand such as triphenylphosphine, and stirring for 3 - 48 hours under room temperature or under heating in an atmosphere of carbon monoxide. Preferably, it is carried out using, as a catalyst,
5 bistriphenylphosphine palladium or palladium acetate and as a base, diisopropylethylamine or tributylalminium, at 60 - 80°C for 12 - 36 hours.

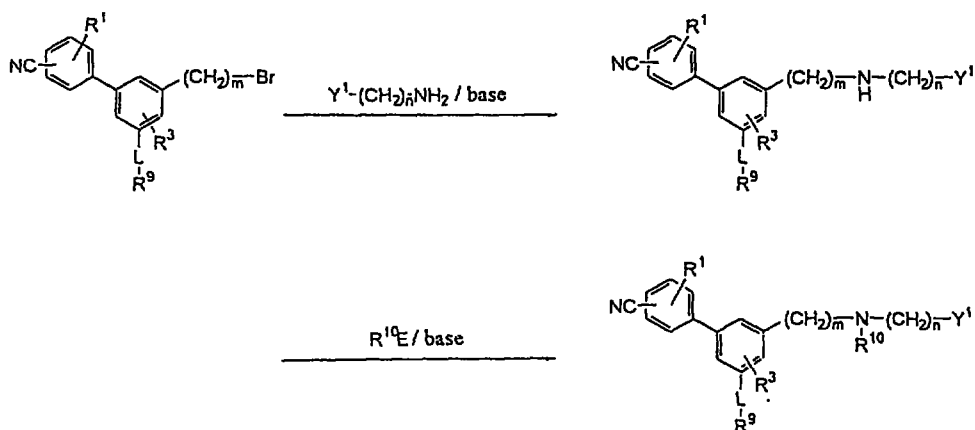
(ii) Monoalkylation using an organic zinc reagent (in the case that L is C_{1-8} alkylene): Iodine can be
10 substituted with alkyl by dissolving the ethers obtained from the first step of reaction (a-1) and 0-valence palladium catalyst such as tetrakistriphenylphosphine palladium into the solvent such as THF or DMF, benzene, or toluene, or a mixture thereof, adding, to this
15 solution, THF solution containing alkyl zinc reagent of formula: $1-Zn-L-COOMe$, and stirring for 3 - 48 hours under room temperature or under heating in an atmosphere of carbon monoxide. Preferably, it is carried out using, as a catalyst, tetrakistriphenylphosphine palladium and
20 as a solvent, THF, at 20 - 80°C for 6 - 36 hours.

The biphenylation which is the third step of the reaction (a-2) can be carried out by reacting monohalide with cyanophenyl boronic acid in presence of palladium catalyst. This reaction proceeds usually by heating,
25 with stirring in DMF, the monohalide obtained from the second step of the reaction (a-2) and bivalent palladium catalyst such as palladium acetate, and additionally, bases such as triethylamine, and triarylphosphines to produce the cyanobiphenyl compound of interest.
30 Preferably, it is carried out at 60 - 100°C for 2 - 24 hours.

Moreover, among nitriles which are precursors of the present compounds of formula (1), compounds having a nitrogen as X can be synthesized, for example, according
35 to the following reactions (b-1) and (b-2):

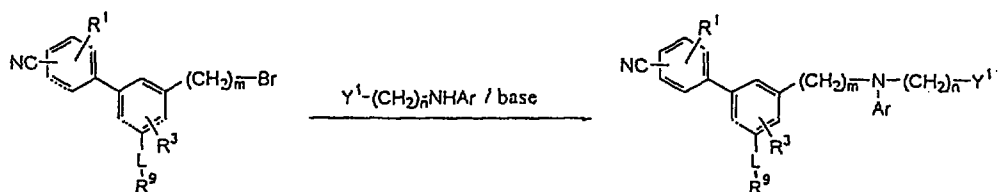
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(b-1)

wherein R^1 , R^3 , L , m , and n are as defined in formula (1); R^9 means fluorine, chlorine, bromine, hydroxyl or protected hydroxyl, amino or protected amino, C_{1-8} alkoxy, or methoxycarbonyl among substituent R^2 defined in formula (1); Y^1 means a substituent Y defined in formula (1) except for the one having the structures defined in the formula I-3 as a substituent Z on Y ; R^{10} means a substituent R^4 except for hydrogen and aryl; E is a leaving group such as chlorine, bromine, iodine, acyloxy or sulfonyloxy.

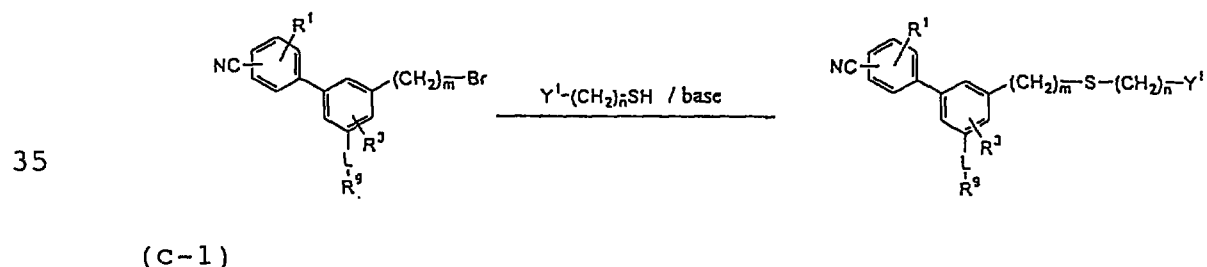


(b-2)

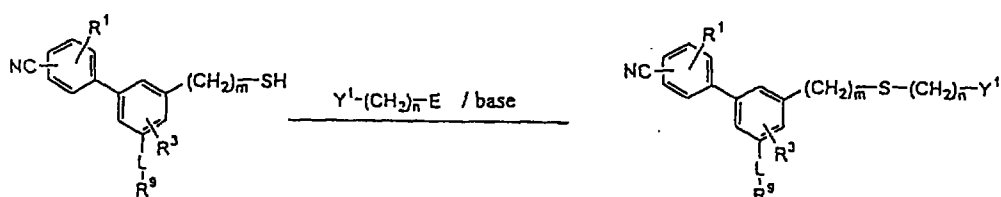
wherein R^1 , R^3 , L , m , and n are as defined in formula (1); R^9 means fluorine, chlorine, bromine, hydroxyl or protected hydroxyl, amino or protected amino, C_{1-8} alkoxy, or methoxycarbonyl among substituent R^2 defined in formula (1); Y^1 means a substituent Y defined in formula (1) except for the one having the structures defined in the formula I-3 as a substituent Z on Y ; Ar means aryl; E is a leaving group such as chlorine, bromine, iodine, acyloxy or sulfonyloxy.

The N-alkylation of reactions (b-1) and (b-2) can be carried out using a condition for alkylation which is known. That is, the starting material, biphenylalkylbromide can be reacted with amines of
 5 formula: $Y^1-(CH_2)_n-NH_2$ in the presence of mineral salts such as potassium carbonate or amines such as tertiary amines which act as a base, to produce a secondary amine which is a compound of the present invention. This compound can be reacted with alkylating agent of formula:
 10 R^4-E to produce a tertiary amine which is a compound of the present invention. The above reactions are carried out usually by mixing amines with alkylating agents at optional rate in suitable solvents, and stirring then for 1 - 96 hours under cooling, under room temperature or
 15 under heating. Usually, the reactions are carried out using, as a base, mineral salts such as potassium carbonate or sodium carbonate or organic tertiary amines such as triethylamine or pyridine, and using, as a solvent, alcohols such as methanol or ethanol,
 20 hydrocarbons such as benzene or toluene, or a solvents which do not influence the reaction such as THF, dioxane, acetonitrile, DMF or DMSO, or a mixture thereof, at the rate of alkylating agents to amines of 1:10 - 10:1. Preferably, it is done at an alkylating agents to amines
 25 rate of 1:5 - 1:1, under room temperature or under heating, for 2 - 24 hours.

Among nitriles which are precursors of the present compounds of formula (1), compounds having a sulfur as X can be synthesized, for example, according to the
 30 following reactions (c-1) and (c-2):



wherein R^1 , R^3 , L , m , and n are as defined in formula (1): R^9 means fluorine, chlorine, bromine, hydroxyl or protected hydroxyl, amino or protected amino, C_{1-8} alkoxy, or methoxycarbonyl among substituent R^2 defined in formula (1); Y^1 means a substituent Y defined in formula (1) except for the one having the structures defined in the formula I-3 as a substituent Z on Y ; and E is a leaving group such as chlorine, bromine, iodine, sulfonate.



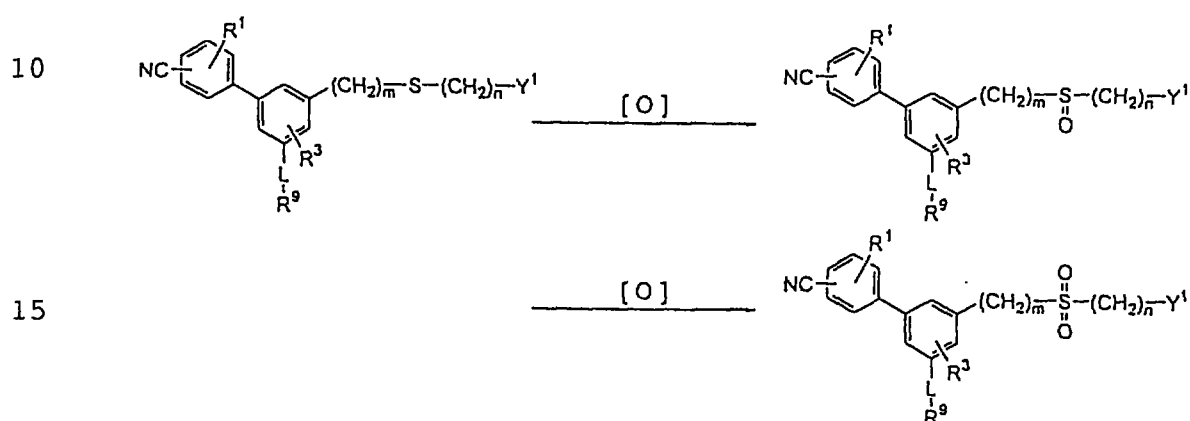
(c-2)

wherein R^1 , R^3 , L , m , and n are as defined in formula (1): R^9 means fluorine, chlorine, bromine, hydroxyl or protected hydroxyl, amino or protected amino, C_{1-8} alkoxy, or methoxycarbonyl among substituent R^2 defined in formula (1); Y^1 means a substituent Y defined in formula (1) except for the one having the structures defined in the formula I-3 as a substituent Z on Y ; and E is a leaving group such as chlorine, bromine, iodine, or sulfonate.

The thioetherification of reactions (c-1) and (c-2) can be carried out using a condition for thioetherification which is known. Usually, it is done by mixing alkyl halides with thiols at an optional rate in suitable solvents in the presence of bases such as sodium hydroxide or ammonia, and stirring them under cooling, under room temperature or under heating for 30 minutes to 96 hours. As a solvent, compounds which do not act on the reaction such as water, ethanol, DMF or toluene are employed, and as a base, sodium hydroxide, ammonia or cesium carbonate, etc. is employed. The reactions are carried out preferably by mixing at the

rate of alkyl halides to thiols being 1:5 - 5:1, and stirring under room temperature or under heating for 30 minutes to 24 hours.

Moreover, the resulting sulfide can be subjected to oxidation such as in the following reaction (d) to produce a compound having sulfoxide or sulfone as X among the compound of formula (1).



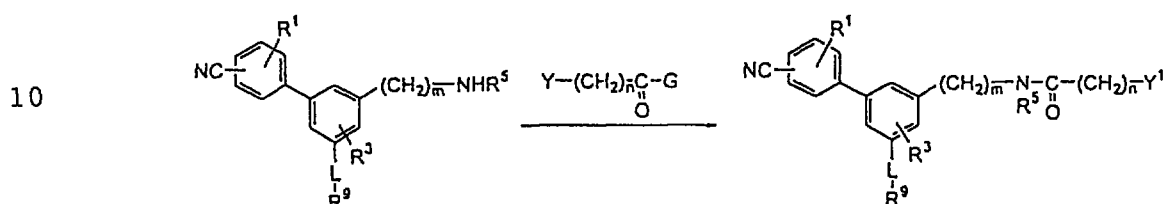
(d)

wherein R^1 , R^3 , L, m, and n are as defined in formula (1): R^9 means fluorine, chlorine, bromine, hydroxyl or protected hydroxyl, amino or protected amino, C_1 - C_8 alkoxy, or methoxycarbonyl among substituent R^2 defined in formula (1): and Y^1 means a substituent Y defined in formula (1) except for the one having the structures defined in the formula I-3 as a substituent Z on Y.

The oxidation of reaction (d) can be carried out according to a process described in Jikken Kagaku Kohza (The 4th Edition), 24, Organic Synthesis VI - heteroelement-metallic element compounds -, p.350 - 373, edited by the Japan Chemical Association. Usually, the reaction is carried out using sulfides or sulfoxides using alcohols such as water or ethanol, etc. as a solvent and hydrogen peroxide, peracetic acid, metaperiodic acid or m-chloroperbenzoic acid, etc. as an oxidizing agent under cooling, under room temperature or under heating with stirring for 30 minutes to 24 hours.

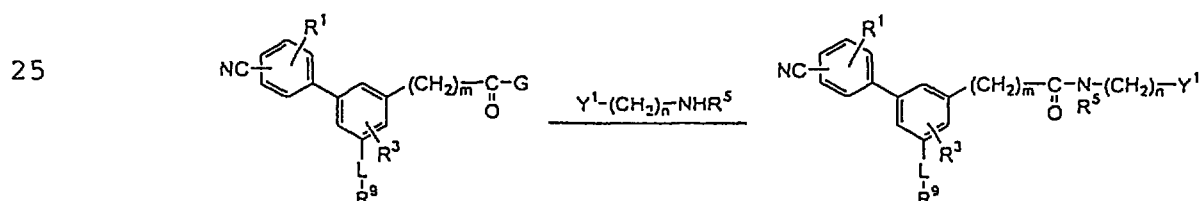
Preferably, the sulfoxide is produced for 30 to 12 hours at 0 - 20°C, while the sulfone is produced for 1 - 12 hours at 0 - 80°C.

Further, among nitriles which are precursors of the present compounds of formula (1), compounds having an amido linkage as X can be synthesized, for example, according to the following reactions (e-1) and (e-2):



(e-1)

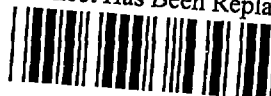
15 wherein R¹, R³, R⁵, L, m, and n are as defined in formula (1); R⁹ means fluorine, chlorine, bromine, hydroxyl or protected hydroxyl, amino or protected amino, C₁-₈ alkoxy, or methoxycarbonyl among substituent R² defined in formula (1): Y¹ means a substituent Y defined in formula (1) except for the one having the structures defined in the formula I-3 as a substituent Z on Y; and G is halogen, acyloxy, p-nitrophenoxy or hydroxyl, etc.



(e-2)

30 wherein R¹, R³, R⁵, L, m, and n are as defined in formula (1): R⁹ means fluorine, chlorine, bromine, hydroxyl or protected hydroxyl, amino or protected amino, C₁-₈ alkoxy, or methoxycarbonyl among substituent R² defined in formula (1); Y¹ means a substituent Y defined in formula (1) except for the one having the structures defined in the formula I-3 as a substituent Z on Y; and G

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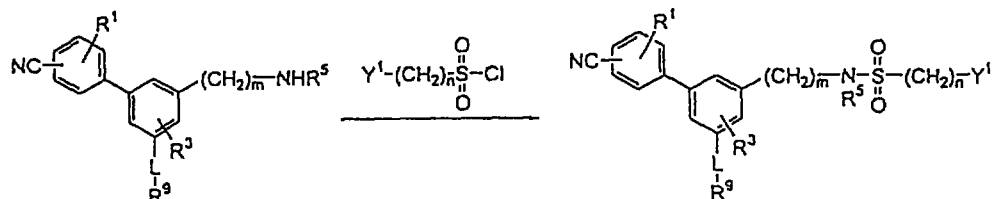


is halogen, acyloxy, p-nitrophenoxy or hydroxyl, etc.

The reactions of (e-1) and (e-2) can be carried out using a condition for amidation which is known. Usually, the amides can be obtained by mixing active derivatives of carboxylic acids with amine compounds in suitable solvents in the presence of bases, for acylation. As the active derivatives of carboxylic acids for use, active esters such as acid halides, mixed acid anhydrides or p-nitrophenol, etc. are employed under cooling or under room temperature for 30 minutes to 24 hours. Preferably, it is done in halogenated hydrocarbons such as dichloromethane, aliphatic ethers such as THF or diethylether, or solvents such as acetonitrile or DMF, or a solvent mixture thereof, using tertiary amines such as triethylamine as bases, at 0 - 20°C for 1 - 18 hours.

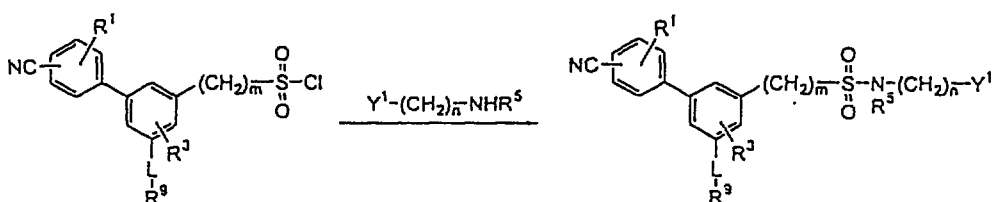
Also, these amides can be obtained by the condensation between amines and carboxylic acids in presence of condensating agents such as carbodiimides. In this case, halogenated hydrocarbons such as DMF or chloroform as solvents are suitable while N,N-dicyclohexylcarbodiimide, 1-ethyl-(3-(N,N-dimethylamino)propyl)carbodiimide, carbonyldiimidazole, diphenylphosphorylazide, or diethylphosphorylcyanide are suitable as condensating agents. The reaction is usually carried out under cooling or under room temperature for 2 - 48 hours.

Moreover, among nitriles which are precursors of the present compounds of formula (1), compounds having a sulfoneamide structure as X can be synthesized, for example, according to the following reactions (f-1) or (f-2):



(f-1)

wherein R^1 , R^3 , R^5 , L , m , and n are as defined in formula (1); R^9 means fluorine, chlorine, bromine, hydroxyl or protected hydroxyl, amino or protected amino, C_{1-8} alkoxy, or methoxycarbonyl among substituent R^2 defined in formula (1); and Y^1 means a substituent Y defined in formula (1) except for the one having the structures defined in the formula I-3 as a substituent Z on Y .



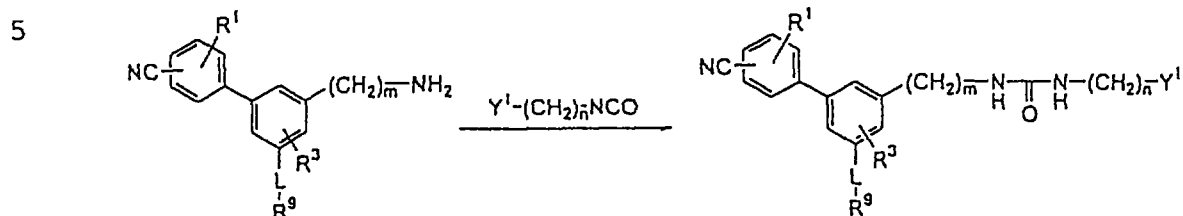
(f-2)

wherein R^1 , R^3 , R^5 , L , m , and n are as defined in formula (1); R^9 means fluorine, chlorine, bromine, hydroxyl or protected hydroxyl, amino or protected amino, C_{1-8} alkoxy, or methoxycarbonyl among substituent R^2 defined in formula (1); and Y^1 means a substituent Y defined in formula (1) except for the one having the structures defined in the formula I-3 as a substituent Z on Y .

The reactions of (f-1) and (f-2) can be carried out by reacting an amine with active derivatives of sulfonic acids in suitable solvents in the presence of bases to produce sulfonamids of interest. As the active derivatives of sulfonic acids, sulfonyl halide is preferable, and the reaction is carried out in halogenated hydrocarbons such as dichloromethane, aliphatic ethers such as THF or diethylether, a solvent such as acetonitrile or DMF, or a mixture of the solvents at 0 - 20°C for 1 - 24 hours, using tertiary amines such as triethylamine as a base.

Also, among nitriles which are precursors of the

present compounds of formula (1), compounds having a urea structure as X can be synthesized, for example, according to the following reaction (g):

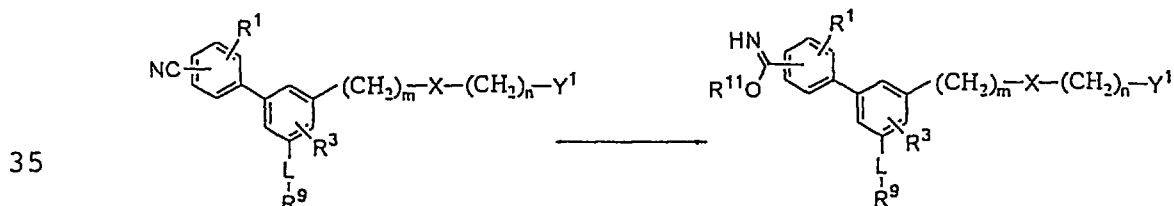


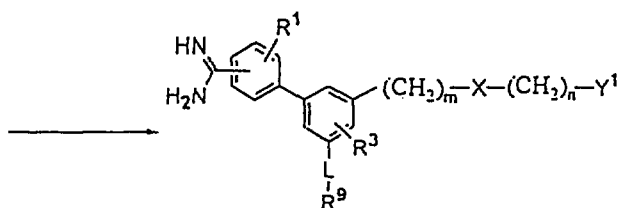
10 (g)

wherein R^1 , R^3 , L , m and n are as defined in formula (1): R^9 means fluorine, chlorine, bromine, hydroxyl or protected hydroxyl, amino or protected amino, C_{1-8} alkoxy, or methoxycarbonyl among substituent R^2 defined in formula (1); and Y^1 means a substituent Y defined in formula (1) except for the one having the structures defined in the formula I-3 as a substituent Z on Y .

That is, compounds having a urea structure as X can be produced by reacting, as a raw material, amine with isocyanate derivatives in a suitable solvent under cooling to heating. A solvent used in this reaction can be DMF, THF, dioxane, dichloroethane, chloroform, acetonitrile, DMSO, benzene, or toluene, etc.

