

DESCRIPTION

CaSR ANTAGONIST

Technical Field

The present invention relates to a compound having a
5 calcium-sensing receptor (CaSR, hereinafter to be simply
referred to as a calcium receptor) antagonistic action, a
pharmaceutical composition containing the compound,
particularly a calcium receptor antagonist and a therapeutic
agent of osteoporosis.

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Background Art

Calcium receptors sense extracellular Ca^{2+} concentration
and increase intracellular Ca^{2+} , thereby acting to suppress the
production of parathyroid hormone (PTH) involved in the
control of Ca^{2+} metabolism and bone metabolism.

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The serum calcium concentration of healthy mammal is
strictly maintained at about 9-10 mg/100 ml (ca. 2.5 mM),
which is referred to as calcium homeostasis of living
organisms. When this value falls to not more than 50%, tetania
occurs, and conversely, when it increases by 50%,

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consciousness is clouded, both cases threatening the lives.

For maintaining calcium homeostasis, duodenum acts as a Ca^{2+}
uptake organ, bone acts as a Ca^{2+} storage organ, and kidney
acts as a Ca^{2+} excretory organ. These Ca^{2+} kinetics are
controlled by various hormones generally referred to as

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"calcium controlling hormone". Representative hormone includes
active vitamin D [$1\alpha, 25(\text{OH})_2\text{D}_3$], PTH, calcitonin, Parathyroid
Hormone-Related Protein (PTH-related Protein (PTHrP)) and the
like.

Bone plays an important role not only as a supporting
30 framework and motor organ of the body, but also as a storage
organ of Ca^{2+} , which is its constituent component. To fulfill
such functions, bone tissues repeat formation thereof
(osteogenesis) and absorption thereof (bone resorption)

throughout the entire life. For osteogenesis, osteoblast derived from mesenchymal cell plays a major role, and for bone resorption, osteoclast derived from hematopoietic cell plays a major role. The mechanism of osteogenesis includes osteoid
5 formation by bone organic matrix (bone matrix proteins such as type I collagen and the like) produced by osteoblast present on the osteogenesis surface, and subsequent calcification. On the other hand, the mechanism of bone resorption includes
10 adhesion of osteoclast to the bone surface, intracellular absorption of Ca^{2+} via protease acid secretion and ion transport, and excretion of absorbed Ca^{2+} to the bone marrow side, thereby releasing Ca^{2+} into blood. The deficient part of the bone absorbed by osteoclast is repaired by osteogenesis by osteoblast. This series of phenomena are called remodeling of
15 bone, and by the remodeling, old bones are replaced by new bones, thus maintaining the strength of the entire bone while maintaining calcium homeostasis.

PTH is a hormone that plays a key role in maintaining the calcium homeostasis. When blood Ca^{2+} concentration
20 decreases, secretion of PTH from the parathyroid gland is promoted immediately, which, in the bone, acts on osteoblast (activation of osteoclast by osteoblast, production of bone organic matrix decomposition enzyme and the like) to promote osteoclastic bone resorption, whereby Ca^{2+} is transferred from
25 the bone into the blood. In kidney, PTH promotes resorption of Ca^{2+} in the distal convoluted tubule, and activates 25(OH) vitamin D_3 in the proximal tubule, thereby promoting the production of active vitamin D_3 [$1\alpha, 25(\text{OH})_2\text{D}_3$] having a function of promoting resorption of Ca^{2+} from the intestine. It
30 also suppresses resorption of phosphorus. As mentioned above, PTH directly or indirectly increases blood Ca^{2+} concentration.

When blood Ca^{2+} concentration increases, calcium receptor senses it, immediately suppresses secretion of PTH from the

parathyroid gland to decrease the amount of Ca^{2+} to be supplied into the blood [Brown, E.M., Homeostatic mechanisms regulating extracellular and intracellular calcium metabolism in the parathyroids, p.19, (1994), Raven press, New York]. Secretion
5 of PTH is also suppressed by active vitamin D [$1\alpha, 25(\text{OH})_2\text{D}_3$].

Because PTH is a hormone assuming an important role in controlling Ca^{2+} metabolism and bone metabolism, attempts have been made to apply PTH to the treatment of osteoporosis. In 1982, Tam et al. found that sustained administration of bovine
10 PTH (1-84) to thyroid/parathyroid gland enucleated rat results in promotion of both osteogenesis and bone resorption of femoral cancellous bone, leading to a decrease in net bone mass, but subcutaneous intermittent administration thereof does not result in promotion of bone resorption but in
15 promotion of osteogenesis alone, leading to an increase in the bone mass [Endocrinology, 110, 506-512 (1982)]. Furthermore, Uzawa et al. compared the actions of sustained administration and intermittent administration of PTH with regard to epiphyseal long bone and metaphyseal cancellous bone of young
20 rat. As a result, they clarified that sustained administration of PTH results in remarkable increase in bone mass in metaphyseal cancellous bone highly susceptible to the effect of endochondral ossification, though associated with abnormal findings such as hyperplasia of epiphyseal plate cartilage,
25 fibrous osteitis and the like, and in marked promotion of bone resorption and decrease in bone mass accompanied by rarefaction of cortical bone, in epiphyseal cancellous bone where the effect is small [Bone, 16, 477-484 (1995)]. In addition, it has been reported that intermittent
30 administration of PTH results in significant increases in bone mass and bone trabecula in both epiphyseal and metaphyseal cancellous bones without increase in osteoclast or decrease of cortical bone.

Moreover, Scutt et al. have reported that, in chicken calvaria derived osteoblast, a short time (10-20 min) treatment with PTH promotes cell growth as compared to a long time (18 hr) treatment [Calcif. Tissue Int., 55, 208-215 (1994)]. This suggests that some of the actions of PTH on osteoblast are temporary and that expression of the action by the treatment for an extremely short time may be related to the fact that sustained administration and intermittent administration of PTH in vivo show different actions on bone tissues.

Ishizuya et al. further clarified through investigation of the action of PTH on differentiation of osteoblast using an in vitro experiment system that the action of PTH varies depending on the treatment time. They have reported that sustained action of PTH on osteoblast derived from rat calvaria resulted in strong inhibition of differentiation of osteoblast and nearly complete inhibition of osteogenesis in vitro, but repeated PTH action for the first 6 hr of 48 hr as one cycle resulted in significant promotion of differentiation of osteoblast and promotion of osteogenesis in vitro.

PTH is considered to not only prevent decrease in bone mass of osteoporosis model, but also has a bone mass recovery effect even on an animal already suffering from marked decrease in bone mass. Wronski et al. intermittently administered human PTH (1-34) to 90-day-old SD rat at 4 weeks post-ovariectomy and showing an obvious decrease in cancellous bone, for 15 weeks from 4 weeks post-ovariectomy. As a result, promotion of osteogenesis and inhibition of bone resorption were observed during the period of from week 5 to week 10 after the start of the administration, showing increased bone mass of about twice the bone mass of sham operation group [Endocrinology, 132, 823-831 (1993)]. They have also reported that, in this experiment, estrogen and bisphosphonate

prevented decrease in bone mass caused by ovariectomy but did not show increase in bone mass, unlike PTH. They analyzed in detail the cortical bone of this experiment system and found images showing promoted osteogenesis and bone mass increase on the periosteal side and endosteal side by intermittent administration of human PTH (1-34), based on which they have clarified that the increase in cancellous bone due to PTH did not accompany decrease in cortical bone [Bone, 15, 51-58 (1994)].

Furthermore, Mosekilde et al. have reported that intermittent administration of human PTH (1-34) or human PTH (1-84) causes not only an increase in bone mass but also a dose-dependent increase in compression strength and bending strength, which are indices of bone substance, of cancellous bone [Endocrinology, 129, 421-428 (1991)] and cortical bone [J. Bone Miner. Res., 8, 1097-1101 (1993)] of rat vertebral bone. As discussed above, since PTH shows an obvious bone mass increasing action in experimental animals, various investigations are ongoing as regards the restrictive conditions expected in actual clinical applications. Mizoguchi studied whether or not a pharmacological effect is observed by intermittent administration of PTH, even when PTH in blood, which is considered to be one of the factors responsible for osteoporosis, has significantly increased, and concluded that the bone mass increased as usual [Journal of Japanese Society of Bone Morphometry, vol. 5, pp. 33 - 39 (1995)]. Takao et al. have studied the frequency of PTH administration and reported that administration of once a week for 12 weeks to healthy rat scarcely promoted bone resorption but dose-dependently increased the bone mass [Japanese Journal of Bone Metabolism, vol. 12 (Suppl.), p. S343 (1994)], suggesting possible effectiveness of clinically useful low frequency administration. The foregoing achievements suggest the

possibility of PTH for making a potent and promising therapeutic drug for the treatment of postmenopausal osteoporosis or postovariectomy osteoporosis, which increases bone mass and decreases bone fracture rate.

5 These results clearly indicate that intermittent administration of PTH would enable treatment of osteoporosis. On the other hand, PTH problematically requires injection as an administration route, which is painful for many patients. However, an orally administrable pharmaceutical agent that can
10 intermittently increase PTH concentration in blood is greatly expected to become a therapeutic drug of osteoporosis, which is based on a new action mechanism different from that of the above-mentioned PTH and conventional calcitonin.

 Calcium receptor is a G protein coupled receptor, which
15 is cloned as a molecule essential for controlling PTH secretion, and which penetrates cell membrane 7 times. Human calcium receptor consists of 1078 amino acids, and shows 93% amino acid homology with bovine calcium receptor. Human calcium receptor consists of a large N terminal extracellular
20 region consisting of 612 amino acids, a cell membrane penetration region consisting of 250 amino acids and a C terminal intracellular region consisting of 216 amino acids.

 Expression of calcium receptor has been found in parathyroid gland, kidney, thyroid C cell, brain and the like,
25 as well as in bone (bone marrow cells).

 When calcium receptor is bound with a ligand such as Ca^{2+} and the like, it activates phospholipase C in conjugation with G protein, causes production of inositol triphosphate and increase in intracellular Ca^{2+} concentration, and as a result,
30 suppresses secretion of PTH [Nature, 366, 575-580 (1993)].

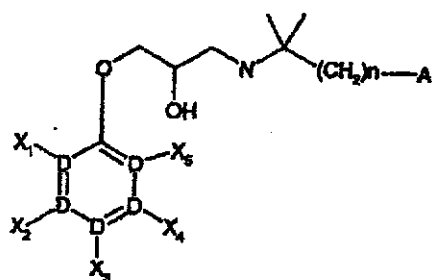
 As mentioned above, a pharmaceutical agent that inhibits activation of calcium receptor, or a pharmaceutical agent that antagonizes calcium receptor, removes suppression of PTH

secretion in parathyroid gland cells, and promotes secretion of PTH. It is considered that, if the antagonistic action can increase blood PTH concentration discontinuously and intermittently, its antagonist is expected to show the same effect as that provided by intermittent administration of PTH, and a pharmaceutical agent extremely effective for the treatment of osteoporosis can be provided.

In contrast, cytochrome (cytochrome P450, hereinafter P450) is a protein having a molecular weight of about 50,000, which contains protoheme, and its physical functions vary over a wide range. For example, it has a function of an enzyme catalyzing various reactions in the drug metabolism. CYP2D6 belonging to the family of P450 (CYP) is an important enzyme for human drug metabolism, and is involved in the metabolism of many compounds. When a drug inhibiting the metabolic function of CYP2D6 is administered, the drug is accumulated in the body and may exert a strong influence. Accordingly, a compound having a weak inhibitory action on the metabolic function of CYP2D6 is desirable as a drug.

Heretofore, various compounds useful as CaSR antagonists have been reported.

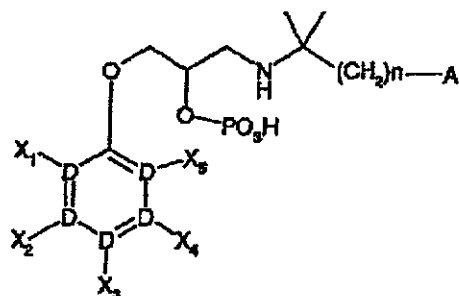
Specifically, for example, a compound represented by the following formula



wherein A is aryl etc., D is C or N, X₁ and X₅ are each hydrogen, cyano etc., and X₂, X₃ and X₄ are each hydrogen, halogen, C₁₋₄ alkyl etc. (WO 02/38106) is mentioned.

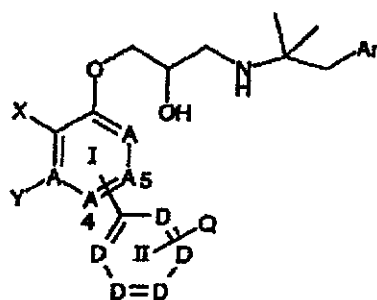
In addition, a compound represented by the following

formula



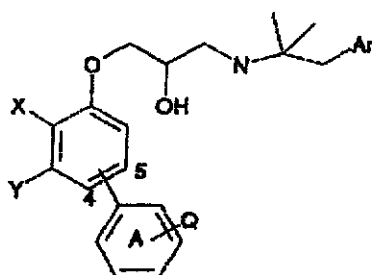
wherein A is aryl etc., D is C or N, X₁ and X₅ are each hydrogen, cyano etc., X₂ is hydrogen etc., and X₃ and X₄ are
 5 each hydrogen, C₁₋₄ alkyl etc. (WO 02/34204) is mentioned.

Furthermore, a compound represented by the following formula



wherein A is C or N, D is C or N, X is cyano, nitro etc., Y is
 10 chlorine, fluorine etc., and Ar is phenyl, naphthyl etc. (WO 02/07673) is mentioned.

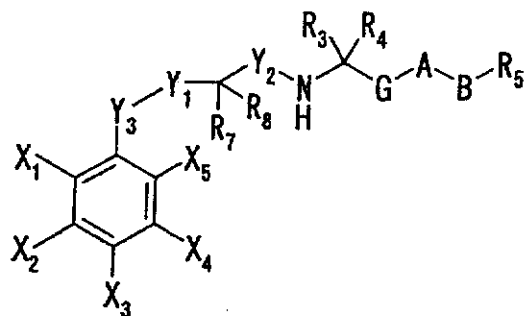
In addition, a compound represented by the following formula



15 wherein X is cyano, nitro etc., Y is chlorine, fluorine etc.,
 and Ar is phenyl, naphthyl etc. (JP 2002-536330-T, WO 00/45816,

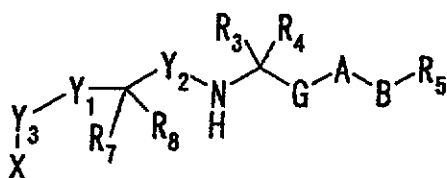
EP 1148876-A, US 6417215), and

a compound represented by the following formula

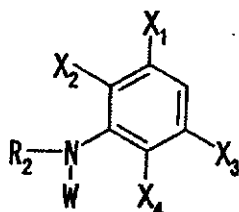


wherein X_1 , X_2 , X_3 , X_4 and X_5 are each H, halogen and the like,
 5 Y_1 is a covalent bond, or a non-substituted or a substituted
 alkylene, etc., Y_2 is a non-substituted or a substituted
 methylene, Y_3 is a covalent bond, O etc., R_3 and R_4 are each
 independently methyl, ethyl etc., R_5 is aryl, fused aryl etc.,
 R_7 is H, OH etc., R_8 is H, C_{1-4} alkyl etc., A and B are
 10 independently a bond, CH_2 etc., G is a covalent bond, CHR_6 (R_6
 is H etc.) etc. (JP 2002-510671-T, WO 99/51569, EP 1070048-A,
 US 6395919) are described.

As a CaSR antagonist, a compound represented by the
 following formula



15 wherein X is a following formula

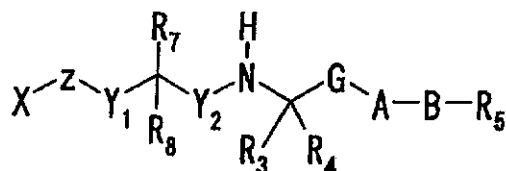


(Ia)

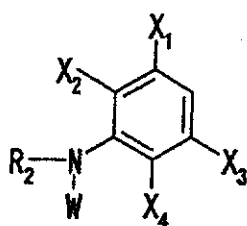
wherein X_1 , X_2 , X_3 and X_4 are each independently CN, NO_2 etc.,
 then W is R_1 , SO_2R_1 etc., R_2 is H, C_{1-4} alkyl etc., and the like,

Y₁ is a covalent bond, or a non-substituted or a substituted alkylene etc., Y₂ is a non-substituted or a substituted methylene, Y₃ is a covalent bond, O etc., R₃ and R₄ are independently methyl, ethyl etc., R₅ is heteroaryl, fused
 5 heteroaryl etc., R₇ is H, OH etc., R₈ is H, C₁₋₄ alkyl etc., A and B are each independently a bond, CH₂ etc., and G is a covalent bond, CHR₆ (R₆ is H etc.) etc. (JP 2002-510636-T, WO 99/51241, EP 1069901-A, US 2002052509-A) is described.

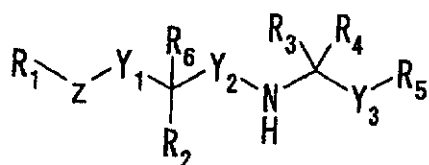
As a CaSR antagonist, a compound represented by the
 10 following formula



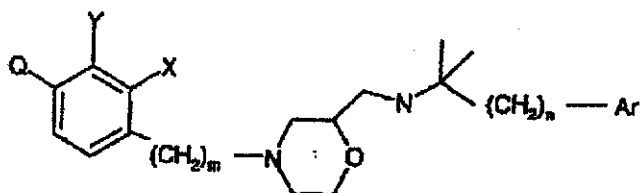
wherein Y₁ is a covalent bond, alkylene etc., Y₂ is a non-substituted or a substituted methylene, C₁₋₄ alkyl etc., Z is a covalent bond, O etc., R₃ and R₄ are each independently methyl,
 15 ethyl etc., R₅ is phenyl, naphthyl etc., G is a covalent bond or C-R₆ wherein R₆ is H, OH etc., R₇ is H, OH etc., R₈ is H, C₁₋₄ alkyl etc., A-B moiety is CH₂CH₂, a covalent bond etc., and X is a following formula



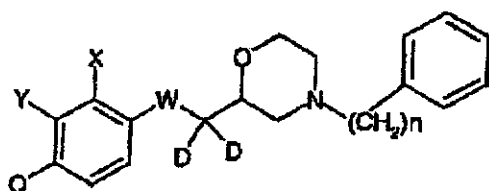
20 wherein W is R₁, SO₂R₁ wherein R₁ is hydrogen, C₁₋₄ alkyl etc., and the like, X₁, X₂, X₃ and X₄ are each independently CN, NO₂ etc., R₂ is hydrogen, C₁₋₄ alkyl etc., and the like (JP 2001-523223-T, WO 98/45255, EP 973730-A, US 6294531),
 a compound represented by the following formula



wherein R_1 is aryl etc., R_2 is hydroxyl group etc., R_3 and R_4 are each lower alkyl etc., R_5 is substituted naphthyl, substituted phenyl etc., Y_1 is alkylene etc., Y_2 is alkylene, Y_3 is alkylene and Z is oxygen etc. (JP 2001-501584-T, WO 97/37967, EP 901459-A, US 6022894),
a compound represented by the following formula

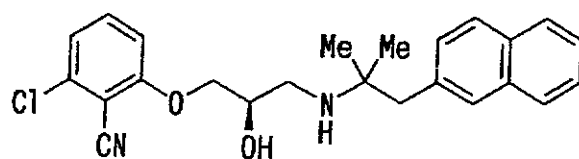


wherein X is nitro etc., Y is hydrogen etc., Q is C_{1-4} alkyl etc., Ar is phenyl, naphthyl etc., m is 0-2 and n is 1-3 (JP 2002-522499-T, WO 00/09132, EP 1112073-A), and
a compound represented by the following formula



wherein X is cyano etc., Y is chlorine etc., Q is hydrogen etc., W is oxygen etc., D is hydrogen etc. and n is 2-4 (JP 2002-522532-T, WO 00/09491, EP 1104411-A) are described.

Maxine Gowen et al. administered a compound having a CaSR antagonistic action, which is called NPS-2143,



NPS-2143

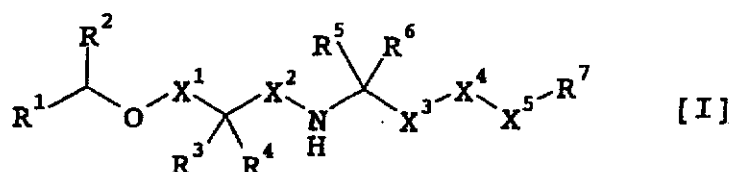
to OVX rats orally and measured blood concentration and bone density thereof, thereby testing the effect of NPS-2143 on osteogenesis, and reported the results thereof (The Journal of Clinical Investigation, vol. 105, pp. 1595-1604 (2000)).

According to the report, NPS-2143 significantly promotes release of PTH, but it did not show any direct effect on osteoblast and osteoclast in vitro and was free of bone decrease or bone increase. One of the reasons pointed out therefor is too long a half-life of NPS-2143 in blood. That is, when rat PTH (1-34) was administered to OVX rat at the dose of 5 µg/kg, blood PTH concentration reached the peak of about 175 pg/ml in 30 minutes and returned to the original level in 2 hours, but when NPS-2143 was administered at the dose of 100 µmol/kg, the blood PTH concentration reached about 115 pg/ml in 30 minutes and kept increasing and showed about 140 pg/ml even 4 hours later (The Journal of Clinical Investigation, vol. 105, p.1595-1604 (2000), especially p. 1598, Fig. 3).

At that time, the blood concentration of NPS-2143 itself was maintained at the level of not less than 100 ng/ml even 8 hours after the administration. It was 24 hours later when the concentration became 10 ng/ml or below the undetectable level.

The above-mentioned Maxine Gowen et al. reference teaches that a calcium receptor antagonist having a too long blood half-life provides results as in continuous administration of PTH, where a bone mass increase cannot be expected. Thus, most of the conventional calcium receptor antagonists continuously increase the blood PTH concentration and cannot be expected to provide a sufficient osteogenesis promoting action. Of the

conventional calcium receptor antagonists, a compound represented by the following formula [I]



wherein R¹ is optionally substituted aryl group etc., R² is C₁₋₆ alkyl group, C₃₋₇ cycloalkyl group etc., R³ is hydroxyl group etc., R⁴ is hydrogen atom etc., R⁵ and R⁶ are C₁₋₆ alkyl group etc., R⁷ is optionally substituted aryl group etc., X¹ is a single bond, C₁₋₆ alkylene etc., X² is optionally substituted C₁₋₆ alkylene, X³ is a single bond or optionally substituted C₁₋₆ alkylene, and X⁴ and X⁵ are linked to form a single bond, methylene etc., which has a superior calcium receptor antagonistic action, which can be administered orally and intermittently, and which can increase blood PTH concentration discontinuously and intermittently, is disclosed (W002/14259).

By comparison of the activities of a compound within the scope disclosed in this publication and the compound of the present invention, the compound of the present invention was surprisingly found to have a higher activity and to be a compound having a lower inhibitory action on the metabolic enzyme CYP2D6.

However, there are not many reports on such an effective compound, and further study is desired.

Disclosure of the Invention

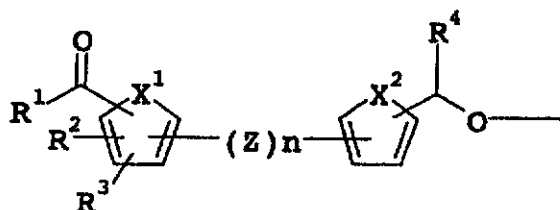
The present invention aims at providing a compound having a superior calcium receptor antagonistic action, which can be administered orally and intermittently, and which can increase blood PTH concentration discontinuously and intermittently. The present invention also aims at providing a pharmaceutical composition permitting oral administration, which comprises this compound, and which is effective as a therapeutic drug

for a disease accompanying abnormal calcium homeostasis, such as osteoporosis, hypoparathyroidism, osteosarcoma, periodontitis, bone fracture, osteoarthritis, chronic rheumatoid arthritis, Paget's disease, humoral hypercalcemia
5 syndrome, autosomal dominant hypocalcemia and the like, particularly a therapeutic drug for osteoporosis.

It has recently reported that the increasing of blood calcium concentration causes an increasing of dopamine in the brain and then improve a condition of Parkinson's disease and
10 dementia. The compound of the present invention is also expected a therapeutic drug for Parkinson's disease and dementia because of increasing blood PTH concentration and consequently increasing blood calcium concentration.

To solve the above-mentioned problems, the present
15 inventors have conducted intensive studies and, as a result, found that a compound represented by the following formula (1) has a superior calcium receptor antagonistic action, and can be administered orally and intermittently, which resulted in the completion of the present invention. A compound
20 represented by the following formula (1) can surprisingly increase the blood PTH concentration discontinuously and intermittently, and is greatly expected to have practicality as a superior therapeutic drug for osteoporosis.

A compound represented by the following formula (1) of
25 the present invention is characterized in that a carbon atom adjacent to an oxygen atom has a structure of

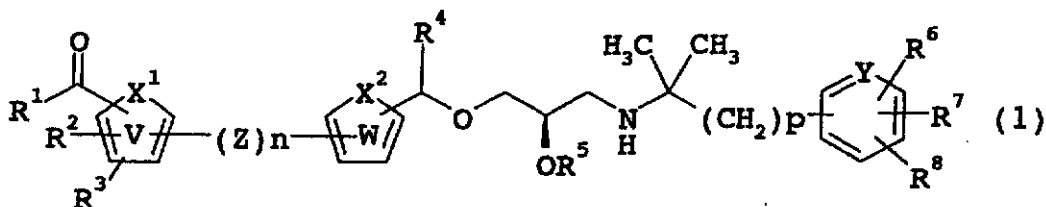


wherein each symbol is as defined below. As is clear from the following Experimental Examples, the compound of the present

invention having this structure is superior in calcium receptor antagonistic action, and also has a discontinuous and transitional PTH secretagogue action. Accordingly, by administration of the compound of the present invention, a similar effect as in the intermittent administration of the PTH can be achieved, which is considered to be extremely effective for the treatment of osteoporosis. In addition, as shown in the Experimental Examples below, the compound of the present invention shows a weak inhibitory action on the metabolic function of P450, especially CYP2D6, which is desirable as a pharmaceutical product. The PTH secretion action of the present invention was shown even low dose compared with a compound as known before. The compound of the present invention was improved a property of absorption and solubility. It is also clear that the compound of the present invention has a weak side effect.

The present invention relates to a compound represented by the following formula (1), a calcium receptor antagonist and a therapeutic drug for osteoporosis, which comprise this compound as an active ingredient. More particularly, the present invention provides the following [1] to [44].

[1] A compound represented by the following formula (1), a pharmaceutically acceptable salt thereof or an optically active form thereof (hereinafter sometimes to be collectively abbreviated as compound (1)):



wherein

n is 0 or 1,

p is an integer of 1 to 3,

R^1 is a hydroxyl group, a C_{1-6} alkoxy group or R^A ,
 wherein R^A is $R^C-OC(=O)O-C_{1-4}$ alkylene-O- or OH-NH-,
 wherein R^C is a C_{1-6} alkyl group or a C_{3-6} cycloalkyl group,
 R^2 and R^3 are the same or different and each is a hydrogen atom,
 5 a hydroxyl group, a halogen atom, an amino group, a C_{1-7}
 acylamino group, a halo C_{1-6} alkyl group, a carboxyl group, a
 C_{1-6} alkoxy-carbonyl group, a C_{1-6} alkoxy group, a halo C_{1-6}
 alkoxy group, a C_{1-6} alkyl group, a hydroxy- C_{1-6} alkyl group, a
 C_{1-7} acylamino- C_{1-6} alkyl group, a C_{2-6} alkenyl group, an aralkyl
 10 group, a phenyl group, a C_{1-6} alkylamino group, a di(C_{1-6}
 alkyl)amino group, a C_{1-6} alkoxy- C_{1-6} alkyl group, a mercapto
 group, a cyano group, a nitro group, a morpholino group, a
 piperidino group or a pyrrolidino group, or R^2 and R^3 are
 joined to form an ethyleneoxy group,
 15 X^1 is $-C=C-$, $-C=N-$, an oxygen atom or a sulfur atom,
 Z is $-S-$, $-SO-$, $-SO_2-$, $-(CH_2)_{m1}-O-$, $-O-(CH_2)_{m1}-$, $-(CH_2)_{m2}-NH-$, $-$
 $NH-(CH_2)_{m2}-$, $-(CH_2)_{m3}-N(CH_3)-$, $-N(CH_3)-(CH_2)_{m3}-$, a C_{1-4} alkylene
 group, $-SO_2-N(CH_3)-$, $-N(CH_3)-SO_2-$, $-NHCO-$, $-CONH-$ or a C_{2-4}
 alkenylene group,
 20 wherein $m1$, $m2$ and $m3$ are each an integer of 0 to 2,
 X^2 is $-C=C-$, an oxygen atom or a sulfur atom,
 R^4 is a C_{1-6} alkyl group or a C_{3-6} cycloalkyl group,
 R^5 is a hydrogen atom or R^B ,
 wherein R^B is a C_{1-7} acyl group optionally substituted by a
 25 carboxyl group,
 Y is a carbon atom or a nitrogen atom, and
 R^6 , R^7 and R^8 are the same or different and each is a hydrogen
 atom, a halogen atom, a C_{1-6} alkyl group, a C_{1-6} alkoxy group, a
 halo C_{1-6} alkyl group, a halo C_{1-6} alkoxy group, a carboxyl group,
 30 a hydroxyl group, a cyano group, a nitro group, a phenyl group,
 a C_{3-6} cycloalkyl group, a di(C_{1-6} alkyl)aminocarbonyl group or a
 hydroxy- C_{1-6} alkyl group, or adjacent R^6 and R^7 are joined to
 form $-CH=CH-CH=CH-$, $-C(OH)=CH-CH=CH-$, $-CH=C(OH)-CH=CH-$, $-O-$

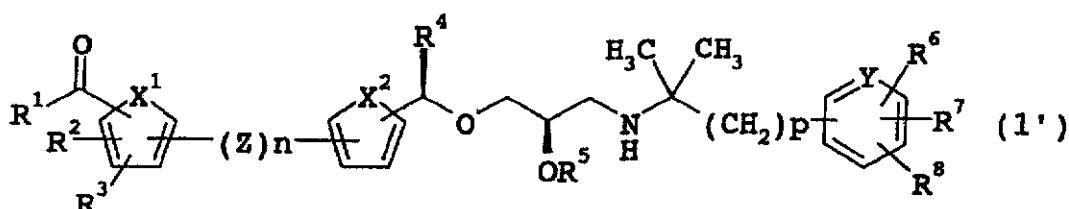
$(\text{CH}_2)_{k1}-\text{O}-$, $-\text{O}-(\text{CH}_2)_{k2}-$ or $-(\text{CH}_2)_{k3}-$,

wherein $k1$ is an integer of 1 to 4, $k2$ is an integer of 2

to 5, $k3$ is an integer of 3 to 6,

provided that when R^2 and R^3 are both hydrogen atoms and n is 1,
5 then Z should be a group other than $-\text{SO}_2-\text{N}(\text{CH}_3)-$ wherein sulfur
atom is bonded to ring V and a nitrogen atom is bonded to ring
W.

[2] The compound of the above-mentioned [1], which has a
10 configuration represented by the following formula (1')



wherein each symbol is as defined above in [1], or a
pharmaceutically acceptable salt thereof.

15 [3] The compound of the above-mentioned [1] or [2], wherein n
is 1, or a pharmaceutically acceptable salt thereof or an
optically active form thereof.