25 The nitriles which are precursors of the compound of the present invention produced by the above reactions (a-1), (a-2), (b-1), (b-2), (c-1), (c-2), (d), (e-1), (e-2), (f-1), (f-2), and (g) can be converted to the benzamidine derivatives which are a compound of the present invention by the reaction of amidination as follows:





5 (h)

wherein R^1 , R^3 , L , X , m and n are as defined in formula (1); Y^1 means a substituent Y defined in formula (1) except for the one having the structures defined in the formula I-3 as a substituent Z on Y ; R^9 means fluorine, chlorine, bromine, hydroxyl or protected hydroxyl, amino or protected amino, C_{1-8} alkoxy, or methoxycarbonyl among substituent R^2 defined in formula (1); and R^{11} means C_{1-4} alkyl. This amidination is carried out according to the condition for reaction detailed in the following (iii) or (iv):

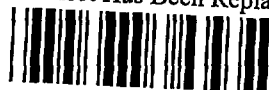
(iii) Amidination through imidation using hydrogen halide in alcohol solution: The reaction by which the imidates are obtained from nitriles and alcohols, proceeds, for example, by dissolving
20 alkoxyethylphenylbenzonitriles in alcohols having 1 to 4 carbons ($R^{11}OH$) containing hydrogen halides such as hydrogen chloride or hydrogen bromide, etc. with stirring. The reaction is usually carried out at -20 - 30°C, for 12 - 96 hours. Preferably, it is done in
25 a hydrogen chloride in methanol or ethanol solution, at -10 - +30°C, for 24 - 72 hours. The reaction between the imidate and ammonia proceeds by stirring the imidate in an alcohol having 1 to 4 carbons such as methanol or ethanol containing ammonia or amines such as
30 hydroxylamine, hydrazine or carbamate ester, or in aliphatic ethers such as diethylether, or in halogenated hydrocarbons such as dichloromethane or chloroform, or a mixture thereof to produce the benzamidine derivative which is a compound of the present invention. The
35 reaction is usually carried out at the temperature of -10 - +50°C, for 1 to 48 hours. Preferably, it is

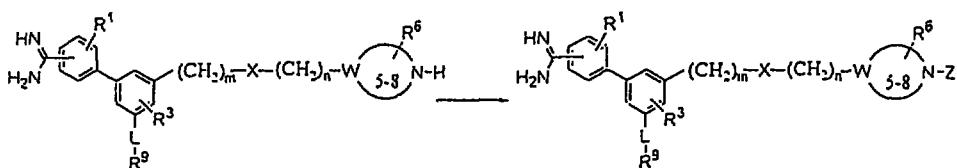


carried out at 0 - 30°C for 2 - 12 hours.

(iv) Amidination through an imidate prepared by direct bubbling of hydrogen halide: The reaction between nitriles and alcohols proceeds, for example by dissolving nitriles in aliphatic ethers such as diethylether, or halogenated hydrocarbons such as chloroform, or aprotic solvents such as benzene, adding the equivalent or an excess of an alcohol having 1 to 4 carbons ($R^{11}OH$), bubbling hydrogen halides such as hydrogen chloride or hydrogen bromide at -30 - 0°C for 30 minutes to 6 hours with stirring, then stopping the bubbling, and stirring at 0 - 50°C for 3 - 96 hours. Preferably, it is done by bubbling hydrogen chloride for 1 - 3 hours at -10 - 0°C with stirring in halogenated hydrocarbons containing the equivalent or excess methanol or ethanol, then stopping the bubbling, and stirring at 10 - 40°C for 8 - 24 hours. The resulting imidates can be converted to benzamidine derivatives (1) which are compounds of the present invention by stirring them in alcohol solvents having 1 to 4 carbons such as methanol or ethanol containing ammonia or amines such as hydroxylamine, hydrazine or carbamate ester, or aliphatic ether solvents such as diethylether, or halogenated hydrocarbon solvents such as chloroform, or a mixture thereof. The reaction is usually carried out at the temperature of -20 - +50°C for 1 - 4 hours. Preferably, it is carried out in saturated ammonia ethanol solution at 0 - 30°C for 2 - 12 hours.

Among the compounds of the present invention of formula (1), compounds having a substituent Y wherein a substituent Z has the structures defined in formula I-3 can be produced by carrying out the imidoylation of the following (j-1) and (j-2), after yielding the benzamidine compounds having a secondary amino group in a substituent Y by the above reaction (h):



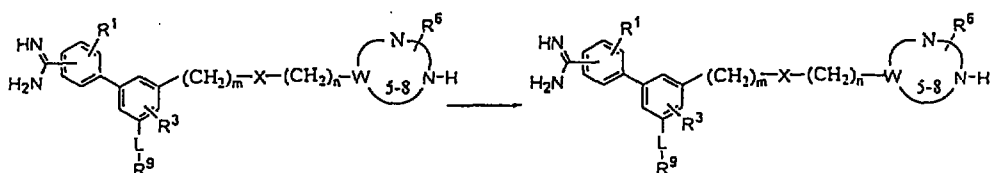


5

(j-1)

wherein R^1 , R^3 , R^6 , L , W , X , Z , m and n are as defined in formula (1); R^9 means fluorine, chlorine, bromine, hydroxyl or protected hydroxyl, amino or protected amino, C_{1-8} alkoxy, or methoxycarbonyl among substituent R^2 defined in formula (1).

10



15

(j-2)

wherein R^1 , R^3 , R^6 , L , W , X , Z , m and n are as defined in formula (1); R^9 means fluorine, chlorine, bromine, hydroxyl or protected hydroxyl, amino or protected amino, C_{1-8} alkoxy, or methoxycarbonyl among substituent R^2 defined in formula (1).

20

This imidoylation proceeds by mixing benzamidine compounds having a secondary amino group in a substituent Y with the equivalent or excess imidates in water, or alcohols having 1 to 4 carbons such as methanol or ethanol, or aliphatic ethers such as diethylether, or halogenated hydrocarbons such as chloroform, or polar solvents such as DMF or DMSO, or a mixture thereof in presence of bases, with stirring. The reaction is usually carried out at room temperature for 1 - 24 hours. As a base, N-methylmorpholine, triethylamine, diisopropylethylamine, sodium hydroxide, or potassium hydroxide, etc. can be used.

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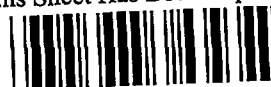
Among the compounds of the present invention of formula (1), compounds having a carboxyl as R^2 are



produced by ester hydrolysis of compounds having methoxycarbonyl as R^9 among the benzamidine compounds produced by the above reaction (h), (j-1) and (j-2). This hydrolysis can be carried out under a basic
5 condition, an acidic condition, or a neutral condition, if necessary. In the reaction under the basic condition, as a base, sodium hydroxide, potassium hydroxide, lithium hydroxide, or barium hydroxide, etc. can be used, and under the acidic condition, hydrochloric acid, sulfuric
10 acid, or Lewis acids such as boron trichloride, trifluoroacetic acid, or p-toluenesulfonic acid, etc., are included, while under the neutral condition, a halogen ion such as lithium iodide or lithium bromide, alkali metal salts with thiol or selenol,
15 iodotrimethylsilane, and enzymes such as esterase are included. The solvent for use includes polar solvents such as water, alcohols, acetone, dioxane, THF, DMF, DMSO, etc., or a mixture thereof. The reaction is usually carried out at room temperature or under heating
20 for 2 - 96 hours. The suitable condition of the reaction temperature or the reaction time, etc. differs, depending on the reaction condition used, and can be selected appropriately by a conventional process.

In the compounds having a carboxyl is a substituent
25 R^2 , obtained from the above process, the carboxyl can be converted to the other esters by the following process (v), (vi), or (vii):

(v) Conversion from carboxyl to alkoxycarbonyl:
The carboxyl can be converted to the alkoxycarbonyl by
30 reacting compounds having carboxyl as a substituent R^2 among compounds of formula (1) with the equivalent or excess alkylating agents (for example, methyl acyloxylchlorides such as methyl acetoxylchloride or methyl pivaloyloxylchloride, or allyl chlorides, or benzyl
35 chlorides) in halogenated hydrocarbons such as dichloromethane, or aliphatic ethers such as THF, or aprotic polar solvents such as DMF, or a mixture thereof,



under presence of tertiary amines such as triethylamine or diisopropylethylamine, at -10 - +80°C for 1 - 48 hours. Preferably, it is done using the equivalent to a slight excess of alkylating agent, in the presence of diisopropylethylamine, at 20 - 60°C, for 2 - 24 hours.

(vi) Conversion from carboxyl to aralkoxycarbonyl: The carboxyl can be converted to the aralkoxycarbonyl by reacting compounds having carboxyl as a substituent R^2 among compounds of formula (1) with the equivalent or excess alcohols such as benzyl alcohol in a solvent of halogenated hydrocarbons such as dichloromethane, in the presence of acid catalysts such as hydrogen chloride, sulfuric acid or sulfonic acid. The reaction is usually carried out at room temperature or under heating for 1 - 72 hours. Preferably, it is done using the equivalent to a slight excess of alcohols under presence of diisopropylethylamine, at 20 - 60°C, for 2 - 24 hours.

(vii) Conversion of carboxyl to aryloxycarbonyl: The carboxyl can be converted to the aryloxycarbonyl by reacting compounds having carboxyl as a substituent R^2 among compounds of formula (1) with the equivalent or an excess of aromatic compound having hydroxyl such as phenol in a solvent of aliphatic ethers such as diethylether, under presence of the condensating agents such as dicyclohexylcarbodiimide. The reaction is usually carried out at 0 - 50°C for 1 - 48 hours. Preferably, it is done at room temperature for 3 - 24 hours.

Also, compounds having a carboxyl as R^2 can be converted to ones having carbamoyl by known techniques, for example, by treating the carboxyl with oxalyl chloride, etc. to produce acid halides, and reacting with ammonia solution. Similarly, it can be converted to N-methyl-N-methoxycarbamoyl by acid halides with N-methyl-N-methoxyamine, and further this can be converted to

alkylcarbonyl by reacting with various alkylmagnesium reactants.

Among the present compounds synthesized by the above processes, compounds having an amidino group as a substituent A can be introduced through one of the electrons in a nitrogen constituting the amidino group with various carbonyls by the following process (ix), (x), or (xi).

(ix) Aryloxycarbonylation of amidino:

Aryloxycarbonyl can be introduced through one of the electrons in a nitrogen constituting an amidino by stirring compounds having an amidino as a substituent A among the compounds of formula (1) with the equivalent to excess aryl chloroformates such as phenyl chloroformate in a mixed solvent of water and halogenated hydrocarbons such as dichloromethane in the presence of bases such as sodium hydroxide or potassium hydroxide. The reaction is usually carried out at $-10 - +40^{\circ}\text{C}$ for 3 - 48 hours. Preferably, it is done using the equivalent or a little excess aryl chloroformate at $0 - 30^{\circ}\text{C}$ for 6 - 24 hours.

(x) Alkoxycarbonylation of amidino: Alkoxycarbonyl can be introduced through one of the electrons in a nitrogen constituting an amidino by reacting compounds having an amidino as a substituent A among the compounds of formula (1) with the equivalent to excess alkylcarbonic acid p-nitrophenyl ester in an absolute solvent such as THF or DMF in the presence of bases such as metal hydrides such as sodium hydride or tertiary amines, at $-10 - +30^{\circ}\text{C}$ for 3 - 48 hours. Preferably, it is done with the equivalent to a slight excess of p-nitrophenyl ester of alkylcarbonates under presence of tertiary amines such as triethylamine or diisopropylethylamine, at $-10 - +40^{\circ}\text{C}$ for 6 - 24 hours.

(xi) Arylcarbonylation of amidino: Arylcarbonyl can be introduced through one of the electrons in a nitrogen constituting an amidino by reacting compounds having an



amidino as a substituent A among the compounds of formula (1) with the equivalent to excess aromatic carboxylic acid chloride such as benzoylchloride in halogenated hydrocarbons such as methylene chloride or solvents such as THF, DMF or pyridine, or a mixture thereof in the presence of bases such as amines, at -10 - +30°C for 1 - 48 hours. Preferably, it is done with the equivalent to a slight excess of aromatic carboxylic acid chloride under presence of amines such as triethylamine, diisopropylethylamine or pyridine, at -10 - +40°C for 2 - 24 hours.

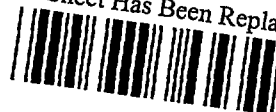
Furthermore, the compounds of formula (1) can be produced by an optional combination of other well-known etherification, amidination, hydrolysis, alkyylimidoylation, amidation or esterification processes, or process which is usually employed by those skilled in the art.

The alkoxymethylphenylbenzamidine derivatives (1) produced as above, can be isolated and purified by the known techniques for example by extraction, precipitation, fractional chromatography, fractional crystallization, or recrystallization, etc. Further, a pharmaceutically acceptable salt of the compound of the present invention can be produced by subjecting it to a usual salt-forming reaction.

The biphenylamidine derivatives and pharmaceutically acceptable salts thereof of the invention have an effect of inhibiting FXa activity, and can be used as a prophylactic agent and/or a therapeutic agent which are clinically applicable against thromboembolism such as myocardial infarction, cerebral thrombosis, thrombosis of peripheral artery or thrombosis of deep vein as a FXa inhibitor.

Moreover, the biphenylamidine derivatives of the invention can constitute pharmaceutical compositions with pharmaceutically acceptable carriers, and be

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administered orally or parenterally in various dosage form. Parenterally administration includes for example, administration by intravenous, subcutaneous, intramuscular, transdermal, intrarectal, transnasal and
5 instillation methods.

The dosage form of the pharmaceutical composition includes the following: For example, in the case of oral administration, tablets, pills: granules, powder, solution, suspension, syrup, or capsules, etc. can be
10 used.

As a method for producing a tablet, it can be formed by conventional techniques using a pharmaceutically acceptable carrier such as excipient, binder or disintegrant, etc. Also, the form of a pill, granules,
15 or powder can be produced by the conventional techniques using excipient, etc. in the same manner as the tablet. The form of a solution, suspension or syrup can be produced by the conventional techniques using glycerol esters, alcohols, water or vegetable oils, etc. The form
20 of capsule can be produced by filling a capsule made of gelatine, etc. with the granules, powder or a solution, etc.

Among the agents for parenteral administration, in the case of intravenous, subcutaneous or intramuscular administration, it can be administered as injection. A
25 injection can be produced by dissolving the biphenylamidine derivatives in water soluble solutions such as, for example physiological salt solution, or water insoluble solutions consisting of organic esters
30 such as for example, propylene glycol, polyethylene glycol, or vegetable oils, etc.

In the case of transdermal administration, for example, a dosage form as an ointment or a cream can be employed. The ointment can be produced by using the
35 biphenylamidine derivative in the mixture of fats and oils or vaseshines, etc., and the cream can be produced by mixing the biphenylamidine derivative with

emulsifiers.

In the case of rectal administration, it may be in the form of suppository using a gelatine soft capsule, etc.

5 In the case of transnasal administration, it can be used as an formulation consisting of a liquid or powdery composition. As a base of a liquid formulation, water, salt solution, phosphate buffer, or acetate buffer, etc. are used, and also, it may contain surfactants,
10 antioxidants, stabilizers, preservatives, or tackifiers. A base of powdery formulation may include water-absorbing materials such as, for example, highly water-soluble polyacrylates, cellulose low-alkylethers, polyethylene glycol polyvinylpyrrolidone, amylose or pullulan, etc.,
15 or water-unabsorbing materials such as, for example, celluloses, starches, proteins, gums or cross-linked vinyl polymers. The water-absorbing materials are preferable. These materials may be mixed for use. Further, antioxidants, colorants, conservatives,
20 preservatives or, antiseptic etc. may be added to the powdery formulation. The liquid or powdery formulation can administrated, for example, using a spray apparatus.

 In the case of eye drop administration, an aqueous or non-aqueous eye drop can be employed. In the aqueous
25 eye drop, as a solvent, sterilized and purified water or physiological salt solution, etc. can be used. When only the sterilized and purified water is employed as a solvent, an aqueous suspended eye drop can be formed by adding a suspension such as surfactants or high-molecular
30 tackifiers, or a soluble eye drop by adding solubilizers such as nonionic surfactants. In the non-aqueous eye drop, a non-aqueous suspended eye drop can be formed by using injectable non-aqueous solvents as a solvent.

 In the case of administering through the eyes by
35 means other than eye drops, the dosage form such as eye-ointments, applicating solutions, diffusing agents or insert agents can be used.

Further, in the case of the inhalation through nose or mouth, a solution or suspension containing a biphenylamidine derivative and a pharmaceutical excipient which is generally utilized is inhaled through, for example, an inhalant aerosol spray, etc. Also, a biphenylamidine derivative which is in the form of dry powder can be administered through inhalator, etc. which contacts directly with lung.

To these formulations, if necessary, pharmaceutically acceptable carriers such as isotonic agents, preservatives, conservatives, wetting agents, buffers, emulsifiers, dispersions or stabilizers, etc. may be added.

Also, if necessary, these formulations can be sterilized by the addition of a sterilant, filtration using a bacteria-retaining filter, or treatment with heat or irradiation, etc. Alternatively, it is possible to produce an aseptic solid formulation, which can be used to be dissolved or suspended in a suitable aseptic solution immediately before use.

The dose of the biphenylamidine of the invention differs depending on kinds of disease, route of administration, or condition, age, sex or weight of the patient, etc., but generally, is about

1 - 500 mg/day/human body, preferably 10 - 300 mg/day/human body in the case of oral administration, while is about 0.1 - 100 mg/day/human body, preferably 0.3 - 30 mg/day/human body in the case of intravenous, subcutaneous, intramuscle, transdermal, intrarectal, transnasal, instillation or inhalation.

When the biphenylamidine of the invention is used as a prophylactic agent, it can be administered according to well-known processes, depending on the respective condition.

Embodiments

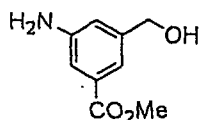
The present invention will be illustrated using the following Productive Examples, Embodiments, and

Experiments. However, the scope of the invention is not restricted in any means by these examples.

Productive Example 1:

Methyl 3-amino-5-hydroxymethylbenzoate:

5

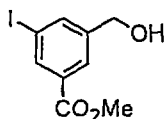


10 85g of 3-nitro-5-methoxycarbonylbenzoic acid was dissolved in 200 ml of THF under a flow of nitrogen, and 43.4 ml of borane dimethylsulfide complex was added with stirring under ice-cooling. After stirring for 18 hours, 200 ml of water was added, and then 96g of potassium
15 carbonate was added. It was extracted with ethyl acetate, and the organic layer was washed with salt solution. After drying with magnesium sulfate, the resulting solid was dissolved in 800 ml of ethyl acetate, 750 mg of 10% Pd/C was added, and stirring was continued
20 under the flow of hydrogen. After the reaction was completed, it was subjected to the filtration, and then the filtrate was concentrated to produce 64g of the title compound.

25 ¹H-NMR (270 MHz, CDCl₃) : δ 2.30 (s, 1 H), 3.89 (s, 3 H), 4.64 (s, 1 H), 6.89 (s, 1 H), 7.26 (s, 1 H), 7.39 (s, 1 H).

Productive Example 2:

30 Methyl 5-hydroxymethyl-3-iodobenzoate:

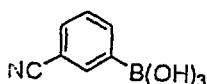


35 34.3g of the compound obtained from Productive Example 1 was dissolved in 200 ml of THF, and 75g of hydroiodic acid was added with stirring under ice-

cooling. A 100 ml solution containing 13.73g of sodium nitrite was added. After stirring at 0°C for 40 min., a 150 ml solution containing 34.6g of potassium iodide was added. After stirring at 40°C for 2 hours, 300 ml of water was added and was concentrated. It was extracted with ethyl acetate, and the organic layer was washed with salt solution. After drying with sodium sulfate, it was purified through silica gel column chromatography to produce 23.1g (42%) of the title compound.

¹H-NMR (270 MHz, CDCl₃) : δ 1.81 (t, 1 H, J = 5.6 Hz), 3.92 (s, 3 H), 4.72 (d, 1 H, J = 5.6 Hz), 7.93 (s, 1 H), 7.98 (s, 1 H), 8.29 (s, 1 H).

Productive Example 3:
Dihydroxy-(3-cyanophenyl)borane:



20g of 3-bromobenzonitrile was dissolved in 100 ml of dry THF and, under a nitrogen atmosphere, 37.6 ml of triisopropoxyborane was added. This solution was cooled to -78°C, and 98.3 ml of 1.6M n-butyllithium hexane solution was dropped for 30 min. with stirring. After stirring at room temperature for 30 min., it was cooled to 0°C, 220 ml of 4M sulfuric acid was added. This solution was refluxed with heating overnight, and then cooled to 0°C again. 340 ml of 5M sodium hydroxide was added, and extracted with 200 ml of diethyl ether. The aqueous layer was removed, and 6M hydrochloric acid was added until the pH was 2. It was extracted twice with 300 ml of ethyl acetate, dried with magnesium sulfate, and then the solvent was removed. The resulting crude product was recrystallized from DMF-water to produce



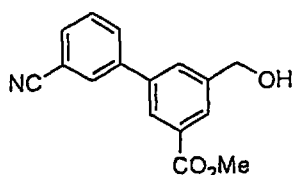
11.6g (72%) of the title compound as acicular light-yellow crystals.

1 H - N M R (2 7 0 M H z , D M S O - d ₆) : δ 7 . 6 ~ 8 .
5 3 (m , 4 H) , 8 . 5 (b r s , 2 H) .

Productive Example 4:

Methyl 3-(3-cyanophenyl)-5-(hydroxymethyl)benzoate:

10



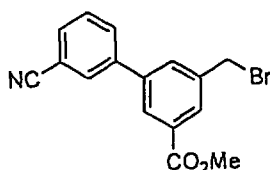
3.08g of the compound obtained from the above
15 Productive Example 2 was dissolved in 500 ml of dry THF
under the flow of nitrogen, and to this solution, 2.32g
of the compound obtained from Productive Example 3, 2.18g
of potassium carbonate, and 456 mg of
tetrakis(triphenylphosphine) palladium were added and
20 stirred with heating at 90°C, overnight. The reaction
was quenched by adding water, extracted with ethyl
acetate, and dried on magnesium sulfate, and then the
solvent was removed. It was purified with silica gel
column chromatography to produce 2.05g (73%) of the title
25 compound as colorless crystals.

1 H - N M R (2 7 0 M H z , C D C l ₃) : δ 2 . 1 (b r s ,
1 H) , 3 . 9 6 (s , 3 H) , 4 . 8 4 (d , 2 H , J = 3 . 7
30 H z) , 7 . 5 ~ 8 . 2 (m , 7 H) .

According to the same process of Productive
Example 4, compounds of Productive Examples 5 - 10 which
are listed in table 2 were synthesized.

Productive Example 11:

35 Methyl 3-(3-cyanophenyl)-5-(bromomethyl)benzoate:



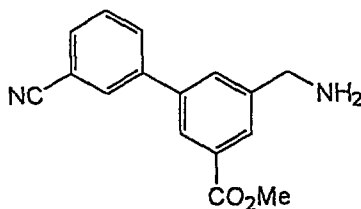
5

To 1.0g of the compound obtained from the above
Productive Example 4, 20 ml of diethyl ether was added to
produce a suspension, and then 0.5 ml of phosphorus
10 tribromide was dropped slowly. The reactant solution was
stirred at room temperature for 19 hours, and subjected
to extraction. The organic layer was washed with
saturated salt solution, dried with sodium sulfate, and
then the solvent was removed under vacuum to produce the
15 title compound in the form of a light-yellow solid (1.2g,
98%)

$^1\text{H-NMR}$ (270 MHz, CDCl_3) : δ 3.97 (s, 3
H), 4.58 (s, 2H), 7.5~7.9 (m, 5H), 8.
20 1~8.2 (m, 2H).