[4] The compound of the above-mentioned [3], wherein
20 n is 1,

p is 1,

R^1 is a hydroxyl group or a C_{1-6} alkoxy group,

R^2 and R^3 are the same or different and each is a hydrogen atom,
a hydroxyl group, a halogen atom, an amino group, a C_{1-7}

25 acylamino group, a trifluoromethyl group, a C_{1-6} alkoxy-carbonyl
group, a C_{1-6} alkoxy group, a C_{1-6} alkyl group, a hydroxy- C_{1-6}
alkyl group, a C_{2-6} alkenyl group, a phenyl group, a benzyl
group, a di(C_{1-6} alkyl)amino group or a nitro group,
or R^2 and R^3 are joined to form an ethyleneoxy group,

X^1 is $-C=C-$ or $-C=N-$,
 X^2 is $-C=C-$,
 Z is $-S-$, $-SO-$, $-SO_2-$, $-(CH_2)_{m1}-O-$, $-O-(CH_2)_{m1}-$, $-(CH_2)_{m2}-NH-$, $-NH-(CH_2)_{m2}-$, $-(CH_2)_{m3}-N(CH_3)-$, $-N(CH_3)-(CH_2)_{m3}-$, a C_{1-4} alkylene
5 group or a C_{2-4} alkenylene group,
wherein $m1$, $m2$ and $m3$ are each an integer of 0 to 2,
 R^4 is a C_{1-6} alkyl group or a C_{3-6} cycloalkyl group,
 R^5 is a hydrogen atom,
 Y is a carbon atom or a nitrogen atom, and
10 R^6 , R^7 and R^8 are the same or different and each is a hydrogen atom, a halogen atom, a C_{1-6} alkyl group or a C_{1-6} alkoxy group, or adjacent R^6 and R^7 are joined to form $-CH=CH-CH=CH-$, a pharmaceutically acceptable salt thereof or an optically active form thereof.

15

[5] The compound of the above-mentioned [4], wherein
 n is 1,
 p is 1,
 R^1 is a hydroxyl group or a C_{1-6} alkoxy group,
20 R^2 and R^3 are the same or different and each is a hydrogen atom, a halogen atom, a C_{1-6} alkoxy group or a C_{1-6} alkyl group,
 X^1 is $-C=C-$,
 Z is $-S-$, $-SO-$, $-SO_2-$, $-(CH_2)_{m1}-O-$, $-O-(CH_2)_{m1}-$, $-CH_2-NH-$, $-NH-CH_2-$, $-N(CH_3)-$, methylene or vinylene,
25 wherein $m1$ is 0 or 1,
 X^2 is $-C=C-$,
 R^4 is a methyl group or a cyclopropyl group,
 R^5 is a hydrogen atom,
 Y is a carbon atom or a nitrogen atom, and
30 R^6 , R^7 and R^8 are the same or different and each is a hydrogen atom, a halogen atom or a C_{1-6} alkyl group, or adjacent R^6 and R^7 are joined to form $-CH=CH-CH=CH-$, a pharmaceutically acceptable salt thereof or an optically

active form thereof.

[6] The compound of the above-mentioned [3], which is selected from the group consisting of

- 5 4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]benzoic acid,
4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]-3-methoxybenzoic acid,
- 10 methyl 4-[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]benzoate,
4-[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]benzoic acid,
4-[2-[1-[(2R)-3-[[1-(quinolin-3-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]benzoic acid,
- 15 4-[2-[1-[(2R)-3-[[1-(4-chloro-2-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]benzoic acid,
4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]benzoic acid,
- 20 3-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]benzoic acid,
4-[2-[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenyl]vinyl]benzoic acid,
3-[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenylthio]benzoic acid,
- 25 4-[2-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenyl]vinyl]benzoic acid,
4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]-3,5-dimethylbenzoic acid,
- 30 4-[2-[1-[(2R)-3-[[1-(4-chloro-2-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]-3,5-

dimethylbenzoic acid,

4-[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]benzyl]benzoic acid,

3-[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]benzyl]benzoic acid,

5 4-[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenylthio]benzoic acid,

4-[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenylsulfinyl]benzoic acid,

10 4-[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenylsulfonyl]benzoic acid,

4-[[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenylamino]methyl]benzoic acid,

15 2-[[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]methyl]benzoic acid,

3-[[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]methyl]benzoic acid,

4-[[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]methyl]benzoic acid,

20 3-[[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]methyl]benzoic acid,

4-[[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]methyl]benzoic acid,

25 3-fluoro-4-[[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]methyl]benzoic acid,

4-[[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]methyl]-3-methylbenzoic acid,

30 4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]-3,5-dimethoxybenzoic acid,

4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]-3-nitrobenzoic acid,

4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]-2-nitrobenzoic acid,

4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]-3-chlorobenzoic acid,

4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]-2-chlorobenzoic acid,

4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]-2-trifluoromethylbenzoic acid,

4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]-3-trifluoromethylbenzoic acid,

4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]-3-fluorobenzoic acid,

4-[2-[1-[(2R)-3-[[1-(4-chloro-3-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]benzoic acid, and

4-[2-[1-[(2R)-3-[[1-(4-chloro-3-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]-5-methylbenzoic acid,

a pharmaceutically acceptable salt thereof or an optically active form thereof.

[7] The compound of the above-mentioned [1] or [2], wherein n is 0, a pharmaceutically acceptable salt thereof or an optically active form thereof.

[8] The compound of the above-mentioned [7], wherein
 n is 0,
 p is 1,
 R¹ is a hydroxyl group or a C₁₋₆ alkoxy group,
 5 R² and R³ are the same or different and each is a hydrogen atom,
 a hydroxyl group, a halogen atom, an amino group, a C₁₋₇
 acylamino group, a trifluoromethyl group, a C₁₋₆ alkoxy-carbonyl
 group, a C₁₋₆ alkoxy group, a C₁₋₆ alkyl group, a hydroxy-C₁₋₆
 alkyl group, a C₂₋₆ alkenyl group, a phenyl group, a benzyl
 10 group, a di(C₁₋₆alkyl)amino group or a nitro group, or
 R² and R³ are joined to form an ethyleneoxy group,
 X¹ is -C=C- or -C=N-,
 X² is -C=C-,
 R⁴ is a C₁₋₆ alkyl group or a C₃₋₆ cycloalkyl group,
 15 R⁵ is a hydrogen atom,
 Y is a carbon atom or a nitrogen atom, and,
 R⁶, R⁷ and R⁸ are the same or different and each is a hydrogen
 atom, a halogen atom, a C₁₋₆ alkyl group or a C₁₋₆ alkoxy group,
 or adjacent R⁶ and R⁷ are joined to form -CH=CH-CH=CH-,
 20 a pharmaceutically acceptable salt thereof or an optically
 active form thereof.

[9] The compound of the above-mentioned [8], wherein
 n is 0,
 25 p is 1,
 R¹ is a hydroxyl group or a C₁₋₆ alkoxy group,
 R² and R³ are the same or different and each is a hydrogen atom,
 a hydroxyl group, a halogen atom, an amino group, a C₁₋₇
 acylamino group, a trifluoromethyl group, a C₁₋₆ alkoxy-carbonyl
 30 group, a C₁₋₆ alkoxy group, a C₁₋₆ alkyl group, a hydroxy-C₁₋₆
 alkyl group, a C₂₋₆ alkenyl group, a phenyl group, a benzyl
 group, a di(C₁₋₆ alkyl)amino group or a nitro group, or R² and
 R³ are joined to form an ethyleneoxy group,

X^1 is $-C=C-$ or $-C=N-$,
 X^2 is $-C=C-$,
 R^4 is a methyl group or a cyclopropyl group,
 R^5 is a hydrogen atom,
5 Y is a carbon atom, and
 R^6 , R^7 and R^8 are the same or different and each is a hydrogen atom, a halogen atom, a C_{1-6} alkyl group or a C_{1-6} alkoxy group, or adjacent R^6 and R^7 are joined to form $-CH=CH-CH=CH-$,
a pharmaceutically acceptable salt thereof or an optically
10 active form thereof.

[10] The compound of the above-mentioned [7], which is
selected from the group consisting of 2'-[1-[(2R)-3-[[1-(3-
fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-
15 hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid,
2'-[1-[(2R)-3-[[1-(4-chloro-3-fluorophenyl)-2-methylpropan-2-
yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-
carboxylic acid,
2'-[1-[(2R)-3-[[1-(3-chloro-4-methylphenyl)-2-methylpropan-2-
20 yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-
carboxylic acid,
2'-[1-[(2R)-3-[[1-(4-chloro-3-methylphenyl)-2-methylpropan-2-
yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-
carboxylic acid,
25 2'-[1-[(2R)-3-[[1-(2,3-difluoro-4-methylphenyl)-2-
methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-
methylbiphenyl-4-carboxylic acid,
2'-[1-[(2R)-3-[[1-(4-chloro-2-fluorophenyl)-2-methylpropan-2-
yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-
30 carboxylic acid,
2'-[1-[(2R)-3-[[1-(2-fluoro-4-methylphenyl)-2-methylpropan-2-
yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-
carboxylic acid,

2'-[1-[(2R)-3-[[1-(4-ethyl-3-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid,

3-methyl-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-5-carboxylic acid,

5 methyl 2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-3,5-dicarboxylate,

2'-[(cyclopropyl) [(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]methyl]-3-methylbiphenyl-4-

10 carboxylic acid,

2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid,

2'-[(cyclopropyl) [(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-

15 methylpropan-2-yl]amino]-2-hydroxypropoxy]methyl]-3-methylbiphenyl-4-carboxylic acid,

2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid,

20 2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-5-carboxylic acid,

2'-[(cyclopropyl) [(2R)-3-[[1-(4-chloro-2-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]methyl]-3-

25 methylbiphenyl-4-carboxylic acid,

2'-[(cyclopropyl) [(2R)-3-[[1-(4-chloro-3-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]methyl]-3-methylbiphenyl-4-carboxylic acid,

2'-[1-[(2R)-3-[[1-(3-fluoro-4-methoxyphenyl)-2-methylpropan-2-

30 yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid,

3-methyl-2'-[1-[(2R)-3-[[1-(3,4-dimethylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-

carboxylic acid,
 2'-[1-[(2R)-3-[[1-(4-methylphenyl)-2-methylpropan-2-yl]amino]-
 2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid,
 2'-[1-[(2R)-3-[[1-(4-chloro-3-methoxyphenyl)-2-methylpropan-2-
 5 yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-
 carboxylic acid,
 2'-[1-[(2R)-3-[[1-(4-ethylphenyl)-2-methylpropan-2-yl]amino]-
 2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid,
 2'-[1-[(2R)-3-[[1-(4-chloro-2,5-difluorophenyl)-2-
 10 methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-
 methylbiphenyl-4-carboxylic acid,
 2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-
 yl]amino]-2-hydroxypropoxy]ethyl]-3-methoxybiphenyl-4-
 carboxylic acid,
 15 2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-
 yl]amino]-2-hydroxypropoxy]ethyl]-2-methoxybiphenyl-4-
 carboxylic acid,
 2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-
 yl]amino]-2-hydroxypropoxy]ethyl]-3-(trifluoromethyl)biphenyl-
 20 4-carboxylic acid,
 2'-[1-[(2R)-3-[[1-(2-fluoro-4-methoxyphenyl)-2-methylpropan-2-
 yl]amino]-2-hydroxypropoxy]ethyl]-3-(trifluoromethyl)biphenyl-
 4-carboxylic acid,
 3-ethyl-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-
 25 yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-carboxylic acid,
 2'-[1-[(2R)-3-[[1-(3,4-dichlorophenyl)-2-methylpropan-2-
 yl]amino]-2-hydroxypropoxy]ethyl]-3-(trifluoromethyl)biphenyl-
 4-carboxylic acid,
 2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-
 30 yl]amino]-2-hydroxypropoxy]ethyl]-3-isopropylbiphenyl-4-
 carboxylic acid,
 3-ethyl-2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-
 methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-

- carboxylic acid,
 2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-isopropylbiphenyl-4-carboxylic acid,
- 5 2-chloro-6-[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenyl]pyridine-3-carboxylic acid,
 2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-propylbiphenyl-4-
- 10 carboxylic acid,
 2,3-dimethyl-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-carboxylic acid,
 2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-
- 15 yl]amino]-2-hydroxypropoxy]ethyl]-3-propylbiphenyl-4-carboxylic acid,
 2-chloro-6-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenyl]pyridine-3-carboxylic acid,
- 20 3,5-dimethyl-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-carboxylic acid,
 2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-m-terphenyl-4'-carboxylic acid,
- 25 2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-2,3-dimethylbiphenyl-4-carboxylic acid,
 2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3,5-dimethylbiphenyl-4-
- 30 carboxylic acid,
 4-(hydroxymethyl)-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-3-carboxylic acid,

3-isobutyl-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-carboxylic acid,
 2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-isobutylbiphenyl-4-
 5 carboxylic acid,
 2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-4-(hydroxymethyl)biphenyl-3-carboxylic acid,
 2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-(2-methyl-1-
 10 propenyl)biphenyl-4-carboxylic acid,
 2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-hydroxybiphenyl-4-carboxylic acid,
 2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-hydroxybiphenyl-4-
 15 carboxylic acid,
 3-ethyl-2'-[1-[(2R)-3-[[1-(4-chloro-3-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-
 20 carboxylic acid,
 2'-[1-[(2R)-3-[[1-(4-chloro-3-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-isopropylbiphenyl-4-carboxylic acid,
 2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-(1-methylpropyl)biphenyl-
 25 4-carboxylic acid,
 2-methyl-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-carboxylic acid,
 3-methyl-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-carboxylic acid,
 30 4-fluoro-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-3-carboxylic acid,
 2'-[1-[(2R)-3-[[1-(3,4-dichlorophenyl)-2-methylpropan-2-

yl]amino]-2-hydroxypropoxy]ethyl]-2-methylbiphenyl-4-carboxylic acid,

6-fluoro-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-3-carboxylic acid,

5 3-fluoro-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-carboxylic acid,

2'-[1-[(2R)-3-[[1-(3-chlorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid,

2'-[1-[(2R)-3-[[1-(3,4-dichlorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-

10 carboxylic acid,

2-fluoro-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-carboxylic acid,

2'-[(cyclopropyl)[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]methyl]-3-methylbiphenyl-4-

15 carboxylic acid,

2'-[(cyclopropyl)[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]methyl]-3-fluorobiphenyl-4-carboxylic acid,

20 2'-[(cyclopropyl)[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]methyl]-2-fluorobiphenyl-4-carboxylic acid,

2'-[(cyclopropyl)[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]methyl]-2-methylbiphenyl-4-

25 carboxylic acid,

2'-[1-[(2R)-3-[[1-(3,4-dichlorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-2-fluorobiphenyl-4-carboxylic acid,

3-chloro-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-carboxylic acid,

30 2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-nitrobiphenyl-4-carboxylic acid,

3-amino-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-carboxylic acid,
 3-(acetylamino)-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-
 5 carboxylic acid,
 3-chloro-2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-carboxylic acid,
 2'-[1-[(2R)-3-[[1-(3-methoxy-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-
 10 carboxylic acid,
 2,3-dihydro-5-[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenyl]benzofuran-7-carboxylic acid,
 15 2,6-dimethyl-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-carboxylic acid,
 2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-2,6-dimethylbiphenyl-4-
 20 carboxylic acid,
 3-(dimethylamino)-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-carboxylic acid,
 2,3-dihydro-5-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenyl]benzofuran-7-carboxylic acid,
 25 methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-carboxylic acid,
 3-benzyl-2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-carboxylic acid,
 30 2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methoxybiphenyl-4-carboxylic acid,
 2'-[1-[(2R)-3-[[1-(4-chloro-2-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methoxybiphenyl-4-carboxylic acid,

yl]amino]-2-hydroxypropoxy]ethyl]-3-methoxybiphenyl-4-carboxylic acid,

2'-[1-[(2R)-3-[[1-(4-chloro-3-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methoxybiphenyl-4-

5 carboxylic acid,

2'-[1-[(2R)-3-[[1-(4-chloro-3-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-2-methylbiphenyl-4-carboxylic acid,

2'-[1-[(2R)-3-[[1-(4-chloro-2-fluorophenyl)-2-methylpropan-2-

10 yl]amino]-2-hydroxypropoxy]ethyl]-2-methylbiphenyl-4-carboxylic acid,

4-methyl-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-3-carboxylic acid,

2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-

15 yl]amino]-2-hydroxypropoxy]ethyl]-4-methylbiphenyl-3-carboxylic acid,

2'-[1-[(2R)-3-[[1-(3,5-dichlorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid,

20 2'-[1-[(2R)-3-[[1-(2,5-difluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid,

2'-[1-[(2R)-3-[[1-(5-chloro-2-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-

25 methylbiphenyl-4-carboxylic acid,

2'-[1-[(2R)-3-[[1-(3-chloro-2-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid,

2'-[1-[(2R)-3-[[1-(3-fluoro-4-trifluoromethylphenyl)-2-

30 methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid,

2'-[1-[(2R)-3-[[1-(5-chloro-3-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-

carboxylic acid,

2'-[1-[(2R)-3-[[1-(3,5-ditrifluoromethylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid,

5 2'-[1-[(2R)-3-[[1-(4-methyl-3,5-dimethoxyphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid,

2'-[1-[(2R)-3-[[1-(3,5-dimethoxyphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-

10 carboxylic acid,

2'-[1-[(2R)-3-[[1-(4-chloro-3-trifluoromethylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid,

2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-

15 yl]amino]-2-hydroxypropoxy]ethyl]-3-t-butylbiphenyl-4-carboxylic acid,

2'-[1-[(2R)-3-[[1-(4-chloro-2-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-t-butylbiphenyl-4-carboxylic acid,

20 2'-[1-[(2R)-3-[[1-(4-chloro-3-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-t-butylbiphenyl-4-carboxylic acid,

2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methoxybiphenyl-4-

25 carboxylic acid,

2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-morpholinobiphenyl-4-carboxylic acid,

2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-

30 yl]amino]-2-hydroxypropoxy]ethyl]-3-(trifluoromethoxy)biphenyl-4-carboxylic acid,

2'-[1-[(2R)-3-[[1-(3-trifluoromethyl-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-

methylbiphenyl-4-carboxylic acid,

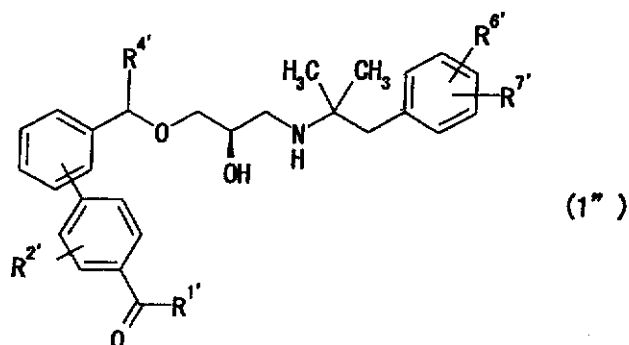
2'-[1-[(2R)-3-[[1-(4-chloro-3-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-(hydroxymethyl)biphenyl-4-carboxylic acid, and

5 2'-[1-[(2R)-3-[[1-(4-chloro-3-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-carboxybiphenyl-4-carboxylic acid,

a pharmaceutically acceptable salt thereof or an optically active form thereof.

10

[11] A compound represented by the following formula (1''), a pharmaceutically acceptable salt thereof or an optically active form thereof:



15 wherein

R^{1'} is a hydroxyl group or a C₁₋₆ alkoxy group,

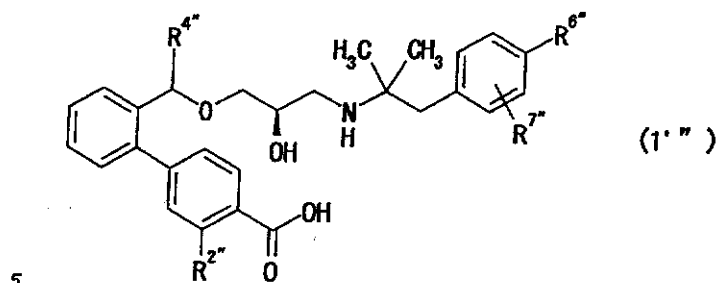
R^{2'} is a hydroxyl group, a halogen atom, an amino group, a C₁₋₇ acylamino group, a halo C₁₋₆ alkyl group, a C₁₋₆ alkoxy-carbonyl group, a C₁₋₆ alkoxy group, a halo C₁₋₆ alkoxy group, a C₁₋₆ alkyl group, a hydroxy-C₁₋₆ alkyl group, a di(C₁₋₆ alkyl)amino group or
20 a nitro group,

R^{4'} is a C₁₋₆ alkyl group or a C₃₋₆ cycloalkyl group,

R^{6'} is a halogen atom, a C₁₋₆ alkyl group, a C₁₋₆ alkoxy group or a halo C₁₋₆ alkyl group, or when R^{7'} is adjacent, R^{6'} and R^{7'} are
25 linked to form -CH=CH-CH=CH-, and

R^{7'} is a hydrogen atom, a halogen atom, a C₁₋₆ alkyl group, a C₁₋₆ alkoxy group or a halo C₁₋₆ alkyl group.

[12] A compound represented by the following formula (1'"), a pharmaceutically acceptable salt thereof or an optically active form thereof:



wherein

- $R^{2''}$ is a C_{1-6} alkyl group,
 $R^{4''}$ is a methyl group or a cyclopropyl group,
 $R^{6''}$ is a halogen atom or a C_{1-6} alkyl group, and
 10 $R^{7''}$ is a hydrogen atom, a halogen atom, a C_{1-6} alkyl group, a C_{1-6} alkoxy group or a halo C_{1-6} alkyl group.

[13] The compound of the above-mentioned [11] or [12], which is selected from the group consisting of

- 15 2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid,
 2'-[1-[(2R)-3-[[1-(4-chloro-3-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-
 20 carboxylic acid,
 2'-[1-[(2R)-3-[[1-(3-chloro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid,
 2'-[1-[(2R)-3-[[1-(4-chloro-3-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-
 25 carboxylic acid,
 2'-[1-[(2R)-3-[[1-(4-chloro-2-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-

- carboxylic acid,
- 2'-[1-[(2R)-3-[[1-(2-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid,
- 5 2'-[1-[(2R)-3-[[1-(4-ethyl-3-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid,
- 2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-
- 10 carboxylic acid,
- 2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-5-carboxylic acid,
- 2'-[(cyclopropyl)[(2R)-3-[[1-(4-chloro-2-fluorophenyl)-2-
- 15 methylpropan-2-yl]amino]-2-hydroxypropoxy]methyl]-3-methylbiphenyl-4-carboxylic acid,
- 2'-[(cyclopropyl)[(2R)-3-[[1-(4-chloro-3-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]methyl]-3-methylbiphenyl-4-carboxylic acid,
- 20 3-methyl-2'-[1-[(2R)-3-[[1-(3,4-dimethylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-carboxylic acid,
- 2'-[1-[(2R)-3-[[1-(4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid,
- 25 2'-[1-[(2R)-3-[[1-(4-chloro-3-methoxyphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid,
- 2'-[1-[(2R)-3-[[1-(4-ethylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid,
- 30 3-ethyl-2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-carboxylic acid,
- 2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-

yl]amino]-2-hydroxypropoxy]ethyl]-3-isopropylbiphenyl-4-carboxylic acid,

2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-propylbiphenyl-4-

5 carboxylic acid,

2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-isobutylbiphenyl-4-carboxylic acid,

3-ethyl-2'-[1-[(2R)-3-[[1-(4-chloro-3-fluorophenyl)-2-

10 methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-carboxylic acid,

2'-[1-[(2R)-3-[[1-(4-chloro-3-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-isopropylbiphenyl-4-carboxylic acid,

15 2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-(1-methylpropyl)biphenyl-4-carboxylic acid,

2'-[1-[(2R)-3-[[1-(3-chlorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid,

20 2'-[1-[(2R)-3-[[1-(3,4-dichlorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid,

2'-[1-[(2R)-3-[[1-(3-methoxy-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-

25 carboxylic acid,

2'-[1-[(2R)-3-[[1-(3,5-dichlorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid,

2'-[1-[(2R)-3-[[1-(4-chloro-3-trifluoromethylphenyl)-2-

30 methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid,

2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-t-butylbiphenyl-4-

carboxylic acid,

2'-[1-[(2R)-3-[[1-(4-chloro-2-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-t-butylbiphenyl-4-carboxylic acid,

5 2'-[1-[(2R)-3-[[1-(4-chloro-3-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-t-butylbiphenyl-4-carboxylic acid and

2'-[1-[(2R)-3-[[1-(3-trifluoromethyl-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid

10 a pharmaceutically acceptable salt thereof or an optically active form thereof.

[14] The compound of the above-mentioned [13], which is
15 selected from the group consisting of

2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid,

2'-[1-[(2R)-3-[[1-(4-chloro-3-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid,

2'-[1-[(2R)-3-[[1-(3-chloro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid and

25 2'-[1-[(2R)-3-[[1-(4-chloro-2-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid,

a pharmaceutically acceptable salt thereof or an optically active form thereof.

30

[15] 2'-[1-[(2R)-3-[[1-(3-Fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid, a pharmaceutically

acceptable salt thereof or an optically active form thereof.

[16] 2'-[1-[(2R)-3-[[1-(4-Chloro-3-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid, a pharmaceutically acceptable salt thereof or an optically active form thereof.

[17] 2'-[1-[(2R)-3-[[1-(3-Chloro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid, a pharmaceutically acceptable salt thereof or an optically active form thereof.

[18] 2'-[1-[(2R)-3-[[1-(4-Chloro-2-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid, a pharmaceutically acceptable salt thereof or an optically active form thereof.

[19] A pharmaceutical composition comprising a pharmaceutically acceptable carrier, and a compound of any one of the above-mentioned [1] to [18], a pharmaceutically acceptable salt thereof or an optically active form thereof as an active ingredient.

[20] The pharmaceutical composition of the above-mentioned [19], wherein the active ingredient is a compound of any one of the above-mentioned [3] to [6], a pharmaceutically acceptable salt thereof or an optically active form thereof.

[21] The pharmaceutical composition of the above-mentioned [19], wherein the active ingredient is a compound of any one of the above-mentioned [7] to [10], a pharmaceutically acceptable salt thereof or an optically active form thereof.

[22] The pharmaceutical composition of the above-mentioned [19], wherein the active ingredient is a compound of any one of the above-mentioned [11] to [18], a pharmaceutically acceptable salt thereof or an optically active form thereof.

5

[23] A therapeutic drug for osteoporosis, which comprises a pharmaceutically acceptable carrier, and a compound of any one of the above-mentioned [1] to [18], a pharmaceutically acceptable salt thereof or an optically active form thereof,
10 as an active ingredient.

[24] The therapeutic drug for osteoporosis of the above-mentioned [23], wherein the active ingredient is a compound of any one of the above-mentioned [3] to [6], a pharmaceutically
15 acceptable salt thereof or an optically active form thereof.

[25] The therapeutic drug for osteoporosis of the above-mentioned [23], wherein the active ingredient is a compound of any one of claims [7] to [10], a pharmaceutically acceptable
20 salt thereof or an optically active form thereof.

[26] The therapeutic drug for osteoporosis of the above-mentioned [23], wherein the active ingredient is a compound of any of the above-mentioned [11] to [18], a pharmaceutically
25 acceptable salt thereof or an optically active form thereof.

[27] The therapeutic drug for osteoporosis of any one of the above-mentioned [23] to [26], which is used for concomitant use with a different therapeutic drug for osteoporosis.

30

[28] The therapeutic drug for osteoporosis of the above-mentioned [25], wherein the different therapeutic drug for osteoporosis is selected from the group consisting of a

calcium agent, a vitamin D preparation, a vitamin K preparation, a female hormone preparation, an estrogen antagonist preparation, an anabolic steroid preparation, a parathyroid hormone preparation, a calcitonin preparation, a
5 bisphosphonate preparation and an ipriflavone preparation.

[29] A method for treating osteoporosis, which comprises administering an effective amount of a compound of any one of the above-mentioned [1] to [18], a pharmaceutically acceptable
10 salt thereof or an optically active form thereof to a patient with osteoporosis.

[30] A calcium receptor antagonist comprising a pharmaceutically acceptable carrier, and a compound of any one
15 of the above-mentioned [1] to [18], a pharmaceutically acceptable salt thereof or an optically active form thereof as an active ingredient.

[31] A calcium receptor antagonist of the above-mentioned [30],
20 wherein the active ingredient is a compound of any one of the above-mentioned [3] to [6], a pharmaceutically acceptable salt thereof or an optically active form thereof.

[32] The calcium receptor antagonist of the above-mentioned
25 [30], wherein the active ingredient is a compound of any one of the above-mentioned [7] to [10], a pharmaceutically acceptable salt thereof or an optically active form thereof.

30 [33] The calcium receptor antagonist of the above-mentioned [30], wherein the active ingredient is a compound of any one of the above-mentioned [11] to [18], a pharmaceutically acceptable salt thereof or an optically active form thereof.

[34] A calcium receptor antagonist having an IC_{50} value of a calcium receptor antagonistic action which is not less than 10 times the IC_{50} value of an inhibitory action of metabolic
5 enzyme P450.

[35] The calcium receptor antagonist of the above-mentioned [34], wherein the IC_{50} value of the calcium receptor antagonistic action is not less than 100 times the IC_{50} value
10 of an inhibitory action of metabolic enzyme P450.

[36] The calcium receptor antagonist of the above-mentioned [34], wherein the metabolic enzyme P450 is CYP2D6.

15 [37] The calcium receptor antagonist of the above-mentioned [35], wherein the metabolic enzyme P450 is CYP2D6.

[38] A calcium receptor antagonist having an IC_{50} value of a calcium receptor antagonistic action is not more than $0.1 \mu M$,
20 and an IC_{50} value of an inhibitory action of the metabolic enzyme CYP2D6 is not less than $1 \mu M$.

[39] The calcium receptor antagonist of the above-mentioned [38], wherein the IC_{50} value of the calcium receptor
25 antagonistic action is not more than $0.1 \mu M$, and the IC_{50} value of the inhibitory action of the metabolic enzyme CYP2D6 is not less than $10 \mu M$.

[40] The calcium receptor antagonist of any one of the above-
30 mentioned [34] to [37], wherein the calcium receptor antagonist is described in any one of the above-mentioned [30] to [33].

[41] A PTH secretagogue comprising a pharmaceutical acceptable carrier and a compound of any one of the above-mentioned [1] to [18], a pharmaceutically acceptable salt thereof or an optically active form thereof as an active ingredient.

5

[42] The PTH secretagogue of the above-mentioned [41], wherein the active ingredient is a compound of any one of claims 3 to 6, a pharmaceutically acceptable salt thereof or an optically active form thereof.

10

[43] The PTH secretagogue of the above-mentioned [41], wherein the active ingredient is a compound of any one of the above-mentioned [7] to [10], a pharmaceutically acceptable salt thereof or an optically active form thereof.

15

[44] The PTH secretagogue of the above-mentioned [41], wherein the active ingredient is a compound of any one of the above-mentioned [11] to [18], a pharmaceutically acceptable salt thereof or an optically active form thereof.

20

Detailed Description of the Invention

The terms used in the present specification are defined as follows.

The "halogen atom" is fluorine atom, chlorine atom,
25 bromine atom or iodine atom, which is preferably fluorine atom or chlorine atom, particularly preferably chlorine atom.

The "C₁₋₆ alkyl group" is straight chain or branched chain alkyl group having 1 to 6, preferably 1 to 4, carbon atoms, for example methyl group, ethyl group, propyl group, isopropyl
30 group, butyl group, isobutyl group, tert-butyl group, pentyl group, isopentyl group, tert-pentyl group or hexyl group and the like, with preference given to C₁₋₄ alkyl group selected from methyl group, ethyl group, propyl group, isopropyl group,

butyl group, isobutyl group and tert-butyl group.

The "halo C₁₋₆ alkyl group" is the aforementioned "C₁₋₆ alkyl group" substituted by one or more halogen atoms of haloalkyl groups, wherein the position of substitution is free
5 of any particularly limitation as long as it is chemically acceptable. Examples of the "halo C₁₋₆ alkyl group" include fluoromethyl group, difluoromethyl group, trifluoromethyl group, chloromethyl group, dichloromethyl group, trichloromethyl group, bromomethyl group, dibromomethyl group,
10 tribromomethyl group, iodomethyl group, diiodomethyl group, triiodomethyl group, 2-fluoroethyl group, 2,2-difluoroethyl group, 2,2,2-trifluoroethyl group, 2-chloroethyl group, 2,2-dichloroethyl group, 2,2,2-trichloroethyl group, 2-bromomethyl group, 2,2-dibromomethyl group, 2,2,2-tribromomethyl group, 3-
15 chloropropyl group or 4-chlorobutyl group and the like, preferably halo C₁₋₂ alkyl group such as trifluoromethyl group and 2,2,2-trichloroethyl group, particularly preferably trifluoromethyl group.

The "hydroxy-C₁₋₆ alkyl group" is a hydroxyalkyl group
20 wherein the aforementioned "C₁₋₆ alkyl group" is substituted by hydroxyl group, wherein the position of substitution is free of any particularly limitation as long as it is chemically acceptable. Examples of the "hydroxy-C₁₋₆ alkyl group" include hydroxymethyl group, 1-hydroxyethyl group, 2-hydroxyethyl
25 group, 1-hydroxypropyl group, 2-hydroxypropyl group, 3-hydroxypropyl group, 2-hydroxy-1-methylethyl group, 1-hydroxybutyl group, 2-hydroxybutyl group, 3-hydroxybutyl group, 4-hydroxybutyl group, 3-hydroxy-2-methylpropyl group, 2-hydroxy-1,1-dimethylethyl group, 5-hydroxypentyl group or 6-
30 hydroxyhexyl group and the like, preferably hydroxy-C₁₋₄ alkyl group selected from hydroxymethyl group, 2-hydroxyethyl group, 3-hydroxypropyl group and 4-hydroxybutyl group.

The "C₁₋₆ alkoxy group" is a straight chain or branched

chain alkoxy group having 1 to 6, preferably 1 to 4, carbon atoms, for example methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, tert-butoxy group, pentyloxy group, tert-pentyloxy group or hexyloxy group and the like, preferably C₁₋₄ alkoxy group selected from methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group and tert-butoxy group.

The "halo C₁₋₆ alkoxy group" is a haloalkoxy group wherein the aforementioned "C₁₋₆ alkoxy group" is substituted by one or more halogen atoms. The position of substitution is free of any particularly limitation as long as it is chemically acceptable. The "halo C₁₋₆ alkoxy group" is, for example, fluoromethoxy group, difluoromethoxy group, trifluoromethoxy group, chloromethoxy group, dichloromethoxy group, trichloromethoxy group, bromomethoxy group, dibromomethoxy group, tribromomethoxy group, iodomethoxy group, diiodomethoxy group, triiodomethoxy group, 2-fluoroethoxy group, 2,2-difluoroethoxy group, 2,2,2-trifluoroethoxy group, 2-chloroethoxy group, 2,2-dichloroethoxy group, 2,2,2-trichloroethoxy group, 2-bromoethoxy group, 2,2-dibromoethoxy group, 2,2,2-tribromoethoxy group, 3-chloropropoxy group or 4-chlorobutoxy group and the like, preferably halo C₁₋₂ alkoxy group such as trifluoromethoxy group and 2,2,2-trichloroethoxy group, particularly preferably trifluoromethoxy group.

The "C₁₋₆ alkoxy-C₁₋₆ alkyl group" is alkoxyalkyl group wherein the aforementioned "C₁₋₆ alkyl group" is substituted by the aforementioned "C₁₋₆ alkoxy group". The position of substitution is free of any particularly limitation as long as it is chemically acceptable. Examples of the "C₁₋₆ alkoxy-C₁₋₆ alkyl group" include methoxymethyl group, ethoxymethyl group, propoxymethyl group, butoxymethyl group, pentyloxymethyl group, hexyloxymethyl group, 1-methoxyethyl group, 1-ethoxyethyl group, 2-methoxyethyl group, 2-ethoxyethyl group, 1-

methoxypropyl group, 1-ethoxypropyl group, 2-methoxypropyl group, 2-ethoxypropyl group, 3-methoxypropyl group, 3-ethoxypropyl group, 2-methoxy-1-methylethyl group, 1-methoxybutyl group, 1-ethoxybutyl group, 2-methoxybutyl group, 5 2-ethoxybutyl group, 3-methoxybutyl group, 3-ethoxybutyl group, 4-methoxybutyl group, 4-ethoxybutyl group, 3-methoxy-2-methylpropyl group, 2-methoxy-1,1-dimethylethyl group, 2-ethoxy-1,1-dimethylethyl group, 5-methoxypentyl group or 6-methoxyhexyl group and the like, preferably C₁₋₄ alkoxy-C₁₋₄ 10 alkyl group selected from methoxymethyl group, ethoxymethyl group, propoxymethyl group, butoxymethyl group, 2-methoxyethyl group, 3-methoxypropyl group and 4-methoxybutyl group.

The "C₁₋₆ alkoxy-carbonyl group" is alkoxy-carbonyl group wherein C₁₋₆ alkoxy moiety is the aforementioned "C₁₋₆ alkoxy 15 group", for example methoxycarbonyl group, ethoxycarbonyl group, propoxycarbonyl group, isopropoxycarbonyl group, butoxycarbonyl group, isobutoxycarbonyl group, tert-butoxycarbonyl group, pentyloxycarbonyl group or hexyloxycarbonyl group and the like, preferably C₁₋₄ alkoxy- 20 carbonyl group selected from methoxycarbonyl group, ethoxycarbonyl group, propoxycarbonyl group, isopropoxycarbonyl group, butoxycarbonyl group and tert-butoxycarbonyl group.

The "C₁₋₆ alkylamino group" is alkylamino group wherein 25 the aforementioned "C₁₋₆ alkyl group" is substituted by amino group, for example methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group, tert-butylamino group, pentylamino group, isopentylamino group, tert-pentylamino group or hexylamino 30 group and the like, preferably C₁₋₄ alkylamino group selected from methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group and tert-butylamino group.

The "di(C₁₋₆ alkyl)amino group" is a dialkylamino group wherein amino group is di-substituted by the aforementioned "C₁₋₆ alkyl group" and the kind of alkyl group may be different. For example, dimethylamino group, ethylmethylamino group, 5 diethylamino group, methylpropylamino group, ethylpropylamino group, dipropylamino group, diisopropylamino group, dibutylamino group, diisobutylamino group, di-tert-butylamino group, dipentylamino group, diisopentylamino group, di-tert-pentylamino group or dihexylamino group and the like can be 10 mentioned, preferably di C₁₋₄ alkylamino group selected from dimethylamino group, diethylamino group, dipropylamino group, diisopropylamino group, dibutylamino group, diisobutylamino group and di-tert-butylamino group.

The "di(C₁₋₆ alkyl)aminocarbonyl group" is . 15 dialkylaminocarbonyl group wherein aminocarbonyl group is di-substituted by the aforementioned "C₁₋₆ alkyl group" and the kind of alkyl group may be different. For example, dimethylaminocarbonyl group, ethylmethylaminocarbonyl group, diethylaminocarbonyl group, methylpropylaminocarbonyl group, 20 ethylpropylaminocarbonyl group, dipropylaminocarbonyl group, diisopropylaminocarbonyl group, dibutylaminocarbonyl group, diisobutylaminocarbonyl group, di-tert-butylaminocarbonyl group, dipentylaminocarbonyl group, diisopentylaminocarbonyl group, di-tert-pentylaminocarbonyl group or 25 dihexylaminocarbonyl group and the like can be mentioned, preferably di(C₁₋₄ alkyl)aminocarbonyl group selected from dimethylaminocarbonyl group, diethylaminocarbonyl group, dipropylaminocarbonyl group, diisopropylaminocarbonyl group, dibutylaminocarbonyl group, diisobutylaminocarbonyl group and 30 di-tert-butylaminocarbonyl group.

The "C₁₋₇ acyl group" is alkanoyl group, alkenoyl group or aroyl group having 1 to 7 carbon atoms, such as formyl group, acetyl group, propionyl group, butyryl group, pivaloyl group,

ethenoyl group, propenoyl group, butenoyl group or benzoyl group and the like can be mentioned, preferably formyl group, acetyl group, pivaloyl group or benzoyl group. The acyl group may be substituted by carboxyl group for example carboxyacetyl
5 group, 3-carboxypropionyl group, 4-carboxybutyryl group and the like.

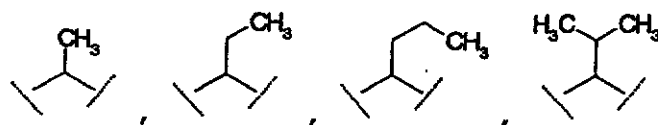
The " C_{1-7} acylamino group" is acylamino group wherein the carbon number of the acyl moiety preferably is 1 to 7, more preferably 2 to 5, wherein the acyl moiety is chain (straight
10 chain and branched chain) or cyclic. As the acyl portion, for example, those exemplified for the aforementioned " C_{1-7} acyl group" can be mentioned. Examples of the acylamino group include alkanoylamino group such as formylamino group, acetylamino group, propionylamino group, butyrylamino group or
15 pivaloylamino group and the like; and aroylamino group such as benzoylamino group and the like, preferably formylamino group, acetylamino group, pivaloylamino group or benzoylamino group.

The " C_{3-6} cycloalkyl group" is a cyclic alkyl group having 3 to 6 carbon atoms, such as cyclopropyl group, cyclobutyl
20 group, cyclopentyl group, cyclohexyl group or cycloheptyl group and the like, preferably C_{3-5} cycloalkyl group such as cyclopropyl group, cyclobutyl group or cyclopentyl group and the like, more preferably cyclopropyl group or cyclobutyl group, particularly preferably cyclopropyl group.

25 The " C_{2-6} alkenyl group" is an alkenyl group having 2 to 6 carbon atoms, such as vinyl group, 1-propenyl group, 2-methyl-1-propenyl group, allyl group, 1-butenyl group, 2-butenyl group, 3-butenyl group, 1-pentenyl group, 2-pentenyl group, 3-pentenyl group, 4-pentenyl group or 5-hexenyl group and the
30 like, preferably C_{2-4} alkenyl group such as vinyl group, 2-methyl-1-propenyl group or allyl group and the like.

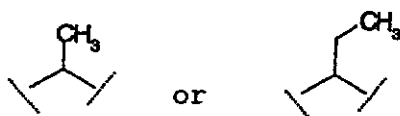
The " C_{1-4} alkylene group" is a linear or branched chain alkylene group having 1 to 4, preferably 1 to 3, carbon atoms,

for example, methylene group, ethylene group, propylene group, butylene group,

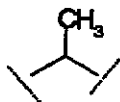


and the like can be mentioned. Preferred are methylene group, 5 ethylene group or propylene group.

As the "C₁₋₄ alkylene group" containing in R^A,



is preferable, particularly



10 is preferable.

The "C₂₋₄ alkenylene group" is an alkenylene group having 2 to 4, preferably 2 or 3, carbon atoms, such as vinylene group, 1-propenylene group, 2-propenylene group, 1-butenylene group, 2-butenylene group, 3-butenylene group and the like, 15 preferably vinylene group, 1-propenylene or 2-propenylene group.

The "C₁₋₇ acylamino-C₁₋₆ alkyl group" is a group wherein the aforementioned "C₁₋₆ alkyl group" is substituted by "C₁₋₇ acylamino group". Examples thereof include alkanoylamino-C₁₋₆ 20 alkyl group such as formylaminomethyl group, acetylaminomethyl group, propionylaminomethyl group, butyrylaminoethyl group, pivaloylaminoethyl group, formylaminoethyl group, acetylaminoethyl group, propionylaminoethyl group, butyrylaminoethyl group, pivaloylaminoethyl group, 25 formylaminopropyl group, acetylaminopropyl group, propionylaminopropyl group, butyrylaminoethyl group, pivaloylaminoethyl group, formylaminobutyl group,

acetylaminobutyl group, propionylaminobutyl group,
butyrylaminobutyl group, pivaloylaminobutyl group,
formylaminopentyl group, acetylaminopentyl group,
propionylaminopentyl group, butyrylaminopentyl group,
5 pivaloylaminopentyl group, formylaminohexyl group,
acetylaminohexyl group, propionylaminohexyl group,
butyrylaminohexyl group, pivaloylaminohexyl group and the like,
and aroylamino-C₁₋₆ alkyl group such as benzoylaminoethyl group,
benzoylaminoethyl group, benzoylaminoethyl group,
10 benzoylaminoethyl group, benzoylaminoethyl group,
benzoylaminoethyl group and the like, with preference given to
acetylaminomethyl group or acetylaminomethyl group.

The "aralkyl group" is a group wherein the "C₁₋₆ alkyl
group" is substituted by the aforementioned "aryl group". As
15 used herein, the "aryl group" is preferably that having 6 to
14 carbon atoms, for example phenyl group, naphthyl group,
anthranyl group or biphenyl group and the like. Examples of
the "aralkyl group" include benzyl group, phenethyl group,
phenylbutyl group, phenylpropyl group, phenylpentyl group,
20 phenylhexyl group, naphthylmethyl group, anthranylmethyl group
or biphenylmethyl group and the like, with preference given to
benzyl group.

As the "salt" of the compound of the present invention,
there can be mentioned, but not limited to, inorganic acid
25 addition salts such as hydrochloride, hydrobromide, sulfate,
phosphate or nitrate and the like; organic acid addition salts
such as acetate, propionate, succinate, glycolate, lactate,
malate, oxalate, tartrate, citrate, maleate, fumarate,
methanesulfonate, benzenesulfonate, p-toluenesulfonate or
30 ascorbate and the like; amino acid addition salts such as
aspartate or glutamate and the like; inorganic base salts such
as sodium, potassium, calcium, magnesium or zinc and the like;
organic base salts such as methylamine, dimethylamine,

ethylamine, diethylamine, triethylamine, triethanolamine, trishydroxymethylaminomethane, dicyclohexylamine, ethylenediamine, guanidine, meglumine or 2-aminoethanol and the like; and base salts of amino acids such as asparagine, 5 glutamine, arginine, histidine or lysin and the like.

Preferable salts are hydrochloride, sodium salt, potassium salt and calcium salt, and hydrochloride or sodium salt are particularly preferable.

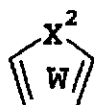
The compound of the present invention includes solvate. 10 As used herein, a "solvate" of a compound means a compound of the present invention being connected with a solvent molecule such as water, alcohol and the like by a comparatively weak bond such as Van der Waals force, static interaction, hydrogen bond, charge transfer bond, coordinate bond and the like. In 15 some cases, solvate may mean a compound incorporated into a solid state with water, alcohol and the like. Preferable solvate is hydrate.

A "prodrug" of a compound is a derivative of the compound of the present invention, which has a chemically or 20 metabolically decomposable group, which decomposes by hydrolysis or solvolysis, or under physiological conditions to show pharmaceutical activity. A substituent represented by R^A and a substituent represented by R^B in the formula (1) of the present invention are substituents directed to a prodrug, and 25 $-COR^A$ and/or $-OR^B$ are/is substituent(s) converted to $-CO_2H$ and/or $-OH$ in the living organism.

The "ring V" in the present invention is a ring represented by



30 in the formula (1), wherein X^1 is as defined above and "ring W" is a ring represented by



is the formula (1), wherein X_2 is as defined above.

The "IC₅₀ value of calcium receptor antagonistic action" is a value measured by the method described in Experimental Example 1 in the present specification.

The "metabolic enzyme P450" indicates cytochrome P450 existing in an animal, especially CYP2C9, CYP2D6 or CYP3A4 can be mentioned.

The "IC₅₀ value of inhibitory action of the metabolic enzyme CYP2D6" is a value measured by the method described in Experimental Example 4 in the present specification.

The "IC₅₀ value of its calcium receptor antagonistic action is not less than 10 times an IC₅₀ value of an inhibitory action of metabolic enzyme CYP2D6", the "IC₅₀ value of the calcium receptor antagonistic action is not less than 100 times the IC₅₀ value of the inhibitory action of the metabolic enzyme CYP2D6" refer to values calculated based on the comparison of the above-mentioned "IC₅₀ value of calcium receptor antagonistic action" and "IC₅₀ value of metabolic enzyme CYP2D6 inhibitory action".

The "IC₅₀ value of the compound of the calcium receptor antagonistic action is not more than 0.1 μM" means that the above-mentioned "IC₅₀ value of the calcium receptor antagonistic action" is 0.1 μM or below.

The "IC₅₀ value of a metabolic enzyme CYP2D6 inhibitory action is not less than 10 μM", and the "IC₅₀ value of the metabolic enzyme CYP2D6 inhibitory action is not less than 1 μM" refer to the above-mentioned "IC₅₀ value of the metabolic enzyme CYP2D6 inhibitory action" of not less than 10 μM and not less than 1 μM, respectively.

The compound represented by the formula (1) of the

present invention has various isomers, such as optical isomers, stereoisomers, geometric isomers, tautomers and the like. The present invention encompasses all these isomers and mixtures thereof.

5 In the compound represented by the formula (1) of the present invention,

R^1 is preferably a hydroxyl group or a C_{1-4} alkoxy group, more preferably a hydroxyl group, a methoxy group or an ethoxy group, particularly preferably a hydroxyl group,

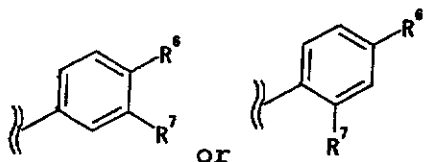
10 R^2 and R^3 are each preferably a hydrogen atom, a hydroxyl group, a halogen atom (particularly preferably chlorine atom, fluorine atom), an amino group, an C_{1-7} acylamino group (particularly preferably C_{1-4} alkylcarbonylamino group), a halo- C_{1-6} alkyl group (particularly preferably a trifluoromethyl group), a carboxyl group, a C_{1-6} alkoxy group (particularly preferably C_{1-4} alkoxy group), a halo- C_{1-6} alkoxy group, a hydroxy- C_{1-6} alkyl group (particularly preferably hydroxy- C_{1-4} alkyl group), a C_{1-7} acylamino- C_{1-6} alkyl group (particularly preferably C_{1-4} alkylcarbonylamino- C_{1-4} alkyl group), a C_{1-6} alkyl group (particularly preferably C_{1-4} alkyl group), a C_{2-4} alkenyl group, a C_{1-6} alkoxy-carbonyl group, a di(C_{1-6} alkyl) amino group (particularly preferably di(C_{1-4} alkyl) amino group) or a phenyl group, or R^2 and R^3 are joined to form an ethyleneoxy group, R^2 is preferably a hydroxyl group, a halogen atom, an amino group, an C_{1-7} acylamino group, a halo- C_{1-6} alkyl group, a C_{1-6} alkoxy-carbonyl group, a C_{1-6} alkoxy group, a halo- C_{1-6} alkoxy group, a C_{1-6} alkyl group, a hydroxy- C_{1-6} alkyl group, a di(C_{1-6} alkyl) amino group or nitro group, more preferably a C_{1-6} alkyl group, particularly preferably a C_{1-4} alkyl group,

25 R^3 is preferably a hydrogen atom,

X^1 is preferably $-C=C-$ or $-C=N-$, particularly preferably $-C=C-$, X^2 is preferably $-C=C-$,

30 Z is preferably $-S-$, $-SO-$, $-SO_2-$, $-(CH_2)_{m1}-O-$, $-O-(CH_2)_{m1}-$, $-$

- $(\text{CH}_2)_{m2}-\text{NH}-$, $-\text{NH}-(\text{CH}_2)_{m2}-$, $-(\text{CH}_2)_{m3}-\text{N}(\text{CH}_3)-$, $-\text{N}(\text{CH}_3)-(\text{CH}_2)_{m3}-$, C_{1-4}
 alkylene or C_{2-4} alkenylene,
 $m1$, $m2$ and $m3$ are each preferably 0 or 1,
 alkylene for Z is preferably methylene or ethylene,
 5 R^4 is preferably a C_{1-6} alkyl group or a cyclopropyl group,
 particularly preferably a C_{1-4} alkyl group such as methyl group
 and the like,
 R^5 is preferably a hydrogen atom,
 p is preferably 1,
 10 Y is preferably a carbon atom, and
 R^6 , R^7 and R^8 are each preferably a hydrogen atom, a halogen
 atom (particularly preferably chlorine atom or fluorine atom),
 a C_{1-4} alkyl group or a C_{1-4} alkoxy group, or adjacent R^6 and R^7
 are joined to form $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$.
 15 The case that R^6 and R^7 are selected from the group consisting
 of halogen atom and a C_{1-4} alkyl group, and that R^8 is a
 hydrogen atom is particularly preferable.
 The position of R^6 and R^7 is preferably



- 20 In the compound represented by the formula (1) of the
 present invention, when n is 1, for example, an embodiment
 wherein
 R^1 is a hydroxyl group or a C_{1-6} alkoxy group,
 R^2 and R^3 are the same or different and each is a hydrogen atom,
 25 a hydroxyl group, a halogen atom, an amino group, a C_{1-7}
 acylamino group, a trifluoromethyl group, a C_{1-6} alkoxy-carbonyl
 group, a C_{1-6} alkoxy group, a C_{1-6} alkyl group, a hydroxy- C_{1-6}
 alkyl group, a C_{2-6} alkenyl group, a phenyl group, a benzyl
 group, a di(C_{1-6} alkyl)amino group or a nitro group, or R^2 and
 30 R^3 are joined to form an ethyleneoxy group,

- X^1 is $-C=C-$ or $-C=N-$,
 X^2 is $-C=C-$,
 Z is $-S-$, $-SO-$, $-SO_2-$, $-(CH_2)_{m1}-O-$, $-O-(CH_2)_{m1}-$, $-(CH_2)_{m2}-NH-$, $-NH-(CH_2)_{m2}-$, $-(CH_2)_{m3}-N(CH_3)-$, $-N(CH_3)-(CH_2)_{m3}-$, a C_{1-4} alkylene group or a C_{2-4} alkenylene group,
 wherein $m1$, $m2$ and $m3$ are each an integer of 0 to 2,
 R^4 is a C_{1-6} alkyl group or a C_{3-6} cycloalkyl group,
 R^5 is a hydrogen atom,
 p is 1,
 10 Y is a carbon atom or a nitrogen atom, and
 R^6 , R^7 and R^8 are the same or different and each is a hydrogen atom, a halogen atom, a C_{1-6} alkyl group or a C_{1-6} alkoxy group, or adjacent R^6 and R^7 are joined to form $-CH=CH-CH=CH-$ is preferable. Of such compounds, a compound wherein
 15 R^1 is a hydroxyl group or a C_{1-4} alkoxy group, particularly a hydroxyl group, a methoxy group or an ethoxy group,
 R^2 and R^3 are the same or different and each is a hydrogen atom, a hydroxyl group, a halogen atom (particularly chlorine atom or fluorine atom), an amino group, a C_{1-7} acylamino group
 20 (particularly C_{1-4} alkylcarbonylamino group), a trifluoromethyl group, a C_{1-4} alkoxy group (particularly methoxy group), a hydroxy- C_{1-4} alkyl group, a C_{1-4} alkyl group, a C_{2-4} alkenyl group, a C_{1-4} alkoxy-carbonyl group or a phenyl group, or R^2 and R^3 are joined to form an ethyleneoxy group,
 25 X^1 and X^2 are $-C=C-$,
 Z is $-S-$, $-SO-$, $-SO_2-$, $-(CH_2)_{m1}-O-$, $-O-(CH_2)_{m1}-$, $-(CH_2)_{m2}-NH-$, $-NH-(CH_2)_{m2}-$, $-(CH_2)_{m3}-N(CH_3)-$, $-N(CH_3)-(CH_2)_{m3}-$, a C_{1-4} alkylene group (particularly methylene or ethylene) or a C_{2-4} alkenylene group,
 30 wherein $m1$, $m2$ and $m3$ are each 0 or 1,
 R^4 is a C_{1-6} alkyl group or a cyclopropyl group, particularly a C_{1-4} alkyl group (methyl group etc.),
 R^5 is a hydrogen atom,

p is 1,

Y is a carbon atom, and

R⁶, R⁷ and R⁸ are the same or different and each is a hydrogen atom, a halogen atom (preferably chlorine atom or fluorine atom), a C₁₋₄ alkyl group or a C₁₋₄ alkoxy group, or adjacent R⁶ and R⁷ are joined to form -CH=CH-CH=CH- is preferable.

In the compound represented by the formula (1) of the present invention, when n is 1, for example, an embodiment wherein

10 R¹ is a hydroxyl group or a C₁₋₆ alkoxy group (preferably methoxy group),

R² and R³ are the same or different and each is a hydrogen atom, a halogen atom (preferably fluorine atom or chlorine atom), a C₁₋₆ alkoxy group (preferably methoxy group) or a C₁₋₆ alkyl group (preferably methyl group, ethyl group, n-propyl group or isopropyl group),

X¹ is -C=C-,

X² is -C=C-,

Z is -S-, -SO-, -SO₂-, -(CH₂)_{m1}-O-, -O-(CH₂)_{m1}-, -CH₂-NH-, -NH-CH₂-, -N(CH₃)-, methylene or vinylene,

wherein m1 is 0 or 1,

R⁴ is a methyl group or a cyclopropyl group,

R⁵ is a hydrogen atom,

p is 1,

25 Y is a carbon atom or a nitrogen atom, and

R⁶, R⁷ and R⁸ are the same or different and each is a hydrogen atom, a halogen atom (preferably fluorine atom or chlorine atom) or a C₁₋₆ alkyl group (preferably methyl group), or adjacent R⁶ and R⁷ are joined to form -CH=CH-CH=CH- is more preferable. Of the above, an embodiment wherein

R¹ is a hydroxyl group or a C₁₋₄ alkoxy group, particularly a hydrogen atom, a methoxy group or an ethoxy group,

R² and R³ are the same or different and each is a hydrogen atom

or a C₁₋₄ alkyl group (particularly methyl group),
 X¹ is -C=C-,
 X² is -C=C-,
 Z is -S-, -SO-, -SO₂-, -(CH₂)_{m1}-O-, -O-(CH₂)_{m1}-, -CH₂-NH-, -NH-
 5 CH₂-, -N(CH₃)-, methylene or vinylene,
 wherein m1 is 0 or 1,
 R⁴ is a methyl group or a cyclopropyl group,
 R⁵ is a hydrogen atom,
 p is 1,
 10 Y is a carbon atom, and
 R⁶, R⁷ and R⁸ are the same or different and each is a hydrogen
 atom, a halogen atom (particularly chlorine atom or fluorine
 atom) or a C₁₋₄ alkyl group (particularly methyl group), or
 adjacent R⁶ and R⁷ are joined to form -CH=CH-CH=CH- is
 15 preferable.

In the compound represented by the formula (1) of the
 present invention, when n is 0, for example, an embodiment
 wherein

R¹ is a hydroxyl group or a C₁₋₆ alkoxy group,
 20 R² and R³ are the same or different and each is a hydrogen atom,
 a hydroxyl group, a halogen atom, an amino group, a C₁₋₇
 acylamino group, a trifluoromethyl group, a C₁₋₆ alkoxy-carbonyl
 group, a C₁₋₆ alkoxy group, a C₁₋₆ alkyl group, hydroxy-C₁₋₆ alkyl
 group, a C₂₋₆ alkenyl group, a phenyl group, a benzyl group,
 25 di(C₁₋₆ alkyl)amino group or a nitro group, or R² and R³ are
 joined to form an ethyleneoxy group,
 X¹ is -C=C- or -C=N-,
 X² is -C=C-,
 R⁴ is a C₁₋₆ alkyl group or a C₃₋₆cycloalkyl group,
 30 R⁵ is a hydrogen atom,
 p is 1,
 Y is a carbon atom or a nitrogen atom, and
 R⁶, R⁷ and R⁸ are the same or different and each is a hydrogen

atom, a halogen atom, a C₁₋₆ alkyl group or a C₁₋₆ alkoxy group, or adjacent R⁶ and R⁷ are joined to form -CH=CH-CH=CH- is preferable, and particularly, an embodiment wherein R¹ is a hydroxyl group or a C₁₋₄ alkoxy group, particularly a hydroxyl group, a methoxy group or an ethoxy group, R² and R³ are the same or different and each is a hydrogen atom, a hydroxyl group, a halogen atom (particularly chlorine atom or fluorine atom), an amino group, a C₁₋₇ acylamino group (particularly C₁₋₄ alkylcarbonylamino group), a trifluoromethyl group, a C₁₋₄ alkoxy group (particularly methoxy group), a hydroxy-C₁₋₄ alkyl group, a C₁₋₄ alkyl group, a phenyl group, a di(C₁₋₆ alkyl)amino group, a C₂₋₄ alkenyl group or a C₁₋₄ alkoxy-carbonyl group, or R² and R³ are joined to form an ethyleneoxy group,

15 X¹ is -C=C- or -C=N-,
 X² is -C=C-,
 R⁴ is a C₁₋₆ alkyl group or a cyclopropyl group, particularly a C₁₋₄ alkyl group (methyl group etc.),
 R⁵ is a hydrogen atom,

20 p is 1,
 Y is a carbon atom,
 R⁶, R⁷ and R⁸ are the same or different and each is a hydrogen atom, a halogen atom (particularly chlorine atom or fluorine atom), a C₁₋₄ alkyl group or a C₁₋₄ alkoxy group, or adjacent R⁶ and R⁷ are joined to form -CH=CH-CH=CH- is preferable.

In the compound represented by the formula (1) of the present invention, when n is 0, for example, an embodiment wherein

R¹ is a hydroxyl group or a C₁₋₆ alkoxy group (preferably methoxy group),
 30 R² and R³ are the same or different and each is a hydrogen atom, a hydroxyl group, a halogen atom (preferably fluorine atom or chlorine atom), an amino group, a C₁₋₇ acylamino group

(preferably acetyl amino group), a trifluoromethyl group, a C₁₋₆ alkoxy-carbonyl group (preferably methoxycarbonyl group), a C₁₋₆ alkoxy group (preferably methoxy group), a C₁₋₆ alkyl group (preferably methyl group, ethyl group, propyl group, isopropyl group, isobutyl group), a hydroxy-C₁₋₆ alkyl group (preferably hydroxymethyl group), a C₂₋₆ alkenyl group (preferably 2-methyl-1-propenyl group), a phenyl group, a benzyl group, a di(C₁₋₆ alkyl)amino group (preferably dimethylamino group) or a nitro group, or R² and R³ are joined to form an ethyleneoxy group,

10 X¹ is -C=C- or -C=N-,
 X² is -C=C-,
 R⁴ is a methyl group or a cyclopropyl group,
 R⁵ is a hydrogen atom,
 p is 1,

15 Y is a carbon atom, and
 R⁶, R⁷ and R⁸ are the same or different and each is a hydrogen atom, a halogen atom (preferably fluorine atom or chlorine atom), a C₁₋₆ alkyl group (preferably methyl group or ethyl group) or a C₁₋₆ alkoxy group (preferably methoxy group), or

20 adjacent R⁶ and R⁷ are joined to form -CH=CH-CH=CH- is more preferable, and particularly, an embodiment wherein
 R¹ is a hydroxyl group or a C₁₋₄ alkoxy group (particularly methoxy group or ethoxy group),
 R² and R³ are the same or different and each is a hydrogen atom,

25 a hydroxyl group, a halogen atom (particularly chlorine atom or fluorine atom), an amino group, a C₁₋₇ acylamino group (particularly C₁₋₄ alkylcarbonylamino group (e.g., acetyl amino group)), a trifluoromethyl group, a C₁₋₄ alkoxy group (particularly methoxy group), a hydroxy-C₁₋₄ alkyl group

30 (particularly hydroxymethyl group), a C₁₋₄ alkyl group (particularly methyl group, ethyl group, isopropyl group, propyl group or isobutyl group), a C₂₋₄ alkenyl group (particularly 2-methyl-1-propenyl group), a C₁₋₄ alkoxy-carbonyl

group (particularly acetylcarbonyl group), a benzyl group or a phenyl group, or R^2 and R^3 are joined to form an ethyleneoxy group,

X^1 is $-C=C-$ or $-C=N-$,

5 X^2 is $-C=C-$,

R^4 is a methyl group or a cyclopropyl group,

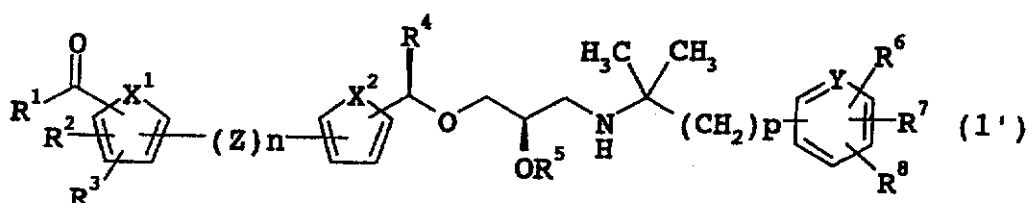
R^5 is a hydrogen atom,

p is 1,

Y is a carbon atom,

10 R^6 , R^7 and R^8 are the same or different and each is a hydrogen atom, a halogen atom (particularly chlorine atom or fluorine atom), a C_{1-4} alkyl group (particularly methyl group) or a C_{1-4} alkoxy group (particularly methoxy group), or adjacent R^6 and R^7 are joined to form $-CH=CH-CH=CH-$ is preferable.