Productive Example 12:

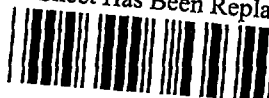
Methyl 3-(3-cyanophenyl)-5-(aminomethyl)benzoate:



25

1.1g of the compound obtained from the above
30 Productive Example 11 was dissolved in 33 ml of DMF, and
325 mg of sodium azide was added. After the reactant
solution was stirred at room temperature for 2 hours,
80 mL of water and 120 mL of ethyl acetate were added to
extract organic substances, and the aqueous layer was
35 extracted twice with 100 mL of ethyl acetate. The
extraction was washed with a saturated salt solution,
dried with anhydrous sodium sulfate solution, and the

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solvent was removed under vacuum to produce light-yellow-colored, oily methyl 3-(3-cyanophenyl)-5-(azidomethyl)benzoate as a crude product.

GC - MS(M - N₂) = 264.

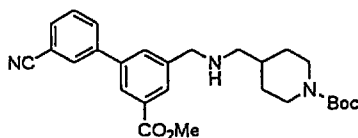
5 The Methyl 3-(3-cyanophenyl)-5-(azidomethyl)benzoate obtained as above was put in a flask, dissolved in 66 mL of ethanol, and after 1.1g of palladium-barium carbonate was added, the air in flask was displaced with hydrogen. Stirring was continued at room temperature for 6 hours, 10 the catalyst was subjected to celite-filtration, and the filtrate was concentrated and purified with silica gel chromatography to produce 794 mg of the title compound (Yield of the two steps: 90%).

GC - MS(M - H) = 265

15 Productive Example 13:

Methyl 3-(3-cyanophenyl)-5-[(N-t-butoxycarbonyl)piperidin-4-ylmethyl)aminomethyl)benzoate:

20



5.5g of the compound obtained from the above Productive Example 12 was dissolved in 150 ml of dry THF. 25 To this solution, 7.92g of 4-aminomethyl-(N-t-butoxycarbonyl)piperidine was added and stirred, at room temperature, overnight. This reaction was quenched by pouring this solution into a 0.5M potassium bisulfate solution, and extracted with ethyl acetate. After drying 30 with sodium sulfate, the solvent was removed to produce 10g of the title compound (potassium bisulfate salt, quantitative).

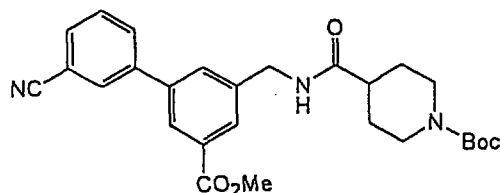


1 H - N M R , (2 7 0 M H z , C D C l ₃) : δ 1 . 0 ~ 1 . 3
(m , 2 H) , 1 . 4 3 (s , 9 H) , 1 . 7 ~ 2 . 0 (m , 3
H) 2 . 6 ~ 2 . 8 (m , 4 H) , 3 . 9 5 (s , 3 H) , 4 . 0
5 ~ 4 . 2 (b r s , 4 H) , 7 . 5 ~ 7 . 7 (m , 2 H) , 7 . 9
~ 8 . 0 (m , 2 H) , 8 . 2 0 (s , 2 H) .

According to the same process of Productive
Example 13, compounds of Productive Example 14 which are
10 listed in table 2 were synthesized.

Productive Example 15:

Methyl 3-(3-cyanophenyl)-5-[(N-t-
butoxycarbonyl)piperidin-4-carbonyl]
aminomethyl)benzoate:



53 mg of the compound obtained from the above
Productive Example 12 was dissolved in 2.0 ml of
chloroform. To this solution, 57 mg of (N-t-
butoxycarbonyl) isonipecotic acid, 27 mg of HOBt, and
25 48 mg of EDCI hydrochloride was added and stirred, at
room temperature, overnight. This reaction was subjected
to the cation exchange resin column SCX for the solid-
phase extraction and the anion exchange resin column SAX
for solid-phase extraction, manufactured by Barian
30 company, and extracted with methanol with removal of
impurity. The extract was concentrated to produce 100 mg
of the title compound, quantitatively.

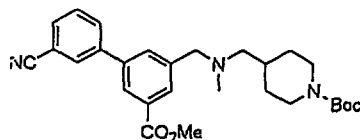
MS(M + 1) = 478

According to the same process of Productive
Example 15, compounds of Productive Examples 16 - 22
35 which are listed in table 2 were synthesized.

Productive Example 23:

Methyl 3-(3-cyanophenyl)-5-[N-[(N-t-butoxycarbonylpiperidin)-4-ylmethyl]-N-methylaminomethyl]benzoate:

5



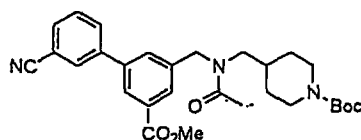
464g of the compound of the above Productive Example 13 was dissolved in 13 mL of dimethylformamide, 276 mg of potassium carbonate and 94 μ L of methyl iodide were added, and after stirring for 6 hours, the extraction was carried out. The organic layer was washed with salt solution and dried with sodium sulfate, the solvent was removed under vacuum, and it was purified through silica gel chromatography to produce 289 mg of the title compound (Yield: 61%).

$^1\text{H-NMR}$ (270 MHz, CDCl_3) : δ 1.0 ~ 1.9 (m, 5 H), 1.49 (s, 9 H), 2.22 (s, 3 H), 2.2 ~ 2.3 (m, 2 H), 2.5 ~ 2.8 (m, 2 H), 2.70 (t, 2 H, $J = 12.0 \text{ Hz}$), 3.57 (s, 2 H), 3.96 (s, 3 H), 4.0 ~ 4.2 (m, 2 H), 4.64 (s, 1 H), 4.72 (s, 1 H), 7.5 ~ 7.7 (m, 2 H), 7.72 (s, 1 H), 7.85 (d, 1 H, $J = 7.6 \text{ Hz}$), 8.01 (s, 1 H), 8.12 (s, 1 H).

According to the same process of Productive Example 23, compounds of Productive Examples 24 - 27 which are listed in table 2 were synthesized.

Productive Example 28:

Methyl 3-(3-cyanophenyl)-5-[N-[(N-t-butoxycarbonylpiperidin)-4-ylmethyl]-N-acetylaminomethyl]benzoate:



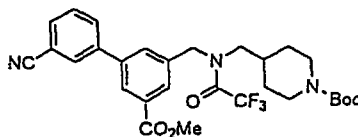
5 464g of the compound of the above Productive
Example 13 was dissolved in 10 mL of dimethylformamide,
and 277 μ L of triethylamine was added. 92 μ L of
acetylchloride was added and stirring was continued for
2 hours. It was poured onto sodium hydrogencarbonate
10 solution and extracted with ethyl acetate. The organic
layer was washed with salt solution and dried with sodium
sulfate, the solvent was removed under vacuum, and it was
purified through silica gel chromatography to produce
349 mg of the title compound (Yield: 69%).

15 $^1\text{H-NMR}$ (270 MHz, CDCl_3) : δ 1.0 ~ 2.0
(m, 5 H), 1.45 & 1.46 (s, 9 H), 2.15 & 2.
21 (s, 3 H), 2.5 ~ 2.8 (m, 2 H), 3.2 ~ 3.
20 3 (m, 2 H), 3.96 & 3.97 (s, 3 H), 4.0 ~ 4.
3 (m, 2 H), 4.64 & 4.72 (s, 2 H), 7.4 ~ 8.
0 (m, 6 H), 8.1 ~ 8.2 (m, 1 H).

 According to the same process of Productive
25 Example 28, compounds of Productive Examples 29 - 32
which are listed in table 2 were synthesized.

 Productive Example 33:

 Methyl 3-(3-cyanophenyl)-5-[N-[(N-t-
butoxycarbonylpiperidin-4-yl) methyl]-N-
30 trifluoroacetylaminomethyl]benzoate:



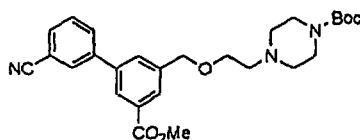
35 Under the atmosphere of nitrogen, 2.0g of the
compound of the above Productive Example 13 was dissolved

in 20 mL of dry DMF, and this solution was cooled to 0°C. With stirring, 1.38 mL of triethylamine was added, and further, 0.70 mL of trifluoroacetic anhydride was added. After stirring under room temperature for 5 hours, water and ethyl acetate were added. The extraction with ethyl acetate was carried out, the organic layer was washed with diluted hydrochloric acid and sodium hydrogencarbonate solution and dried with magnesium sulfate, and the solvent was removed. The purification through silica gel column chromatography resulted in 1.46g (78%) of the title compound.

MS(M + 1) = 560

Productive Example 34:

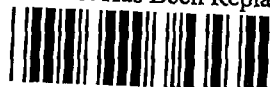
Methyl 3-(3-cyanophenyl)-5-[2-[(4-t-butoxycarbonyl)piperazin-1-yl]-ethoxy]methyl]benzoate:



20

After 24g of sodium hydride (60% in oil) was suspended in 2.0 mL of dimethylformamide, 2.0 mL of dimethylformamide solution containing 154 mg of 1-t-butoxycarbonyl-4-(2-hydroxyethyl)piperazine was added, and it was stirred for 10 min. After cooling to -30°C, 143 mg of the compound of the Productive Example 11 dissolved in 2.0 mL of dimethylformamide was added, and stirred at -30°C to room temperature for 4 hours. It was poured onto aqueous saturated ammonium chloride solution, and extracted with ethyl acetate. The combined organic layer was washed with saturated salt solution and dried on magnesium sulfate. After the solvent was removed under vacuum, the purification with silica gel chromatography resulted in 21 mg (Yield: 10%) of the title compound.

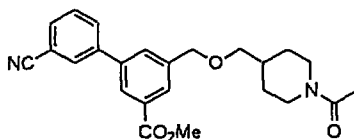
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1 H-NMR (270 MHz, CDCl₃) : δ 1.45 (s, 9 H), 2.4~2.5 (m, 4 H), 2.66 (t, 2 H, j = 5.9 Hz), 3.4~3.5 (m, 4 H), 3.66 (t, 2 H, j = 5.8 Hz), 3.97 (s, 3 H), 4.65 (s, 2 H), 7.5~8.2 (m, 7 H)

Productive Example 35:

Methyl 3-(3-cyanophenyl)-5-[(1-acetylpiperidin-4-yl)-methoxymethyl]benzoate:



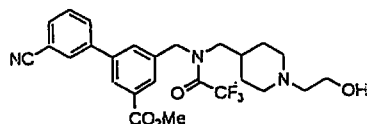
400 mg of the compound of the Productive Example 9 was dissolved in 20 mL of methanol, and 20 mL of 2N hydrochloric acid was added with stirring under ice-cooling. After stirring at 0°C to room temperature for 7 hours, the concentration yielded the crude product of methyl 3-(3-cyanophenyl)-5-(piperidin-4-ylmethoxymethyl)benzoate. This product was dissolved in 20 mL of dichloromethane, and 3.0 mL of triethylamine was added. 460 µL of acetyl chloride was added with stirring under ice-cooling, the stirring was continued at 0°C to room temperature for 18 hours, it was poured onto saturated potassium hydrogensulfate solution, and extracted with ethyl acetate. The organic layer was washed with saturated sodium hydrogencarbonate solution and then saturated salt water, dried with magnesium sulfate. After the solvent was removed under vacuum, the purification with silica gel column chromatography resulted in 260 mg (Yield: 74%) of the title compound.

1 H - N M R (2 7 0 M H z , C D C l ₃) : δ 1 . 0 ~ 1 . 3
(m , 2 H) , 1 . 7 ~ 2 . 0 (m , 3 H) , 2 . 0 9 (s , 3
H) , 2 . 5 6 (t d , 1 H , J = 1 2 . 8 , 2 . 9 H z) , 3 .
5 0 6 (t d , 1 H , J = 1 3 . 2 , 2 . 0 H z) , 3 . 2 ~ 3 . 5
(m , 2 H) , 3 . 8 3 (b r d , 1 H , J = 1 3 . 5 H z) , 3 .
9 7 (s , 3 H) , 4 . 6 5 (s , 2 H) , 4 . 5 ~ 4 . 8 (m ,
1 H) , 7 . 5 8 (t , 1 H , J = 7 . 8 H z) , 7 . 6 ~ 7 . 8
(m , 1 H) , 7 . 7 2 (s , 1 H) , 7 . 8 5 (d , 1 H , J =
7 . 9 H z) , 7 . 9 0 (s , 1 H) , 8 . 0 3 (s , 1 H) , 8 .
1 7 (s , 1 H)

15 Productive Example 36:

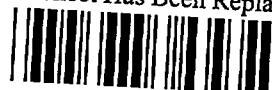
Methyl 3-(3-cyanophenyl)-5-((1-(t-
butoxycarbonylmethyl)-4-piperidyl)-
methoxymethyl)benzoate:

20



Under the atmosphere of nitrogen, 100 mg of Methyl
3-(3-cyanophenyl)-5-(piperidin-4-yl-
25 methoxymethyl)benzoate which is obtained as Productive
Example 37 was dissolved in 5 ml of dry ethanol, and
56 mg of potassium carbonate and 69 μ L of t-Butyl
Bromoacetate are added and stirred at 60°C, overnight.
The solvent was removed and the purification through
30 silica gel chromatography to produce 10 mg (7.6%) of the
title compound.

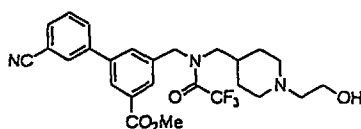
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¹H-NMR (270 MHz, CDCl₃) : δ 1.2 ~ 1.4 (m, 2H), 1.46 (s, 9H), 1.6 ~ 1.8 (m, 3H), 2.17 (d, J = 11 Hz, 2H),
 2.96 (d, J = 9 Hz, 2H), 3.11 (s, 2H), 3.38 (d, J = 6.3 Hz), 3.96 (s, 3H), 4.60 (s, 2H), 7.5 ~ 7.9 (m, 5H), 8.03 (s, 1H), 8.15 (s, 1H)

Productive Example 37:

Methyl 3-(3-cyanophenyl)-5-((2,2,2-trifluoro-N-((1-(2-hydroxyethyl)(4-piperidyl)methyl)acetylamino)methyl)benzoate:

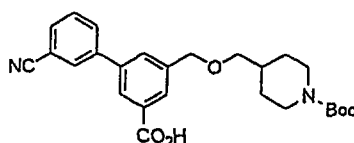


To the compound obtained from the Productive Example 35, 5 mL of trifluoroacetic acid was added at 0°C, and stirred for 30 min. The solvent was removed. Under the atmosphere of nitrogen, to this solution, 20 mL of dry methanol was added, and 300 mg of potassium carbonate and 250 µL of 2-bromoethanol were added and stirred at 60°C, overnight. The solvent was removed, and the purification with silica gel chromatography resulted in 220 mg (71%) of the title compound.

MS(M + H) = 504

Productive Example 38:

3-(3-cyanophenyl)-5-[2-(N-t-butoxycarbonylpiperidin-4-yl)-methoxymethyl]benzoic acid:

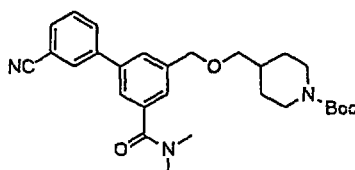


1.43g of the compound of the Productive Example 9 was dissolved in 20 mL of methanol, and 2 mL of water was added. 1.54 mL of 4N lithium hydroxide solution was added and stirred at room temperature for 3 hours. After acidification by adding a saturated ammonium chloride aqueous solution, the extraction with ethyl acetate was carried out. The organic layer was washed with saturated salt water and dried with magnesium sulfate, the solvent was removed, and the purification through silica gel column chromatography results in 1.03g (Yield: 74%) of the title compound.

$^1\text{H-NMR}$ (270 MHz, CDCl_3) : δ 1.0 ~ 1.3 (m, 2H), 1.46 (s, 9H), 1.7 ~ 2.0 (m, 3H), 2.56 (td, 1H, $J = 12.8, 2.9$ Hz), 3.05 (td, 1H, $J = 13.2, 2.0$ Hz), 3.2 ~ 3.5 (m, 2H), 3.83 (brd, 1H, $J = 13.5$ Hz), 4.65 (s, 2H), 4.6 ~ 4.8 (m, 1H), 7.60 (t, 1H, $J = 7.8$ Hz), 7.6 ~ 7.8 (m, 1H), 7.74 (s, 1H), 7.85 (d, 1H, $J = 7.9$ Hz), 7.90 (s, 1H), 8.03 (s, 1H), 8.16 (s, 1H)

Productive Example 39:

3-(3-cyanophenyl)-5-[2-(1-t-butoxycarbonylpiperidin-4-yl)methoxymethyl]benzoic acid dimethylamide:



300 mg of the compound of the Productive Example 38 was dissolved in 10 mL of dichloromethane, 116 μL of

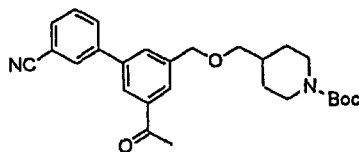
oxalyl chloride and then 135 μ L of pyridine were added at 0°C and it was stirred at 0°C for 1 hour. To this reaction solution, 40% dimethylamine solution was dropped and it was stirred at room temperature for 1 hour.

5 Saturated sodium hydrogencarbonate solution was added and extracted with ethyl acetate. The organic layer was washed with saturated salt water, and dried with magnesium sulfate, and the solvent was removed. The resulting crude product was purified through silica gel
10 column chromatography to produce 268 mg (Yield: 84%) of the title compound.

1 H - N M R (2 7 0 M H z , C D C l ₃) : δ 1 . 0 ~ 1 . 3 (m, 2 H) , 1 . 4 6 (s, 9 H) , 1 . 7 ~ 2 . 0 (m, 3
15 H) , 2 . 5 6 (t d, 1 H, J = 1 2 . 8 , 2 . 9 H z) , 3 . 0 (b r s, 4 H) , 3 . 1 4 (s, 3 H) , 3 . 2 ~ 3 . 5 (m, 2 H) , 3 . 8 3 (b r d, 1 H, J = 1 3 . 5 H z) , 4 . 6 5
20 (s, 2 H) , 4 . 6 ~ 4 . 9 (m, 1 H) , 7 . 6 0 (t, 1 H, J = 7 . 8 H z) , 7 . 6 ~ 7 . 8 (m, 1 H) , 7 . 7 4 (s, 1 H) , 7 . 8 6 (d, 1 H, J = 7 . 8 H z) , 7 . 9 2 (s, 1 H) , 8 . 0 4 (s, 1 H) , 8 . 1 7 (s, 1 H) .

Productive Example 40:

1-acetyl-3-(3-cyanophenyl)-5-[2-(N-t-butoxycarbonylpiperidin-4-yl) methoxymethyl]benzene:



291 mg of the compound of the Productive Example 38
35 was dissolved in 10 mL of dichloromethane, 116 μ L of oxalyl chloride and then 135 μ L of pyridine were added at

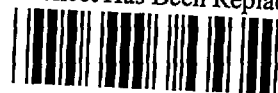
0°C and it was stirred at 0°C for 1 hour. Then, 76 mg of N,O-dimethylhydroxylamine hydrochloride was added and stirred at room temperature for 1 hour. Saturated sodium hydrogencarbonate aqueous solution was added and
5 extracted with ethyl acetate. The organic layer was washed with saturated salt solution, dried with magnesium sulfate, and the solvent was removed. The resulting crude product was dissolved in 10 mL of tetrahydrofuran, and under an atmosphere of nitrogen, at 0°C, 2.29 mL of
10 methylmagnesium bromide was added. After stirring at 0°C for 40 minutes, diluted hydrochloric acid solution was added and extracted with ethyl acetate. The organic layer was washed with saturated salt water and dried with magnesium sulfate. The solvent was removed under vacuum
15 and the purification through silica gel column chromatography resulted in 190 mg (Yield: 65%) of the title compound.

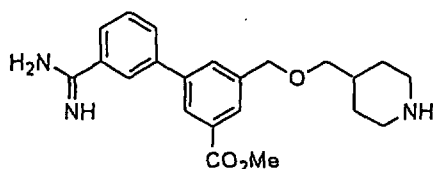
¹H-NMR (270 MHz, CDCl₃) : δ 1.0 ~ 1.3
20 (m, 2H), 1.46 (s, 9H), 1.7 ~ 2.0 (m, 3H), 2.09 (s, 3H), 2.56 (td, 1H, J = 12.8, 2.9 Hz), 3.06 (td, 1H, J = 13.2, 2.0 Hz), 3.2 ~ 3.5 (m, 2H), 3.83 (brd, 1H, J = 13.5 Hz), 4.65 (s, 2H), 4.5 ~ 4.7 (m,
25 1H), 7.60 (t, 1H, J = 7.9 Hz), 7.6 ~ 7.8 (m, 1H), 7.70 (s, 1H), 7.85 (d, 1H, J = 7.9 Hz), 7.90 (s, 1H), 8.02 (s, 1H), 8.
30 16 (s, 1H).

Example 1

Methyl 3-(3-amidinophenyl)-5-[(4-piperidinyl)methoxymethyl]-5-benzoate·salt:

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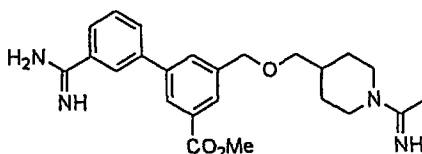
6.0g of the compound of the Productive Example 9 was dissolved in 60 mL of dichloromethane and 3.0 mL of methanol was added. The gas of hydrochloric acid was bubbled into the solution with stirring under ice-cooling. After stirring at 0°C for 30 minutes and then at room temperature for 20 hours, it was concentrated to a dry solid. 30 mL of saturated ammonia-ethanol solution was added, stirred at room temperature for 5 hours, and concentrated. The resulting crude product was purified using HP-20 column chromatography (30g, Eluent: water-methanol) to produce the title compound (4.89g, Yield: 99%).

¹H-NMR (270 MHz, DMSO-d₆) : δ 1.31.5 (m, 2H), 1.72.0 (m, 3H), 2.72.9 (m, 2H), 3.23.3 (m, 2H), 3.38 (d, 2H, J = 6.3 Hz), 3.91 (s, 3H), 4.64 (s, 2H), 7.69 (t, 1H, J = 7.9 Hz), 7.86 (d, 1H, J = 7.9 Hz), 7.99 (s, 1H), 8.02 (s, 1H), 8.07 (d, 1H, J = 7.6 Hz), 8.15 (s, 1H), 8.28 (s, 1H), 8.55 & 8.85 (brs, 1H), 9.19 & 9.52 (s, 2H).