15 The compound represented by the formula (1) of the present invention preferably has a configuration represented by the following formula (1')



wherein each symbol is as defined above for the formula (1).

20 Preferable examples when $n=0$ are shown in the following, wherein the number placed before each compound name corresponds to Example number.

1-1

2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid

1-2

2'-[1-[(2R)-3-[[1-(4-chloro-3-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-

- carboxylic acid
1-3
2'-[1-[(2R)-3-[[1-(3-chloro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid
- 5 1-4
2'-[1-[(2R)-3-[[1-(4-chloro-3-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid
- 10 1-5
2'-[1-[(2R)-3-[[1-(2,3-difluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid
- 1-6
15 2'-[1-[(2R)-3-[[1-(4-chloro-2-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid
- 1-7
2'-[1-[(2R)-3-[[1-(2-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid
- 20 1-8
2'-[1-[(2R)-3-[[1-(4-ethyl-3-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid
- 25 1-9
3-methyl-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-5-carboxylic acid
- 1-10
30 methyl 2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-3,5-dicarboxylate
- 1-11
2'-[(cyclopropyl)[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-

- 2-yl]amino]-2-hydroxypropoxy)methyl]-3-methylbiphenyl-4-carboxylic acid
1-12, 1-13
- 2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid
5 1-14
- 2'-[(cyclopropyl)[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy)methyl]-3-methylbiphenyl-4-carboxylic acid
10 1-15, 1-16
- 2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid
15 1-17
- 2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-5-carboxylic acid
1-18
- 2'-[(cyclopropyl)[(2R)-3-[[1-(4-chloro-2-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy)methyl]-3-methylbiphenyl-4-carboxylic acid
20 1-19
- 2'-[(cyclopropyl)[(2R)-3-[[1-(4-chloro-3-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy)methyl]-3-methylbiphenyl-4-carboxylic acid
25 1-20
- 2'-[1-[(2R)-3-[[1-(3-fluoro-4-methoxyphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid
30 1-21
- 3-methyl-2'-[1-[(2R)-3-[[1-(3,4-dimethylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-

carboxylic acid

1-22

2'-[1-[(2R)-3-[[1-(4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid

5 1-23

2'-[1-[(2R)-3-[[1-(4-chloro-3-methoxyphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid

1-24

10 2'-[1-[(2R)-3-[[1-(4-ethylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid

1-25

2'-[1-[(2R)-3-[[1-(4-chloro-2,5-difluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-

15 methylbiphenyl-4-carboxylic acid

1-26

2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methoxybiphenyl-4-carboxylic acid

20 1-27

2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-2-methoxybiphenyl-4-carboxylic acid

1-28

25 2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-(trifluoromethyl)biphenyl-4-carboxylic acid

1-29

2'-[1-[(2R)-3-[[1-(2-fluoro-4-methoxyphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-(trifluoromethyl)biphenyl-4-carboxylic acid

30 1-30

3-ethyl-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-

- yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-carboxylic acid
1-31
- 2'-[1-[(2R)-3-[[1-(3,4-dichlorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-(trifluoromethyl)biphenyl-4-carboxylic acid
5 1-32
- 2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-isopropylbiphenyl-4-carboxylic acid
10 1-33
- 3-ethyl-2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-carboxylic acid
1-34
- 2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-isopropylbiphenyl-4-carboxylic acid
15 1-35
- 2-chloro-6-[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenyl]pyridine-3-carboxylic acid
20 1-36
- 2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-propylbiphenyl-4-carboxylic acid
25 1-37
- 2,3-dimethyl-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-carboxylic acid
30 1-38
- 2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-propylbiphenyl-4-carboxylic acid

1-39

2-chloro-6-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenyl]pyridine-3-carboxylic acid

5 1-40

3,5-dimethyl-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-carboxylic acid

1-41

10 2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-m-terphenyl-4'-carboxylic acid

1-42

2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-2,3-dimethylbiphenyl-4-carboxylic acid

1-43

2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3,5-dimethylbiphenyl-4-carboxylic acid

20 1-44

4-(hydroxymethyl)-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-3-carboxylic acid

1-45

25 3-isobutyl-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-carboxylic acid

1-46

2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-isobutylbiphenyl-4-carboxylic acid

1-47

2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-4-(hydroxymethyl)biphenyl-3-

- carboxylic acid
1-48
2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-(2-methyl-1-propenyl)biphenyl-4-carboxylic acid
5 1-49
2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-hydroxybiphenyl-4-carboxylic acid
10 1-50
2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-hydroxybiphenyl-4-carboxylic acid
1-51
15 3-ethyl-2'-[1-[(2R)-3-[[1-(4-chloro-3-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-carboxylic acid
1-52
2'-[1-[(2R)-3-[[1-(4-chloro-3-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-isopropylbiphenyl-4-carboxylic acid
20 1-53
2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-(1-methylpropyl)biphenyl-4-carboxylic acid
25 1-54
2-methyl-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-carboxylic acid
1-55
30 3-methyl-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-carboxylic acid
1-56
4-fluoro-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-

- yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-3-carboxylic acid
1-57
- 2'-[1-[(2R)-3-[[1-(3,4-dichlorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-2-methylbiphenyl-4-
5 carboxylic acid
1-58
- 6-fluoro-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-3-carboxylic acid
1-59
- 10 3-fluoro-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-carboxylic acid
1-60
- 2'-[1-[(2R)-3-[[1-(3-chlorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid
15 1-61
- 2'-[1-[(2R)-3-[[1-(3,4-dichlorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-
carboxylic acid
1-62
- 20 2-fluoro-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-carboxylic acid
1-63
- 2'-[(cyclopropyl)[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]methyl]-3-methylbiphenyl-4-
25 carboxylic acid
1-64
- 2'-[(cyclopropyl)[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]methyl]-3-fluorobiphenyl-4-
carboxylic acid
30 1-65
- 2'-[(cyclopropyl)[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]methyl]-2-fluorobiphenyl-4-
carboxylic acid

1-66

2'-[(cyclopropyl)[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy)methyl]-2-methylbiphenyl-4-carboxylic acid

5 1-67

2'-[1-[(2R)-3-[[1-(3,4-dichlorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-2-fluorobiphenyl-4-carboxylic acid

1-68

10 3-chloro-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-carboxylic acid

1-69

2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-nitrobiphenyl-4-carboxylic
15 acid

1-70

3-amino-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-carboxylic acid

1-71

20 3-(acetylamino)-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-carboxylic acid

1-72

3-chloro-2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-carboxylic acid

1-73

2'-[1-[(2R)-3-[[1-(3-methoxy-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid

30 1-74

2,3-dihydro-5-[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-

- hydroxypropoxy]ethyl]phenyl]benzofuran-7-carboxylic acid
1-75
- 2,6-dimethyl-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-
5 carboxylic acid
1-76
- 2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-2,6-dimethylbiphenyl-4-carboxylic acid
10 1-77
- 3-(dimethylamino)-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-carboxylic acid
1-78
- 15 2,3-dihydro-5-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenyl]benzofuran-7-carboxylic acid
1-79
- 3-benzyl-2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-4-carboxylic acid
20 1-80
- 2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methoxybiphenyl-4-
25 carboxylic acid
1-81
- 2'-[1-[(2R)-3-[[1-(4-chloro-2-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methoxybiphenyl-4-carboxylic acid
30 1-82
- 2'-[1-[(2R)-3-[[1-(4-chloro-3-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methoxybiphenyl-4-carboxylic acid

1-83

2'-[1-[(2R)-3-[[1-(4-chloro-3-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-2-methylbiphenyl-4-carboxylic acid

5 1-84

2'-[1-[(2R)-3-[[1-(4-chloro-2-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-2-methylbiphenyl-4-carboxylic acid

1-85

10 4-methyl-2'-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]biphenyl-3-carboxylic acid

1-86

2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-4-methylbiphenyl-3-

15 carboxylic acid

1-87

2'-[1-[(2R)-3-[[1-(3,5-dichlorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid

20 1-89

2'-[1-[(2R)-3-[[1-(2,5-difluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid

1-90

25 2'-[1-[(2R)-3-[[1-(5-chloro-2-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid

1-91

2'-[1-[(2R)-3-[[1-(3-chloro-2-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid

30

1-92

2'-[1-[(2R)-3-[[1-(3-fluoro-4-trifluoromethylphenyl)-2-

methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-
methylbiphenyl-4-carboxylic acid

1-93

2'-[1-[(2R)-3-[[1-(5-chloro-3-fluorophenyl)-2-methylpropan-2-
5 yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-
carboxylic acid

1-94

2'-[1-[(2R)-3-[[1-(3,5-ditrifluoromethylphenyl)-2-
methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-
10 methylbiphenyl-4-carboxylic acid

1-95

2'-[1-[(2R)-3-[[1-(4-methyl-3,5-dimethoxyphenyl)-2-
methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-
methylbiphenyl-4-carboxylic acid

15 1-96

2'-[1-[(2R)-3-[[1-(3,5-dimethoxyphenyl)-2-methylpropan-2-
yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-
carboxylic acid

1-97

20 2'-[1-[(2R)-3-[[1-(4-chloro-3-trifluoromethylphenyl)-2-
methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-
methylbiphenyl-4-carboxylic acid

1-98

2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-
25 yl]amino]-2-hydroxypropoxy]ethyl]-3-t-butylbiphenyl-4-
carboxylic acid

1-99

2'-[1-[(2R)-3-[[1-(4-chloro-2-fluorophenyl)-2-methylpropan-2-
yl]amino]-2-hydroxypropoxy]ethyl]-3-t-butylbiphenyl-4-
30 carboxylic acid

1-100

2'-[1-[(2R)-3-[[1-(4-chloro-3-fluorophenyl)-2-methylpropan-2-
yl]amino]-2-hydroxypropoxy]ethyl]-3-t-butylbiphenyl-4-

carboxylic acid

1-101

2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methoxybiphenyl-4-

5 carboxylic acid

1-102

2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-morpholinobiphenyl-4-

carboxylic acid

10 1-103

2'-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-

(trifluoromethoxy)biphenyl-4-carboxylic acid

1-104

15 2'-[1-[(2R)-3-[[1-(3-trifluoromethyl-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-

methylbiphenyl-4-carboxylic acid

1-106

2'-[1-[(2R)-3-[[1-(4-chloro-3-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-(hydroxymethyl)biphenyl-4-

20 carboxylic acid

1-107

2'-[1-[(2R)-3-[[1-(4-chloro-3-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-carboxylbiphenyl-4-

25 carboxylic acid

Preferable examples when n=1 are shown in the following.

2-1

4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]benzoic acid

30 2-2

4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]-3-methoxybenzoic acid

- 2-3
methyl 4-[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]benzoate
- 2-4
5 4-[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]benzoic acid
- 2-5
4-[2-[1-[(2R)-3-[[1-(quinolin-3-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]benzoic acid
- 10 2-6
4-[2-[1-[(2R)-3-[[1-(4-chloro-2-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]benzoic acid
- 2-7
4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]benzoic acid
- 15 2-8
3-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]benzoic acid
- 2-9
20 4-[2-[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenyl]vinyl]benzoic acid
- 2-10
3-[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenylthio]benzoic acid
- 25 2-11
4-[2-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenyl]vinyl]benzoic acid
- 2-12
30 4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]-3,5-dimethylbenzoic acid
- 2-13

- 4-[2-[1-[(2R)-3-[[1-(4-chloro-2-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]-3,5-dimethylbenzoic acid
2-14
- 5 4-[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]benzyl]benzoic acid
2-15
- 3-[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]benzyl]benzoic acid
10 2-16
- 4-[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenylthio]benzoic acid
2-17
- 4-[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenylsulfinyl]benzoic acid
15 2-18
- 4-[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenylsulfonyl]benzoic acid
2-19
- 20 4-[[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenylamino]methyl]benzoic acid
2-20
- 2-[[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]methyl]benzoic acid
25 2-21
- 3-[[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]methyl]benzoic acid
2-22
- 30 4-[[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]methyl]benzoic acid
2-23
- 3-[[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-

- 2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]methyl]benzoic acid
2-24
- 4-[[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-
2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]methyl]benzoic acid
5 2-25
- 3-fluoro-4-[[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-
methylpropan-2-yl]amino]-2-
hydroxypropoxy]ethyl]phenoxy]methyl]benzoic acid
2-26
- 10 4-[[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-
2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]methyl]-3-
methylbenzoic acid
2-27
- 4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-
15 2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]-3,5-
dimethoxybenzoic acid
2-28
- 4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-
2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]-3-nitrobenzoic
20 acid
2-29
- 4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-
2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]-2-nitrobenzoic
acid
25 2-30
- 4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-
2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]-3-chlorobenzoic
acid
2-31
- 30 4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-
2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]-2-chlorobenzoic
acid
2-32

- 4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]-2-trifluoromethylbenzoic acid
2-33
- 5 4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]-3-trifluoromethylbenzoic acid
2-34
- 10 4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]-3-fluorobenzoic acid
2-35
- 15 4-[2-[1-[(2R)-3-[[1-(4-chloro-3-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]benzoic acid
2-36
- 4-[2-[1-[(2R)-3-[[1-(4-chloro-3-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]-5-methylbenzoic acid

The form of the compound of the present invention to be
20 used as a pharmaceutical product is a compound itself (free form), a salt of the compound, a solvate of the compound or a prodrug of the compound. Preferable form is a free form, a salt of the compound or a solvate of the compound, particularly preferably a salt of the compound.

25 The compound of the present invention can be used in the form of a prodrug. In this case, for example, a compound represented by the formula (1), wherein R^1 is a hydroxyl group, is converted to a compound wherein R^1 is R^A , i.e., C_{1-6} alkyl- $OC(=O)O-C_{1-4}$ alkylene-O-, C_{3-6} cycloalkyl- $OC(=O)O-C_{1-4}$ alkylene-O-
30 or $OH-NH-$ and used as a prodrug, and/or a compound wherein R^5 is a hydrogen atom is converted to a compound wherein R^5 is R^B , i.e., a C_{1-7} acyl group optionally substituted by carboxyl group and used as a prodrug.

A therapeutic drug for osteoporosis, which contains the compound of the present invention as an active ingredient can be used along with a different therapeutic drug for osteoporosis. The different therapeutic drug for osteoporosis is, for example, a calcium agent (Calcium Lactate, Calcium Gluconate, Calcium L-Aspartate, Calcium Chloride, Calcium Hydrogen Phosphate etc.), a vitamin D preparation (Alfacalcidol, Calcitriol, Maxacalcitol, Falecalcitriol etc.), a vitamin K preparation (Menatetrenone etc.), a female hormone preparation (Estradiol, Estriol etc.), an estrogen antagonist preparation (Raloxifen etc.), an anabolic steroid preparation, a parathyroid hormone preparation (Teriparatide, PTH(1-84) etc.), a calcitonin preparation (Elcatonin, Calcitonin salmon etc.), a bisphosphonate preparation (Alendronate sodium hydrate, Sodium risedronate hydrate, Etidronate disodium, Pamidronate disodium, Incadronate didodium ect.), an ipriflavone preparation (Ipriflavone) and other therapeutic drug for osteoporosis such as Strontium Ranelate, a WNT inhibitor, a PPAR gamma agonist, Osteopontin, a statin preparation, a RANK/RANKL inhibitor, a Src inhibitor, a Pyk2 inhibitor, Osteoprotegerin and the like. A therapeutic drug for osteoporosis containing the compound of the present invention and a different therapeutic drug for osteoporosis can be administered in an effective amount for osteoporosis patients.

The calcium receptor antagonist preferably shows an IC_{50} value of its calcium receptor antagonistic action of not less than 10 times, more preferably not less than 100 times, that of the metabolic enzyme CYP2D6 inhibitory action.

In addition, the calcium receptor antagonist preferably shows an IC_{50} value of its calcium receptor antagonistic action of not more than 0.1 μM and an IC_{50} value of the metabolic enzyme P450, specially CYP2D6 inhibitory action of not less

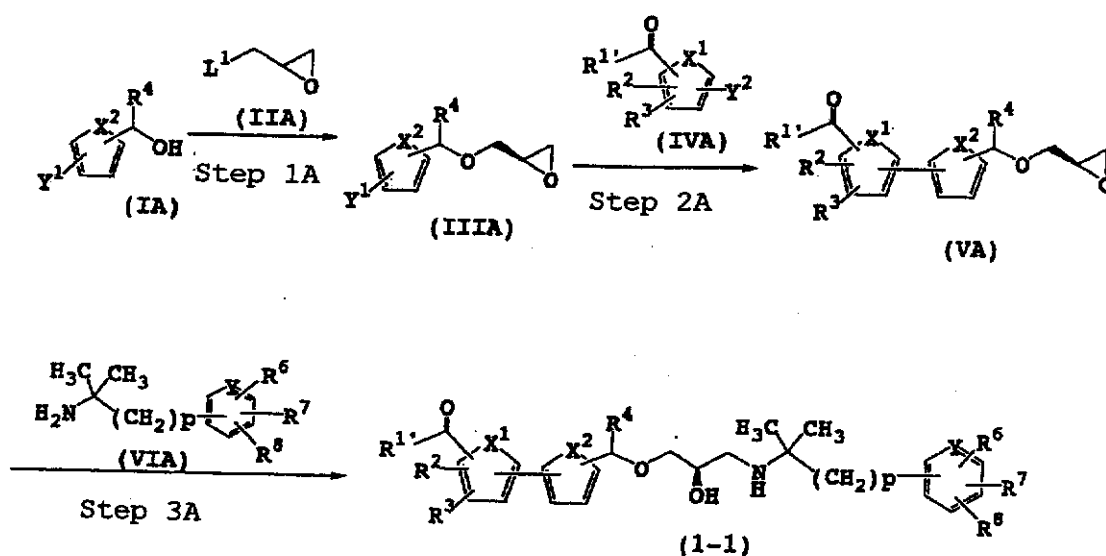
than 1 μM , more preferable an IC_{50} value of the calcium receptor antagonistic action of not more than 0.1 μM , and an IC_{50} value of metabolic enzyme P450, specially CYP2D6 inhibitory action of not less than 10 μM .

5 The production methods of the compound of the formula (1) of the present invention are concretely explained in the following. It is needless to say that the present invention is not limited to these production methods. For synthesis of the compound of the present invention, the synthesis may start
10 from a moiety easily synthesized. When a reactive functional group is contained in a step, appropriate protection and deprotection may be performed, and to facilitate the reaction, any reagent other than those exemplified may be appropriately used.

15 The compound obtained in each step may be isolated and purified by conventional methods. In some cases, the compound may be used in the next step without isolation and purification.

The production methods of compound (1) are explained in
20 the following separately for $n=0$ and $n=1$.

<Production method when $n=0$ >



wherein $\text{R}^{1'}$ is a C_{1-6} alkoxy group, Y^1 and Y^2 are the same or

different and each is a halogen atom (as defined above) or a trifluoromethanesulfonyloxy group, L^1 is a leaving group, such as a halogen atom (as defined above) or a sulfonyloxy group such as a 3-nitrobenzenesulfonyloxy group, a p-toluenesulfonyloxy group, a benzenesulfonyloxy group, a p-bromobenzenesulfonyloxy group, a methanesulfonyloxy group or a trifluoromethanesulfonyloxy group and the like, and other symbols are as defined above.

Step 1A

10 The compound (IA) is reacted with compound (IIA) in N,N-dimethylformamide, dimethyl sulfoxide, tetrahydrofuran, water and the like or a mixed solvent thereof, in the presence of a base such as sodium hydride, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium
15 hydrogencarbonate, potassium hydrogen carbonate, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, pyridine, 4-dimethylaminopyridine and the like at 0°C to room temperature, whereby compound (IIIA) is obtained. In this case, alkylammonium hydrogensulfate such as tetrabutylammonium
20 hydrogensulfate and the like can be added.

A stereoselective reaction can be carried out by selecting a reagent and a leaving group to be used.

For example, compound (IA) is reacted with (R)-glycidyl mesylate in N,N-dimethylformamide in the presence of sodium
25 hydride to give compound (IIIA).

Step 2A

In this step, compound (VA) is obtained from compound (IIIA) or (IVA) by Suzuki coupling.

The compound (IVA) is reacted with bispinacolatodiboron
30 in dimethyl sulfoxide, N,N-dimethylformamide, 1,4-dioxane and the like or a mixed solvent thereof using bis(diphenylphosphino)ferrocenepalladium(II) chloride and a base such as potassium acetate and the like to give a boronic

acid ester of compound (IVA), which is then reacted with compound (IIIA) in toluene, ethanol, benzene, acetone, 1,4-dioxane, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, 1,2-dimethoxyethane, dimethyl sulfoxide, water and the like or
5 a mixed solvent thereof, using a palladium catalyst such as bis(diphenylphosphino)ferrocenepalladium(II) chloride, tetrakis(triphenylphosphine)palladium(0) and the like and a base such as sodium carbonate, tripotassium phosphate (K_3PO_4), potassium carbonate, sodium hydrogencarbonate, potassium
10 hydrogen carbonate and the like, whereby compound (VA) is obtained.

Alternatively, compound (IIIA) obtained in Step 1A is reacted with a palladium catalyst such as bis(diphenylphosphino)ferrocenepalladium(II) chloride,
15 tetrakis(triphenylphosphine)palladium(0) and the like, potassium acetate and bispinacolatodiboron in dimethyl sulfoxide, N,N-dimethylformamide, 1,4-dioxane and the like or a mixed solvent thereof to give a boronic acid ester of compound (IIIA), which is then reacted with compound (IVA) in
20 toluene, ethanol, benzene, acetone, 1,4-dioxane, tetrahydrofuran, acetonitrile, 1,2-dimethoxyethane, dimethyl sulfoxide, water and the like or a mixed solvent thereof, using a palladium catalyst such as bis(diphenylphosphino)ferrocenepalladium(II) chloride,
25 tetrakis(triphenylphosphine)palladium(0) and the like, and a base such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogen carbonate, tripotassium phosphate and the like to give compound (VA).

Step 3A

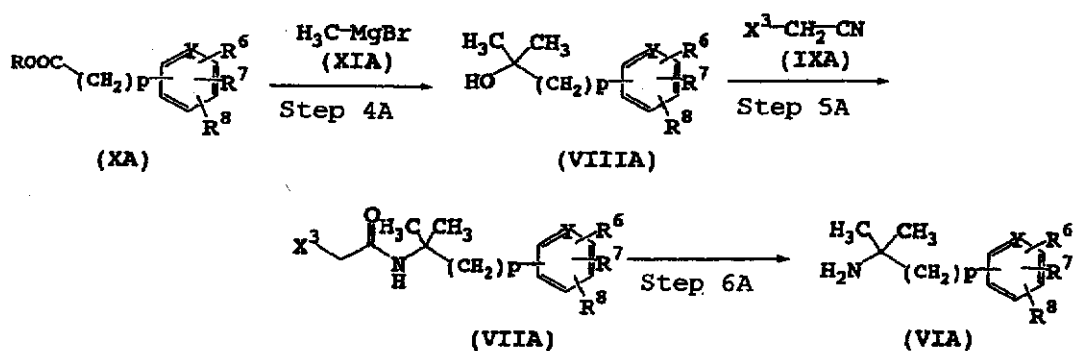
30 The compound (VA) obtained in Step 2A is reacted with compound (VIA) in methanol, ethanol, n-propanol, isopropanol, tetrahydrofuran, 1,4-dioxane, acetonitrile, toluene and the like or a mixed solvent thereof at room temperature-reflux

temperature to give compound (1-1). In this case, alkali perchlorate such as lithium perchlorate and the like is preferably added.

Hydrolysis of compound (1-1) by conventional methods results in conversion of R^{1'} (C₁₋₆ alkoxy group) to a hydroxyl group.

The compound (VIA) used in Step 3A can be prepared by various methods. In the following, preparation methods of compound (VIA) are explained.

10 Preparation method of compound (VIA) 1



wherein X³ is a hydrogen atom or a halogen atom (as defined above), R is an alkyl group (preferably a methyl group or an ethyl group), and other symbols are as defined above.

15 Step 4A

The compound (XA) is reacted with compound (XIA) in tetrahydrofuran or diethyl ether to give compound (VIIIA).

Step 5A

In this step, compound (VIIA) is obtained from compound (VIIIA) by Ritter reaction. The compound (VIIIA) obtained in Step 4A is reacted with compound (IXA) in acetic acid with addition of sulfuric acid to give compound (VIIA).

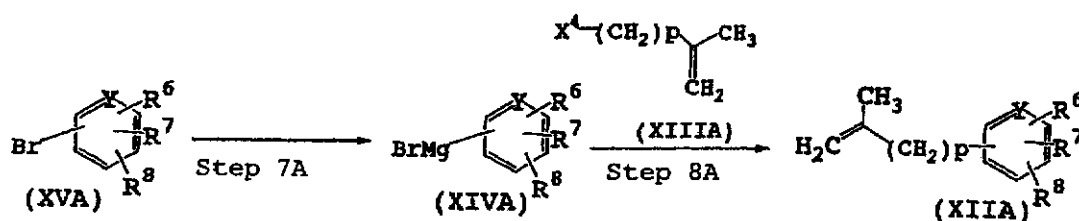
Step 6A

When X³ in compound (VIIA) obtained in Step 5A is a halogen atom, this step is performed under the conditions generally used for removing a haloacetyl group. For example,

reaction in water, methanol, ethanol, n-propanol, isopropanol, tetrahydrofuran, 1,4-dioxane, acetic acid and the like or a mixed solvent thereof, using thiourea under heating gives compound (VIA).

5 When X^3 in compound (VIIA) is a hydrogen atom, this step is performed under the conditions generally used for removing an acetyl group. For example, reaction in water, methanol, ethanol, n-propanol, isopropanol, tetrahydrofuran, 1,4-dioxane, diethylene glycol and the like using a base such as sodium
10 hydroxide, potassium hydroxide, lithium hydroxide and the like under heating affords compound (VIA).

Preparation method of compound (VIA) 2



wherein X^4 is a halogen atom (as defined above), and other
15 symbols are as defined above.

Step 7A

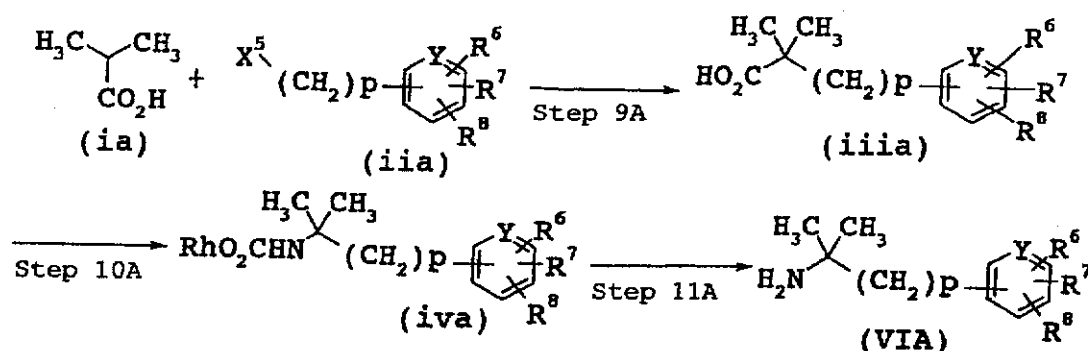
The compound (XVA) is reacted with magnesium in tetrahydrofuran or diethyl ether to give compound (XIVA).

Step 8A

20 The compound (XIVA) obtained in Step 7A is reacted with compound (XIIIA) in tetrahydrofuran or diethyl ether, using copper iodide as a catalyst as necessary to give compound (XIIA).

The compound (XIIA) obtained in Step 8A is subjected to a
25 similar reaction as in Step 5A to give compound (VIIA), which is then subjected to a similar reaction as in Step 6A to give compound (VIA).

Preparation method of compound (VIA) 3



wherein X^5 is a halogen atom (as defined above), $\text{RhO}_2\text{C}-$ is an amino-protecting group such as a benzyloxycarbonyl group, a tert-butoxycarbonyl group and the like, and other symbols are as defined above.

Step 9A

The compound (ia) is reacted with compound (iia) in a solvent such as tetrahydrofuran, n-hexane and the like in the presence of a base such as n-butyllithium and the like and hexamethylphosphoramide to give compound (iia).

Step 10A

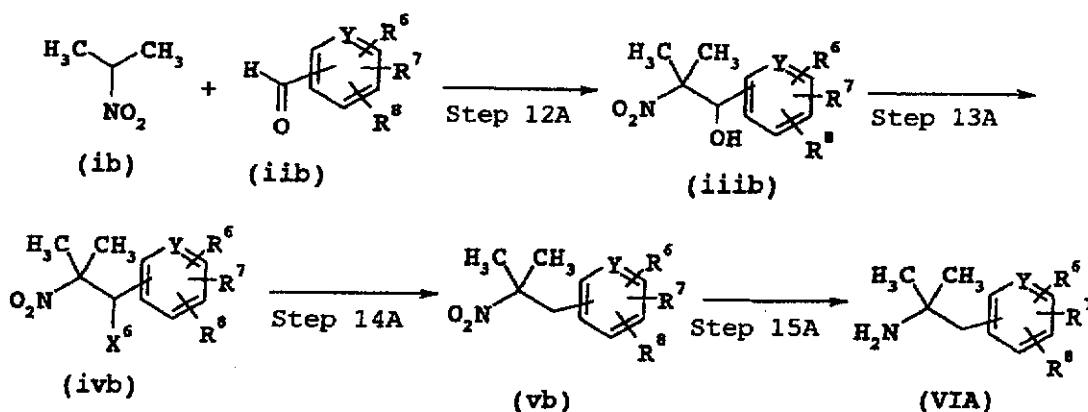
In this step, compound (iia) obtained in Step 9A is subjected to Curtius rearrangement to give compound (iva). The compound (iia) is reacted with halogenated alkyl carbonate such as chloroethyl carbonate and the like in water, acetone, methyl ethyl ketone and the like or a mixed solvent thereof, in the presence of a base such as triethylamine, N,N-diisopropylethylamine and the like. Then, sodium azide is reacted to give a compound. The obtained compound is rearranged under heating and then reacted with alcohol of the formula: Rh-OH wherein Rh is a benzyl group, a tert-butyl group and the like to give compound (iva).

Step 11A

In this step, $-\text{CO}_2\text{Rh}$ wherein $-\text{CO}_2\text{Rh}$ is as defined above of compound (iva) obtained in Step 10A is removed, which is performed by a method generally employed for deprotection of a

compound wherein an amino group is protected with $-\text{CO}_2\text{Rh}$. For example, when $-\text{CO}_2\text{Rh}$ is benzyloxycarbonyl group, compound (iva) is subjected to hydrogenation using a catalyst such as palladium carbon, palladium black, palladium hydroxide on carbon, Raney-nickel and the like in a solvent such as methanol, ethanol, n-propanol, isopropanol, tetrahydrofuran, 1,4-dioxane and the like to give compound (VIA). When, for example, $-\text{CO}_2\text{Rh}$ is tert-butoxycarbonyl group, a reaction using an acid such as hydrogen chloride, sulfuric acid, hydrogen bromide and the like in water, methanol, ethanol, n-propanol, isopropanol, tetrahydrofuran, 1,4-dioxane, acetic acid and the like or a mixed solvent thereof gives compound (VIA).

Preparation method of compound (VIA) 4 (p=1)



wherein X^6 is a halogen atom (as defined above), and other symbols are as defined above.

Step 12A

By reacting compound (iib) with compound (ib) in a solvent such as tetrahydrofuran, N,N-dimethylformamide, dimethyl sulfoxide and the like, in the presence of tetraalkylammonium halide such as tetrabutylammonium fluoride and the like and trialkylhalosilane such as tert-butyldimethylchlorosilane and the like, compound (iiib) can be obtained.

Step 13A

By subjecting compound (iii**b**) to be obtained in Step 12A to halogenation using a halogenating agent such as thionyl chloride, oxalyl chloride and the like, compound (iv**b**) can be obtained. In this reaction, the halogenating agent itself to
5 be used may be used as a solvent, or a solvent such as dichloromethane, chloroform, 1,2-dichloroethane, tetrahydrofuran, 1,4-dioxane and the like may be used.

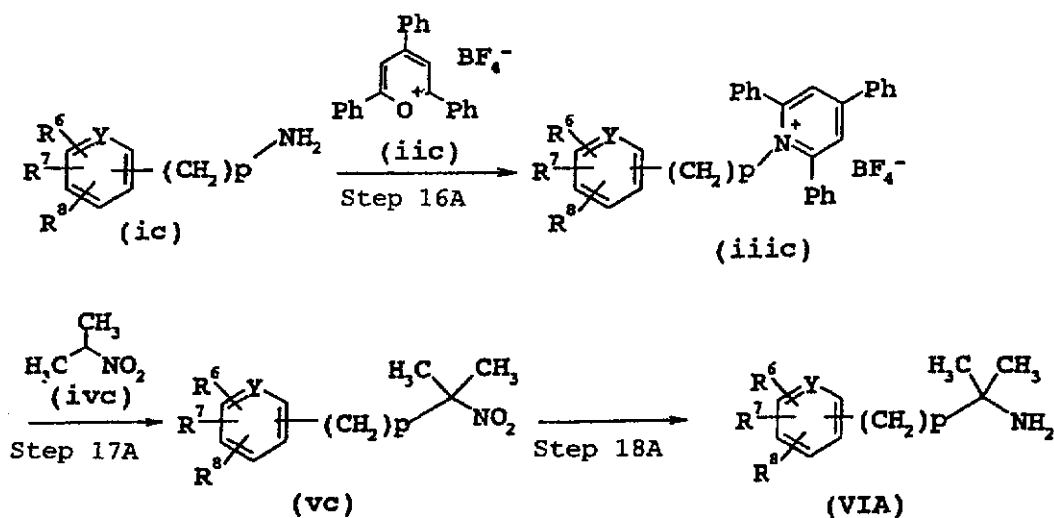
Step 14A

By subjecting compound (iv**b**) to be obtained in Step 13A
10 to hydrogenation in a solvent such as methanol, ethanol, n-propanol, isopropanol, tetrahydrofuran, 1,4-dioxane, ethyl acetate and the like in the presence of a catalyst such as palladium carbon, palladium black, palladium hydroxide on carbon and the like, compound (v**b**) can be obtained. In this
15 reaction, pressurization to some extent is preferable.

Step 15A

By subjecting compound (v**b**) to be obtained in Step 14A to hydrogenation using a catalyst such as Raney-nickel, platinum oxide, palladium-carbon and the like in a solvent
20 such as methanol, ethanol, n-propanol, isopropanol, tetrahydrofuran, 1,4-dioxane and the like, compound (VIA) can be obtained. In this reaction, pressurization to some extent is preferable. In addition, compound (VIA) can be also obtained by reduction with iron, tin chloride and the like in
25 the above-mentioned solvent.

Preparation method of compound (VIA) 5



wherein Ph is a phenyl group, and other symbols are as defined above.

Step 16A

- 5 The compound (ic) is reacted with compound (iic) in ethanol, isopropanol, tert-butanol, acetone, water, methylene chloride, diethyl ether, N,N-dimethylformamide and the like or a mixed solvent thereof at room temperature-reflux temperature to give compound (iiic).

10 Step 17A

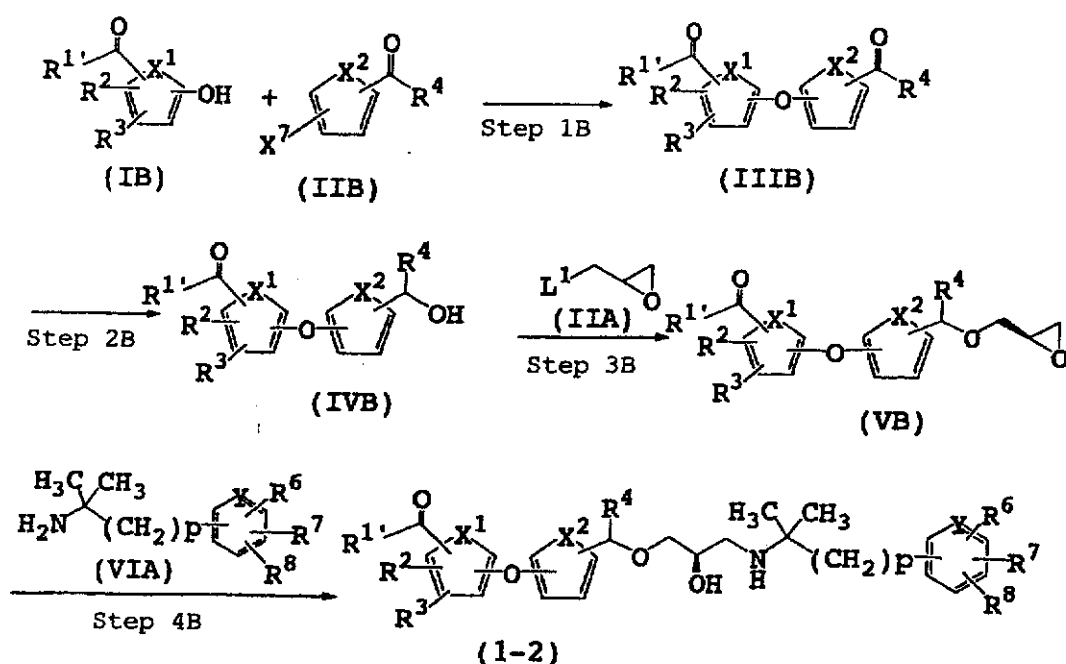
- The compound (ivc) is reacted with compound (iiic) obtained in Step 16A in dimethyl sulfoxide, N,N-dimethylformamide, tetrahydrofuran, diethyl ether and the like or a mixed solvent thereof, in the presence of sodium methoxide, sodium hydride and the like to give compound (vc).

Step 18A

The compound (vc) obtained in Step 17A is subjected to a similar reaction as in Step 15A to give compound (VIA).

<Production method when n is 1>

- 20 In the case Z is -O-



wherein X^7 is a halogen atom (as defined above), and other symbols are as defined above.

Step 1B

- 5 By reacting compound (IB) with compound (IIB) in N,N-dimethylacetamide, N,N-dimethylformamide, dimethyl sulfoxide and the like or a mixed solvent thereof, in the presence of a base such as potassium carbonate, sodium carbonate and the like, at room temperature-reflux temperature, compound (IIIB)
- 10 is obtained.

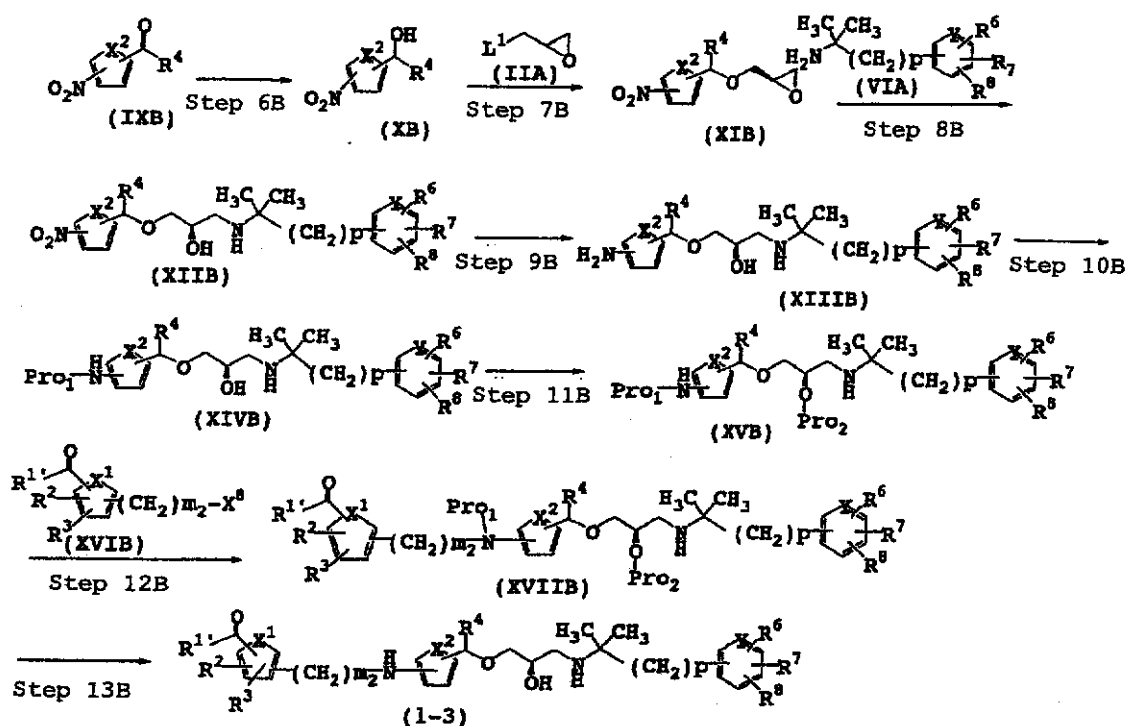
Step 2B

- By reduction of compound (IIIB) obtained in Step 1B with a reducing agent such as lithium aluminum hydride, sodium borohydride, lithium borohydride and the like in isopropanol,
- 15 tetrahydrofuran, toluene, methanol and the like or a mixed solvent thereof, at -10°C to room temperature, compound (IVB) can be obtained. In addition, by subjecting compound (IIIB) to reduction reaction using an asymmetric reducing agent such as B-chlorodiisopinocampheylborane, (S)-5,5-diphenyl-2-methyl-
- 20 3,4-propano-1,3,2-oxazaborolidine and the like, or to an

By reacting compound (VIB) with compound (VIIB) in acetonitrile, N,N-dimethylformamide, toluene and the like or a mixed solvent thereof, in the presence of a base such as triethylamine, potassium carbonate, sodium carbonate and the like and tri(o-tolyl)phosphine or triphenylphosphine, using a palladium catalyst such as diacetoxypalladium, dichloropalladium and the like at room temperature-reflux temperature, compound (VIIIB) can be obtained.

By subjecting compound (VIIIB) obtained in Step 5B to a step similar to Step 4B, compound (1-9) wherein Z is a C₂₋₄ alkenylene group can be obtained.

In the case Z is $-(CH_2)_{m2}-NH-$



wherein Pro₁ is an amino-protecting group (e.g., a trifluoroacetyl group, a tert-butoxycarbonyl group and the like), Pro₂ is a hydroxyl-protecting group (e.g., an acetyl group, a benzoyl group, a chloroacetyl group, a trichloroacetyl group and the like), X⁸ is a halogen atom (as defined above), and other symbols are as defined above.

Step 6B

By reacting compound (IXB) in methanol, ethanol, tetrahydrofuran, diethyl ether and the like or a mixed solvent thereof, using sodium borohydride, lithium borohydride and the like, compound (XB) can be obtained.

Step 7B

By subjecting compound (XB) obtained in Step 6B and compound (IIA) to a reaction similar to Step 1A, compound (XIB) can be obtained.

10 Step 8B

By subjecting compound (XIB) obtained in Step 7B and compound (VIA) to a reaction similar to Step 3A, compound (XIIB) can be obtained.

Step 9B

15 By reacting compound (XIIB) in tetrahydrofuran, ethanol, water, methanol and the like or a mixed solvent thereof, using iron and ammonium chloride, compound (XIIIB) can be obtained.

Step 10B

By protecting an amino group of compound (XIIIB) obtained in Step 9B by conventional methods, compound (XIVB) can be obtained. For example, when an amino group is protected with a trifluoroacetyl group, the compound is reacted with trifluoroacetic anhydride in chloroform, methylene chloride, tetrahydrofuran, toluene, ethyl acetate and the like or a mixed solvent thereof in the presence of a base such as pyridine, triethylamine and the like.

Step 11B

By protecting a hydroxyl group of compound (XIVB) obtained in Step 10B by conventional methods, compound (XVB) can be obtained. For example, when a hydroxyl group is protected with an acetyl group, the compound is reacted with acetic anhydride in chloroform, methylene chloride, tetrahydrofuran, toluene, ethyl acetate and the like or a

mixed solvent thereof in the presence of a base such as pyridine, triethylamine and the like.

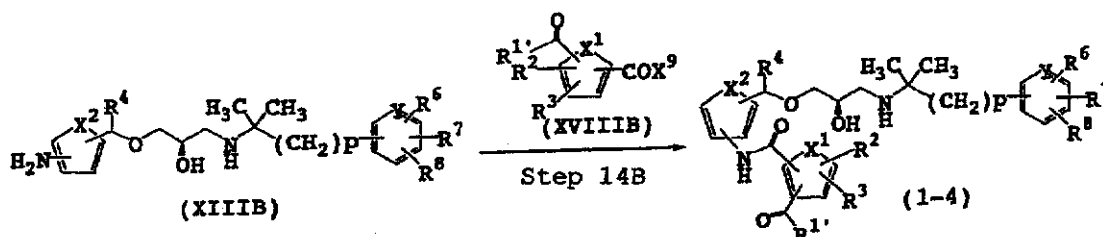
Step 12B

By reacting compound (XVB) obtained in Step 11B with compound (XVIB) in N,N-dimethylformamide, tetrahydrofuran, diethyl ether, dimethyl sulfoxide, acetone, acetonitrile or a mixed solvent thereof in the presence of a base such as sodium hydride, potassium carbonate, sodium carbonate and the like, compound (XVIIIB) can be obtained.

Step 13B

By deprotection of compound (XVIIIB) obtained in Step 12B by conventional methods, compound (1-3) can be obtained. For example, when an amino group is protected with a trifluoroacetyl group and a hydroxyl group is protected with an acetyl group, the compound is reacted in tetrahydrofuran-methanol in the presence of sodium hydroxide.

In the case Z is -CONH-



wherein X^9 is a halogen atom (as defined above), and other symbols are as defined above.

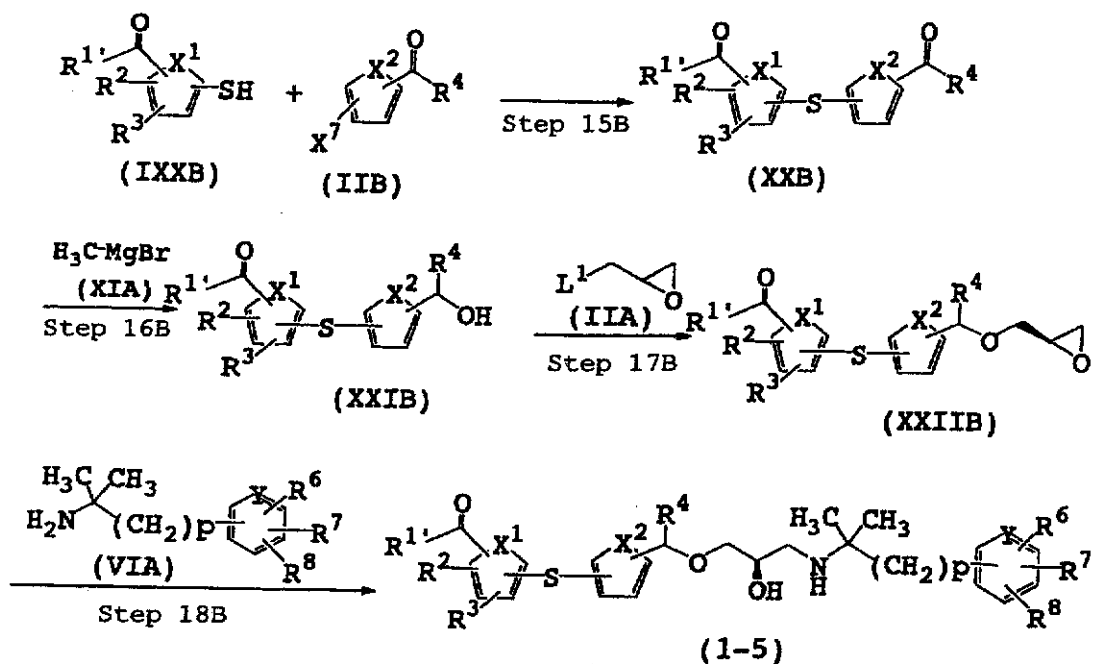
Step 14B

By reacting compound (XIIIB) obtained in Step 9B with compound (XVIIIIB) in chloroform, methylene chloride, tetrahydrofuran, toluene, ethyl acetate, or a mixed solvent thereof, in the presence of a base such as pyridine, triethylamine, N,N-diisopropylethylamine and the like, compound (1-4) can be obtained.

Hydrolysis of compound (1-4) by conventional methods affords conversion of $R^{1'}$ (C_{1-6} alkoxy group) to a hydroxyl

group. For example, compound (1-4) is hydrolyzed in a mixed solvent of methanol-tetrahydrofuran-water using sodium hydroxide.

In the case Z is -S-



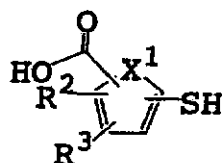
5

wherein each symbol is as defined above.

Step 15B

By subjecting compound (IXXB) and compound (IIB) to a reaction similar to Step 1B, compound (XXB) can be obtained.

10 When a compound of the formula



wherein each symbol is as defined above, is used as a starting material, a -CO₂H group is converted to a -COR^{1'} group in advance to give compound (IXXB). For example, the group can be converted using concentrated sulfuric acid in C₁₋₆ alcohol such as methanol, ethanol and the like.

Step 16B

By subjecting compound (XXB) obtained in Step 15B and compound (XIA) to a reaction similar to Step 4A, compound (XXIB) can be obtained.

Step 17B

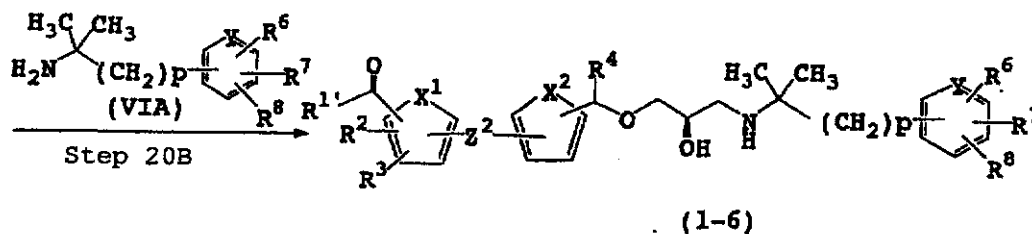
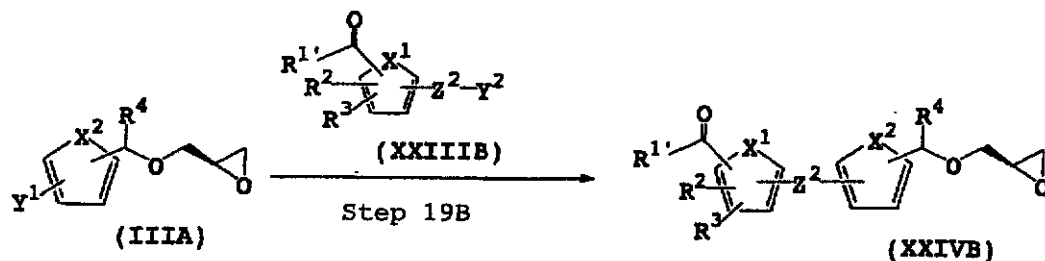
5 By subjecting compound (XXIB) obtained in Step 16B and compound (IIA) to a reaction similar to Step 1A, compound (XXIIB) can be obtained.

Step 18B

10 By subjecting compound (XXIIB) obtained in Step 17B and compound (VIA) to a reaction similar to Step 3A, compound (1-5) can be obtained.

Hydrolysis of compound (1-5) by conventional methods affords conversion of $R^{1'}$ (C_{1-6} alkoxy group) to a hydroxyl group. For example, hydrolysis is performed in tetrahydrofuran, 15 methanol and the like or a mixed solvent thereof in the presence of sodium hydroxide.

In the case Z is a C_{1-4} alkylene group



wherein Z^2 is a C_{1-4} alkylene group (as defined for C_{1-4} alkylene group for Z), and other symbols are as defined above.

Step 19B

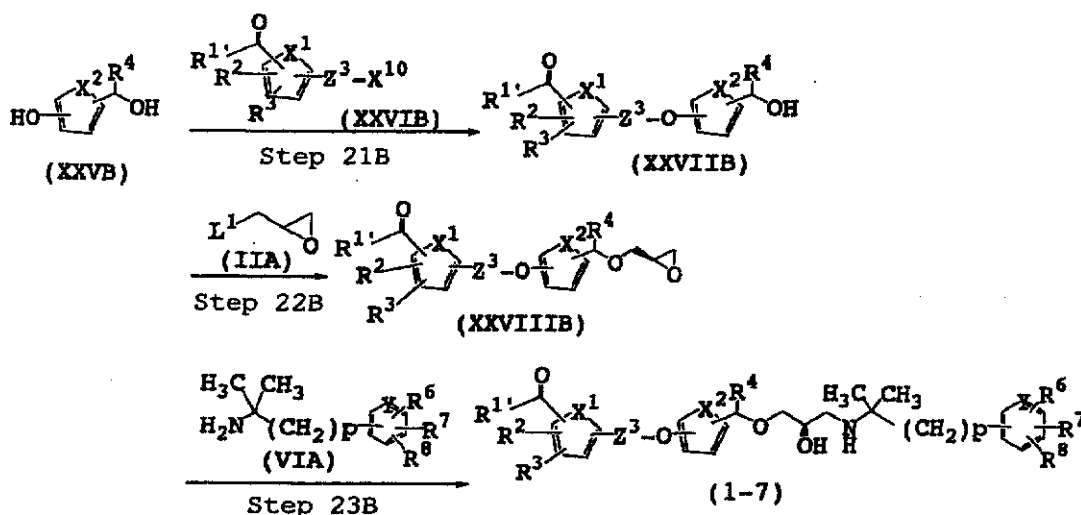
By subjecting compound (IIIA) and compound (XXIIIB) to a reaction similar to Step 2A, compound (XXIVB) can be obtained.

Step 20B

By subjecting compound (XXIVB) obtained in Step 19B and
5 compound (VIA) to a reaction similar to Step 3A, compound (1-6) can be obtained.

Hydrolysis of compound (1-6) by conventional methods affords conversion of $R^{1'}$ (C_{1-6} alkoxy group) to a hydroxyl group. For example, compound (1-6) is hydrolyzed in
10 tetrahydrofuran, methanol and the like or a mixed solvent thereof in the presence of sodium hydroxide.

In the case Z is $-(CH_2)_{m1}-O-$ (1)



wherein Z^3 is $-(CH_2)_{m1}-$ ($m1$ here is as defined for $m1$ for Z), X^{10}
15 is a halogen atom (as defined above), and other symbols are as defined above.

Step 21B

By reacting compound (XXVB) with compound (XXVIB) in N,N-dimethylformamide, tetrahydrofuran, diethyl ether, dimethyl
20 sulfoxide, acetone, acetonitrile and the like or a mixed solvent thereof, in the presence of a base such as sodium hydride, potassium carbonate, sodium carbonate and the like, compound (XXVIIIB) can be obtained.

Step 22B

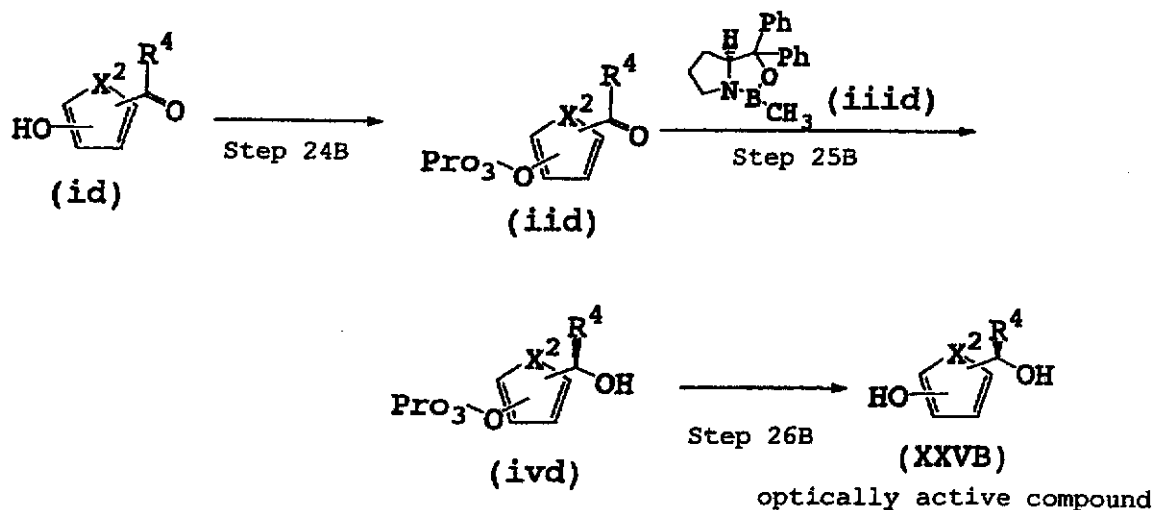
By subjecting compound (XXVIIIB) obtained in Step 21B and compound (IIA) to a reaction similar to Step 1A, compound (XXVIIIB) can be obtained.

5 Step 23B

By subjecting compound (XXVIIIB) obtained in Step 22B and compound (VIA) to a reaction similar to Step 3A, compound (1-7) can be obtained.

Hydrolysis of compound (1-7) by conventional methods
10 affords conversion of R^{1'} (C₁₋₆ alkoxy group) to a hydroxyl group. For example, compound (1-7) is hydrolyzed in tetrahydrofuran, methanol and the like or a mixed solvent thereof in the presence of sodium hydroxide.

It is also possible to use an optically active compound
15 (XXVB), and an optically active compound (XXVB) can be produced by a method as shown in the following.



wherein Pro₃ is as defined for Pro₂, and other symbols are as defined above.

20 Step 24B

By protection of a hydroxyl group of compound (id) by conventional methods, compound (iid) can be obtained. For example, when a hydroxyl group is protected with a benzyl

group, the compound is reacted with benzyl halide (e.g., benzyl bromide) in N,N-dimethylformamide in the presence of a base such as potassium carbonate, sodium hydride and the like.

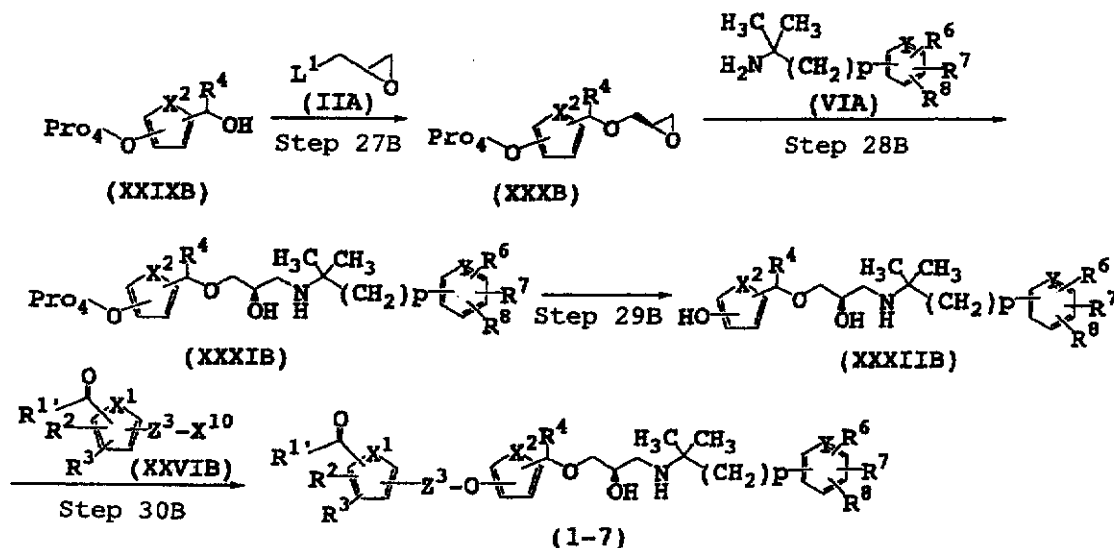
Step 25B

5 By reacting compound (iid) obtained in Step 24B with compound (iiid) in tetrahydrofuran, toluene, methylene chloride, hexane and the like or a mixed solvent thereof, in the presence of a boran dimethylsulfide complex salt, compound (ivd) can be obtained.

10 Step 26B

By deprotection of compound (ivd) obtained in Step 25B by conventional methods, an optically active compound (XXVB) can be obtained. For example, when a hydroxyl group is protected with a benzyl group, hydrogenation is performed in

15 tetrahydrofuran, methanol, ethanol, ethyl acetate and the like or a mixed solvent thereof in the presence of palladium carbon. In the case Z is $-(CH_2)_{m1}-O-$ (2)



wherein Pro_4 is as defined for Pro_2 and other symbols are as

20 defined above.

Step 27B

By subjecting compound (XXIXB) and compound (IIA) to a reaction similar to Step 1A, compound (XXXB) can be obtained.

Step 28B

By subjecting compound (XXXB) obtained in Step 27B and compound (VIA) to a reaction similar to Step 3A, compound (XXXIB) can be obtained.

5 Step 29B

By subjecting compound (XXXIB) obtained in Step 28B to deprotection by conventional methods, compound (XXXIIB) can be obtained. For example, when hydroxyl group of compound (XXXIB) is protected with a 2-(trimethylsilyl)ethoxymethyl group,
10 deprotection is performed in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone in the presence of tetrabutylammonium halide (e.g., tetrabutylammonium fluoride and the like) and MS4A.

Step 30B

15 By subjecting compound (XXXIIB) obtained in Step 29B and compound (XXVIB) to a reaction similar to Step 21B, compound (1-7) can be obtained.

Hydrolysis of compound (1-7) by conventional methods affords conversion of R^{1'} (C₁₋₆ alkoxy group) to a hydroxyl
20 group. For example, compound (1-7) is hydrolyzed in tetrahydrofuran-methanol in the presence of sodium hydroxide.