According to the same reaction of the above Example 1 except that HPLC (ODS, Eluent: water-methanol) was used instead of HP-20 column chromatography for isolation and purification, the compounds of Example 2 - 40 which are listed in table 3 were synthesized.

Example 41

Methyl 3-(3-amidinophenyl)-5-[(1-acetoimidoyl-4-piperidiny)methoxymethyl]benzoate·salt:



To 4.79g of the compound of the Example 1 and 3.10g of ethylacetoimidate·monohydrochloride, 50 mL of ethanol was added. 5.25 ml of triethylamine was dropped with stirring under ice-cooling. After increasing the temperature from 0°C to room temperature, stirring was continued for 36 hours and the product was concentrated to form a dry solid. The purification with HPLC (ODS, Eluent: water-methanol) resulted in the title compound (4.37g, Yield: 82%).

$^1\text{H-NMR}$ (270 MHz, DMSO- d_6) : δ 1.1 ~ 1.4 (m, 2 H), 1.7 ~ 2.1 (m, 3 H), 2.50 (s, 3 H), 3.0 ~ 3.5 (m, 4 H), 3.8 ~ 4.0 (m, 1 H), 3.91 (s, 3 H), 4.0 ~ 4.2 (m, 1 H), 4.64 (s, 2 H), 7.74 (t, 1 H, $J = 7.8$ Hz), 7.87 (d, 1 H, $J = 7.6$ Hz), 8.00 (s, 1 H), 8.03 (s, 1 H), 8.07 (d, 1 H, $J = 7.6$ Hz), 8.16 (s, 1 H), 8.28 (s, 1 H), 8.64 & 9.20 (brs, 1 H), 9.25 & 9.54 (brs, 2 H).

According to the same reaction of the above Example 41, the compounds of Example 42 - 57 which are listed in table 3 were synthesized.

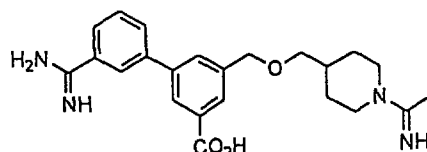
Further, using the same reaction as above except for using ethyl propionimide·monohydrochloride instead of ethylacetoimidate·monohydrochloride, the compounds of

Examples 58 - 59 which are listed in table 3 were synthesized.

Further, using the same reaction as above except for using ethyl hydroxyacetoimide·monohydrochloride instead of ethylacetoimide·monohydrochloride, the compounds of Example 60 which are listed in table 3 were synthesized.

Example 61

3-(3-amidinophenyl)-5-[(1-acetoimidoyl-4-piperidinyl)methoxymethyl]benzoic acid·hydrochloride:



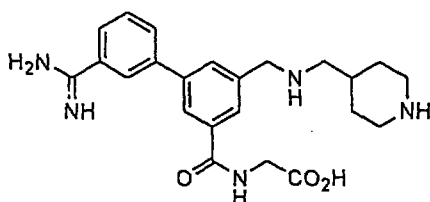
2.71g of the compound of the Example 41 was dissolved in 27 ml of 2N hydrochloric acid, stirred at 70°C for 24 hours, concentrated to form a dry solid, and isolated and purified using HPLC (ODS, Eluent: water-methanol) to produce the title compound (2.00g, Yield: 76%).

$^1\text{H-NMR}$ (270 MHz, DMSO- d_6) : δ 1.2 ~ 1.6 (m, 2 H), 1.9 ~ 2.2 (m, 3 H), 2.31 (s, 3 H), 3.0 ~ 3.4 (m, 2 H), 3.47 (d, 2 H, $J = 5.9$ Hz), 3.9 ~ 4.1 (m, 2 H), 4.65 (s, 2 H), 7.6 ~ 7.8 (m, 3 H), 8.0 ~ 8.1 (m, 2 H), 8.10 (s, 1 H), 8.24 (s, 1 H).

According to the same reaction of the above Example 61, the compounds of Examples 62 - 68, 70 and 72 - 83 which are listed in table 3 were synthesized.

Example 69

3-(3-amidinophenyl)-5-[[4-(4-piperidyl)methyl]aminomethyl]phenylcarbonylaminoacetic acid·salt:



5

73 mg of the compound of the Example 68 was dissolved in 5 mL of DMF, and to this solution, 38 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 20 mg of glycine, and 50 mg of triethylamine were added and stirred at room temperature, overnight. The solvent was removed and the isolation and purification using HPLC (ODS, Eluent: water-methanol) results in the title compound (25 mg, Yield: 30%).

According to the same reaction of the above Example 69, the compounds of Example 71 which are listed in table 3 were synthesized.

Experiment 1

(1) Determination of inhibiting activity of activated blood coagulation factor X (FXa):

The substance for analysis was dissolved in water or water wherein a suitable concentration of organic solvents (DMSO, ethanol or methanol) had been added, as a specimen. To 70 μ L of the specimen serially diluted with water, 90 μ L of 100 mM Tris buffer (pH 8.4), 20 μ L of 50 mM Tris buffer (pH 8.4) containing 50 mU/mL human FXa, and 2 mM substrate (Daiichi Chemical S-2765) were added and incubated for 30 min., 50 μ L of 50% acetic acid was added, and the absorbance (A405) were determined. As a blank, Tris buffer was added instead of FXa while, as a control, water was added instead of the specimen. The 50% inhibition activity (IC50) was determined as the indication of FXa inhibiting activity. The inhibiting activity of human FXa by the present compound was listed in table 4.

(2) Determination of thrombin inhibiting activity:

To 70 μ L of the specimen serially diluted with water, 90 μ L of 100 mM Tris buffer (pH 8.4), 20 μ L of 50 mM Tris buffer (pH 8.4) containing 1 U/mL human thrombin, and 2 mM substrate (Daiichi Chemical S-2238) were added and incubated for 30 min., 50 μ L of 50% acetic acid was added, and the absorbance (A_{405}) were determined. As a blank, Tris buffer was added instead of thrombin while as a control, water is added instead of the specimen. The 50% inhibition activity (IC_{50}) was determined as the indication of thrombin inhibiting activity. The inhibiting activity of human thrombin by the present compound is listed in table 4.

(3) Determination of anticoagulation activity (APTT):

To 100 μ L of normal human plasma (Ci-Trol®) manufactured by DADE, 100 μ L of the specimen was added, and incubated at 37°C for 1 minute. To this solution, 100 μ L of APTT reagent (manufactured by DADE) which was retained at 37°C was added, and after incubating at 37°C for 2 minutes, 100 μ L of 25 mM calcium chloride solution was added, and the coagulation time was determined using the coagulation measurement apparatus manufactured by AMELUNG. The coagulation time when physiological salt solution was added instead of the analyte is used as a control, the concentration of the specimen corresponding to the 2-fold elongation of this coagulation time (CT2) is calculated, and this value is used as the indication of the anticoagulation activity. The human APTT elongation activities of the present compounds were listed in table 4.

(4) Determination of acetylcholine esterase (AChE) inhibiting activity:

The substance for analysis was dissolved in distilled water as specimen. To 50 μ L of the specimen

serially diluted, 50 μ L of enzyme solution, wherein human acetylcholine esterase (manufactured by Sigma, C-5400) had been dissolved in distilled water at 0.1 U/ mL was added. To this solution, 50 μ L of the solution which was
5 prepared by dissolving 5,5'-dithiobis (manufactured by Nacarai Tesque, 141-01) in phosphate buffer (0.1M NaH_2PO_4 - Na_2HPO_4 , pH 7.0) at 0.5 mM is added and mixed, and reacted with 50 μ L of the solution wherein
10 acetylthiocholine iodide (Wako Company, 017-09313) had been dissolved in phosphate buffer at 3 mM, at room temperature. As a control, distilled water was added instead of the substance for analysis and the absorbance (A450) was determined over time. As a blank, phosphate buffer was added instead of the enzyme solution and the
15 50% inhibition activity (IC_{50}) was determined.

The human AChE inhibiting activity of the present compound was listed in table 4.

(5) Determination of bioavailability (BA):

The substance for analysis was dissolved in
20 distilled water (for oral administration; 10 mg/kg) or physiological salt solution (for intravenous administration; 3 mg/kg) to prepare a solution for administration. This solution was administered to fasted ICR mice (male, 6 weeks aged), the whole blood was
25 extracted from the heart under ether anesthesia at 5 min. (intravenous administration group only), 15 min., 30 min., 1 hr., 2 hr., and 4 hr. after the administration, and the plasma was separated by the centrifugation (3,500 rpm, 30 min., 4°C) to produce the
30 specimen (n = 4). Using the above method for determining FXa inhibiting activity, the calibration curve for the substance for analysis was previously prepared and the concentration of the substance for analysis in the specimen was determined. The lower area of the
35 concentration in plasma - time curve (AUC) was calculated

and then the bioavailavility in the mouse (BA) was calculated according to the following formula:

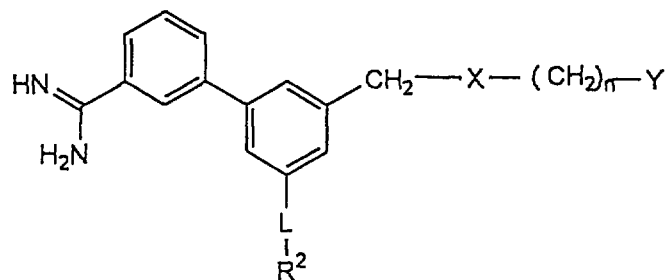
$$BA(\%) = (AUC\ po)/(AUC\ iv) \times (Dose\ iv)/(Dose\ po) \times 100$$

5 The bioavailability for the compound of the invention in the mouse was listed in table 4.

Industrial Applicability

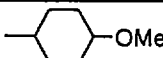
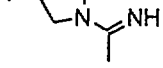
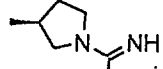
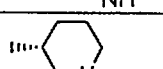
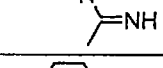
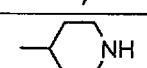
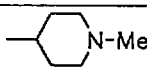
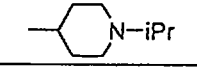
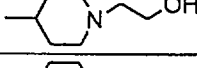
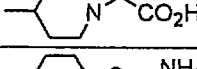
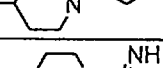
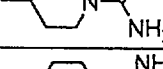
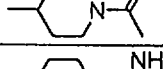
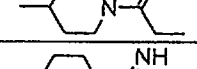
10 A biphenylamidine derivative, and pharmaceutically acceptable salt thereof, of the invention have an effect of inhibiting FXa activity, and can be used as a prophylactic agent and/or a therapeutic agent which are clinically applicable against thromboembolisms such as myocardial infarction, cerebral thrombosis, thrombosis of peripheral arteries or thrombosis of deep veins as a FXa
15 inhibitor.

Table 1

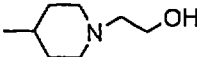
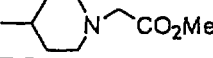
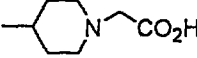
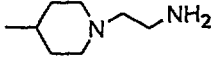
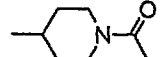
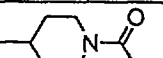
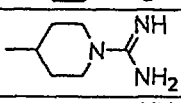
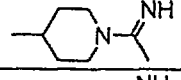
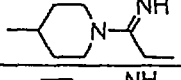
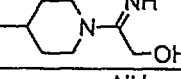
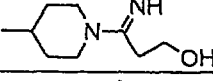
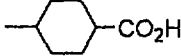
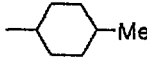
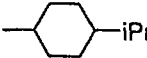
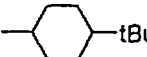


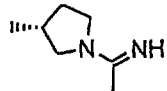
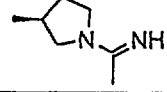
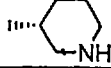
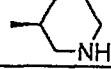
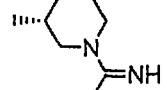
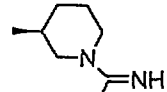
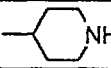
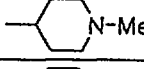
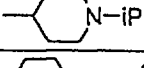
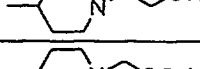
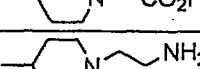
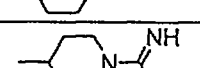
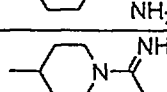
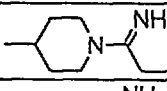
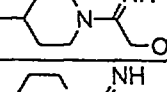
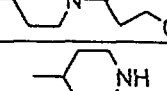
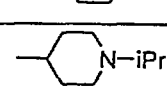
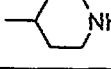
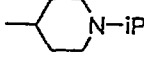
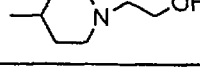
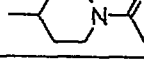
Compound No.	L	R ²	X	n	Y
1	Bond	$-\text{CO}_2\text{Me}$	$-\text{NH}-$	1	
2	Bond	$-\text{CO}_2\text{Me}$	$-\text{NH}-$	1	
3	Bond	$-\text{CO}_2\text{Me}$	$-\text{NH}-$	1	
4	Bond	$-\text{CO}_2\text{Me}$	$-\text{NH}-$	1	
5	Bond	$-\text{CO}_2\text{Me}$	$-\text{NH}-$	1	
6	Bond	$-\text{CO}_2\text{Me}$	$-\text{NH}-$	1	
7	Bond	$-\text{CO}_2\text{Me}$	$-\text{NH}-$	1	
8	Bond	$-\text{CO}_2\text{Me}$	$-\text{NH}-$	1	
9	Bond	$-\text{CO}_2\text{Me}$	$-\text{NH}-$	1	
10	Bond	$-\text{CO}_2\text{Me}$	$-\text{NH}-$	1	
11	Bond	$-\text{CO}_2\text{Me}$	$-\text{NH}-$	1	
12	Bond	$-\text{CO}_2\text{Me}$	$-\text{NH}-$	1	
13	Bond	$-\text{CO}_2\text{Me}$	$-\text{NH}-$	1	
14	Bond	$-\text{CO}_2\text{Me}$	$-\text{NH}-$	1	
15	Bond	$-\text{CO}_2\text{Me}$	$-\text{NH}-$	1	
16	Bond	$-\text{CO}_2\text{Me}$	$-\text{NH}-$	1	
17	Bond	$-\text{CO}_2\text{Me}$	$-\text{NH}-$	1	

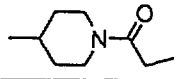
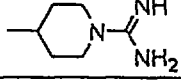
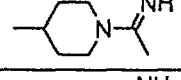
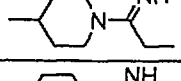
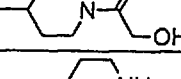
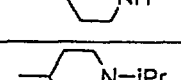
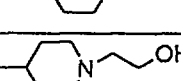
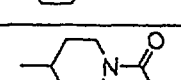
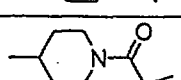
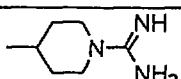
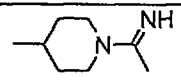
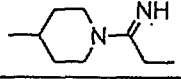
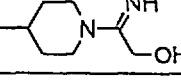
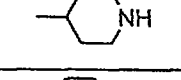
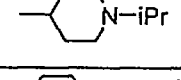
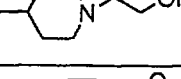
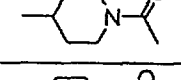
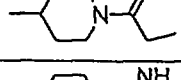
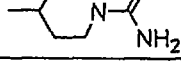
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22	Bond	-CO ₂ Me	-NH-	1	
23	Bond	-CO ₂ Me	-NH-	1	
24	Bond	-CO ₂ Me	-NH-	1	
25	Bond	-CO ₂ Me	-NH-	1	
26	Bond	-CO ₂ Me	-NH-	1	
27	Bond	-CO ₂ Me	-NH-	1	
28	Bond	-CO ₂ Me	-NH-	1	
29	Bond	-CO ₂ Me	-NH-	1	
30	Bond	-CO ₂ Me	-NH-	1	
31	Bond	-CO ₂ Me	-NH-	1	
32	Bond	-CO ₂ Me	-NH-	1	
33	Bond	-CO ₂ Me	-NH-	1	
34	Bond	-CO ₂ H	-NH-	1	
35	Bond	-CO ₂ H	-NH-	1	
36	Bond	-CO ₂ H	-NH-	1	
37	Bond	-CO ₂ H	-NH-	1	
38	Bond	-CO ₂ H	-NH-	1	
39	Bond	-CO ₂ H	-NH-	1	

4 0	Bond	-CO ₂ H	-NH-	1	
4 1	Bond	-CO ₂ H	-NH-	1	
4 2	Bond	-CO ₂ H	-NH-	1	
4 3	Bond	-CO ₂ H	-NH-	1	
4 4	Bond	-CO ₂ H	-NH-	1	
4 5	Bond	-CO ₂ H	-NH-	1	
4 6	Bond	-CO ₂ H	-NH-	1	
4 7	Bond	-CO ₂ H	-NH-	1	
4 8	Bond	-CO ₂ H	-NH-	1	
4 9	Bond	-CO ₂ H	-NH-	1	
5 0	Bond	-CO ₂ H	-NH-	1	
5 1	Bond	-CO ₂ H	-NH-	1	
5 2	Bond	-CO ₂ H	-NH-	1	
5 3	Bond	-CO ₂ H	-NH-	1	
5 4	Bond	-CO ₂ H	-NH-	1	
5 5	Bond	-CO ₂ H	-NH-	1	
5 6	Bond	-CO ₂ H	-NH-	1	
5 7	Bond	-CO ₂ H	-NH-	1	
5 8	Bond	-CO ₂ H	-NH-	1	
5 9	Bond	-CO ₂ H	-NH-	1	
6 0	Bond	-CO ₂ H	-NH-	1	

6 1	Bond	-CO ₂ H	--NH--	1	
6 2	Bond	-CO ₂ Me	-O-	1	
6 3	Bond	-CO ₂ Me	-O-	1	
6 4	Bond	-CO ₂ Me	-O-	1	
6 5	Bond	-CO ₂ Me	-O-	1	
6 6	Bond	-CO ₂ Me	-O-	1	
6 7	Bond	-CO ₂ Me	-O-	1	
6 8	Bond	-CO ₂ Me	-O-	1	
6 9	Bond	-CO ₂ Me	-O-	1	
7 0	Bond	-CO ₂ Me	-O-	1	
7 1	Bond	-CO ₂ Me	-O-	1	
7 2	Bond	-CO ₂ Me	-O-	1	
7 3	Bond	-CO ₂ Me	-O-	1	
7 4	Bond	-CO ₂ Me	-O-	1	
7 5	Bond	-CO ₂ Me	-O-	1	
7 6	Bond	-CO ₂ Me	-O-	1	
7 7	Bond	-CO ₂ Me	-O-	1	
7 8	Bond	-CO ₂ Me	-O-	1	
7 9	Bond	-CO ₂ Me	-O-	1	
8 0	Bond	-CO ₂ Me	-O-	1	
8 1	Bond	-CO ₂ Me	-O-	1	
8 2	Bond	-CO ₂ Me	-O-	1	

8 3	Bond	-CO ₂ Me	-O-	1	
8 4	Bond	-CO ₂ Me	-O-	1	
8 5	Bond	-CO ₂ Me	-O-	1	
8 6	Bond	-CO ₂ Me	-O-	1	
8 7	Bond	-CO ₂ Me	-O-	1	
8 8	Bond	-CO ₂ Me	-O-	1	
8 9	Bond	-CO ₂ Me	-O-	1	
9 0	Bond	-CO ₂ Me	-O-	1	
9 1	Bond	-CO ₂ Me	-O-	1	
9 2	Bond	-CO ₂ Me	-O-	1	
9 3	Bond	-CO ₂ Me	-O-	1	
9 4	Bond	-CO ₂ Me	-O-	1	
9 5	Bond	-CO ₂ H	-O-	1	
9 6	Bond	-CO ₂ H	-O-	1	
9 7	Bond	-CO ₂ H	-O-	1	
9 8	Bond	-CO ₂ H	-O-	1	
9 9	Bond	-CO ₂ H	-O-	1	
1 0 0	Bond	-CO ₂ H	-O-	1	
1 0 1	Bond	-CO ₂ H	-O-	1	
1 0 2	Bond	-CO ₂ H	-O-	1	
1 0 3	Bond	-CO ₂ H	-O-	1	
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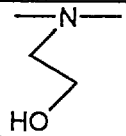
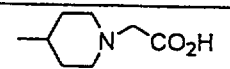
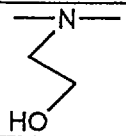
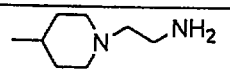
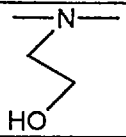
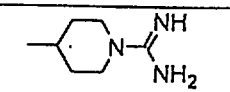
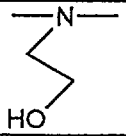
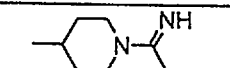
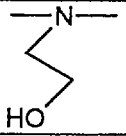
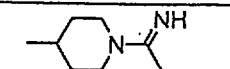
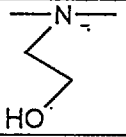
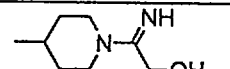
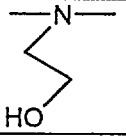
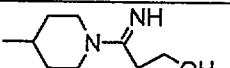
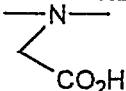
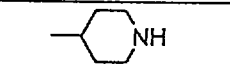
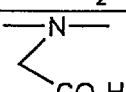
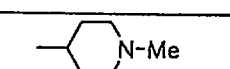
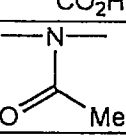
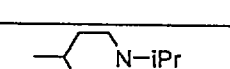
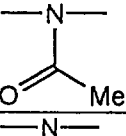
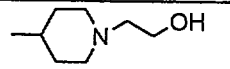
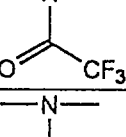
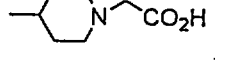
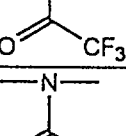
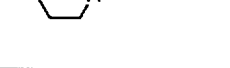
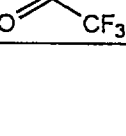
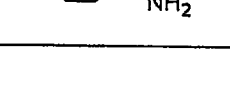
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107	Bond	-CO ₂ H	-O-	1	
108	Bond	-CO ₂ H	-O-	1	
109	Bond	-CO ₂ H	-O-	1	
110	Bond	-CO ₂ H	-O-	1	
111	Bond	-CO ₂ H	-O-	1	
112	Bond	-CO ₂ H	-O-	1	
113	Bond	-CO ₂ H	-O-	1	
114	Bond	-CO ₂ H	-O-	1	
115	Bond	-CO ₂ H	-O-	1	
116	Bond	-CO ₂ H	-O-	1	
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118	Bond	-CO ₂ H	-O-	1	
119	Bond	-CO ₂ H	-O-	1	
120	Bond	-CO ₂ H	-O-	1	
121	Bond	-CO ₂ H	-O-	1	
122	Bond	-CO ₂ H	-O-	1	
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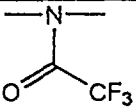
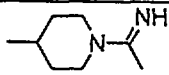
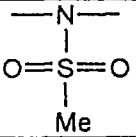
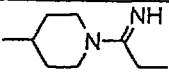
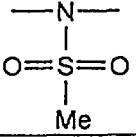
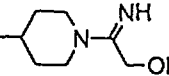
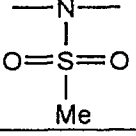
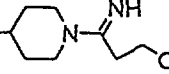
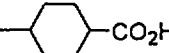
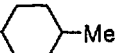
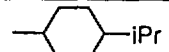
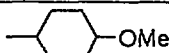
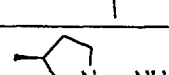
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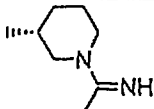
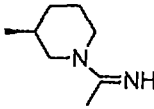
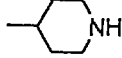
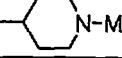
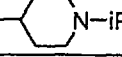
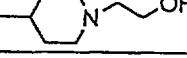
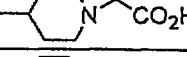
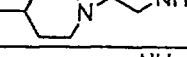
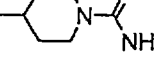
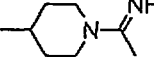
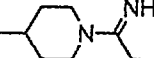
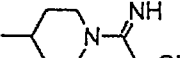
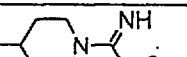
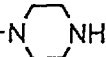
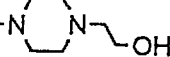
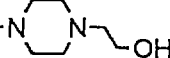
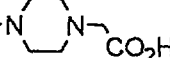
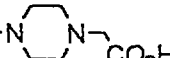
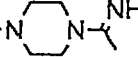
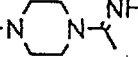
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156	Bond		-O-	1	
157	Bond		-O-	1	
158	Bond		-O-	1	
159	Bond		-O-	1	
160	Bond		-NH-	1	
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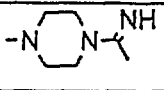
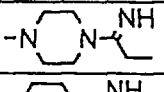
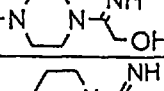
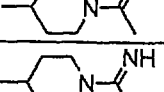
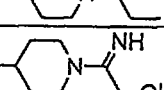
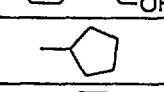
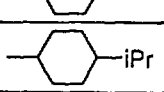
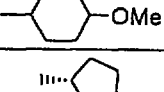
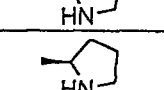
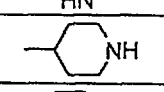
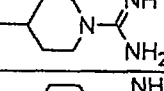
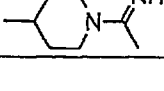
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2 1 8	Bond	-CO ₂ H		1	
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2 5 2	Bond	-CO ₂ H	-NH-	2	
2 5 3	Bond		-NH-	2	
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2 5 5	-CH ₂ CH ₂ -	-CO ₂ H	-NH-	2	