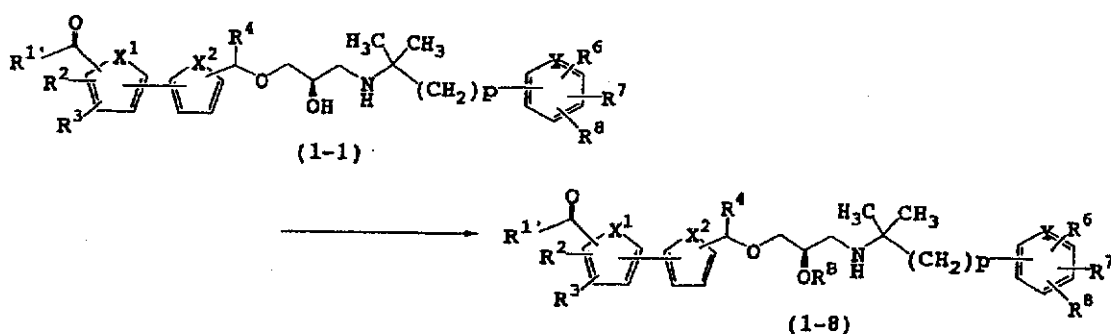
It is also possible to perform Step 27B using an optically active compound (XXIXB). For example, compound (id) is subjected to Step 24B and Step 25B, an optically active
25 compound (XXIXB) can be obtained. For example, when an optically active compound (XXIXB), wherein a hydroxyl group is protected with a 2-(trimethylsilyl)ethoxymethyl group, is desired, in Step 24B compound (id) is reacted with 2-(trimethylsilyl)ethoxymethyl halide (e.g., 2-
30 (trimethylsilyl)ethoxymethyl chloride) in chloroform in the presence of diisopropylethylamine.

When, in the present invention, a compound (1) wherein R¹ is R^A, particularly R^C-OC(=O)O-C₁₋₄ alkylene-O-, is desired,

compound (1) wherein R^1 is a hydroxyl group is reacted with R^C - $OC(=O)O-C_{1-4}$ alkylene- L^2 (L^2 is a leaving group such as a halogen atom and the like) in N,N-dimethylformamide, tetrahydrofuran, diethyl ether, dimethyl sulfoxide, acetone, 5 acetonitrile and the like or a mixed solvent thereof in the presence of a base such as sodium hydride, potassium carbonate, sodium carbonate and the like, whereby compound (1) wherein R^1 is $R^C-OC(=O)O-C_{1-4}$ alkylene-O- can be obtained.

When a compound wherein R^1 is R^A , particularly OH-NH-, is 10 desired, compound (1) wherein R^1 is a hydroxyl group is reacted with trimethylsilyloxyamine in N,N-dimethylformamide, tetrahydrofuran, diethyl ether, dimethyl sulfoxide, acetone, acetonitrile and the like or a mixed solvent thereof, in the presence of a condensation agent such as 15 dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, diisopropylcarbodiimide, diphenylphosphoryl azide, 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) and the like and an additive such as 1-hydroxybenzotriazole, 4-dimethylaminopyridine and the like. 20 Then, tetrabutylammonium fluoride is reacted in the above-mentioned solvent to give compound (1) wherein R^1 is OH-NH-.

For the production of compound (1) wherein R^5 is R^B , for example, as shown by the following formulas, compound (1-1) obtained in Step 3A is reacted with acid anhydride such as 25 acetic anhydride, succinic anhydride, maleic anhydride and the like or acyl halide in chloroform, methylene chloride, tetrahydrofuran, toluene, ethyl acetate and the like or a mixed solvent thereof, in the presence of a base such as pyridine, triethylamine, dimethylaminopyridine and the like, 30 whereby compound (1-8) can be obtained.



wherein each symbol is as defined above.

When a salt of a compound represented by the formula (1) is desired, known methods can be used. For example, when an acid addition salt is desired, a compound represented by the formula (1) is dissolved in water, methanol, ethanol, n-propanol, isopropanol, diethyl ether, tetrahydrofuran, 1,4-dioxane, ethyl acetate, dichloromethane, 1,2-dichloroethane, chloroform and the like or a mixed solvent thereof, the above-mentioned solvent wherein the desired acid has been dissolved is added and the precipitated crystals are collected by filtration, or concentrated under reduced pressure.

When a crystal of a salt is desired with using several solvents, a preferable method is as follows; a compound is dissolved in a solvent with high solvent power, and a solvent wherein the desired acid has been dissolved is added, and a solvent which has low solvent power is added and then the precipitated crystals are collected.

When a basic salt is desired, a compound represented by the formula (1) is dissolved in water, methanol, ethanol, n-propanol, isopropanol, tetrahydrofuran, 1,4-dioxane and the like or a mixed solvent thereof, the above-mentioned solvent wherein an equivalent amount of the desired base has been dissolved is added and the precipitated crystals are collected by filtration, or concentrated under reduced pressure.

When a crystal of a salt is desired with using several solvents, a preferable method is as follows; a compound is

dissolved in a solvent with high solvent power, and a solvent wherein the desired base has been dissolved is added, and a solvent which has low solvent power is added and then the precipitated crystals are collected.

5 When an acid addition salt of a compound represented by the formula (1) is to be converted to a free form, acid addition salt of a compound represented by the formula (1) is added to an aqueous solution of a base such as sodium hydrogencarbonate, potassium hydrogen carbonate, sodium
10 carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, lithium hydroxide and the like to adjust pH of the aqueous solution to neutral-weakly acidic, and the solution is separated into two layers including a solvent such as ethyl acetate, dichloromethane, 1,2-dichloroethane, chloroform,
15 methyl ethyl ketone or toluene and the like, whereby a free form of the compound represented by the formula (1) can be obtained.

 When a basic salt of a compound represented by the formula (1) is to be converted to a free form, an aqueous
20 solution of acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, acetic acid, citric acid and the like is added to an aqueous solution of a basic salt of a compound represented by the formula (1) and the precipitated solid is collected by filtration, or the solution is separated into two
25 layers including a solvent such as ethyl acetate, dichloromethane, 1,2-dichloroethane, chloroform, methyl ethyl ketone or toluene and the like, whereby a free form of the compound represented by the formula (1) can be obtained.

 When a salt of an optically active compound is desired, a
30 compound represented by the formula (1) is suspended in methanol, ethanol, n-propanol, isopropanol, tetrahydrofuran, 1,4-dioxane, water and the like, and the suspension is heated to dissolve, and then the solution is cooled to precipitate a

crystal. The crystal of the salt is obtained by the method described above with using thus obtained crystal.

The thus-obtained compound of the formula (1) of the present invention has a superior calcium receptor antagonistic
5 action. When the compound of the present invention is to be used as a therapeutic agent of osteoporosis, hypoparathyreosis, osteosarcoma, periodontal disease, bone fracture, osteoarthritis, chronic rheumatoid arthritis, Paget's disease, humoral hypercalcemia, autosomal dominant
10 hypocalcemia, Parkinson's disease, dementia and the like, it is generally administered systemically or topically, and orally or parenterally.

While the dose varies depending on age, body weight, condition, treatment effect, administration method, treatment
15 period and the like, it is generally administered from 0.01 mg to 10 g for an adult per day, which is given once or in several portions a day by oral or parenteral administration.

When the compound of the present invention is prepared into a solid composition for oral administration, a dosage
20 form of tablet, pill, powder, granule and the like can be employed. In such a solid composition, one or more active ingredient is admixed with at least one inert diluent, dispersing agent, absorbent and the like, such as lactose, mannitol, glucose, hydroxypropyl cellulose, crystalline
25 cellulose, starch, polyvinyl hydrin, magnesium aluminometasilicate, anhydrous silicic acid powder and the like. The composition may contain an additive other than diluent according to a conventional method.

For preparation of tablets or pills, gastric or enteric
30 film of sucrose, gelatin, hydroxypropyl cellulose, hydroxymethylcellulose phthalate and the like may be applied or two or more layers may be formed. In addition, they may be prepared into capsules of gelatin or ethylcellulose.

For preparation of liquid composition for oral administration, a dosage form such as pharmaceutically acceptable emulsion, solution, suspension, syrup, elixir and the like can be employed. The diluent to be used is, for
5 example, purified water, ethanol, vegetable oil, emulsifier and the like. This composition may contain diluent and an adjuvant other than the diluent, such as wetting agent, suspending agent, sweetener, flavor, aromatic agent, preservative and the like.

10 For preparation of parenteral injection, sterile aqueous or nonaqueous solvent, solubilizer, suspending agent or emulsifier is used. Examples of the aqueous solvent, solubilizer and suspending agent include distilled water for injection, physiological saline cyclodextrin and derivatives
15 thereof, organic amines such as triethanolamine, diethanolamine, monoethanolamine, triethylamine and the like, inorganic alkali solution and the like.

When a water-soluble solution preparation is to be prepared, for example, propylene glycol, polyethylene glycol,
20 vegetable oil such as olive oil, alcohol such as ethanol, and the like may be used. As the solubilizer, for example, surfactant (forming a mixed micelle) such as polyoxyethylene hydrogenated castor oil, sucrose esters of fatty acid and the like, lecithin or hydrogenated lecithin (forming a liposome)
25 and the like can be used. In addition, an emulsion preparation consisting of a water-insoluble solvent such as vegetable oil and the like, and lecithin, polyoxyethylene hydrogenated castor oil, polyoxyethylene polyoxypropylene glycol and the like may be formed.

30 As other compositions for parenteral administration, an external liquid, liniment such as ointment, suppository, pessary and the like, containing one or more active ingredients and prepared by a method known *per se* may be

formulated.

The form of the compound of the present invention for use as a pharmaceutical product is a compound itself (free form), a salt of the compound, a solvate of the compound or a prodrug of the compound, wherein preferred form is a free form, a salt of the compound or a solvate of the compound, particularly preferably a salt of the compound.

Examples

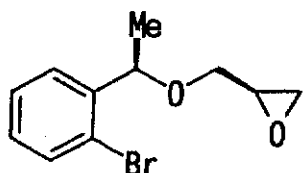
The compound of the formula (1) of the present invention and its production methods are explained in detail by referring to the following Examples, which are not to be construed as limitative.

Example 1-1

2'-[(1R)-[(2R)-3-[[1-(3-Fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid

Step 1

(2R)-2-[[[(1R)-(2-Bromophenyl)ethoxy)methyl]oxirane

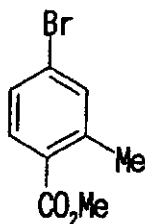


(1R)-(2-Bromophenyl)ethanol (30.0 g) and (R)-glycidyl 3-nitrobenzenesulfonate (50.3 g) were dissolved in dimethylformamide (300 ml) and sodium hydride (7.76 g, 60% in oil) was added. The mixture was stirred at room temperature for 2 hrs. 10% Aqueous citric acid solution (600 ml) was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=6:1) to give the title compound (32.9 g).

$^1\text{H-NMR}$ (300MHz, δ ppm, CDCl_3) 7.53-7.49 (2H,m), 7.37-7.32 (1H,m), 7.16-7.10 (1H,m), 4.89 (1H,q, $J=6.4\text{Hz}$), 3.62-3.57 (1H,m), 3.34-3.28 (1H,m), 3.18-3.12 (1H,m), 2.79-2.76 (1H,m), 2.58-2.55 (1H,m), 1.44 (3H,d, $J=6.4$).

5 Step 2

Methyl 4-bromo-2-methylbenzoate

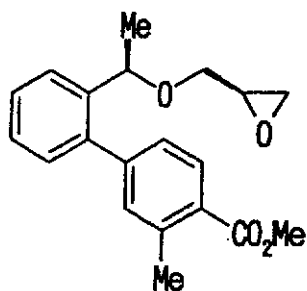


4-Bromo-2-methylbenzoic acid (75.0 g) was dissolved in methanol (500 ml) and concentrated sulfuric acid (10 ml) was
 10 added. The mixture was heated at reflux for 20 hrs. The reaction mixture was cooled to room temperature, and concentrated under reduced pressure. Water (150 ml) was added to the obtained residue, and the mixture was extracted with ethyl acetate (150 ml). The organic layer was washed
 15 successively with water, saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over sodium sulfate, and concentrated under reduced pressure to give the title compound (78.0 g).

$^1\text{H-NMR}$ (400MHz, δ ppm, CDCl_3) 8.20 (1H,s), 8.86 (1H,d, $J=8.0\text{Hz}$),
 20 7.30 (1H,d, $J=8.0\text{Hz}$), 3.91 (3H,s), 2.45 (3H,s).

Step 3

Methyl 3-methyl-2'-[(1R)-((R)-oxiranylmethoxy)ethyl]biphenyl-4-carboxylate

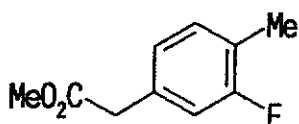


Methyl 4-bromo-2-methylbenzoate (9.16 g) obtained in Step 2 was dissolved in dimethyl sulfoxide (120 ml), and bis(diphenylphosphino)ferrocene dichloropalladium(II) (1.46 g), potassium acetate (11.8 g) and bispinacolatodiboron (11.2 g) were added at 80°C. The mixture was stirred for 3 hrs. The reaction mixture was cooled to room temperature, water was added and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=9:1) and the resulting compound was dissolved in toluene (80 ml) and ethanol (80 ml). Thereto was added a solution of bis(diphenylphosphino)ferrocene dichloropalladium(II) (1.17 g) and (2R)-2-(((1R)-(2-bromophenyl)ethoxy)methyl)oxirane (10.5 g) obtained in Step 1 in ethanol (80 ml) and 2M aqueous sodium carbonate solution (80 ml) was added. The mixture was heated under reflux for 3 hrs. The reaction mixture was allowed to return to room temperature, and extracted with diethyl ether. The organic layer was washed successively with water and saturated brine, dried over sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=5:1) to give the title compound (8.93 g).

¹H-NMR(300MHz, δppm, CDCl₃) 7.96(1H, d, J=8.6Hz), 7.60(1H, d, J=6.7Hz), 7.43-7.28(4H, m), 7.18-7.13(1H, m), 4.55(1H, q, J=6.4Hz), 3.92(3H, s), 3.44-3.40(1H, m), 3.18-3.12(1H, m), 3.07-3.02(1H, m), 2.73-2.70(1H, m), 2.65(3H, s), 2.47-2.45(1H, m), 1.37(3H, d, J=6.4Hz).

Step 4

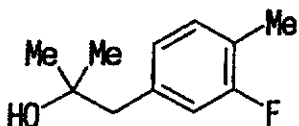
Methyl (3-fluoro-4-methylphenyl)acetate



(3-Fluoro-4-methylphenyl)acetic acid (105.3 g) was dissolved in methanol (740 ml) and concentrated sulfuric acid (9.9 ml) was added. The mixture was stirred at 85°C for 1 hr. The reaction mixture was cooled to room temperature, and concentrated under reduced pressure. Water was added to the obtained residue and the mixture was extracted with ethyl acetate (1 L). The organic layer was washed successively with water, aqueous sodium hydrogencarbonate solution, water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give the title compound (114.2 g).
¹H-NMR (300MHz, δppm, CDCl₃) 7.14-7.10 (1H, m), 6.96-6.93 (2H, m), 3.70 (3H, s), 3.58 (2H, s), 2.25-2.24 (3H, s).

Step 5

15 1-(3-Fluoro-4-methylphenyl)-2-methylpropan-2-ol

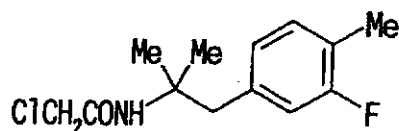


Methyl (3-fluoro-4-methylphenyl) acetate (114.2 g) obtained in Step 4 was dissolved in tetrahydrofuran (800 ml) and 1M-methylmagnesium bromide (1.56 L) was added dropwise at 0°C under argon streams. The mixture was stirred at room temperature for 1 hr. The reaction mixture was ice-cooled, saturated aqueous ammonium chloride solution (155 ml) was added dropwise and magnesium sulfate (280 g) was added. The reaction mixture was filtered off and the filtrate was concentrated under reduced pressure to give the title compound (130.1 g).

¹H-NMR (300MHz, δppm, CDCl₃) 7.11-7.08 (1H, m), 6.88-6.86 (2H, m), 2.71 (2H, s), 2.25 (3H, s), 1.22 (6H, s).

Step 6

2-Chloro-N-[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]acetamide

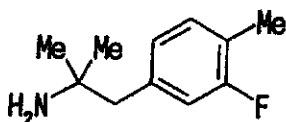


1-(3-Fluoro-4-methylphenyl)-2-methylpropan-2-ol (130.1 g)
 5 obtained in Step 5 was dissolved in chloroacetonitrile (139 ml) and acetic acid (115 ml), and concentrated sulfuric acid (33.4 ml) was added dropwise under ice-cooling. The mixture was stirred at room temperature for 2 hrs and 4N-aqueous sodium hydroxide solution (16 ml) was added dropwise under
 10 ice-cooling. The mixture was extracted twice with toluene and twice with ethyl acetate. The organic layer was washed twice with 10% brine and concentrated under reduced pressure to give the title compound (131.6 g).

¹H-NMR(300MHz,δppm,CDCl₃) 7.10-7.06(1H,m), 6.80-6.76(2H,m),
 15 6.19(1H,brs), 3.95(2H,s), 3.00(2H,s), 2.24(3H,s), 1.37(6H,s).

Step 7

(1-(3-Fluoro-4-methylphenyl)-2-methylpropan-2-yl)amine



2-Chloro-N-[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]acetamide (131.6 g) obtained in Step 6 was dissolved in
 20 acetic acid (200 ml) and ethanol (1 L), and thiourea (46.6 g) was added. The mixture was stirred overnight at 100°C. The reaction mixture was cooled to room temperature, and the precipitated crystals were filtered. The filtrate was
 25 concentrated under reduced pressure, and 4N-sodium hydroxide solution (300 ml) was added to the obtained residue. The mixture was extracted 3 times with toluene. The organic layer was washed with brine, and concentrated under reduced pressure.

The obtained residue was dissolved in diethyl ether (1 L) and 4N-hydrochloric acid/ethyl acetate solution (255 ml) was added dropwise under ice-cooling. The mixture was stirred for 1 hr and the precipitated crystals were collected by filtration.

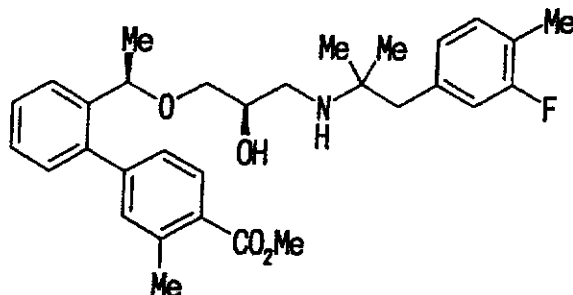
5 The obtained crystals were added to a mixture of toluene and 4N-aqueous sodium hydroxide solution. The toluene layer was separated, washed twice with water, and concentrated under reduced pressure to give the title compound (57.9 g).

¹H-NMR (300MHz, δ ppm, CDCl₃) 7.11-7.07 (1H, m), 6.85-6.82 (2H, m),
10 2.61 (2H, s), 2.25 (3H, s), 1.11 (6H, s).

MS (APCI, m/z) 182 (M+H)⁺.

Step 8

Methyl 2'-[(1R)-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylate



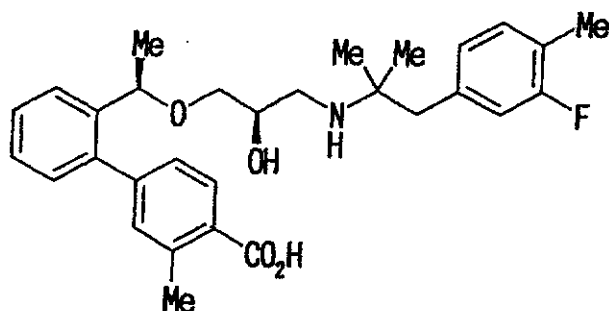
Methyl 3-methyl-2'-[(1R)-((R)-oxiranylmethoxy)ethyl]biphenyl-4-carboxylate (2.26 g) obtained in Step 3 was dissolved in toluene (50 ml). (1-(3-Fluoro-4-methylphenyl)-2-methylpropan-2-yl)amine (1.38 g) obtained in
20 Step 7 and lithium perchlorate (815 mg) were added successively, and the mixture was stirred overnight at room temperature. The reaction mixture was washed successively with water and saturated brine, dried over sodium sulfate, and
25 concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform:methanol=9:1) to give the title compound (3.37 g).

¹H-NMR (400MHz, δ ppm, DMSO-d₆) 7.95 (1H, d, J=8.6 Hz), 7.56-7.53 (1H, m), 7.41-7.37 (1H, m), 7.32-7.28 (1H, m), 7.17-7.12 (3H, m), 7.06-7.02 (1H, m), 6.80-6.77 (2H, m), 4.48 (1H, q, J=6.3Hz), 3.92 (3H, s), 3.66-3.63 (1H, m), 3.21-3.13 (2H, m), 2.72-2.68 (1H, m), 2.64 (3H, s), 2.59-2.54 (3H, m), 2.23 (3H, m), 1.35 (3H, d, J=6.3Hz), 1.02 (3H, s), 1.00 (3H, s).

MS (ESI, m/z) 508 (M+H)⁺.

Step 9

2'-[(1R)-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid



Methyl 2'-[(1R)-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylate (3.37 g) obtained in Step 8 was dissolved in methanol (25 ml) and tetrahydrofuran (25 ml), and 2N-sodium hydroxide (13.5 ml) was added. The mixture was stirred at 60°C for 3 hrs and concentrated under reduced pressure. The obtained residue was diluted with water and the mixture was neutralized by adding 10% aqueous citric acid solution. The resulting white precipitate was collected by filtration and dried to give the title compound (3.06 g).

¹H-NMR (300MHz, δ ppm, DMSO-d₆) 7.85 (1H, d, J=8.3Hz), 7.56-7.53 (1H, m), 7.47-7.42 (1H, m), 7.37-7.32 (1H, m), 7.19-7.13 (4H, m), 6.97-6.89 (2H, m), 4.47 (1H, q, J=6.4Hz), 3.70 (1H, s), 3.14 (2H, d, J=5.3Hz), 2.85-2.80 (1H, m), 2.73 (2H, s), 2.63-2.59 (1H, m), 2.56 (3H, s), 2.19 (3H, s), 1.28 (3H, d, J=6.4 Hz), 1.05 (3H, s), 1.04 (3H, s).

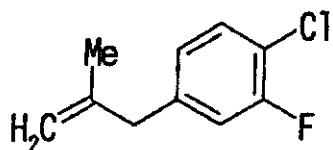
MS (ESI, m/z) 494 (M+H)⁺.

Example 1-2

2'-[(1R)-[(2R)-3-[[1-(4-Chloro-3-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-
5 carboxylic acid

Step 1

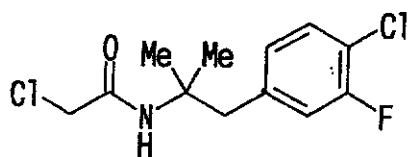
1-Chloro-2-fluoro-4-(2-methylallyl)benzene



Magnesium (2.43 g) and iodine (10 mg) were added to
10 tetrahydrofuran (40 ml) and a solution of 4-bromo-1-chloro-2-fluorobenzene (21.0 g) in tetrahydrofuran (40 ml) was added dropwise, and the mixture was stirred at room temperature for 1 hr to give a Grignard's reagent. The reaction mixture was ice-cooled and copper iodide (1.90 g) was added. 3-Chloro-2-
15 methyl-1-propene (14.8 ml) was added and the mixture was stirred at room temperature for 1 hr. The reaction mixture was ice-cooled and saturated aqueous ammonium chloride solution (10 ml) was added. The mixture was stirred at room temperature for 20 min and magnesium sulfate (40 g) was added. The
20 reaction mixture was filtered and the filtrate was concentrated under reduced pressure. Hexane (100 ml) was added to the obtained residue and insoluble materials were filtered off. The resulting solution was concentrated under reduced pressure to give the title compound (16.9 g).
25 ¹H-NMR (300 MHz, δ ppm, CDCl₃) 7.40-7.20 (1H, m), 6.99 (1H, dd, J=9.9, 1.8 Hz), 6.91 (1H, d, J=8.1 Hz), 4.84 (1H, s), 4.73 (1H, s), 3.28 (2H, s), 1.66 (3H, s).

Step 2

2-Chloro-N-[1-(4-chloro-3-fluorophenyl)-2-methylpropan-2-yl]acetamide
30

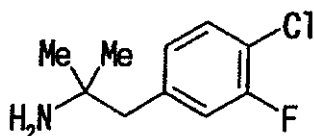


In the same manner as in Step 6 of Example 1-1, the title compound (10.1 g) was obtained from 1-chloro-2-fluoro-4-(2-methylallyl)benzene (16.9 g) obtained in Step 1.

5 $^1\text{H-NMR}$ (400MHz, δppm , CDCl_3) 7.30 (1H, dd, $J=7.9$, 7.9Hz), 6.92 (1H, dd, $J=9.9$, 1.8Hz) 6.85 (1H, dd, $J=8.1$, 1.8Hz), 6.14 (1H, brs), 3.96 (2H, s), 3.06 (2H, s), 1.36 (6H, s).
MS (ESI, m/z) 278 ($M+H$) $^+$.

Step 3

10 1-(4-Chloro-3-fluorophenyl)-2-methylpropan-2-ylamine

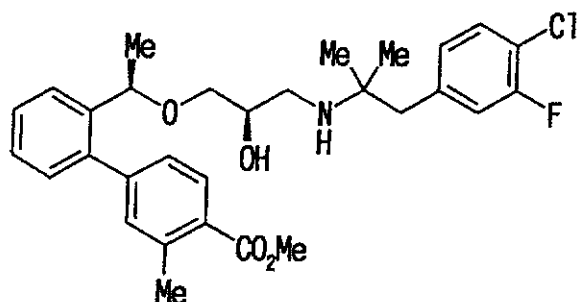


In the same manner as in Step 7 of Example 1-1, the title compound (6.90 g) was obtained from 2-chloro-N-[1-(4-chloro-3-fluorophenyl)-2-methylpropan-2-yl]acetamide (10.1 g) obtained
15 in Step 2.

$^1\text{H-NMR}$ (400MHz, δppm , CDCl_3) 7.30 (1H, dd, $J=7.9$, 7.9Hz), 6.99 (1H, dd, $J=10.2$, 2.0Hz) 6.91 (1H, dd, $J=8.1$, 1.9Hz), 2.62 (2H, s), 1.15 (6H, s).
MS (ESI, m/z) 202 ($M+H$) $^+$.

20 Step 4

Methyl 2'--[(1R)-[(2R)-3-[[1-(4-chloro-3-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylate



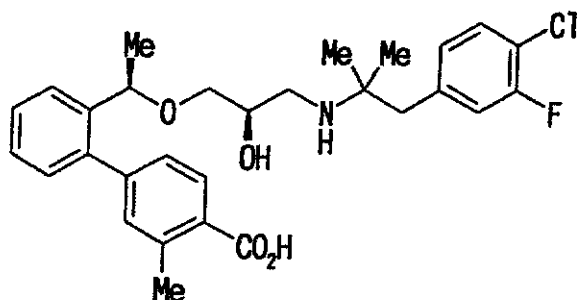
In the same manner as in Step 8 of Example 1-1, the title compound (413 mg) was obtained from methyl 3-methyl-2'-[(1R)-((R)-oxiranylmethoxy)ethyl]biphenyl-4-carboxylate (248 mg) obtained in Step 3 of Example 1-1 and 1-(4-chloro-3-fluorophenyl)-2-methylpropan-2-ylamine (170 mg) obtained in Step 3.

$^1\text{H-NMR}$ (300MHz, δ ppm, DMSO- d_6) 7.96 (1H, d, $J=8.4\text{Hz}$), 7.56-7.53 (1H, m), 7.45-7.39 (2H, m), 7.19-7.11 (3H, m), 6.98-6.88 (2H, m), 4.48 (1H, q, $J=6.6\text{Hz}$), 3.98 (1H, m), 3.92 (3H, s), 3.29-3.19 (2H, m), 3.05-3.00 (1H, m), 2.93 (1H, m), 2.83 (2H, s), 2.64 (3H, s), 1.34 (3H, d, $J=6.6\text{Hz}$), 1.21 (3H, s), 1.19 (3H, s).

MS (ESI, m/z) 528 ($M+H$) $^+$.

Step 5

2'-[(1R)-[(2R)-3-[[1-(4-chloro-3-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylic acid



In the same manner as in Step 9 of Example 1-1, the title compound (345 mg) was obtained from methyl 2'-[(1R)-[(2R)-3-[[1-(4-chloro-3-fluorophenyl)-2-methylpropan-2-yl]amino]-2-

hydroxypropoxy]ethyl]-3-methylbiphenyl-4-carboxylate (413 mg)
obtained in Step 4.

¹H-NMR (400MHz, δppm, DMSO-d₆) 7.84 (1H, d, J=8.6Hz), 7.55-7.52 (1H, m),
7.47-7.41 (2H, m), 7.36-7.32 (1H, m), 7.25-7.22 (1H, m), 7.18-
5 7.15 (3H, m), 7.05-7.03 (1H, m), 4.47 (1H, q, J=6.5Hz), 3.68 (1H, m),
3.13 (2H, d, J=5.5Hz), 2.81-2.78 (1H, m), 2.76 (2H, s), 2.60-
2.57 (1H, m), 2.56 (3H, s), 1.28 (3H, d, J=6.2Hz), 1.05 (3H, s),
1.03 (3H, s).

MS (ESI, m/z) 514 (M+H)⁺.

10 **Examples 1-3 to 1-110**

Examples 1-3 to 1-110 were obtained based on Examples 1-1
and 1-2. The results are shown in Tables 1 and 2-44.

Table 1

Ex. No.	Structural formula	Property data	Reporter gene assay (μM)
1-1		$^1\text{H-NMR}$ (300MHz, δppm , DMSO- d_6) 7.85 (1H, d, J=8.3Hz), 7.56-7.53 (1H, m), 7.47-7.42 (1H, m), 7.37-7.32 (1H, m), 7.19-7.13 (4H, m), 6.97-6.89 (2H, m), 4.47 (1H, q, J=6.4Hz), 3.70 (1H, s), 3.14 (2H, d, J=5.3Hz), 2.85-2.80 (1H, m), 2.73 (2H, s), 2.63-2.59 (1H, m), 2.56 (3H, s), 2.19 (3H, s), 1.28 (3H, d, J=6.4Hz), 1.05 (3H, s), 1.04 (3H, s). MS (ESI, m/z) 494 (M+H) $^{+}$.	0.024
1-2		$^1\text{H-NMR}$ (400MHz, δppm , DMSO- d_6) 7.84 (1H, d, J=8.6Hz), 7.55-7.52 (1H, m), 7.47-7.41 (2H, m), 7.36-7.32 (1H, m), 7.25-7.22 (1H, m), 7.18-7.15 (3H, m), 7.05-7.03 (1H, m), 4.47 (1H, q, J=6.5Hz), 3.68 (1H, m), 3.13 (2H, d, J=5.5Hz), 2.81-2.78 (1H, m), 2.76 (2H, s), 2.60-2.57 (1H, m), 2.56 (3H, s), 1.28 (3H, d, J=6.2Hz), 1.05 (3H, s), 1.03 (3H, s). MS (ESI, m/z) 514 (M+H) $^{+}$.	0.013

Table 2

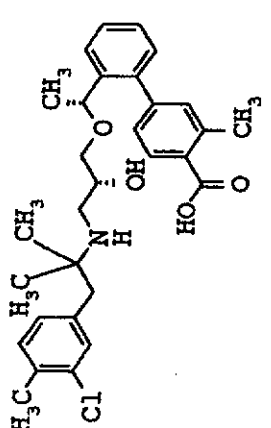
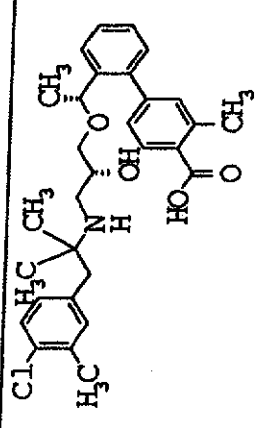
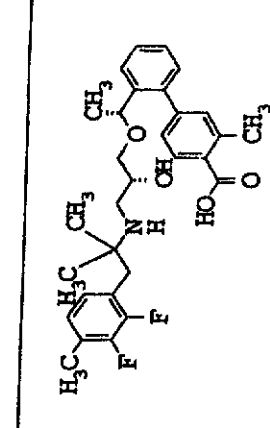
1-3		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.82 (1H, d, J=8.4Hz), 7.54 (1H, d, J=7.9Hz), 7.43 (1H, dd, J=7.4, 7.4Hz), 7.33 (1H, dd, J=7.2, 7.2Hz), 7.25-7.10 (5H, m), 7.04 (1H, d, J=7.7Hz), 4.48 (1H, q, J=6.5Hz), 3.77-3.66 (1H, m), 3.14 (2H, d, J=5.8Hz), 2.90-2.40 (7H, m), 2.27 (3H, s), 1.27 (3H, d, J=6.2Hz), 1.05 (3H, s), 1.04 (3H, s) MS (ESI, m/z) 510 (M+H) ⁺	0.010
1-4		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.83 (1H, d, J=8.4Hz), 7.54 (1H, d, J=7.9Hz), 7.44 (1H, dd, J=7.5, 7.5Hz), 7.34 (1H, dd, J=7.5, 7.5Hz), 7.28 (1H, d, 8.2Hz), 7.20-7.10 (4H, m), 7.01 (1H, d, J=8.1Hz), 4.48 (1H, q, J=6.3Hz), 3.80-3.65 (1H, m), 3.14 (2H, d, J=5.6Hz), 2.90-2.40 (7H, m), 2.28 (3H, s), 1.27 (3H, d, J=6.2Hz), 1.04 (3H, s), 1.03 (3H, s) MS (ESI, m/z) 510 (M+H) ⁺	0.014
1-5		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.85 (1H, d, J=8.4Hz), 7.54 (1H, d, J=7.9Hz), 7.44 (1H, dd, J=7.4, 7.4Hz), 7.34 (1H, dd, J=7.4, 7.4Hz), 7.20-7.12 (3H, m), 7.01-6.90 (2H, m), 4.47 (1H, q, J=6.5Hz), 3.75-3.60 (1H, m), 3.13 (2H, d, J=5.8Hz), 2.90-2.70 (3H, m), 2.65-2.40 (4H, m), 2.24 (3H, s), 1.27 (3H, d, J=6.3Hz), 1.03 (3H, s), 1.02 (3H, s) MS (ESI, m/z) 512 (M+H) ⁺	0.003

Table 3

1-6		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.84 (1H, d, J=8.4Hz), 7.54 (1H, dd, J=7.9, 1.2Hz), 7.44 (1H, ddd, J=7.4, 7.4, 1.2Hz), 7.38-7.25 (3H, m), 7.20-7.13 (4H, m), 4.47 (1H, q, J=6.2Hz), 3.75-3.60 (1H, m), 3.12 (2H, d, J=5.8Hz), 2.85-2.65 (3H, m), 2.60-2.40 (4H, m), 1.27 (3H, d, J=6.2Hz), 1.02 (3H, s), 1.00 (3H, s) MS (ESI, m/z) 514 (M+H) ⁺	0.020
1-7		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.84 (1H, d, J=8.3Hz), 7.54 (1H, dd, J=7.9, 1.2Hz), 7.44 (1H, ddd, J=7.5, 7.5, 1.2Hz), 7.34 (1H, ddd, J=7.4, 7.4, 1.2Hz), 7.20-7.07 (4H, m), 6.96 (1H, d, J=10.9Hz), 6.91 (1H, d, 7.9Hz), 4.48 (1H, q, J=6.3Hz), 3.80-3.60 (1H, m), 3.14 (2H, d, J=5.5Hz), 2.95-2.70 (3H, m), 2.65-2.40 (4H, m), 2.27 (3H, s), 1.27 (3H, d, J=6.3Hz), 1.04 (6H, s) MS (ESI, m/z) 494 (M+H) ⁺	0.015

Table 4

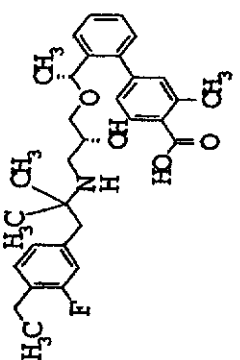
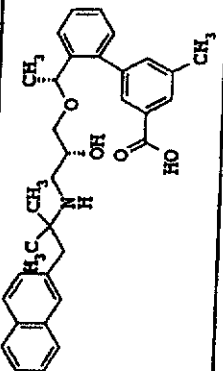
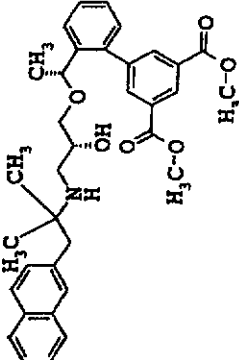
1-8		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.83 (1H, d, J=8.3Hz), 7.53 (1H, dd, J=7.8, 1.2Hz), 7.43 (1H, ddd, J=7.7, 7.7, 1.2Hz), 7.33 (1H, ddd, J=7.6, 7.6, 1.2Hz), 7.20-7.12 (4H, m), 6.98-6.87 (2H, m), 4.48 (1H, q, J=6.3Hz), 3.75-3.60 (1H, m), 3.14 (2H, d, J=5.5Hz), 2.85-2.65 (3H, m), 2.60-2.45 (6H, m), 1.27 (3H, d, J=6.3Hz), 1.14 (2H, t, J=7.5Hz) 1.03 (3H, s), 1.02 (3H, s) MS (ESI, m/z) 508 (M+H) ⁺	0.015
1-9		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.87-7.18 (14H, m), 4.45 (1H, q, J=6.3Hz), 3.80-3.65 (1H, m), 3.18 (2H, d, J=5.1Hz), 2.95-2.80 (3H, m), 2.70-2.60 (1H, m), 2.40 (3H, s), 1.26 (3H, d, J=6.3Hz), 1.08 (3H, s), 1.07 (3H, s). MS (ESI, m/z) 512 (M+H) ⁺	0.016
1-10		¹ H-NMR (300MHz, δ ppm, CDCl ₃) 8.69 (1H, s), 8.16 (1H, d, J=1.6Hz), 7.78-7.17 (11H, m), 4.43 (1H, q, J=6.4Hz), 3.95 (6H, s), 3.80-3.70 (1H, m), 3.30-3.15 (2H, m), 2.90-2.75 (3H, m), 2.75-2.65 (1H, m), 1.33 (3H, d, J=6.4Hz), 1.12 (3H, s), 1.10 (3H, s). MS (ESI, m/z) 570 (M+H) ⁺	0.029

Table 5

1-11		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.88-7.16 (14H, m), 3.89 (1H, d, J=7.4Hz), 3.87-3.75 (1H, m), 3.40-3.15 (2H, m), 3.00-2.85 (3H, m), 2.80-2.65 (1H, m), 2.43 (3H, s), 1.20-0.95 (7H, m), 0.50-0.35 (1H, m), 0.30-0.20 (2H, m), -0.05--0.15 (1H, m). MS (ESI, m/z) 538 (M+H) ⁺ .	0.018
1-12		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 12.7 (1H, bs), 9.15 (1H, bs), 8.70 (1H, bs), 8.00-7.15 (14H, m), 5.59 (1H, bs), 4.49 (1H, q, J=6.4Hz), 4.00-3.90 (1H, m), 3.40-3.05 (5H, m), 2.90-2.75 (1H, m), 2.60 (3H, s), 1.30 (3H, d, J=6.3Hz), 1.25 (6H, s). MS (ESI, m/z) 512 (M+H-HCl) ⁺ .	0.013
1-13		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.90-7.70 (3H, m), 7.65 (1H, s), 7.60-7.25 (7H, m), 7.15-7.12 (1H, m), 6.96-6.93 (2H, m), 4.62 (1H, bs), 4.51 (1H, q, J=6.4Hz), 3.55 (1H, bs), 3.35-3.30 (1H, m), 3.12 (2H, d, J=5.7Hz), 2.80-2.60 (3H, m), 2.48 (3H, s), 1.24 (3H, d, J=6.4Hz), 0.97 (3H, s), 0.95 (3H, s). MS (ESI, m/z) 512 (M+2H-Na) ⁺ .	0.015

Table 6

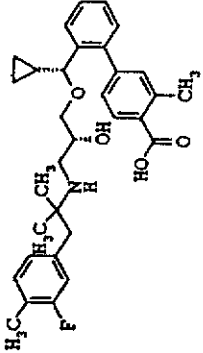
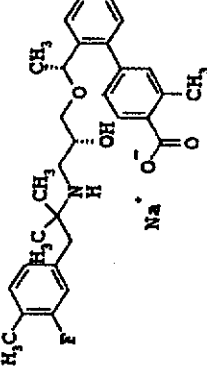
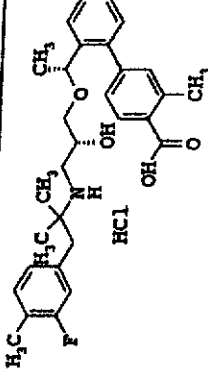
1-14		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.85 (1H, d, J=7.8Hz), 7.60 (1H, d, J=6.6Hz), 7.50-7.30 (2H, m), 7.20-7.10 (4H, m), 7.00-6.90 (2H, m), 3.86 (1H, d, J=7.5Hz), 3.80-3.70 (1H, m), 3.35-3.15 (2H, m), 2.95-2.90 (1H, m), 2.77 (2H, s), 2.76-2.60 (1H, m), 2.56 (3H, s), 2.19 (3H, s), 1.15-1.00 (7H, m), 0.50-0.40 (1H, m), 0.35-0.20 (2H, m), -0.15--0.20 (1H, m). MS (ESI, m/z) 520 (M+H) ⁺ .	0.006
1-15		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.55-7.45 (2H, m), 7.40-7.25 (2H, m), 7.15-7.05 (2H, m), 6.95-6.80 (4H, m), 4.49 (1H, q, J=6.4Hz), 3.55-3.50 (1H, m), 3.09 (2H, s), 2.60-2.35 (6H, m), 2.18 (3H, s), 1.24 (3H, d, J=6.4Hz), 0.89 (3H, s), 0.86 (3H, s). MS (ESI, m/z) 494 (M+2H-Na) ⁺ .	0.012
1-16		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 12.7 (1H, bs), 8.94 (1H, bs), 8.49 (1H, bs), 7.90 (1H, d, J=8.0Hz), 7.60-7.15 (7H, m), 7.00-6.90 (2H, m), 5.55 (1H, d, J=4.0Hz), 4.46 (1H, q, J=6.3Hz), 3.95-3.85 (1H, m), 3.20-2.65 (6H, m), 2.59 (3H, s), 2.21 (3H, s), 1.31 (3H, d, J=6.3Hz), 1.18 (6H, s). MS (ESI, m/z) 494 (M+H-Cl) ⁺ .	0.011

Table 7

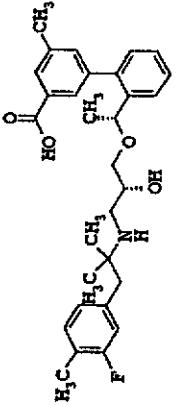
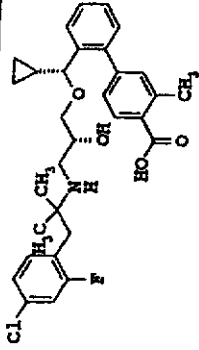
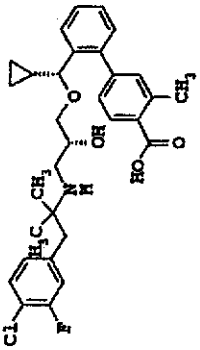
1-17		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.64 (1H, s), 7.60-7.10 (6H, m), 7.00-6.85 (2H, m), 4.43 (1H, q, J=6.4Hz), 3.80-3.65 (1H, m), 3.15 (2H, d, J=5.1Hz), 3.80-3.55 (4H, m), 2.40 (3H, s), 2.18 (3H, s), 1.26 (3H, d, J=6.4Hz), 1.05 (6H, s). MS (ESI, m/z) 494 (M+H) ⁺ .	0.015
1-18		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.86 (1H, d, J=8.4Hz), 7.65-7.10 (9H, m), 3.85 (1H, d, J=7.8Hz), 3.75-3.65 (1H, m), 3.35-3.10 (2H, m), 2.90-2.50 (7H, m), 1.15-0.95 (7H, m), 0.50-0.40 (1H, m), 0.30-0.20 (2H, m), -0.05--0.20 (1H, m). MS (ESI, m/z) 540 (M+H) ⁺ .	0.016
1-19		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.84 (1H, d, J=8.4Hz), 7.59 (1H, d, J=7.9Hz), 7.50-7.15 (7H, m), 7.10-7.00 (1H, m), 3.85 (1H, d, J=7.4Hz), 3.75-3.65 (1H, m), 3.30-3.15 (2H, m), 2.90-2.75 (3H, m), 2.70-2.60 (1H, m), 2.56 (3H, s), 1.15-1.10 (7H, m), 0.50-0.40 (1H, m), 0.30-0.20 (2H, m), -0.15--0.15 (1H, m). MS (ESI, m/z) 540 (M+H) ⁺ .	0.005

Table 8

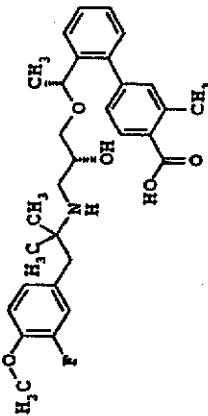
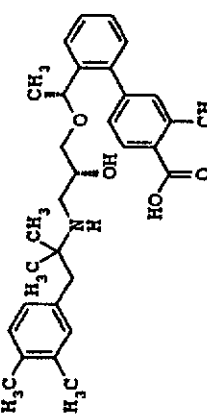
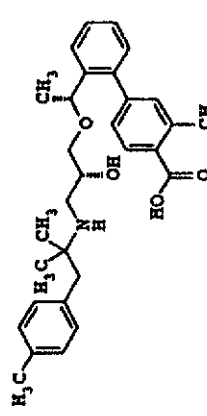
1-20		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.86 (1H, d, $J=8.4$ Hz), 7.57-7.54 (1H, m), 7.47-7.42 (1H, m), 7.37-7.32 (1H, m), 7.19-7.13 (4H, m), 6.79-6.68 (2H, m), 4.48 (1H, q, $J=6.2$ Hz), 3.74 (3H, s), 3.70 (1H, m), 3.14 (2H, d, $J=5.5$ Hz), 2.84-2.81 (1H, m), 2.71 (2H, s), 2.62-2.59 (1H, m), 2.56 (3H, s), 1.28 (3H, d, $J=6.2$ Hz), 1.03 (6H, m). MS (ESI, m/z) 510 (M+H) ⁺ .	0.040
1-21		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.82-7.79 (1H, m), 7.54-7.52 (1H, m), 7.45-7.41 (1H, m), 7.35-7.31 (1H, m), 7.17-7.12 (3H, m), 7.02-7.00 (1H, m), 6.93 (1H, s), 6.88-6.86 (1H, m), 4.49 (1H, q, $J=6.5$ Hz), 3.77 (1H, m), 3.15 (2H, d, $J=5.8$ Hz), 2.92-2.89 (1H, m), 2.73 (2H, s), 2.66-2.64 (1H, m), 2.54 (3H, s), 2.16 (6H, s), 1.26 (3H, d, $J=6.2$ Hz), 1.06 (6H, s). MS (ESI, m/z) 490 (M+H) ⁺ .	0.013
1-22		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.83 (1H, d, $J=8.3$ Hz), 7.55-7.53 (1H, m), 7.46-7.42 (1H, m), 7.36-7.32 (1H, m), 7.19-7.15 (3H, m), 7.09-7.04 (4H, m), 4.49 (1H, q, $J=6.5$ Hz), 3.76 (1H, m), 3.16-3.14 (2H, m), 2.91-2.88 (1H, m), 2.76 (2H, s), 2.66-2.64 (1H, m), 2.56 (3H, s), 2.26 (3H, s), 1.27 (3H, d, $J=6.5$ Hz), 1.06 (6H, s). MS (ESI, m/z) 476 (M+H) ⁺ .	0.012

Table 9

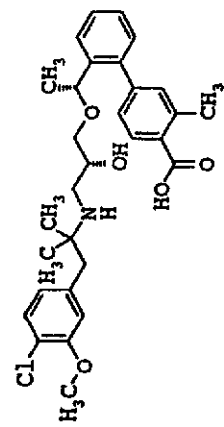
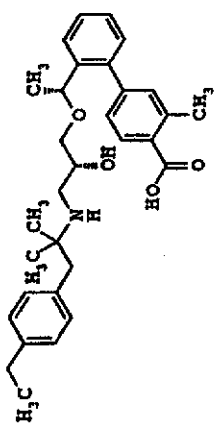
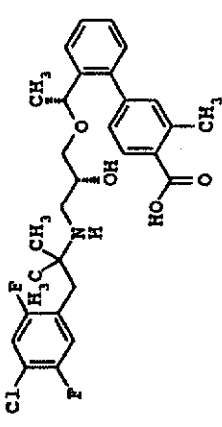
1-23		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.83 (1H, d, $J=8.6$ Hz), 7.54-7.52 (1H, m), 7.46-7.42 (1H, m), 7.36-7.29 (2H, m), 7.19-7.14 (3H, m), 6.95 (1H, m), 6.78-6.75 (1H, m), 4.48 (1H, q, $J=6.2$ Hz), 3.81 (3H, s), 3.77-3.75 (1H, m), 3.14 (2H, d, $J=5.8$ Hz), 2.89-2.87 (1H, m), 2.80 (2H, s), 2.66-2.61 (1H, m), 2.56 (3H, s), 1.28 (3H, d, $J=6.2$ Hz), 1.11 (3H, m), 1.09 (3H, m). MS (ESI, m/z) 526 (M+H) ⁺ .	0.016
1-24		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.85 (1H, d, $J=8.1$ Hz), 7.56-7.54 (1H, m), 7.48-7.43 (1H, m), 7.38-7.33 (1H, m), 7.20-7.16 (3H, m), 7.13-7.07 (4H, m), 4.49 (1H, q, $J=6.2$ Hz), 3.75-3.74 (1H, m), 3.15 (2H, d, $J=5.5$ Hz), 2.90-2.86 (1H, m), 2.75 (2H, s), 2.67-2.55 (6H, m), 1.27 (3H, d, $J=6.2$ Hz), 1.16 (3H, t, $J=7.6$ Hz), 1.05 (6H, s). MS (ESI, m/z) 490 (M+H) ⁺ .	0.020
1-25		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.84 (1H, d, $J=8.3$ Hz), 7.56-7.52 (2H, m), 7.45-7.41 (1H, m), 7.38-7.31 (2H, m), 7.18-7.15 (3H, m), 4.46 (1H, q, $J=6.5$ Hz), 3.66 (1H, m), 3.12 (2H, d, $J=5.5$ Hz), 2.78-2.71 (3H, m), 2.78-2.71 (3H, m), 2.56 (4H, m), 1.28 (3H, d, $J=6.5$ Hz), 1.04 (3H, s), 1.03 (3H, s). MS (ESI, m/z) 532 (M+H) ⁺ .	0.019

Table 10

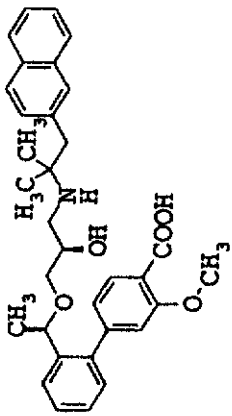
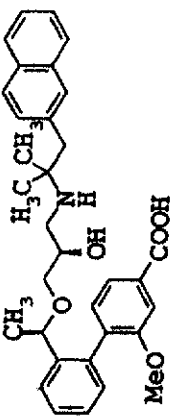
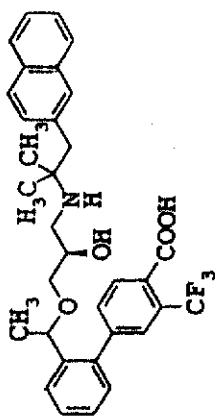
1-26		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.89-7.81 (3H, m), 7.71 (1H, s), 7.66 (1H, d, J=7.5Hz), 7.57-7.35 (6H, m), 7.23 (1H, d, J=7.5Hz), 6.95 (1H, s), 6.90 (1H, d, J=7.9Hz), 4.52 (1H, q, J=6.4Hz), 3.81-3.75 (4H, m), 3.18 (2H, d, J=4.9Hz), 2.96-2.91 (3H, m), 2.72-2.65 (1H, m), 1.30 (3H, d, J=6.4Hz), 1.11 (3H, s). MS (ESI, m/z) 528 (M+H) ⁺ .	0.014
1-27		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.93-7.88 (3H, m), 7.76 (1H, d, J=7.0Hz), 7.67-7.20 (9H, m), 7.13-7.08 (1H, m), 4.23-4.16 and 3.93-3.91 (1H, m), 3.81-3.76 (4H, m), 3.25-2.58 (6H, m), 1.31 and 1.11 (3H, d, J=6.2Hz), 1.26 (3H, s), 1.22 (3H, s). MS (ESI, m/z) 528 (M+H) ⁺ .	0.014
1-28		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.90-7.84 (3H, m), 7.74-7.68 (2H, m), 7.63-7.57 (2H, m), 7.53-7.47 (4H, m), 7.41-7.36 (2H, m), 7.25-7.22 (1H, m), 4.556-4.47 (1H, m), 3.93-3.92 (1H, m), 3.26-3.07 (4H, m), 2.94-2.80 (2H, m), 1.31-1.22 (9H, m). MS (ESI, m/z) 566 (M+H) ⁺ .	0.007

Table 11

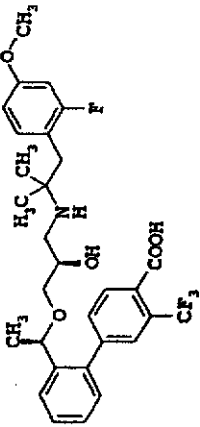
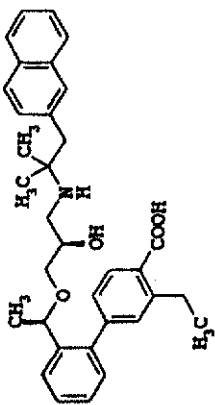
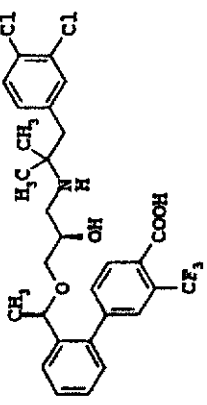
1-29		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.71 (1H, d, J=8.0Hz), 7.60-7.57 (2H, m), 7.52-7.47 (2H, m), 7.25-7.18 (2H, m), 6.82-6.74 (2H, m), 4.51 (1H, q, J=6.6Hz), 3.88-3.86 (1H, m), 3.75 (3H, s), 3.22-2.73 (6H, m), 1.29 (3H, d, J=6.6Hz), 1.14 (6H, s). MS (ESI, m/z) 564 (M+H) ⁺ .	0.082
1-30		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.87-7.80 (4H, m), 7.71 (1H, s), 7.57-7.42 (4H, m), 7.38-7.33 (2H, m), 7.21-7.17 (3H, m), 4.48 (1H, q, J=6.3Hz), 3.77-3.76 (1H, m), 3.17-2.91 (8H, m), 2.72-2.68 (1H, m), 1.28 (3H, d, J=6.3Hz), 1.18 (3H, t, J=7.4Hz), 1.12 (3H, s), 1.11 (3H, s). MS (ESI, m/z) 526 (M+H) ⁺ .	0.007
1-31		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.70 (1H, d, J=7.7Hz), 7.59-7.46 (6H, m), 7.39 (1H, ddd, J=7.3, 7.3, 1.4Hz), 7.24-7.19 (2H, m), 4.51 (1H, q, J=6.3Hz), 3.85-3.84 (1H, m), 3.21-2.92 (5H, m), 2.74-2.70 (1H, m), 1.28 (3H, d, J=6.3Hz), 1.15 (6H, s). MS (ESI, m/z) 584 (M+H) ⁺ .	0.005

Table 12

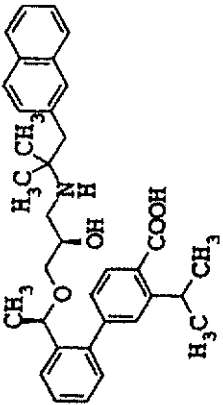
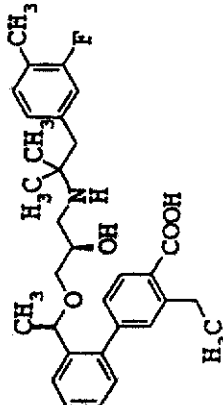
1-32		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.87-7.77 (3H, m), 7.68 (1H, s), 7.62 (1H, d, J=8.1Hz), 7.54 (1H, m), 7.50-7.31 (5H, m), 7.20-7.18 (2H, m), 7.10 (1H, dd, J=7.7, 1.5Hz), 4.47 (1H, q, J=6.2Hz), 3.84 (1H, sept, J=7.0Hz), 3.72-3.71 (1H, m), 3.20-3.10 (2H, m), 2.90 (2H, s), 2.85-2.80 (1H, m), 2.63-2.57 (1H, m), 1.26 (3H, d, J=6.2Hz), 1.19 (6H, d, J=7.0Hz), 1.07 (3H, s), 1.05 (3H, s). MS (ESI, m/z) 540 (M+H) ⁺ .	0.002
1-33		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.76 (1H, d, J=8.5Hz), 7.54 (1H, dd, J=7.7, 1.1Hz), 7.44 (1H, ddd, J=7.7, 1.1Hz), 7.20-7.13 (4H, m), 6.96-6.88 (2H, m), 4.48 (1H, q, J=6.6Hz), 3.70-3.69 (1H, m), 3.15-3.13 (2H, m), 2.97 (2H, q, J=7.3Hz), 2.81-2.71 (3H, m), 2.59-2.47 (1H, m), 2.18 (3H, s), 1.27 (3H, d, J=6.6Hz), 1.17 (3H, t, J=7.3Hz), 1.02 (3H, s), 1.01 (3H, s). MS (ESI, m/z) 508 (M+H) ⁺ .	0.005

Table 13

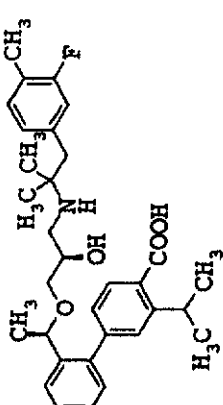
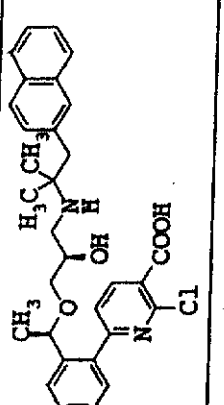
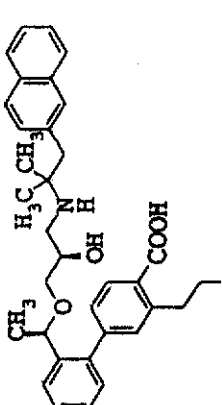
1-34		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.64 (3H, d, J=8.1Hz), 7.54 (1H, dd, J=8.1, 1.1Hz), 7.44 (1H, ddd, J=7.3, 7.3, 1.1Hz), 7.34 (1H, ddd, J=7.3, 7.3, 1.1Hz), 7.20-7.10 (4H, m), 6.96-6.88 (2H, m), 4.45 (1H, q, J=6.3Hz), 3.82 (1H, sept, J=6.6Hz), 3.69-3.68 (1H, m), 3.17-3.07 (2H, m), 2.80-2.70 (3H, m), 2.58-2.51 (1H, m), 2.18 (3H, s), 1.27 (3H, d, J=6.3Hz), 1.20 (6H, d, J=6.6Hz), 1.02 (3H, s), 1.00 (3H, s). MS (ESI, m/z) 522 (M+H) ⁺ .	0.005
1-35		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.90-7.83 (4H, m), 7.74 (1H, s), 7.60-7.36 (8H, m), 4.79 (1H, q, J=6.1Hz), 3.78-3.76 (1H, m), 3.28-3.02 (6H, m), 2.82-2.75 (1H, m), 1.39 (3H, d, J=6.1Hz), 1.20 (6H, s). MS (ESI, m/z) 533 (M+H) ⁺ .	0.010
1-36		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.85-7.71 (4H, m), 7.66 (1H, s), 7.53-7.38 (4H, m), 7.34-7.30 (2H, m), 7.17-7.05 (3H, m), 4.49 (1H, q, J=6.3Hz), 3.71-3.70 (1H, m), 3.17-3.10 (2H, m), 2.94-2.79 (5H, m), 2.61-2.56 (1H, m), 1.58 (2H, tq, J=7.2, 7.2Hz), 1.24 (3H, d, J=6.3Hz), 1.06 (3H, s), 1.04 (3H, s), 0.85 (3H, t, J=7.2Hz). MS (ESI, m/z) 540 (M+H) ⁺ .	0.002

Table 14

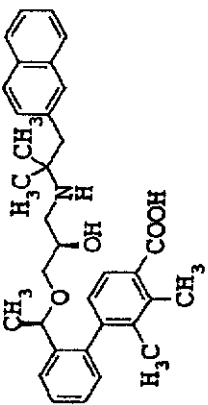
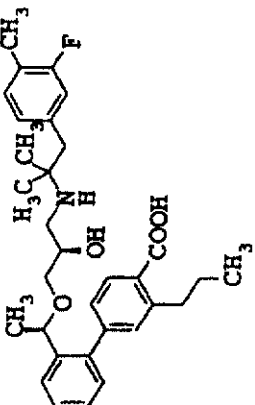
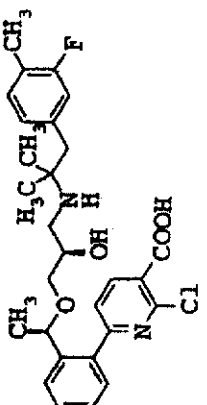
1-37		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.88-7.79 (3H, m), 7.71 (1H, s), 7.55-7.31 (7H, m), 7.06-6.88 (2H, m), 4.31-4.25 and 4.13-4.07 (1H, m), 3.77-3.76 (1H, m), 3.25-3.14 (2H, m), 2.96-2.88 (3H, m), 2.71-2.64 (1H, m), 2.43 (3H, s), 2.00 and 1.91 (3H, s), 1.17-1.09 (9H, m). MS (ESI, m/z) 526 (M+H) ⁺ .	0.003
1-38		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.78 (1H, d, J=7.9Hz), 7.53 (1H, dd, J=7.9, 1.2Hz), 7.43 (1H, ddd, J=7.6, 7.6, 1.4Hz), 7.33 (1H, ddd, J=7.6, 7.6, 1.4Hz), 7.18-7.11 (4H, m), 6.95-6.92 (1H, m), 6.89 (1H, dd, J=7.8, 1.2Hz), 4.45 (1H, q, J=6.3Hz), 3.71-3.70 (1H, m), 3.11-3.10 (2H, m), 2.99-2.82 (3H, m), 2.74 (2H, s), 2.62-2.57 (1H, m), 2.17 (3H, s), 1.57 (2H, tq, J=7.4, 7.4Hz), 1.26 (3H, d, J=6.3Hz), 1.04 (3H, s), 1.03 (3H, s), 0.86 (3H, t, J=7.4Hz). MS (ESI, m/z) 522 (M+H) ⁺ .	0.002
1-39		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.95 (1H, d, J=7.6Hz), 7.58-7.47 (3H, m), 7.38-7.36 (2H, m), 7.20 (1H, dd, J=7.6, 7.6Hz), 6.99-6.91 (2H, m), 4.76 (1H, q, J=6.3Hz), 3.78-3.76 (1H, m), 3.23-3.12 (2H, m), 2.96-2.87 (2H, m), 2.79-2.73 (1H, m), 2.18 (3H, s), 1.39 (3H, d, J=6.3Hz), 1.15 (6H, s). MS (ESI, m/z) 515 (M+H) ⁺ .	0.012