2 5 6	Bond		-NH-	2	
2 5 7	Bond	-CO ₂ H	-NH-	2	
2 5 8	Bond	-CO ₂ H	-NH-	2	
2 5 9	-CH ₂ -	-CO ₂ H	-NH-	1	
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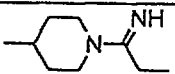
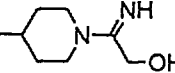
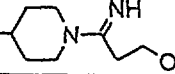
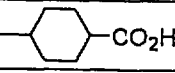
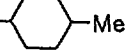
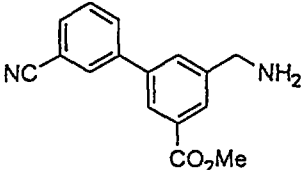
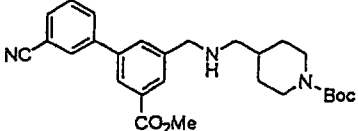
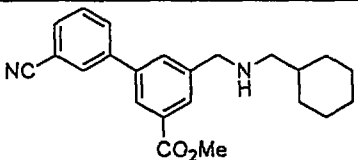
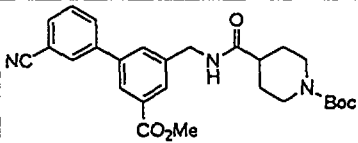
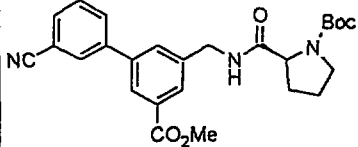
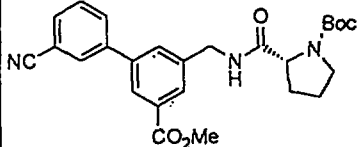
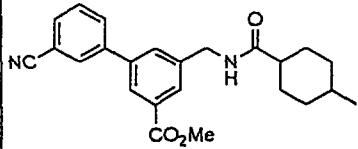
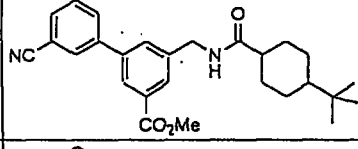
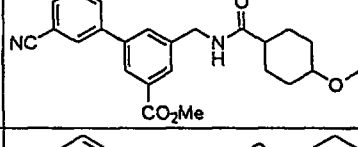
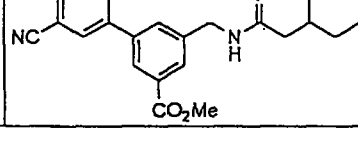
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2 8 2	Bond	-CO ₂ H	-NHCO-	1	
2 8 3	Bond	-CO ₂ H	-NHCO-	1	
2 8 4	Bond	-CO ₂ H	-NHCO-	1	

Table 2

Production Example	Structure	Structural data
4		$^1\text{H-NMR}$ (270MHz, CDCl_3) δ 2.1 (br s, 1H), 3.96 (s, 3H), 4.84 (d, 2H, $J=3.7\text{Hz}$), 7.5-8.2 (m, 7H).
5		$^1\text{H-NMR}$ (270MHz, CDCl_3) δ 0.9-1.2 (m, 2H), 1.4-1.8 (m, 4H), 1.9-2.2 (m, 4H), 3.36 (d, 2H, $J=6.3\text{Hz}$), 3.97 (s, 3H), 7.5-8.2 (m, 7H).
6		$^1\text{H-NMR}$ (270MHz, CDCl_3) δ 1.0-1.3 (m, 5H), 1.45 (s, 9H), 1.7-1.9 (m, 4H), 2.6-2.8 (m, 4H), 3.03 (t, 2H, $J=7.6\text{Hz}$), 3.36 (d, 2H, $J=6.3\text{Hz}$), 4.0-4.2 (m, 3H), 4.53 (s, 2H), 7.1-7.9 (m, 7H).
7		$^1\text{H-NMR}$ (270MHz, CDCl_3) δ 1.46 (s, 9H), 1.5-2.0 (m, 4H), 3.0-3.2 (m, 2H), 3.5-3.7 (m, 1H), 3.7-3.9 (m, 2H), 3.97 (s, 3H), 4.66 (s, 2H), 7.5-8.2 (m, 7H).
8		$^1\text{H-NMR}$ (270MHz, CDCl_3) δ 1.44 (s, 9H), 1.1-2.0 (m, 5H), 2.6-3.0 (m, 2H), 3.40 (d, 2H, $J=6.3\text{Hz}$), 3.8-4.1 (m, 2H), 3.97 (s, 3H), 4.60 (s, 2H), 7.5-8.2 (m, 7H).
9		$^1\text{H-NMR}$ (270MHz, CDCl_3) δ 1.0-1.3 (m, 2H), 1.45 (s, 9H), 1.5-1.6 (m, 1H), 1.6-1.9 (m, 2H), 2.71 (t, 2H, $J=12.2\text{Hz}$), 3.38 (d, 2H, $J=5.9\text{Hz}$), 3.97 (s, 3H), 4.0-4.2 (m, 2H), 4.60 (s, 2H), 7.5-7.9 (m, 4H), 7.90 (s, 1H), 8.03 (s, 1H), 8.16 (s, 1H).
10		$^1\text{H-NMR}$ (270MHz, CDCl_3) δ 1.04 (d, 6H, $J=6.6\text{Hz}$), 1.6-1.9 (m, 4H), 2.13 (dt, 2H, $J=11.6, 2.3\text{Hz}$), 2.70 (quint., 1H, $J=6.6\text{Hz}$), 2.90 (d, 2H, $J=11.6\text{Hz}$), 3.38 (d, 2H, $J=6.6\text{Hz}$), 3.96 (s, 3H), 4.60 (s, 2H), 7.5-7.7 (m, 2H), 7.74 (s, 1H), 7.8-7.9 (m, 1H), 7.90 (s, 1H), 8.03 (s, 1H), 8.15 (s, 1H).
11		$^1\text{H-NMR}$ (270MHz, CDCl_3) δ 3.97 (s, 3H), 4.58 (s, 2H), 7.5-7.9 (m, 5H), 8.1-8.2 (m, 2H).

12		MS 265[M-H]
13		¹ H-NMR (270MHz,CDCl ₃)δ 1.0-1.3(m, 2H), 1.43(s, 9H), 1.7-2.0(m, 3H), 2.6-2.8(m, 4H), 3.95(s, 3H), 4.0-4.2(br S, 4H), 7.5-7.7(m, 2H), 7.9-8.0(m, 2H), 8.09(s, 2H), 8.20(s, 1H).
14		¹ H-NMR (270MHz,CDCl ₃)δ 0.8-1.0(m, 2H), 1.0-1.3(m, 3H), 1.4-1.8(m, 6H), 2.49(d, J=6.6Hz, 2H), 3.90(s, 2H), 3.96(s, 3H), 7.57(dd, J=7.8,7.8Hz, 1H), 7.65(d, J=7.8Hz, 1H), 7.76(s, 1H), 7.85(d, J=7.8Hz, 1H), 7.91(s, 1H), 8.03(s, 1H), 8.12(s, 1H).
15		MS 478[M+H]
16		MS 464[M+H]
17		MS 464[M+H]
18		MS 391[M+H]
19		MS 433[M+H]
20		MS 407[M+H]
21		MS 391[M+H]

22		MS 405[M+H]
23		¹ H-NMR (270MHz,CDCl ₃)δ 1.0~1.9 (m, 5H), 1.49 (s, 9H), 2.22 (s, 3H), 2.2~2.3 (m, 2H), 2.5~2.8 (m, 2H), 2.70 (t, 2H, J= 12.0Hz), 3.57 (s, 2H), 3.96 (s, 3H), 4.0~4.2 (m, 2H), 4.64 & 4.72 (s, 2H), 7.5~7.7 (m, 2H), 7.72 (s, 1H), 7.85 (d, 1H, J= 7.6Hz), 8.01 (s, 1H), 8.12 (s, 1H).
24		¹ H-NMR (270MHz,CDCl ₃)δ 0.9~1.1 (m, 5H), 1.2~1.8 (m, 17H), 2.26 (d, 2H, J=7.0Hz), 2.42 (t, 2H, J=7.0Hz), 2.67 (brt, 2H, J=11.3Hz), 3.63 (s, 2H), 3.96 (s, 3H), 4.0~4.2 (m, 1H), 7.5~8.2 (m, 7H).
25		¹ H-NMR (270MHz,CDCl ₃)δ 0.8~1.1 (m, 5H), 1.1~1.7 (m, 15H), 1.43 (s, 9H), 1.76 (d, J=13.8Hz, 2H), 2.2~2.3 (m, 2H), 2.40 (t, J=7.3Hz, 2H), 2.67 (t, J=12Hz, 2H), 3.62 (s, 2H), 3.96 (s, 3H), 3.9~4.1 (m, 2H), 7.57 (dd, J=7.8,7.8Hz, 1H), 7.67 (d, J=7.8Hz, 1H), 7.72 (s, 1H), 7.84 (d, J=7.9Hz, 1H), 7.89 (s, 1H), 8.02 (s, 1H), 8.11 (s, 1H).
26		¹ H-NMR (270MHz,CDCl ₃)δ 0.02 (s, 6H), 0.84 (m, 9H), 0.8~1.1 (m, 2H), 1.43 (s, 9H), 1.5~2.0 (m, 4H), 2.32 (d, 2H, J=7.0Hz), 2.5~2.7 (m, 4H), 3.5~3.7 (m, 4H), 3.94 (s, 3H), 4.0~4.1 (brs, 1H), 7.5~8.2 (m, 7H).
27		¹ H-NMR (270MHz,CDCl ₃)δ 0.9~1.1 (m, 2H), 1.5~1.7 (m, 1H), 1.7~1.8 (m, 2H), 2.50 (d, 2H), 2.68 (m, 2H), 3.21 (s, 2H), 3.88 (s, 2H), 3.93 (s, 3H), 4.04 (m, 2H), 7.54 (m, 1H), 7.64 (d, 1H), 7.75 (s, 1H), 7.82 (d, 1H), 7.86 (s, 1H), 8.00 (s, 1H), 8.11 (s, 1H).
28		¹ H-NMR (270MHz,CDCl ₃)δ 1.0~2.0 (m, 5H), 1.45 & 1.46 (s, 9H), 2.15 & 2.21 (s, 3H), 2.5~2.8 (m, 2H), 3.2~3.3 (m, 2H), 3.96 & 3.97 (s, 3H), 4.0~4.3 (m, 2H), 4.64 & 4.72 (s, 2H), 7.4~8.0 (m, 6H), 8.1~8.2 (m, 1H).
29		¹ H-NMR (270MHz,CDCl ₃)δ 0.93&1.00 (t, 3H, J=7.6 Hz), 1.0~2.0 (m, 17 H), 2.32&2.37 (t, 2H, J=7.6Hz), 2.5~2.8 (m, 2H), 3.18&3.21 (s, 2H), 3.95&3.97 (s, 3H), 4.0~4.3 (brs, 1H), 4.68&4.73 (s, 2H), 7.4~8.3 (m, 7H).

30		¹ H-NMR (270MHz,CDCl ₃)δ 0.86(brs, 3H), 1.0-1.7(m, 16H), 1.54(d, J=3.9Hz, 9H), 2.35(dt, J=7.5, 20.5Hz, 2H), 2.5-2.8(m, 2H), 3.19(d, J=7.6Hz, 1H), 3.96(d, J=3.7Hz, 3H), 4.0-4.3(m, 2H), 4.7(d, J=12Hz, 2H), 7.4-7.7(m, 3H), 7.8-7.9(m, 3H), 8.15(d, J=11Hz, 1H).
31		¹ H-NMR (270MHz,CDCl ₃)δ 1.0~1.8 (m, 5H), 1.42 (s, 9H), 2.53 (t, 2H, J= 13.0Hz), 2.88 (s, 3H), 3.0~ 3.2 (m, 2H), 3.9~4.2 (m, 2H), 3.98 (s, 3H), 4.50 (s, 2H), 7.60 (t, 1H, J= 7.8Hz), 7.69 (d, 1H, J= 7.6Hz), 7.8~7.9 (m, 1H), 7.89 (s, 1H), 8.03 (s, 1H), 8.20 (s, 1H).
32		¹ H-NMR (270MHz,CDCl ₃)δ 0.8-0.9 (m, 3H), 0.9-1.2(m, 2H), 1.2-1.7(m, 15H), 1.42(s, 9H), 2.50(t, J=13Hz, 2H), 2.9-3.0(m, 2H), 3.1-3.2(m, 2H), 3.97(s, 3H), 3.9-4.2(m, 2H), 4.51(s, 2H), 7.61(dd, J=7.7, 7.7Hz, 1H), 7.70(d, J=7.7Hz, 1H), 7.8-7.9(m, 3H), 8.03(s, 1H), 8.19(s, 1H).
33		MS 560[M+H]
34		¹ H-NMR (270MHz,CDCl ₃)δ 1.45 (s, 9H), 2.4~2.5 (m, 4H), 2.66 (t, 2H, J= 5.9 Hz), 3.4~3.5 (m, 4H), 3.66 (t, 2H, J= 5.8 Hz), 3.97 (s, 3H), 4.65 (s, 2H), 7.5~8.2 (m, 7H).
35		¹ H-NMR (270MHz,CDCl ₃)δ 1.0~1.3 (m, 2H), 1.7~2.0 (m, 3H), 2.09 (s, 3H), 2.56 (td, 1H, J= 12.8, 2.9 Hz), 3.06 (td, 1H, J= 13.2, 2.0 Hz), 3.2~3.5 (m, 2H), 3.83 (brd, 1H, J= 13.5 Hz), 3.97 (s, 3H), 4.65 (s, 2H), 4.5~4.8 (m, 1H), 7.58 (t, 1H, J= 7.8 Hz), 7.6~7.8 (m, 1H), 7.72 (s, 1H), 7.85 (d, 1H, J= 7.9 Hz), 7.90 (s, 1H), 8.03 (s, 1H), 8.17 (s, 1H).
36		¹ H-NMR (270MHz,CDCl ₃)δ 1.2-1.4(m, 2H), 1.46(s, 9H), 1.6-1.8(m, 3H), 2.17(d, J=11Hz, 2H), 2.96(d,J=9Hz, 2H), 3.11(s, 2H), 3.38(d, J=6.3Hz, 2H), 3.96(s, 3H), 4.60(s, 2H), 7.5-7.9(m, 5H), 8.03(s, 1H), 8.15(s, 1H).



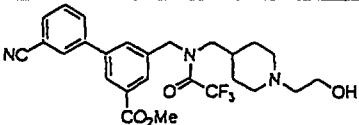
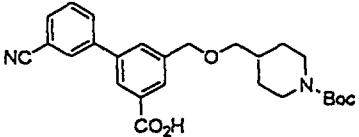
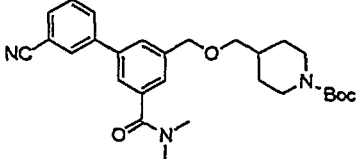
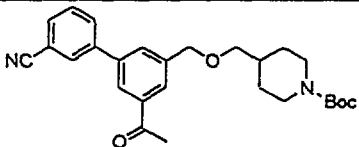
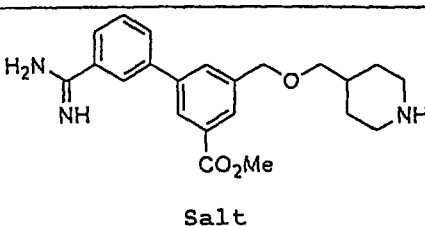
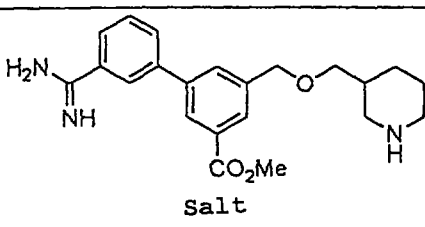
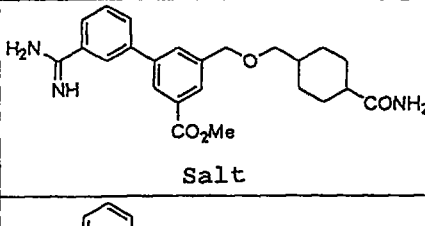
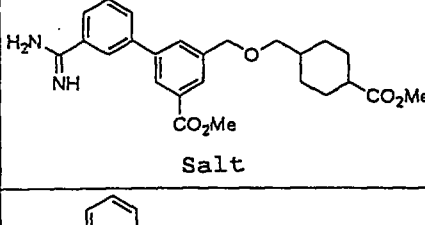
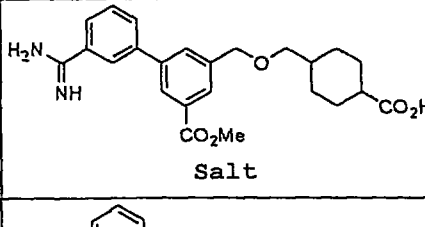
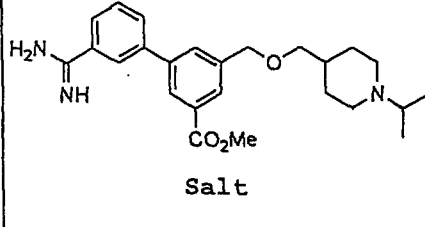
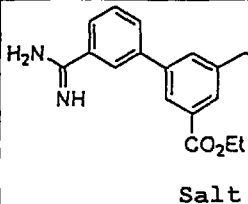
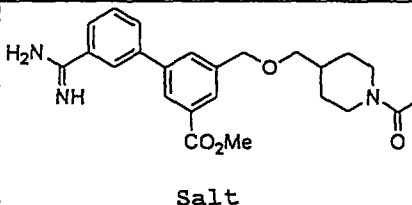
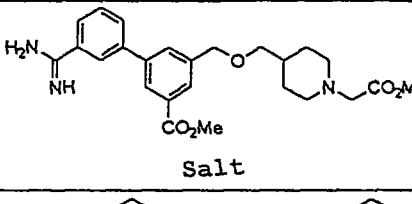
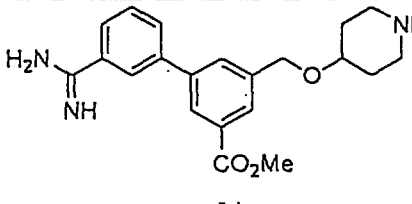
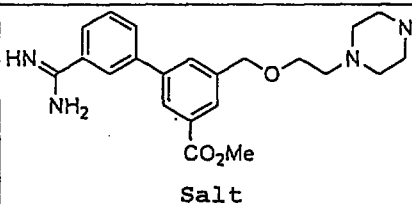
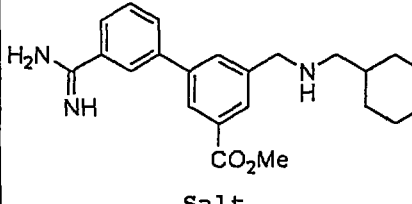
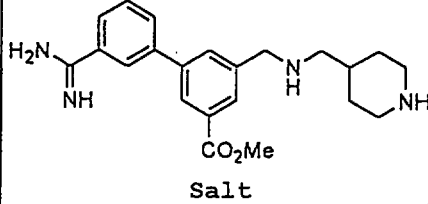
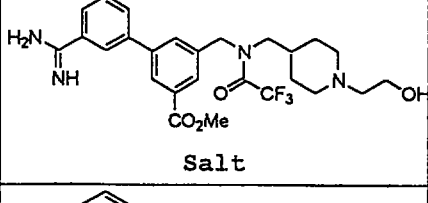
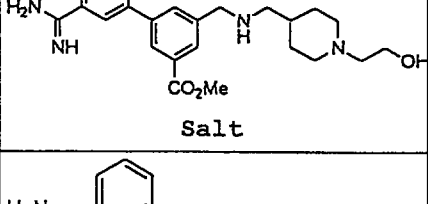
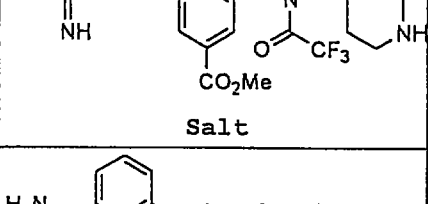
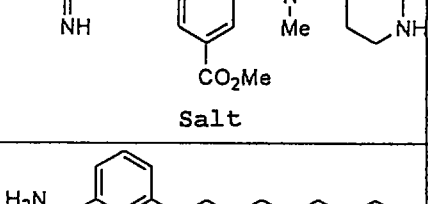
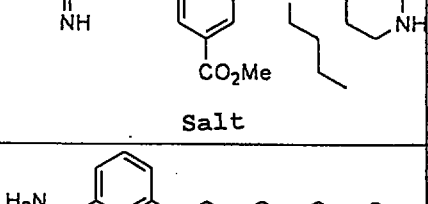
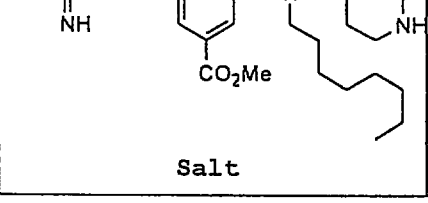
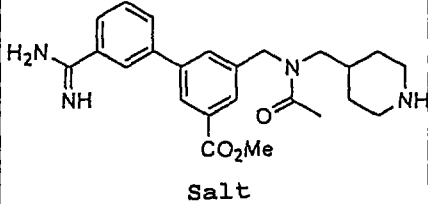
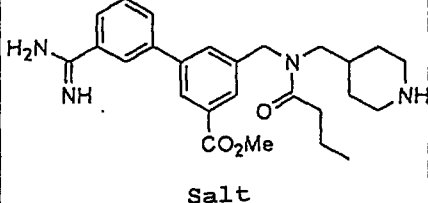
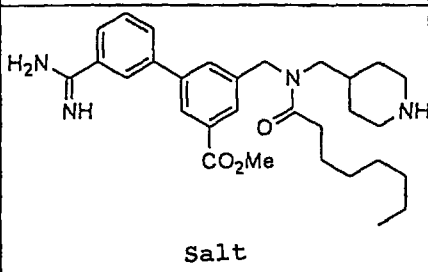
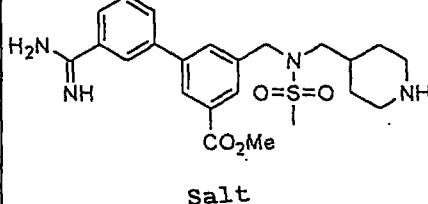
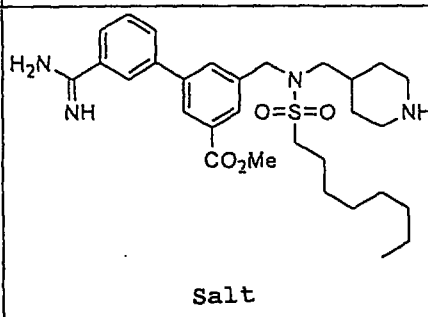
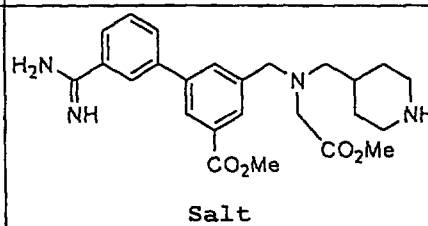
37		MS 504[M+H]
38		¹ H-NMR (270MHz,CDCl ₃)δ 1.0~1.3(m, 2H), 1.46(s, 9H), 1.7~2.0(m, 3H), 2.56(td, 1H, J=12.8, 2.9Hz), 3.05(td, 1H, J=13.2, 2.0Hz), 3.2~3.5(m, 2H), 3.83(brd, 1H, J=13.5Hz), 4.65(s, 2H), 4.6~4.8(m, 1H), 7.60(t, 1H, J=7.8Hz), 7.6~7.8(m, 1H), 7.74(s, 1H), 7.85(d, 1H, J=7.9Hz), 7.90(s, 1H), 8.03(s, 1H), 8.16(s, 1H).
39		¹ H-NMR (270MHz,CDCl ₃)δ 1.0~1.3(m, 2H), 1.46(s, 9H), 1.7~2.0(m, 3H), 2.56(td, 1H, J=12.8, 2.9Hz), 3.0(brs, 4H), 3.14(s, 3H), 3.2~3.5(m, 2H), 3.83(brd, 1H, J=13.5Hz), 4.65(s, 2H), 4.6~4.9(m, 1H), 7.60(t, 1H, J=7.8Hz), 7.6~7.8(m, 1H), 7.74(s, 1H), 7.86(d, 1H, J=7.8Hz), 7.92(s, 1H), 8.04(s, 1H), 8.17(s, 1H).
40		¹ H-NMR (270MHz,CDCl ₃)δ 1.0~1.3(m, 2H), 1.46(s, 9H), 1.7~2.0(m, 3H), 2.09(s, 3H), 2.56(td, 1H, J=12.8, 2.9Hz), 3.06(td, 1H, J=13.2, 2.0Hz), 3.2~3.5(m, 2H), 3.8s(brd, 1H, J=13.5Hz), 4.65(s, 2H), 4.5~4.7(m, 1H), 7.60(t, 1H, J=7.9Hz), 7.6~7.8(m, 1H), 7.70(s, 1H), 7.85(d, 1H, J=7.9Hz), 7.90(s, 1H), 8.02(s, 1H), 8.16(s, 1H).

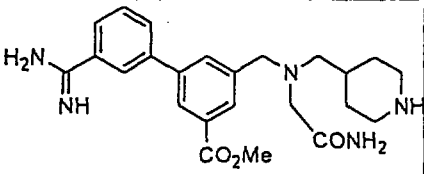
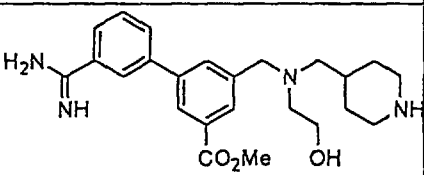
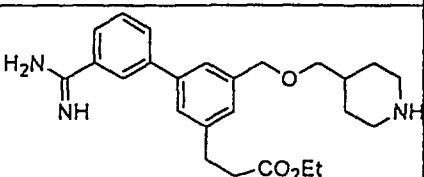
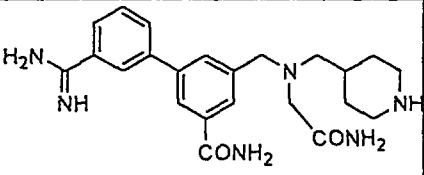
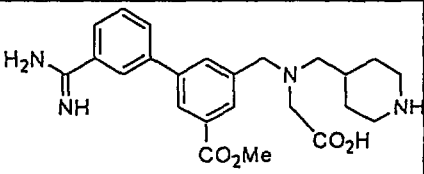
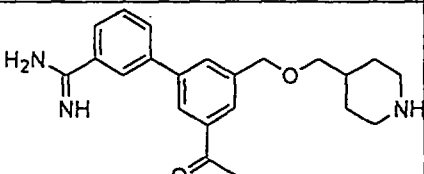
Table 3

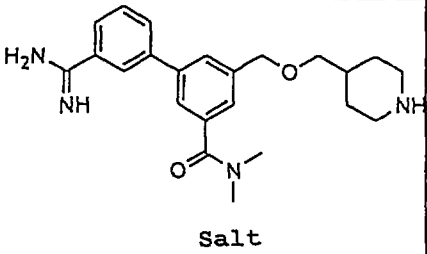
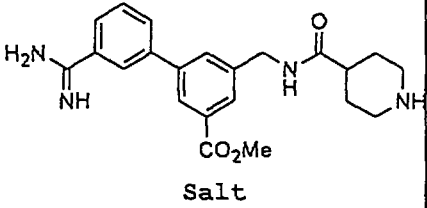
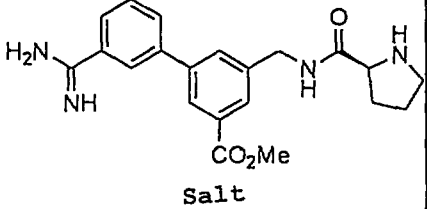
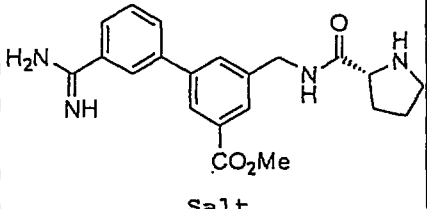
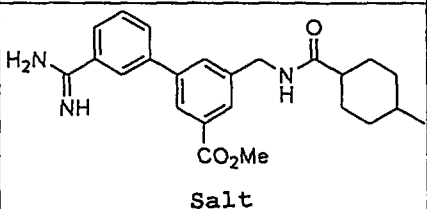
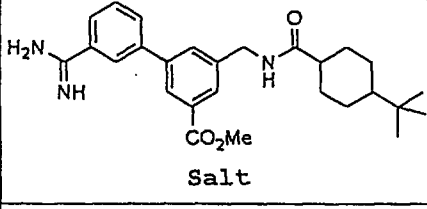
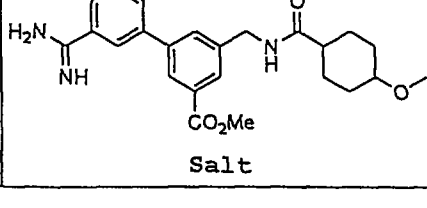
Example	Structure	Structural data
1	 Salt	$^1\text{H-NMR(DMSO-d}_6\text{)}\delta$ 1.3~1.5 (m, 2H), 1.7~2.0 (m, 3H), 2.7~2.9 (m, 2H), 3.15~3.3 (m, 2H), 3.38 (d, 2H, $J=6.3$ Hz), 3.91 (s, 3H), 4.64 (s, 2H), 7.69 (t, 1H, $J=7.9$ Hz), 7.86 (d, 1H, $J=7.9$ Hz), 7.99 (s, 1H), 8.02 (s, 1H), 8.07 (d, 1H, $J=7.6$ Hz), 8.15 (s, 1H), 8.28 (s, 1H), 8.55 & 8.85 (brs, 1H), 9.19 & 9.52 (s, 2H).
2	 Salt	$^1\text{H-NMR(DMSO-d}_6\text{)}\delta$ 1.1~2.3 (m, 5 H), 2.5~2.9 (m, 2 H), 3.1~3.6 (m, 4 H), 3.92 (s, 3 H), 4.63 (s, 2 H), 7.6~8.3 (m, 7 H), 9.1~9.6 (m, 4 H).
3	 Salt	$^1\text{H-NMR(DMSO-d}_6\text{)}\delta$ 0.8~2.2 (m, 10H), 3.2~3.4 (br s, 2H), 3.91 (s, 2H), 6.6~6.7 (brs, 1H), 7.1~7.2 (brs, 1H), 7.7~8.3 (m, 7H), 9.0~9.2 (brs, 1H), 9.4~9.5 (brs, 2H).
4	 Salt	$^1\text{H-NMR(DMSO-d}_6\text{)}\delta$ 0.9~2.3 (m, 10H), 3.0~3.4 (brs, 2H), 3.58 (s, 3H), 3.91 (s, 3H), 4.61 (s, 2H), 7.6~8.4 (m, 7H).
5	 Salt	$^1\text{H-NMR(DMSO-d}_6\text{)}\delta$ 0.8~2.2 (m, 10H), 3.1~3.4 (brs, 2H), 3.91 (s, 3H), 4.61 (s, 2H), 7.6~8.3 (m, 7H).
6	 Salt	$^1\text{H-NMR(DMSO-d}_6\text{)}\delta$ 1.26 (d, 6H, $J=6.9$ Hz), 1.6~2.0 (m, 5H), 2.8~3.0 (m, 2H), 3.1~3.5 (m, 5H), 3.92 (s, 3H), 4.65 (s, 2H), 7.74 (t, 1H, $J=7.8$ Hz), 7.90 (d, 1H, $J=7.9$ Hz), 7.98 (s, 1H), 8.07 (s, 1H), 8.08 (d, 1H, $J=8.3$ Hz), 8.18 (s, 1H), 8.27 (s, 1H), 9.40 & 9.62 (brs, 3H).

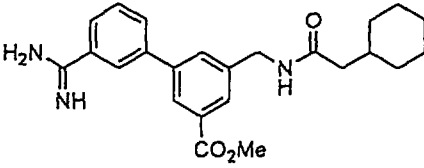
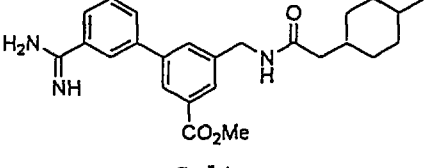
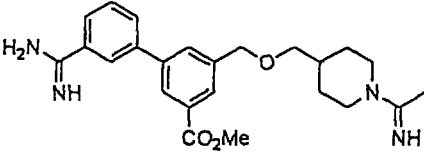
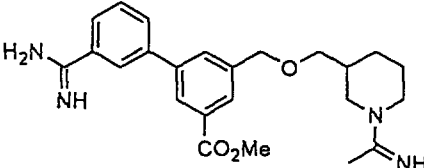
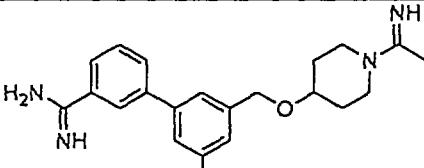
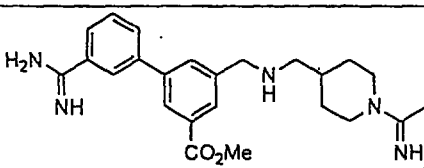
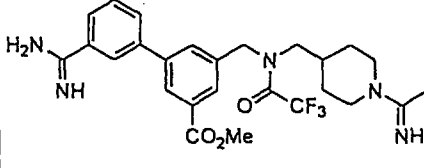
7	 Salt	¹ H-NMR(DMSO-d ₆) δ 1.25 (d, 6H, J= 6.9Hz), 1.36 (t, 3H, J= 7.1Hz), 1.6~2.0 (m, 5H), 2.8~3.0 (m, 2H), 3.1~3.5 (m, 5H), 4.38 (q, 2H, J= 7.0Hz), 4.65 (s, 2H), 7.74 (t, 1H, J= 7.9Hz), 7.87 (d, 1H, J= 7.9Hz), 7.98 (s, 1H), 8.05 (s, 1H), 8.07 (d, 1H, J= 12.2Hz), 8.17 (s, 1H), 8.26 (s, 1H), 9.33 & 9.58 (brs, 3H).
8	 Salt	¹ H-NMR(DMSO-d ₆) δ 0.9~1.3 (m, 2H), 1.6~2.0 (m, 3H), 1.97 (s, 3H), 2.4~2.65 (m, 1H), 3.00 (brt, 1H, J= 11.7 Hz), 3.2~3.5 (m, 2H), 3.80 (brd; 1H, J= 14.9 Hz), 3.91 (s, 3H), 4.37 (brd, 1H, J= 4.37 Hz), 4.63 (s, 2H), 7.71 (t, 1H, J= 7.7 Hz), 7.83 (d, 1H, J= 7.9 Hz), 7.98 (s, 2H), 8.02 (d, 1H, J= 7.9 Hz), 8.11 (s, 1H), 8.25 (s, 1H), 8.17 (s, 1H), 9.4~10.0 (br, 3H).
9	 Salt	¹ H-NMR(DMSO-d ₆) δ 1.5~2.0(m, 5H), 2.9~3.7(m, 6H), 3.74(s, 3H), 3.92(s, 3H), 4.64(s, 2H), 7.7~8.3(m, 7H), 9.14(br s, 2H), 9.51(br s, 2H).
10	 Salt	¹ H-NMR(DMSO-d ₆) δ 1.8~2.2 (m, 4H), 2.8~3.3 (m, 4H), 3.7~3.8 (m, 1H), 3.92 (s, 3H), 4.69 (s, 2H), 7.7~8.3 (m, 7H), 8.7~9.0 (brs, 1H), 9.1~9.2 (brs, 2H), 9.5~9.6 (brs, 2H).
11	 Salt	¹ H-NMR(DMSO-d ₆) δ 2.6~2.8 (m, 6H), 3.0~3.2 (m, 4H), 3.5~3.8 (m, 2H), 3.92 (s, 3H), 4.66 (s, 2H), 7.6~8.3 (m, 7H), 9.06 & 9.48 (brs, 3H).
12	 Salt	¹ H-NMR(DMSO-d ₆) δ 0.8~2.0 (m, 11 H), 2.82 (brs, 2H), 3.94 (s, 3H), 4.31 (brs, 2H), 7.7~8.5(m, 7H), 9.1~9.6 (m, 3H).

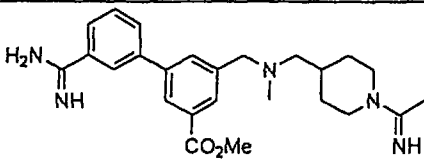
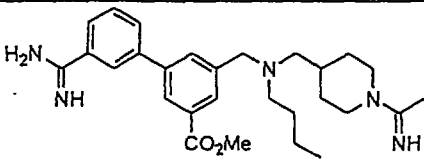
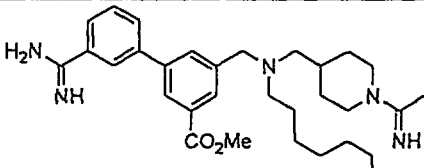
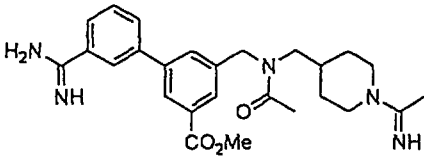
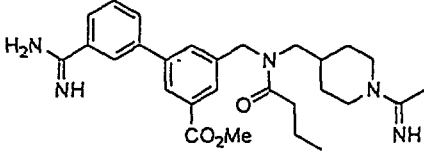
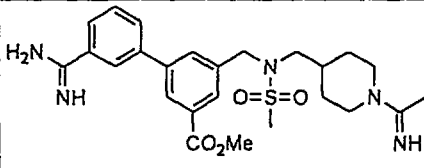
13	 Salt	¹ H-NMR(DMSO-d ₆ +D ₂ O)δ 1.3-1.5(m,2H), 1.96-2.0(m, 2H), 2.1(brs, 1H),2.7-3.0(m,4H), 3.97(s, 3H), 4.32(s, 2H), 7.76(t, J=7.8Hz, 1H), 7.89(d, J=7.8Hz, 1H), 8.1-8.5(m, 5H).
14	 Salt	¹ H-NMR (270MHz,DMSO-d ₆ +D ₂ O)δ 1.4-1.7(m, 2H), 1.7-1.9(m, 2H), 2.0-2.3(m, 1H), 2.8-3.2(m, 2H), 3.2-4.0(m, 8H), 3.88(s, 3H), 4.82(d, J=21Hz, 2H), 7.6-8.3(m, 7H).
15	 Salt	¹ H-NMR(270MHz,DMSO-d ₆ +D ₂ O)δ 1.4-2.3(m, 5H), 2.7-4.0(m, 10H), 3.91(s, 3H), 4.30(s, 2H), 7.74(t, J=7.6Hz, 1H), 7.88(d, J=7.6Hz, 1H), 8.1-8.3(m, 3H), 8.37(s, 1H), 8.48(s, 1H).
16	 Salt	¹ H-NMR(DMSO-d ₆)δ 1.2~1.5(m, 2H), 1.6~1.8(m, 2H), 2.1(br s, 1H), 2.7~3.0(m, 2H), 3.2~3.4(m, 2H), 3.92(s, 3H), 4.85(d, J=20Hz, 2H), 7.7~8.5(m, 7H).
17	 Salt	¹ H-NMR(DMSO-d ₆)δ 1.1~1.6 (m, 2H), 1.8~2.3 (m, 3H), 2.4~3.2 (m, 9H), 3.93 (s, 3H), 4.3~4.7 (m, 3H), 7.8~8.0 (m, 2H), 8.1~8.6 (m, 4H), 9.2 & 9.55 (brs, 3H).
18	 Salt	¹ H-NMR(DMSO-d ₆)δ 0.83 (t, 3H, J=5.7 Hz), 1.0~1.6 (m, 6H), 1.8~2.0 (m, H), 2.3~2.5 (m, 4H), 3.0~3.5 (m, 4H), 3.68 (s, 2H), 3.91 (s, 3H), 3.9~4.1 (brs, 1H), 7.5~8.5 (m, 7H).
19	 Salt	¹ H-NMR(DMSO-d ₆)δ 0.7-0.8(m, 3H), 1.1-2.2(m, 15H), 2.3-2.7(m, 4H), 2.8(brs, 2H), 3.2-3.4(m, 4H), 3.97(s, 3H), 4.5(brs, 2H), 7.7-8.3(m, 7H),9.26(brs, 2H), 9.57(brs, 2H).

20	 Salt	¹ H-NMR(DMSO-d ₆) δ 1.3~1.5 (m, 2H), 1.7~2.2 (m, 3H), 2.05 & 2.13 (s, 3H), 2.7~2.9 (m, 2H), 3.2~3.5 (m, 2H), 3.91 (s, 3H), 4.66 & 4.75 (s, 2H), 7.4~8.3 (m, 7H), 9.13 (m, 3H).
21	 Salt	¹ H-NMR(DMSO-d ₆) δ 0.84&0.92 (t, 3H, J=7.3 Hz), 1.0~1.3 (m, 2H), 1.5~2.0 (m, 5H), 2.31&2.36 (t, 2H, J=7.6Hz), 2.4~2.6 (m, 2H), 2.9~3.1 (m, 2H), 3.20&3.25 (d, 2H, J=7.6 Hz), 3.91 (s, 3H), 4.65&4.71 (s, 2H), 7.2~8.2 (m, 7H).
22	 Salt	¹ H-NMR(DMSO-d ₆) δ 0.7-0.85(m, 3H), 1.1-2.2(m, 16H), 2.29(t, J=7.6Hz, 1H), 2.38(t, J=7.3Hz, 1H), 2.8(brs, 2H), 3.2-3.4(m, 3H), 3.89(d, J=2.7Hz, 3H), 4.70(d, J=25.9Hz, 2H), 7.7-8.3(m, 7H), 9.26(brs, 2H), 9.57(brs, 2H).
23	 Salt	¹ H-NMR(DMSO-d ₆) δ 1.2~1.4 (m, 2H), 1.6~1.9 (m, 3H), 2.64 (t, 2H, J= 11.5Hz), 3.02 (s, 3H), 3.0~3.2 (m, 6H), 3.92 (s, 3H), 4.52 (s, 2H), 7.75 (t, 1H, J= 7.7Hz), 7.90 (d, 1H, J= 7.8Hz), 8.05 (d, 1H, J= 10.5Hz), 8.07 (s, 1H), 8.13 (s, 1H), 8.20 (s, 1H), 8.31 (s, 1H).
24	 Salt	¹ H-NMR(DMSO-d ₆) δ 0.7-0.85(m, 3H), 1.1-2.2(m, 16H), 2.29(t, J=7.6Hz, 1H), 2.38(t, J=7.3Hz, 1H), 2.8(brs, 2H), 3.2-3.4(m, 3H), 3.93(d, J=2.7Hz, 3H), 4.5-4.70(m, 4H), 7.74(dd, J=7.7, 7.7Hz, 1H), 7.90(d, J=7.7Hz, 1H), 8.05(d, J=7.8Hz, 1H), 8.08(s, 1H), 8.13(s, 1H), 8.20(s, 1H), 8.30(s, 1H), 9.26(brs, 2H), 9.57(brs, 2H).
25	 Salt	¹ H-NMR(DMSO-d ₆) δ 1.8~1.9(m, 2H), 2.4~2.6 (m, 2H), 2.8 (m, 2H), 3.21 (d, 2H), 3.53 (brs, 2H), 3.63 (s, 3H), 3.92 (s, 3H), 4.00 (brs, 2H), 7.75 (t, 1H), 7.86 (d, 1H), 8.0~8.1 (brs, 3H), 8.14 (s, 1H), 8.27 (s, 1H), 9.22 (s, 1H), 9.52 (s, 2H).

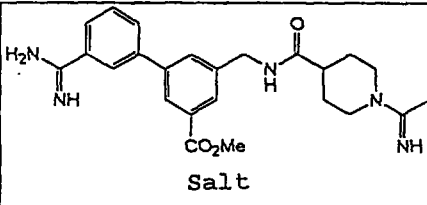
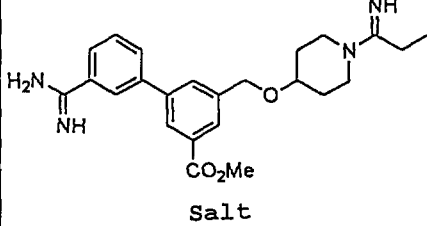
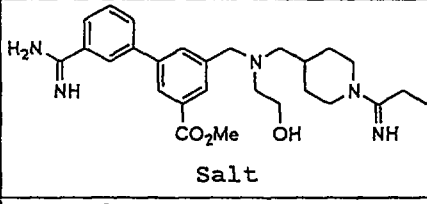
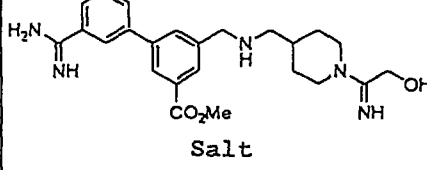
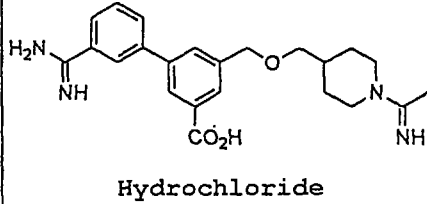
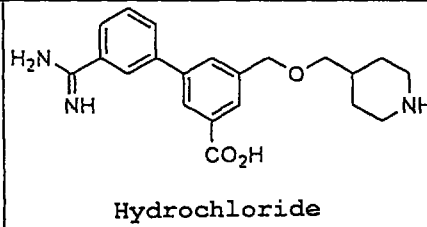
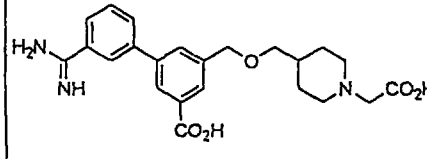
26	 Salt	MS 438[M+H]
27	 Salt	¹ H-NMR(DMSO-d ₆)δ 1.0~1.3 (m, 2H), 1.5~2.0 (m, 3H), 2.30 (d, 2H, J=6.5Hz), 2.4~2.6 (m, 2H), 3.13 (brd, 2H, J=12.4 Hz), 3.50 (t, 2H, J=5.9 Hz), 3.73 (s, 2H), 3.89 (s, 3H), 7.5~8.4 (m, 7H).
28	 Salt	¹ H-NMR(DMSO-d ₆)δ 1.15 (t, J=7.0 Hz, 3H), 1.33~1.52 (m, 2H), 1.73~1.95 (m, 3H), 2.63~2.75 (m, 2H), 2.75~3.00 (m, 4H), 3.25~3.55 (m, 4H), 4.08 (q, J=7.0 Hz, 2H), 4.53 (s, 2H), 7.23 (s, 1H), 7.52~7.63 (m, 2H), 7.64~7.72 (m, 1H), 7.80~7.87 (m, 1H), 7.98~8.03 (m, 1H), 8.10 (s, 1H), 9.2 (br s, 3H).
29	 Salt	MS 423[M+H]
30	 Salt	MS 439[M+H]
31	 Salt	¹ H-NMR(DMSO-d ₆)δ 1.3~1.5 (m, 2H), 1.7~2.0 (m, 3H), 2.7~2.9 (m, 2H), 2.97(s, 3H), 3.15~3.3 (m, 2H), 3.38 (d, 2H, J= 6.3 Hz), 4.64 (s, 2H), 7.69 (t, 1H, J= 7.9 Hz), 7.86 (d, 1H, J= 7.9 Hz), 7.99 (s, 1H), 8.01 (s, 1H), 8.07 (d, 1H, J= 7.6 Hz), 8.14 (s, 1H), 8.27 (s, 1H).

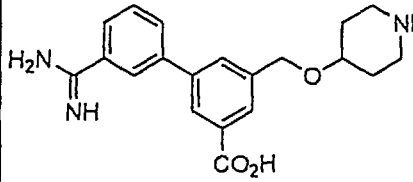
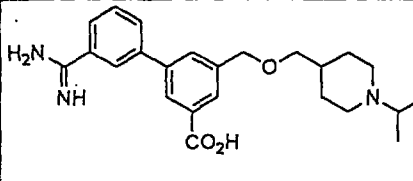
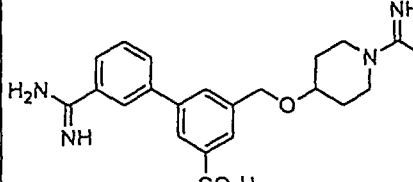
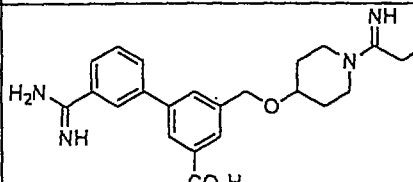
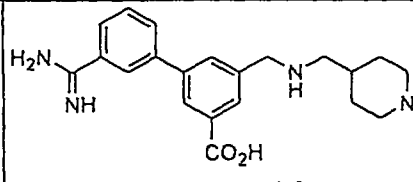
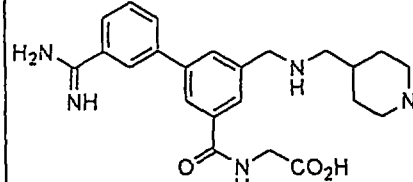
32	 Salt	¹ H-NMR(DMSO-d ₆) δ 1.3~1.4(m, 2H), 1.7~2.0 (m, 3H), 2.7~2.9 (m, 2H), 2.97(s, 3H), 3.02(s, 3H), 3.1~3.3 (m, 2H), 3.3~3.5 (m, 2H), 4.62(s, 2H), 7.67 (t, 1H, J= 7.8 Hz), 7.86 (d, 1H, J= 7.98Hz), 7.97 (s, 1H), 8.00 (s, 1H), 8.07 (d, 1H, J= 7.6 Hz), 8.14 (s, 1H), 8.27 (s, 1H).
33	 Salt	MS 395[M+H]
34	 Salt	MS 381[M+H]
35	 Salt	MS 381[M+H]
36	 Salt	MS 408[M+H]
37	 Salt	MS 450[M+H]
38	 Salt	MS 424[M+H]

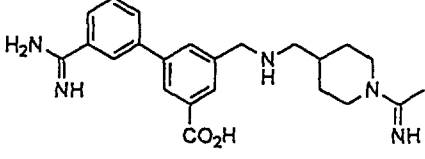
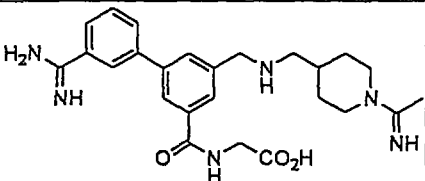
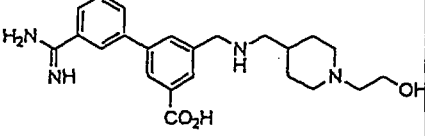
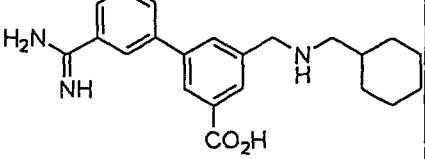
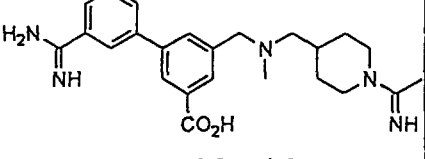
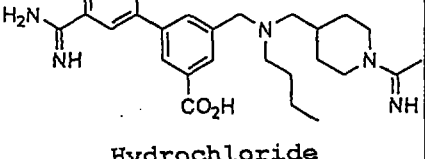
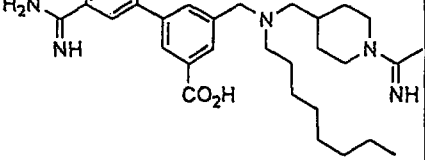
39	 Salt	MS 408[M+H]
40	 Salt	MS 422[M+H]
41	 Salt	¹ H-NMR (270MHz,DMSO-d ₆)δ 1.1~1.4 (m, 2H), 1.7~2.1 (m, 3H), 2.50 (s, 3H), 3.0~3.5 (m, 4H), 3.8~4.0 (m, 1H), 3.91 (s, 3H), 4.0~4.2 (m, 1H), 4.64 (s, 2H), 7.74 (t, 1H, J= 7.8 Hz), 7.87 (d, 1H, J= 7.6 Hz), 8.00 (s, 1H), 8.03 (s, 1H), 8.07 (d, 1H, J= 7.6 Hz), 8.16 (s, 1H), 8.28 (s, 1H), 8.64 & 9.20 (brs, 1H), 9.25 & 9.54 (brs, 2H).
42	 Salt	¹ H-NMR (270MHz,DMSO-d ₆)δ 1.3~2.1 (m, 5 H), 2.27 (s, 3 H), 2.9~3.2 (m, 2 H), 3.44 (d, 2 H, J=5.6 Hz), 3.92 (s, 3 H), 3.7~4.1 (m, 3 H), 4.65 (s, 2 H), 7.7~8.3 (m, 7 H), 9.1~9.6 (m, 4 H).
43	 Salt	¹ H-NMR (270MHz,DMSO-d ₆)δ 1.6~2.2 (m, 4H), 2.28 (s, 3H), 3.2~3.8 (m, 5H), 3.92 (s, 3H), 4.71 (s, 2H), 7.6~8.4 (m, 7H).
44	 Salt	¹ H-NMR (270MHz,DMSO-d ₆ +D ₂ O)δ 1.2~1.5(m, 2H), 1.8~2.0(m, 2H), 2.1(br s, 1H), 2.26(s, 3H), 2.9~3.2(m, 4H), 3.94(s, 3H), 3.9~4.1(m, 2H), 4.35(s, 2H), 7.8~8.2(m, 6H), 8.43(s, 1H).
45	 Salt	¹ H-NMR (270MHz,DMSO-d ₆ +D ₂ O)δ 1.1~1.5(m, 2H), 1.9~1.7(m, 2H), 2.26(s, 3H), 2.1~2.3(m, 2H), 3.0~3.5(m, 4H), 3.92(s, 3H), 3.9~4.1(m, 2H), 4.8~5.0(m, 2H), 7.7~8.1(m, 5H), 8.13(s, 1H), 8.3(m, 1H).

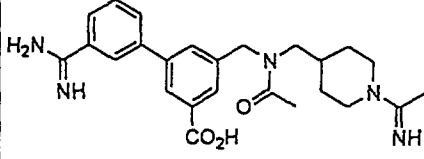
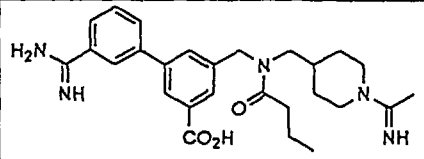
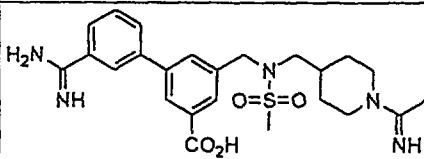
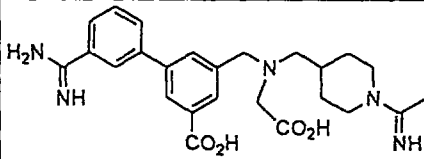
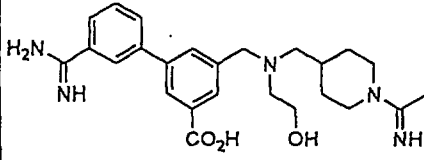
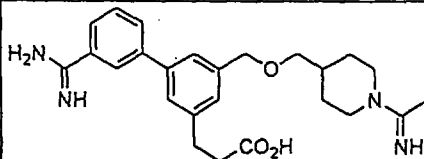
46	 Salt	¹ H-NMR (270MHz,DMSO-d ₆)δ 1.1~1.4 (m, 2H), 1.8~2.3 (m, 3H), 2.27 (s, 6H), 3.0~4.3 (m, 8H), 3.93 (s, 3H), 7.7~8.8 (m, 7H), 9.47 & 9.70 (brs, 3H).
47	 Salt	¹ H-NMR (270MHz,DMSO-d ₆)δ 0.83 (t, 3H, J=5.7 Hz), 1.0~1.6 (m, 6H), 1.8~2.0 (m, 1H), 2.24 (s, 3H), 2.3~2.5 (m, 4H), 3.0~3.5 (m, 4H), 3.68 (s, 2H), 3.91 (s, 3H), 3.9~4.1 (brs, 1H), 7.5~8.5 (m, 7H).
48	 Salt	¹ H-NMR (270MHz,DMSO-d ₆)δ 0.7-0.8(m, 3H), 1.1-2.2(m, 15H), 2.24(s, 3H), 2.3-2.6(m, 2H), 2.6-3.4(m, 4H), 3.7-4.2(m, 2H), 3.93(s, 3H), 4.45(brs, 2H), 7.8-8.3(m, 7H), 9.3(brs, 2H), 9.6(brs, 2H).
49	 Salt	¹ H-NMR (270MHz,DMSO-d ₆)δ 1.1~1.5 (m, 2H), 1.7~1.9 (m, 2H), 2.09 & 2.14 (s, 3H), 2.0~2.3 (m, 1H), 2.21 & 2.29 (s, 3H), 3.0~4.3 (m, 6H), 3.91 (s, 3H), 4.67 & 4.77 (s, 2H), 7.7~8.4 (m, 7H), 9.41 (brs, 3H).
50	 Salt	¹ H-NMR (270MHz,DMSO-d ₆)δ 0.84&0.92 (t, 3H; J=7.3 Hz), 1.0~1.3 (m, 2H), 1.5~2.0 (m, 5H), 2.22&2.24 (s, 3H), 2.31&2.36 (t, 2H, J=7.6Hz), 2.4~2.6 (m, 2H), 2.9~3.1 (m, 2H), 3.20&3.25 (d, 2H, J=7.6 Hz), 3.91 (s, 3H), 4.65&4.71 (s, 2H), 7.2~8.2 (m, 7H).
51	 Salt	¹ H-NMR (270MHz,DMSO-d ₆)δ 1.0~1.3 (m, 2H), 1.6~2.0 (m, 3H), 2.24 (s, 3H), 2.8~3.5 (m, 6H), 3.02 (s, 3H), 3.93 (s, 3H), 4.54 (s, 2H), 7.75 (t, 1H, J= 7.7Hz), 7.91 (d, 1H, J= 8.1Hz), 8.03 (d, 1H, J= 7.8Hz), 8.08 (s, 1H), 8.18 (s, 1H), 8.23 (s, 1H), 8.29 (s, 1H), 9.4 (m, 3H).

52	Salt	¹ H-NMR (270MHz,DMSO-d ₆)δ 1.1~1.3 (m, 2H), 1.8~1.9(m, 3H), 2.22 (s, 3H), 2.5~2.8 (m, 4H), 3.2~3.4 (m, 4H), 3.62 (s, 3H), 3.9~4.0 (brs, 2H), 3.91 (s, 3H), 7.76 (t, 1H), 7.85 (d, 1H), 7.9~8.1 (m, 3H), 8.25 (s, 1H), 8.44 (s, 1H), 9.00 (s, 1H), 9.19 (s, 1H), 9.44 (s, 2H).
53	Salt	¹ H-NMR (270MHz,DMSO-d ₆)δ 1.0~1.3 (m, 2H), 1.5~2.0 (m, 3H), 2.24 (s, 3H), 2.30 (d, 2H, J=6.5Hz), 2.4~2.6 (m, 2H), 3.13 (brd, 2H, J=12.4 Hz), 3.50 (t, 2H, J=5.9 Hz), 3.73 (s, 2H), 3.89 (s, 3H), 7.5~8.4 (m, 7H).
54	Salt	¹ H-NMR (270MHz,DMSO-d ₆)δ 1.16 (t, J=7.0Hz, 3H), 1.17~1.45 (m, 2H), 1.79~1.88 (m, 2H), 2.27 (s, 3H), 2.65~2.75 (m, 2H), 2.27 (s, 3H), 2.65~2.75 (m, 2H), 2.89~3.00(m, 2H), 3.00~3.35 (m, 2H), 3.95~4.0 (m, 1H), 4.1 (q, J=7.0 Hz,2H), 4.55 (s, 2H), 7.22 (s, 1H), 7.55~7.59 (m, 2H), 7.65~7.73(m, 1H), 7.78~7.85 *(m, 1H), 7.98~8.02 (m, 1H), 8.03~8.08 (m, 1H), 8.14 (S, 1H), 9.2 (br s, 1H), 9.55 (br s, 1H).
55	salt	¹ H-NMR (270MHz,DMSO-d ₆ +D ₂ O)δ 1.1~1.4 (m, 2H), 1.7~2.1 (m, 3H), 2.28 (s, 3H), 2.67 (s, 3H),3.0~3.5 (m,4H), 3.8~4.0 (m, 1H), 4.0~4.2 (m, 1H), 4.64 (s, 2H), 7.74 (t, 1H, J= 7.8 Hz), 7.87 (d, 1H, J= 7.6 Hz), 8.00 (s, 1H), 8.03 (s, 1H), 8.07 (d, 1H, J= 7.6 Hz), 8.16 (s, 1H), 8.28 (s, 1H).
56	Salt	¹ H-NMR (270MHz,DMSO-d ₆ +D ₂ O)δ 1.1~1.4 (m, 2H), 1.7~2.1 (m, 3H), 2.28 (s, 3H), 2.95 (s, 3H),3.01(s, 3H), 3.0~3.5 (m,4H), 3.8~4.0 (m, 1H), 4.0~4.2 (m, 1H), 4.63 (s, 2H), 7.74 (t, 1H, J= 7.8 Hz), 7.87 (d, 1H, J= 7.6 Hz), 8.00 (s, 1H), 8.03 (s, 1H), 8.07 (d, 1H, J= 7.7 Hz), 8.15 (s, 1H), 8.30 (s, 1H).

57	 Salt	MS 436[M+H]
58	 Salt	¹ H-NMR (270MHz,DMSO-d ₆ +D ₂ O)δ 1.52 (t, 3H, J=7.6 Hz), 1.6~1.8 (brs, 2H), 1.9~2.1 (brs, 2H), 2.61 (q, 2H, J=7.6 Hz), 3.3~3.8 (m, 5H), 3.92 (s, 3H), 4.72 (s, 2H), 7.6~8.3 (m, 7H).
59	 Salt	MS 480[M+H]
60	 Salt	MS 438[M+H]
61	 Hydrochloride	¹ H-NMR (270MHz,DMSO-d ₆)δ 1.2~1.6 (m, 2H), 1.9~2.2 (m, 3H), 2.31 (s, 3H), 3.0~3.4 (m, 2H), 3.47 (d, 2H, J= 5.9 Hz), 3.9~4.1 (m, 2H), 4.65 (s, 2H), 7.6~7.8 (m, 3H), 8.0~8.1 (m, 2H), 8.10 (s, 1H), 8.24 (s, 1H).
62	 Hydrochloride	¹ H-NMR (270MHz,DMSO-d ₆)δ 1.3~1.5 (m, 2H), 1.7~2.0 (m, 3H), 2.85 (t, 2H, J= 11.5 Hz), 3.2~3.4 (m, 4H), 4.62 (s, 2H), 7.74 (t, 1H, J= 7.8 Hz), 7.85 (d, 1H, J= 7.9 Hz), 7.9~8.0 (m, 2H), 8.06 (d, 1H, J= 7.9 Hz), 8.14 (s, 1H), 8.27 (s, 1H), 9.45 (brs, 3H).
63		¹ H-NMR (270MHz,DMSO-d ₆ +D ₂ O)δ 1.4-1.6(m, 2H), 1.83(br d, J=12Hz, 3H), 2.86(t, J=12Hz, 2H), 3.3-3.5(m, 6H), 4.59(s, 2H), 7.6-8.1(m, 6H), 8.21(s, 1H).

64	 Hydrochloride	¹ H-NMR (270MHz,DMSO-d ₆)δ 1.8~2.2 (m, 4H), 2.9~3.3 (m, 4 H), 3.6~3.8 (m, 1H), 4.65 (s, 2H), 7.4~7.5 (brs, 1H), 7.6~8.5 (m, 7 H), 8.8~9.0 (brs, 1H), 9.1~9.3 (brs, 2H), 9.6~9.7 (brs, 2H).
65	 Hydrochloride	¹ H-NMR (270MHz,DMSO-d ₆)δ 1.18 (d, 6H, J= 6.6Hz), 1.4~1.65 (m, 2H), 1.75~1.95 (m, 3H), 2.6~2.9 (m, 2H), 3.1~3.5 (m, 5H), 4.33 (m, 2H), 4.62 (s, 2H), 7.73 (t, 1H, J= 7.9Hz), 7.84 (d, 1H, J= 7.6Hz), 7.94 (s, 1H), 7.97 (s, 1H), 8.06 (d, 1H, J= 7.6Hz), 8.13 (s, 1H), 8.27 (s, 1H), 9.45 (brs, 3H).
66	 Hydrochloride	¹ H-NMR (270MHz,DMSO-d ₆)δ 1.6~1.8 (m, brs, 2H), 1.9~2.1 (brs, 2H), 2.28 (s, 3H), 3.2~3.5 (m, 2H), 3.6~3.9 (m, 3H), 4.70 (s, 2H), 7.6~8.4 (m, 7H).
67	 Hydrochloride	¹ H-NMR (270MHz,DMSO-d ₆)δ 1.16 (t, 3H, J=7.6 Hz), 2.53 (q, 2H, J=7.6 Hz), 3.2~4.0 (m, 5 H), 4.69 (s, 2H), 7.6~8.3 (m, 7 H).
68	 Hydrochloride	¹ H-NMR (270MHz,DMSO-d ₆ +D ₂ O)δ 1.3-1.5(m, 2H), 1.96(d, J=14Hz, 2H), 2.11(br s, 1H), 2.7-3.0(m, 4H), 4.30(s, 2H), 7.74(t, J=7.7Hz, 1H), 7.87(d, J=7.7Hz, 1H), 8.1-8.5(m, 5H).
69	 Salt	MS 424[M+H]

70	 Hydrochloride	¹ H-NMR (270MHz,DMSO-d ₆ +D ₂ O)δ 1.2~1.5(m, 2H), 1.9~2.0(m, 2H), 2.28(s, 3H), 2.1~2.3(m, 1H), 2.9~3.4(m, 4H), 4.02(dd, J=13.5, 53 Hz, 2H), 4.34(s, 2H), 7.7~8.0(m, 2H), 8.1~8.3(m, 3H), 8.41(s, 1H), 8.47(s, 1H).
71	 Salt	MS 465[M+H]
72	 Hydrochloride	¹ H-NMR (270MHz,DMSO- d ₆ +D ₂ O)δ 1.4-2.3(m, 5H), 2.9-3.9(m, 10H), 4.33(s, 2H), 7.80(t, J=7.6Hz, 1H), 7.89(d, J=7.6Hz, 1H), 8.1-8.3(m, 4H), 8.41(s, 1H).
73	 Hydrochloride	¹ H-NMR (270MHz,DMSO-d ₆)δ 0.8~2.0 (m, 11 H), 2.81 (d, 2H, J=5.9 Hz), 4.29 (s, 2H), 7.7~8.5(m, 7H), 9.1~9.7 (m, 3H).
74	 Hydrochloride	¹ H-NMR (270MHz,DMSO-d ₆)δ 1.1~1.4 (m, 2H), 1.8~2.3 (m, 3H), 2.25 (s, 6H), 3.0~4.3 (m, 8H), 7.7~8.6 (m, 7H), 9.16 & 9.51 (brs, 3H).
75	 Hydrochloride	¹ H-NMR (270MHz,DMSO-d ₆)δ 0.83 (t, 3H, J=5.7 Hz), 1.0~1.6 (m, 6H), 1.8~2.0 (m, H), 2.24 (s, 3H), 2.3~2.5 (m, 4H), 3.0~3.5 (m, 4H), 3.68 (s, 2H), 3.9~4.1 (brs, 1H), 7.5~8.5 (m, 7H).
76	 Hydrochloride	¹ H-NMR (270MHz,DMSO-d ₆)δ 0.85(brs, 3H), 1.0-2.0 (m, 15H), 2.23(s, 3H), 2.3-2.6(m, 2H), 2.7-3.3(m, 4H), 3.8-4.2(m, 2H), 4.67(brs, 2H), 7.74(dd, 7.9,7.9Hz, 1H), 7.88(d, 7.8Hz, 1H), 7.9-8.3(m, 3H), 8.46(brs, 1H), 8.56(brs, 1H).

77	 Hydrochloride	¹ H-NMR (270MHz,DMSO-d ₆)δ 1.1~1.5 (m, 2H), 1.7~1.9 (m, 2H), 2.0~2.3 (m, 1H), 2.08 & 2.14 (s, 3H), 2.27 (s, 3H), 3.0~4.3 (m, 6H), 4.66 & 4.73 (s, 2H), 7.7~8.5 (m, 7H), 9.28 (brs, 3H).
78	 Hydrochloride	¹ H-NMR (270MHz,DMSO-d ₆)δ 0.92&0.97 (t, 3H, J=7.3 Hz), 1.2~1.5 (m, 2H), 1.5~2.0 (m, 4H), 2.0~2.2 (m, 2H), 2.30 (s, 3H), 2.4~2.5 (m, 2H), 3.0~3.5 (m, 4H), 4.00 (brs, 1H), 4.67 (s, 2H), 7.0~8.3 (m, 7H).
79	 Hydrochloride	¹ H-NMR (270MHz,DMSO-d ₆)δ 1.1~1.3 (m, 2H), 1.7~2.0 (m, 3H), 2.21 (s, 3H), 2.8~3.5 (m, 6H), 3.00 (s, 3H), 4.49 (s, 2H), 7.7~7.9 (m, 2H), 7.86 (s, 1H), 8.04 (s, 1H), 8.0~8.1 (m, 1H), 8.22 (s, 1H), 8.46 (s, 1H), 9.21 (m, 3H).
80	 Hydrochloride	¹ H-NMR (270MHz,DMSO-d ₆)δ 1.1~1.3 (m, 2H), 1.8~1.9(m, 3H), 2.25 (s, 3H), 2.5~2.9 (m, 4H), 3.2~3.4 (m, 4H), 3.38 (brs, 1H), 4.09 (brs, 1H), 7.75 (t, 1H), 7.89 (d, 1H), 8.08 (brs, 2H), 8.32 (brs, 2H), 8.67 (brs, 1H), 9.23 (s, 1H), 9.39 (s, 1H), 9.58 (s, 2H).
81	 Hydrochloride	¹ H-NMR (270MHz,DMSO-d ₆)δ 1.0~1.3 (m, 2H), 1.5~2.0 (m, 3H), 2.24 (s, 3H), 2.30 (d, 2H, J=6.5Hz), 2.4~2.6 (m, 2H), 3.13 (brd, 2H, J=12.4 Hz), 3.50 (t, 2H, J=5.9 Hz), 3.73 (s, 2H), 7.5~8.4 (m, 7H).
82	 Hydrochloride	¹ H-NMR (270MHz,DMSO-d ₆)δ 1.21~1.43 (m, 2H), 1.78~1.90 (m, 2H), 1.90~2.08 (m, 1H), 2.25 (s, 3H), 2.45~2.55 (m, 5H), 2.88~2.98 (m, 2H), 3.5 (br s, 6H), 4.0 (m, 1H), 4.55 (s, 2H), 7.25 (s, 1H), 7.50 (s, 1H), 7.61 (s, 1H), 7.60~7.78 (m, 2H), 7.92 (m, 2H), 8.3 (s, 1H).

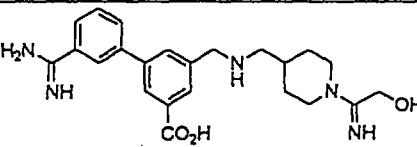
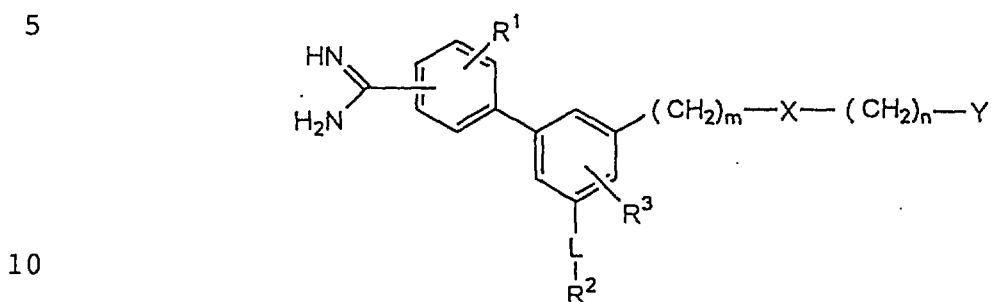
83	 Hydrochloride	MS 424[M+H]
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Table 4

	Fxa inhibition activity IC ₅₀ (μ M)	Thrombin inhibition activity IC ₅₀ (μ M)	APTT CT 2 (μ M)	AChE inhibition activity IC ₅₀ (μ M)	Mouse BA (%)
Compound of Example 61	0.063	> 1000	0.76	49	10
Compound of Example 70	0.19	> 1000	2.0	140	11
Compound of Example 72	1.2	> 1000	11	>250	13
Compound of Example 73	1.7	> 1000	13	>250	ND
Compound of Example 74	0.59	> 1000	5.4	150	13
Compound of Example 81	0.21	820	2.8	130	7
Compound of Example 82	0.13	> 1000	1.9	170	11
Compound of Example 83	0.16	> 1000	1.9	760	12

CLAIMS

1. A biphenylamidine derivative of general formula (1):



. . . (1)

wherein

15 R^1 is a hydrogen atom, a fluorine atom, a chlorine atom, a bromine atom, a hydroxyl group, an amino group, a nitro group, a C_{1-8} alkyl group, or a C_{1-8} alkoxy group;

L is a direct bond or a C_{1-4} alkylene group;

20 R^2 is a fluorine atom; a chlorine atom; a bromine atom; a hydroxyl group; an amino group; a C_{1-8} alkoxy group; a carboxyl group; a C_{1-8} alkoxycarbonyl group; an aryloxy carbonyl group; an aralkoxycarbonyl group; a carbamoyl group wherein a nitrogen atom constituting the carbamoyl group may be substituted with a mono- or
 25 di- C_{1-8} alkyl group or may be a nitrogen atom in an amino acid; a C_{1-8} alkylcarbonyl group; a C_{1-8} alkylsulfenyl group; a C_{1-8} alkylsulfinyl group; a C_{1-8} alkylsulfonyl group; a mono- or di- C_{1-8} alkylamino group; a mono- or di- C_{1-8} alkylaminosulfonyl group; a sulfo group; a
 30 phosphono group; a bis(hydroxycarbonyl)methyl group; a bis(alkoxycarbonyl)methyl group; a or 5-tetrazolyl group;

R^3 is a hydrogen atom, a fluorine atom, a chlorine atom, a bromine atom, a hydroxyl group, an amino group, a nitro group, a C_{1-8} alkyl group, a C_{1-8} alkoxy group, a
 35 carboxyl group, or a C_{1-8} alkoxycarbonyl group;

X is any of the formulae:

-O-, -S-, -SO-, -SO₂-, -NH-CO-NH-, -N(R⁴)-,



* C L M S *

$-\text{CO}-\text{N}(\text{R}^5)-$, $-\text{N}(\text{R}^5)-\text{CO}-$, $-\text{N}(\text{R}^5)-\text{SO}_2-$, $-\text{SO}_2-\text{N}(\text{R}^5)-$,

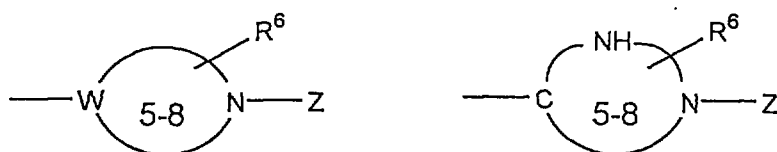
wherein

R^4 is a hydrogen atom, a C_1-10 alkyl group, a C_1-10 alkylcarbonyl group, a C_1-10 alkylsulfonyl group, a C_3-8 cycloalkyl group, or an aryl group,

R^5 is a hydrogen atom, a C_1-10 alkyl group, a C_3-8 cycloalkyl group, or an aryl group,

wherein an alkyl group in the R^4 and R^5 may be substituted with an aryl group, a hydroxyl group, an amino group, a fluorine atom, a chlorine atom, a bromine atom, a C_1-8 alkoxy group, a carboxyl group, a C_1-8 alkoxycarbonyl group, an aryloxycarbonyl group, an aralkoxycarbonyl group, a carbamoyl group, or a 5-tetrazolyl group;

Y is a C_4-8 cycloalkyl group wherein a methylene group in the C_4-8 cycloalkyl may be replaced with a carbonyl group, or may be substituted with a fluorine atom, a chlorine atom, a bromine atom, a hydroxyl group, an amino group, a C_1-8 alkyl group, a C_1-8 alkoxy group, a carbamoyl group, a C_1-8 alkoxycarbonyl group, a carboxyl group, an aminoalkyl group, a mono- or di-alkylamino group, or a mono- or di-alkylaminoalkyl group; or the following 5 - 8-membered ring of the formulae I-1 or I-2:



[I - 1]

[I - 2]

wherein, in the formulae I-1 and I-2,

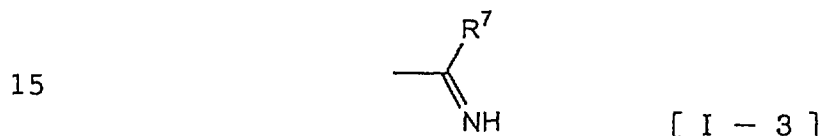
in each cyclic system, the methylene group may be replaced with a carbonyl group, and the cycle may have unsaturated bonds,

R^6 is a hydrogen atom, a fluorine atom, a chlorine atom, a bromine atom, a hydroxyl group, an amino group, a nitro group, a C_1-8 alkyl group, or a C_1-8 alkoxy group,



W is C-H, or a nitrogen atom, with the proviso that W is not a nitrogen atom when the cycle is a 5-membered ring,

5 Z is a hydrogen atom; a C₁₋₁₀ alkyl group wherein the alkyl group may be substituted with a hydroxyl group except when Z is a C₁ alkyl group, an amino group, a C₁₋₈ alkoxy group except when Z is a C₁ alkyl group, a carboxyl group, a C₁₋₈ alkoxycarbonyl group, an aryloxycarbonyl group or an aralkoxycarbonyl group; a 10 C₁₋₈ alkylcarbonyl group; an arylcarbonyl group; an aralkylcarbonyl group; an amidino group; or the following group of the formula I-3:



wherein, in the formula I-3,

R⁷ is a C₁₋₈ alkyl group wherein the alkyl group may be substituted with a hydroxyl atom or a C₁₋₈ alkoxy 20 group; an aralkyl group; or an aryl group;

m is an integer of 1 - 3;

n is an integer of 0 - 3, with the proviso that W is not a nitrogen atom when n is 0 - 1;

or a pharmaceutically acceptable salt thereof.

25 2. A biphenylamidine derivative according to claim 1 wherein, in said formula (1),

R¹ is a hydrogen atom, a fluorine atom, a chlorine atom, a bromine atom, a hydroxyl group, an amino group, a C₁₋₄ alkyl group, or a C₁₋₄ alkoxy group;

30 L is a direct bond or a C₁₋₄ alkylene group;

R² is a fluorine atom; a chlorine atom; a bromine atom; a hydroxyl group; an amino group; a C₁₋₈ alkoxy group; a carboxyl group; a C₁₋₈ alkoxycarbonyl group; an aryloxycarbonyl group; an aralkoxycarbonyl group; a 35 carbamoyl group wherein a nitrogen atom in the carbamoyl group may be substituted with a mono- or di-C₁₋₈ alkyl group or may be a nitrogen atom in an amino acid; a C₁₋₈



alkylcarbonyl group; a C₁₋₈ alkylsulfenyl group; a C₁₋₈ alkylsulfinyl group; a C₁₋₈ alkylsulfonyl group; a mono- or di-C₁₋₈ alkylamino group; a mono- or di-C₁₋₈ alkylaminosulfonyl group; a sulfo group; a phosphono group; a bis(hydroxycarbonyl)methyl group; a bis(alkoxycarbonyl)methyl group; or a 5-tetrazolyl group;

R³ is a hydrogen atom;

X is any of the formulae:

-O-, -S-, -N(R⁴)-, -CO-N(R⁵)-, -N(R⁵)-CO-,
-N(R⁵)-SO₂-, or -SO₂-N(R⁵)-;

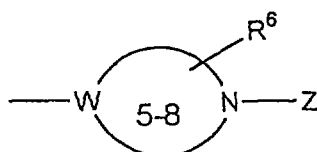
wherein

R⁴ is a hydrogen atom, a C₁₋₁₀ alkyl group, a C₁₋₁₀ alkylcarbonyl group, or a C₁₋₁₀ alkylsulfonyl group,

R⁵ is a hydrogen atom, or a C₁₋₁₀ alkyl group,

wherein an alkyl group in the R⁴ and R⁵ may be substituted with an aryl group, a hydroxyl group, an amino group, a fluorine atom, a chlorine atom, a bromine atom, a C₁₋₈ alkoxy group, a carboxyl group, a C₁₋₈ alkoxycarbonyl group, an aryloxycarbonyl group, an aralkoxycarbonyl group, a carbamoyl group, or a 5-tetrazoyl group;

Y is a C₄₋₈ cycloalkyl group wherein a methylene group constituting the C₄₋₈ cycloalkyl group may be replaced with a carbonyl group, or may be substituted with a fluorine atom, a chlorine atom, a bromine atom, a hydroxyl group, an amino group, a C₁₋₈ alkyl group, a C₁₋₈ alkoxy group, a carbamoyl group, a C₁₋₈ alkoxycarbonyl group, a carboxyl group, an aminoalkyl group, a mono- or di-alkylamino group, or a mono- or di-alkylaminoalkyl group; or the following 5 - 8-membered ring of the formula II-1:



[I I - 1]



wherein, in formula II-1,

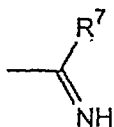
in the cyclic system, the methylene group may be replaced with a carbonyl group,

5 R^6 is a hydrogen atom, a fluorine atom, a chlorine atom, a bromine atom, a hydroxyl group, an amino group, a C_{1-4} alkyl group, or a C_{1-4} alkoxy group;

W is C-H, or a nitrogen atom, with the proviso that W is not a nitrogen group when the cycle is a 5-membered ring,

10 Z is a hydrogen atom; a C_{1-10} alkyl group wherein the alkyl group may be substituted with a hydroxyl group except when Z is a C_1 alkyl group, an amino group, a C_{1-8} alkoxy group except when Z is a C_1 alkyl group, a carboxyl group, a C_{1-8} alkoxy carbonyl group, an
15 aryloxy carbonyl group, or an aralkoxy carbonyl group; a C_{1-8} alkyl carbonyl group; an aryl carbonyl group; an aralkyl carbonyl group; an amidino group; or the following group of the formula II-2:

20



[I I - 2]

wherein, in formula II-2,

25 R^7 is a C_{1-8} alkyl group wherein the alkyl group may be substituted with a hydroxyl group or a C_{1-4} alkoxy group; an aralkyl group; or an aryl group;

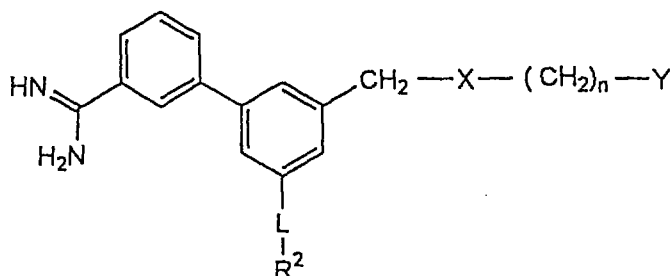
m is an integer of 1 - 3;

n is an integer of 0 - 3, with the proviso that W is not a nitrogen atom when n is 0 - 1;

30 or a pharmaceutically acceptable salt thereof.

3. A biphenylamidine derivative according to claim 1 or 2, of general formula (2):





· · · (2)

wherein

L is a bond or a C₁₋₄ alkylene group;

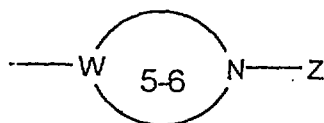
R² is a carboxyl group; a C₁₋₄ alkoxy carbonyl group; an aralkoxy carbonyl group; a carbamoyl group wherein a nitrogen atom constituting the carbamoyl group may be substituted with a mono- or di-C₁₋₄ alkyl group or may be a nitrogen atom in an amino acid; or a C₁₋₄ alkyl carbonyl group;

X is -O-, -N(R⁴)-, or -NH-CO-,

wherein

R⁴ is a hydrogen atom, a C₁₋₁₀ alkyl group, a C₁₋₁₀ alkyl carbonyl group or a C₁₋₁₀ alkyl sulfonyl group, the alkyl being optionally substituted with a hydroxyl group, an amino group, a fluorine atom, a carboxyl group or a C₁₋₈ alkoxy carbonyl group;

Y is a C₅₋₆ cycloalkyl group wherein a methylene group constituting the C₅₋₆ cycloalkyl group may be substituted with a carbamoyl group, a C₁₋₄ alkoxy group or a carboxyl group; or the following 5 - 6-membered ring of the formula III-1:



[III - 1]

wherein, in formula III-1:

W is C-H, or a nitrogen atom, with the proviso that W is not a nitrogen atom when the cycle is a 5-membered



ring,

Z is a hydrogen atom; a C₁₋₄ alkyl group wherein the alkyl group may be substituted with a hydroxyl group except when Z is a C₁ alkyl group, an amino group, a
5 carboxyl group or a C₁₋₄ alkoxy carbonyl group; a C₁₋₄ alkyl carbonyl group; an amidino group; or the following group of the formula III-2:



wherein, in formula III-2,

R⁷ is a C₁₋₄ alkyl group wherein the alkyl group may
15 be substituted with a hydroxyl group;

n is an integer of 0 - 2; with the proviso that W is not a nitrogen group when n is 0 - 1;
or a pharmaceutically acceptable salt thereof.

4. A biphenylamidine derivative according to
20 claim 3, wherein, in said formula (2),

X is -O-, or -N(R⁴)-,

wherein

R⁴ is a hydrogen atom, a C₁₋₁₀ alkyl group, a C₁₋₁₀ alkyl carbonyl group or a C₁₋₁₀ alkyl sulfonyl group, the
25 alkyl group being optionally substituted with a hydroxyl group, an amino group, a fluorine atom, a carboxyl group or a C₁₋₈ alkoxy carbonyl group;
or a pharmaceutically acceptable salt thereof.

5. A biphenylamidine derivative according to
30 claim 3, wherein, in said formula (2),

X is -NH-CO-,

or a pharmaceutically acceptable salt thereof.

6. A biphenylamidine derivative according to
claim 3 or 4, wherein, in general formula (2),

35 L is a bond;

R² is a carboxyl group or a methoxycarbonyl group;

X is -O-, or -N(R⁴)-.

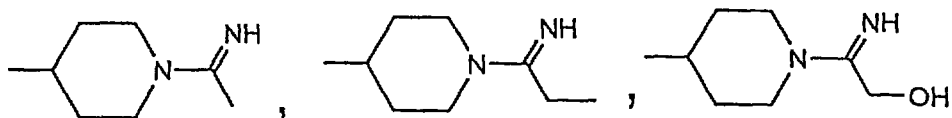


wherein

R⁴ is a hydrogen atom, a methyl group or a 2-hydroxyethyl group;

Y is any of the formulae:

5



10

n is 1;

or a pharmaceutically acceptable salt thereof.

7. A prodrug which generates a biphenylamidine derivative or a pharmaceutically acceptable salt thereof according to any one of claims 1 - 6, in vivo.

15

8. A blood coagulation inhibitor comprising at least a biphenylamidine derivative or a pharmaceutically acceptable salt thereof according to any one of claims 1 - 7, and a pharmaceutically acceptable carrier.

20

9. A prophylactic agent for thrombosis or embolus, comprising at least a biphenylamidine derivative or a pharmaceutically acceptable salt thereof according to any one of claims 1 - 7, and a pharmaceutically acceptable carrier.

25

10. A therapeutic agent for thrombosis or embolus, comprising at least a biphenylamidine derivative or a pharmaceutically acceptable salt thereof according to any one of claims 1 - 7, and a pharmaceutically acceptable carrier.