Table 15

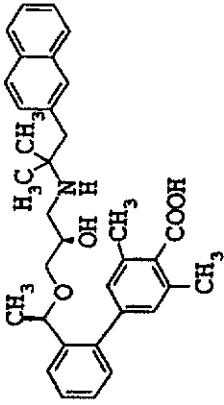
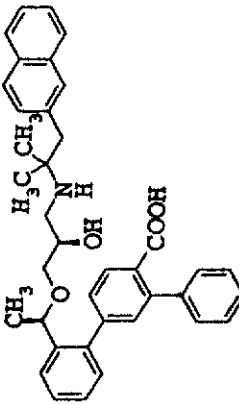
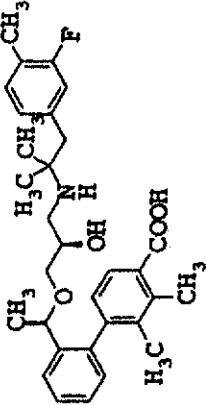
1-40		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.90-7.82 (3H, m), 7.72 (1H, s), 7.54-7.30 (6H, m), 7.15 (1H, dd, J=7.7, 1.5Hz), 6.93 (2H, s), 4.53 (1H, q, J=6.3Hz), 3.81-3.80 (1H, m), 3.21-3.16 (2H, m), 3.02-2.98 (3H, m), 2.77-2.70 (1H, m), 2.30 (6H, s), 1.29 (3H, d, J=6.3Hz), 1.16 (6H, s). MS (ESI, m/z) 526 (M+H) ⁺ .	0.003
1-41		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.85-7.76 (3H, m), 7.61-7.59 (2H, m), 7.53 (1H, dd, J=7.6, 1.0Hz), 7.47-7.39 (5H, m), 7.34-7.19 (7H, m), 7.13 (1H, d, J=1.6Hz), 4.60 (1H, q, J=6.3Hz), 3.74-3.73 (1H, m), 3.17-3.15 (2H, m), 2.83-2.80 (3H, m), 2.60-2.56 (1H, m), 1.27 (3H, d, J=6.3Hz), 0.97 (6H, s). MS (ESI, m/z) 574 (M+H) ⁺ .	0.003
1-42		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.53-7.39 (3H, m), 7.33-7.29 (1H, m), 7.15-7.11 (1H, m), 7.03-6.99 (1H, m), 6.95-6.86 (3H, m), 4.26-4.22 and 4.08-4.03 (1H, m), 3.71-3.70 (1H, m), 3.20-3.10 (2H, m), 2.83-2.80 (1H, m), 2.73-2.71 (2H, m), 2.61-2.56 (1H, m), 2.41 and 2.40 (3H, s), 2.16 (3H, s) 1.97 and 1.89 (3H, s), 1.15-1.12 (3H, m), 1.04-1.01 (6H, m). MS (ESI, m/z) 508 (M+H) ⁺ .	0.024

Table 16

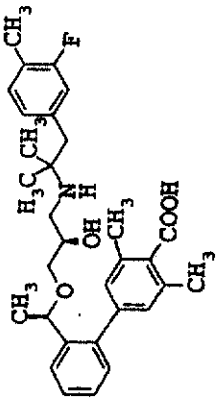
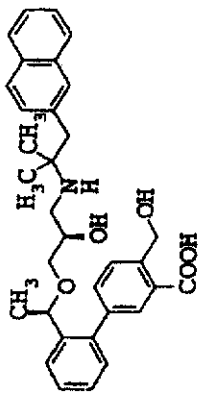
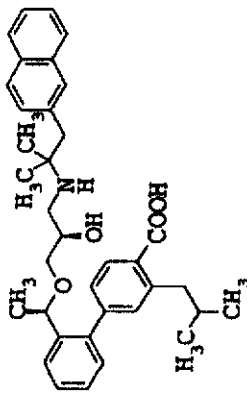
1-43		¹ H-NMR (300MHz, δ ppm, DMSO-d ₆) 7.51 (1H, dd, J=7.6, 1.2Hz), 7.40 (1H, ddd, J=7.6, 7.6, 1.2Hz), 7.31 (1H, ddd, J=7.6, 7.6, 1.4Hz), 7.20-7.16 (1H, m), 7.13 (1H, dd, J=7.6, 1.4Hz), 6.98-6.89 (4H, m), 4.50 (1H, q, J=6.3Hz), 3.78-3.77 (1H, m), 3.18-3.10 (1H, m), 2.97-2.94 (1H, m), 2.82 (2H, s), 2.71-2.66 (1H, m), 2.27 (6H, s), 2.18 (3H, s), 1.28 (3H, d, J=6.3Hz), 1.10 (3H, s), 1.09 (3H, s). MS (ESI, m/z) 508 (M+H) ⁺	0.016
1-44		¹ H-NMR (300MHz, δ ppm, DMSO-d ₆) 7.86-7.77 (3H, m), 7.70 (1H, s), 7.53-7.29 (8H, m), 7.26 (1H, dd, J=7.9, 1.8Hz), 7.18 (1H, dd, J=7.6, 1.4Hz), 4.68 (1H, d, J=13.8Hz), 4.64 (1H, d, J=13.8Hz), 4.47 (1H, q, J=6.2Hz), 3.88-3.87 (1H, m), 3.22-3.21 (2H, m), 3.05 (2H, s), 3.00-2.96 (1H, m), 2.80-2.75 (1H, m), 1.26 (3H, d, J=6.2Hz), 1.16 (6H, s). MS (ESI, m/z) 528 (M+H) ⁺	0.009
1-45		¹ H-NMR (300MHz, δ ppm, DMSO-d ₆) 7.88-7.76 (3H, m), 7.68 (1H, s), 7.56-7.31 (7H, m), 7.19-7.13 (2H, m), 7.04-7.03 (1H, m), 4.50 (1H, q, J=6.6Hz), 3.71-3.70 (1H, m), 3.18-3.09 (2H, m), 2.93-2.78 (5H, m), 2.62-2.58 (1H, m), 1.91-1.84 (1H, m), 1.26 (3H, d, J=6.6Hz), 1.07 (3H, s), 1.05 (3H, s), 0.85 (3H, d, J=2.6Hz), 0.83 (3H, d, J=2.6Hz). MS (ESI, m/z) 554 (M+H) ⁺	0.002

Table 17

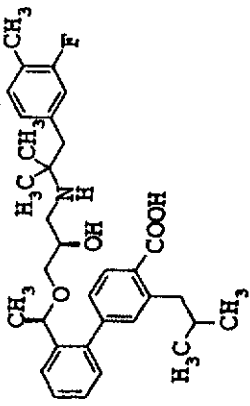
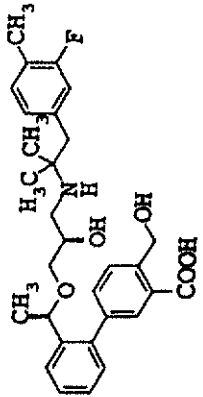
1-46		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.76 (1H, d, J=7.7Hz), 7.54 (1H, dd, J=7.7, 1.1Hz), 7.43 (1H, ddd, J=7.7, 7.7, 1.1Hz), 7.34 (1H, ddd, J=7.7, 7.7, 1.1Hz), 7.18-7.04 (4H, m), 6.95-6.87 (2H, m), 4.48 (1H, q, J=6.2Hz), 3.65-3.64 (1H, m), 3.12-3.09 (2H, m), 2.93-2.78 (2H, m), 2.70-2.66 (3H, m), 2.54-2.47 (1H, m), 2.18 (3H, s), 1.88 (1H, sept, J=6.6Hz), 1.26 (3H, d, J=6.2Hz), 0.99 (3H, s), 0.98 (3H, s), 0.85 (3H, d, J=6.6Hz), 0.84 (3H, d, J=6.6Hz). MS (ESI, m/z) 536 (M+H) ⁺ .	0.003
1-47		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.78 (1H, d, J=1.8Hz), 7.55 (1H, dd, J=7.7, 1.2Hz), 7.50 (1H, d, J=8.0Hz), 7.43 (1H, ddd, J=7.3, 7.3, 1.5Hz), 7.35 (1H, ddd, J=7.3, 7.3, 1.5Hz), 7.30 (1H, dd, J=7.7, 1.2Hz), 7.22-7.17 (2H, m), 7.01-6.92 (2H, m), 4.72 (1H, q, J=13.5Hz), 4.66 (1H, d, J=13.5Hz), 4.48 (1H, q, J=6.3Hz), 3.85-3.84 (1H, m), 3.23-3.21 (2H, m), 2.96-2.91 (1H, m), 2.86 (2H, s), 2.76-2.70 (1H, m), 2.20 (3H, s), 1.29 (3H, d, J=6.3Hz), 1.12 (6H, s). MS (ESI, m/z) 510 (M+H) ⁺ .	0.065

Table 18

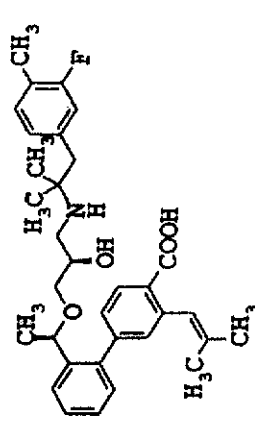
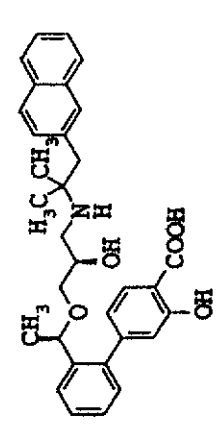
1-48		¹ H-NMR (300MHz, δ ppm, DMSO-d ₆) 7.77 (1H, d, J=7.9Hz), 7.51 (1H, dd, J=7.7, 1.1Hz), 7.41 (1H, ddd, J=7.4, 7.4, 1.4Hz), 7.31 (1H, ddd, J=7.4, 7.4, 1.1Hz), 7.15-7.10 (3H, m), 7.00 (1H, d, J=1.6Hz), 6.93-6.90 (1H, m), 6.86 (1H, dd, J=7.7, 1.4Hz), 6.72 (1H, s), 4.51 (1H, q, J=6.5Hz), 3.69-3.68 (1H, m), 3.10-3.08 (2H, m), 2.80-2.76 (1H, m), 2.70 (2H, s), 2.56-2.51 (1H, m), 2.16 (3H, s), 1.78 (3H, s), 1.67 (3H, s), 1.25 (3H, d, J=6.5Hz), 1.02 (3H, s), 1.00 (3H, s). MS (ESI, m/z) 534 (M+H) ⁺ .	0.002
1-49		¹ H-NMR (300MHz, δ ppm, DMSO-d ₆) 7.87-7.81 (3H, m), 7.70-7.68 (2H, m), 7.49-7.43 (3H, m), 7.37 (1H, ddd, J=7.4, 7.4, 1.4Hz), 7.33 (1H, dd, J=8.5, 1.8Hz), 7.28 (1H, ddd, J=7.4, 7.4, 1.4Hz), 7.14 (1H, dd, J=7.6, 1.4Hz), 6.50-6.47 (2H, m), 4.54 (1H, q, J=6.3Hz), 3.81-3.80 (1H, m), 3.17-3.03 (5H, m), 2.80-2.75 (1H, m), 1.27 (3H, d, J=6.3Hz), 1.17 (6H, s). MS (ESI, m/z) 514 (M+H) ⁺ .	0.002

Table 19

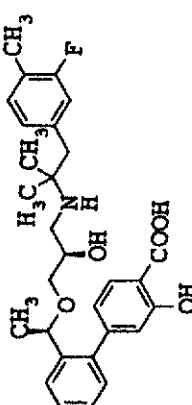
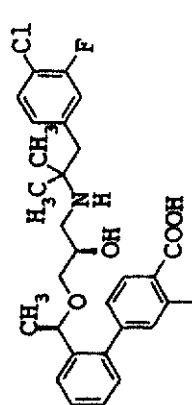
1-50		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.67 (3H, d, J=7.7Hz), 7.84 (1H, dd, J=7.9, 1.2Hz), 7.37 (1H, ddd, J=7.4, 7.4, 1.2Hz), 7.28 (1H, ddd, J=7.4, 7.4, 1.2Hz), 7.17 (1H, dd, J=7.9, 7.9Hz), 7.13 (1H, dd, J=7.4, 1.2Hz), 6.97-6.89 (2H, m), 6.48-6.45 (2H, m), 4.53 (1H, q, J=6.3Hz), 3.77-3.76 (1H, m), 3.14-3.07 (2H, m), 2.98-2.70 (4H, m), 2.17 (3H, s), 1.27 (3H, d, J=6.3Hz), 1.10 (6H, s). MS (ESI, m/z) 496 (M+H) ⁺	0.002
1-51		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.76 (1H, d, J=8.4Hz), 7.55-7.52 (1H, m), 7.45-7.40 (2H, m), 7.34 (1H, ddd, J=7.3, 7.3, 1.5Hz), 7.24-7.12 (4H, m), 7.03 (1H, dd, J=8.1, 1.5Hz), 4.46 (1H, q, J=6.3Hz), 3.66-3.59 (1H, m), 3.12-3.11 (2H, m), 2.96 (2H, q, J=7.3Hz), 2.72-2.67 (3H, m), 2.53-2.47 (1H, m), 1.26 (3H, d, J=6.3Hz), 1.17 (3H, t, J=7.3Hz), 0.99 (3H, s), 0.97 (3H, s). MS (ESI, m/z) 528 (M+H) ⁺	0.004

Table 20

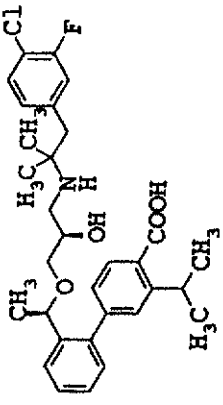
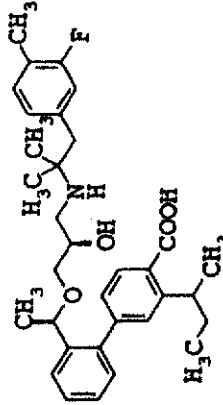
1-52		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.56 (1H, d, J=7.9Hz), 7.49 (1H, dd, J=7.9, 1.4Hz), 7.41-7.36 (2H, m), 7.30 (1H, ddd, J=7.4, 7.4, 1.4Hz), 7.18 (1H, dd, J=10.7, 1.8Hz), 7.15-7.13 (2H, m), 7.06 (1H, dd, J=7.9, 1.6Hz), 6.99 (1H, dd, J=8.3, 1.6Hz), 4.40 (1H, q, J=6.3Hz), 3.77 (1H, sept, J=7.0Hz), 3.63-3.57 (1H, m), 3.11-3.03 (2H, m), 2.71-2.43 (4H, m), 1.24 (3H, d, J=6.3Hz), 1.16 (3H, d, J=7.0Hz), 1.15 (3H, d, J=7.0Hz), 0.96 (3H, s), 0.94 (3H, s). MS (ESI, m/z) 542 (M+H) ⁺ .	0.003
1-53		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.62 (1H, d, J=7.7Hz), 7.55-7.31 (3H, m), 7.19-7.08 (4H, m), 6.95-6.87 (2H, m), 4.45 (1H, q, J=6.2Hz), 3.64-3.57 (2H, m), 3.13-3.09 (2H, m), 2.78-2.69 (3H, m), 2.56-2.53 (1H, m), 2.18 (3H, s), 1.67-1.47 (2H, m), 1.27 (3H, d, J=6.2Hz), 1.19 (3H, d, J=1.5Hz), 1.01 (3H, s), 0.99 (3H, s), 0.79-0.74 (3H, s). MS (ESI, m/z) 536 (M+H) ⁺ .	0.015

Table 21

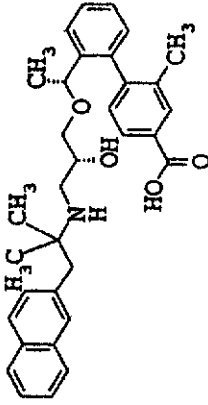
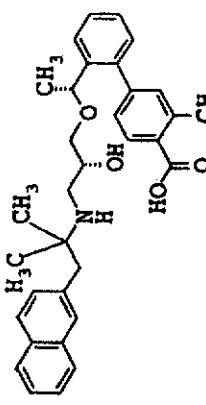
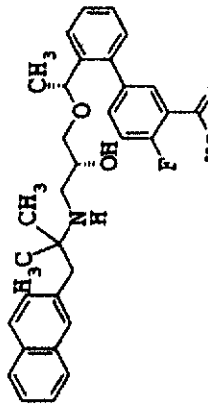
1-54		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.92-7.80 (5H, m), 7.71 (1H, s), 7.59-7.08 (8H, m), 4.23 and 4.05 (1H, q, J=6.2Hz), 3.75 (1H, brs), 3.63-3.58 (1H, m), 3.23-3.13 (1H, m), 2.96-2.91 (2H, m), 2.73-2.71 (1H, m), 2.11 and 2.04 (3H, s), 1.44 (1H, m), 1.21 (3H, d, J=6.2Hz), 1.11 (6H, brs). MS (ESI, m/z) 512 (M+H) ⁺ .	0.023
1-55		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.90-7.81 (4H, m), 7.71 (1H, s), 7.57-7.32 (6H, m), 7.21-7.18 (3H, m), 4.48 (1H, q, J=6.3Hz), 3.72 (1H, brs), 3.17-3.15 (2H, m), 2.96-2.87 (3H, m), 2.73-2.65 (1H, m), 2.58 (3H, s), 1.28 (3H, d, J=6.3Hz), 1.12 (3H, s), 1.11 (3H, s). MS (ESI, m/z) 512 (M+H) ⁺ .	0.010
1-56		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.89-7.81 (3H, m), 7.72 (1H, s), 7.63-7.13 (10H, m), 4.45 (1H, q, J=6.5Hz), 3.81 (1H, brs), 3.24-3.21 (2H, m), 3.01 (2H, s), 2.93-2.83 (1H, m), 2.77-2.67 (1H, m), 1.27 (3H, d, J=6.5Hz), 1.14 (6H, brs). MS (ESI, m/z) 516 (M+H) ⁺ .	0.019

Table 22

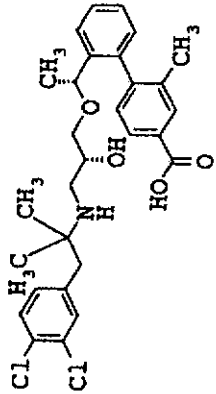
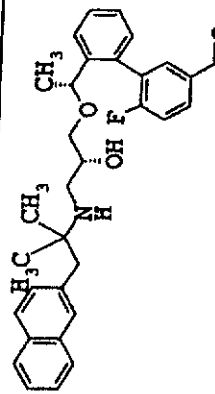
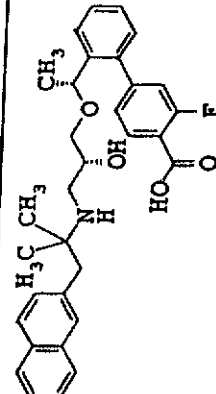
1-57		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.92 (1H, s), 7.84 (1H, t, J=6.5Hz), 7.59-7.34 (5H, m), 7.27-7.08 (3H, m), 4.21 and 4.03 (1H, q, J=6.4Hz), 3.70 (1H, brs), 3.62-3.58 (2H, m), 3.21-3.14 (2H, m), 2.80 (2H, m), 2.10 and 2.05 (3H, s), 1.22 and 1.16 (3H, d, J=6.4Hz), 1.08 (6H, brs). MS (ESI, m/z) 530 (M+H) ⁺ .	0.027
1-58		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.98-7.94 (1H, m), 7.85-7.77 (4H, m), 7.67 (1H, s), 7.56-7.50 (1H, m), 7.46-7.42 (3H, m), 7.36-7.26 (3H, m), 7.21-7.15 (1H, m), 4.25 (1H, q, J=6.5Hz), 3.78 (1H, brs), 3.13 (2H, brs), 2.97 (2H, brs), 2.93-2.85 (1H, m), 2.68-2.62 (1H, m), 1.23 (3H, brs), 1.10 (6H, brs). MS (ESI, m/z) 516 (M+H) ⁺ .	0.021
1-59		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.90-7.82 (4H, m), 7.74 (1H, s), 7.58-7.34 (6H, m), 7.23-7.12 (3H, m), 4.53 (1H, q, J=6.3Hz), 3.86 (1H, brs), 3.21-3.19 (2H, m), 3.07-3.00 (3H, m), 2.83-2.71 (1H, m), 1.29 (3H, d, J=6.3Hz), 1.19 (6H, brs). MS (ESI, m/z) 516 (M+H) ⁺ .	0.016

Table 23

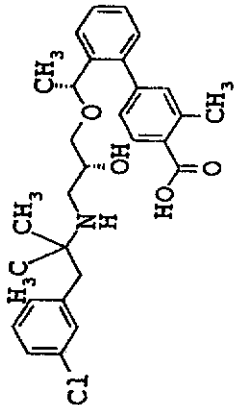
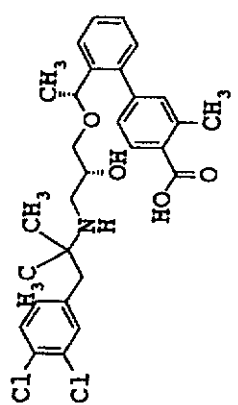
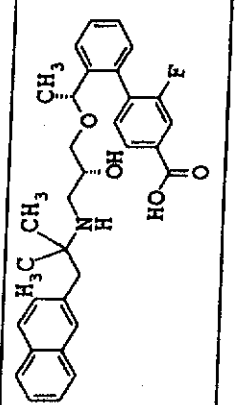
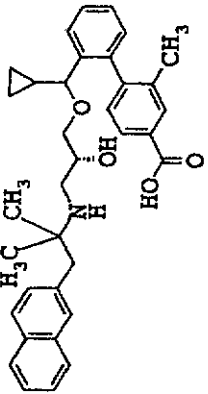
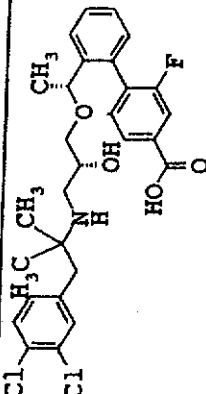
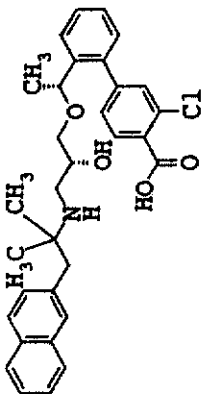
1-60		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.85-7.82 (1H, d, J=8.5Hz), 7.55 (1H, d, J=7.7Hz), 7.44 (1H, t, J=7.5Hz), 7.34 (1H, t, J=7.5Hz), 7.28-7.13 (7H, m), 4.48 (1H, q, J=6.2Hz), 3.66 (1H, brs), 3.19-3.12 (3H, m), 2.77-2.71 (3H, m), 2.56 (3H, brs), 1.27 (3H, d, J=6.2Hz), 1.01 (3H, s), 1.00 (3H, s). MS (ESI, m/z) 496 (M+H) ⁺ .	0.096
1-61		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.83 (1H, d, J=8.2Hz), 7.55-7.31 (5H, m), 7.18-7.14 (4H, m), 4.47 (1H, q, J=6.4Hz), 3.61 (1H, brs), 3.13-3.11 (3H, m), 2.70-2.64 (3H, m), 2.55 (3H, brs), 1.26 (3H, d, J=6.4Hz), 0.98 (3H, s), 0.97 (3H, s). MS (ESI, m/z) 530 (M+H) ⁺ .	0.004
1-62		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.89-7.82 (4H, m), 7.74 (2H, s), 7.59-7.35 (7H, m), 7.22-7.19 (1H, d, J=7.7Hz), 4.34 (1H, brs), 3.84 (1H, brs), 3.18 (1H, brs), 3.05-2.95 (2H, m), 2.80-2.68 (1H, m), 2.53-2.49 (2H, brs), 1.28-1.08 (9H, brs). MS (ESI, m/z) 516 (M+H) ⁺ .	0.008

Table 24

1-63		¹ H-NMR (300MHz, δ ppm, DMSO-d ₆) 7.91-7.77 (4H, m), 7.69 (1H, s), 7.61-7.57 (1H, m), 7.49-7.28 (5H, m), 7.19-7.15 (3H, m), 3.90-3.84 (2H, m), 3.68 (1H, brs), 3.34-3.21 (2H, m), 2.89-2.75 (3H, m), 2.55 (3H, s), 1.07-0.97 (7H, m), 0.42 (1H, brs), 0.30-0.18 (2H, m), -0.12 (1H, brs). MS (ESI, m/z) 538 (M+H) ⁺ .	0.016
1-64		¹ H-NMR (300MHz, δ ppm, DMSO-d ₆) 7.88-7.73 (5H, m), 7.63-7.60 (1H, m), 7.50-7.33 (5H, m), 7.22-7.04 (3H, m), 3.94-3.80 (2H, m), 3.42-3.24 (3H, m), 3.06-3.00 (2H, m), 2.88-2.75 (1H, m), 1.25-1.00 (7H, m), 0.44 (1H, brs), 0.35-0.20 (2H, m), -0.14 (1H, brs). MS (ESI, m/z) 542 (M+H) ⁺ .	0.017
1-65		¹ H-NMR (400MHz, δ ppm, DMSO-d ₆) 7.85-7.56 (7H, m), 7.47-7.23 (6H, m), 7.17 (1H, d, J=7.5Hz), 3.84 (1H, brs), 3.74-3.72 (1H, m), 3.43-3.18 (3H, m), 3.07-2.90 (2H, m), 2.78-2.68 (1H, m), 1.16-1.13 (6H, m), 0.95 (1H, brs), 0.45 (1H, brs), 0.22 (2H, brs), -0.18 (1H, brs). MS (ESI, m/z) 542 (M+H) ⁺ .	0.016

Table 25

1-66		¹ H-NMR (300MHz, δ ppm, DMSO-d ₆) 7.90-7.57 (7H, m), 7.50-7.33 (5H, m), 7.24-7.07 (2H, m), 3.87-3.85 (1H, m), 3.70 (1H, brs), 3.57-3.53 (1H, m), 3.31-3.17 (2H, m), 2.95-2.80 (2H, m), 2.77-2.65 (1H, m), 2.09 (3H, s), 1.12-1.05 (6H, brs), 0.95 (1H, brs), 0.38 (1H, brs), 0.30-0.20 (2H, m), -0.34 (1H, brs). MS (ESI, m/z) 538 (M+H) ⁺ .	0.017
1-67		¹ H-NMR (300MHz, δ ppm, DMSO-d ₆) 7.70 (1H, d, J=6.8Hz), 7.58-7.47 (4H, m), 7.39-7.27 (2H, m), 7.19 (2H, d, J=6.8Hz), 4.30 (1H, brs), 3.70 (1H, brs), 3.13 (2H, brs), 2.88-2.75 (3H, m), 2.63-2.53 (1H, m), 1.22 (3H, brs), 1.06 (6H, brs). MS (ESI, m/z) 534 (M+H) ⁺ .	0.019
1-68		¹ H-NMR (300MHz, δ ppm, DMSO-d ₆) 7.89-7.82 (3H, m), 7.73 (1H, s), 7.62-7.33 (7H, m), 7.25-7.18 (3H, m), 4.56 (1H, q, J=6.2Hz), 3.88 (1H, brs), 3.24-3.17 (2H, m), 3.08-3.03 (3H, m), 2.82-2.72 (1H, m), 1.26 (3H, d, J=6.2Hz), 1.19 (6H, brs). MS (ESI, m/z) 532 (M+H) ⁺ .	0.003

1-69		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.90-7.75 (5H, m), 7.59-7.35 (8H, m), 7.24 (1H, d, J=7.7Hz), 4.55 (1H, q, J=6.5Hz), 3.87 (1H, brs), 3.24-3.23 (2H, m), 3.05 (3H, brs), 2.83-2.73 (1H, m), 1.27 (3H, d, J=6.5Hz), 1.17 (6H, brs). MS (ESI, m/z) 543 (M+H) ⁺ .	0.002
1-70		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.88-7.77 (4H, m), 7.69 (1H, s), 7.55-7.28 (6H, m), 7.15 (1H, d, J=7.7Hz), 6.61 (1H, s), 6.40 (1H, d, J=8.0Hz), 4.55 (1H, q, J=6.6Hz), 3.70 (1H, brs), 3.16-3.14 (2H, m), 2.89 (2H, brs), 2.84-2.83 (1H, m), 2.63-2.57 (1H, m), 1.26 (3H, d, J=6.6Hz), 1.07 (3H, s), 1.05 (3H, s). MS (ESI, m/z) 513 (M+H) ⁺ .	0.005
1-71		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 8.05 (1H, d, J=7.9Hz), 7.87-7.81 (3H, m), 7.72 (1H, s), 7.53-7.29 (6H, m), 7.16 (1H, d, J=7.4Hz), 6.88 (1H, d, J=7.9Hz), 4.57 (1H, q, J=6.3Hz), 3.84 (1H, brs), 3.17-3.16 (2H, m), 3.06 (3H, brs), 2.81-2.79 (1H, m), 2.02 (3H, s), 1.29 (3H, d, J=6.3Hz), 1.19 (6H, brs). MS (ESI, m/z) 555 (M+H) ⁺ .	0.005

Table 27

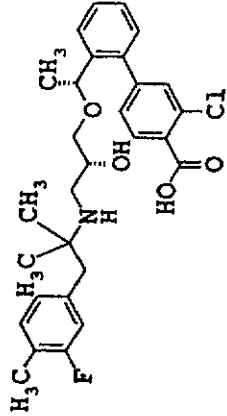
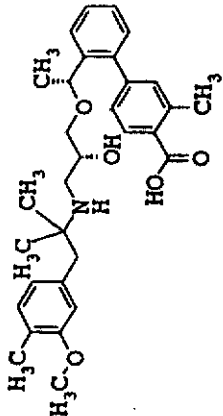
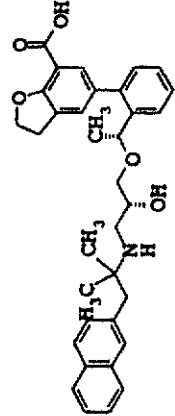
1-72		¹ H-NMR (400MHz, δ ppm, CDCl ₃) 8.01 (1H, d, J=6.7Hz), 7.60-7.54 (2H, m), 7.45 (1H, t, J=7.3Hz), 7.35 (1H, t, J=7.5Hz), 7.24-7.17 (3H, m), 6.99-6.92 (2H, m), 4.55 (1H, q, J=6.0Hz), 3.85 (1H, brs), 3.60 (1H, brs), 3.21-3.17 (1H, m), 3.03-2.95 (1H, m), 2.87 (2H, s), 2.77-2.68 (1H, m), 2.19 (3H, s), 1.28 (3H, d, J=6.0Hz), 1.13 (6H, brs). MS (ESI, m/z) 514 (M+H) ⁺ .	0.015
1-73		¹ H-NMR (300MHz, δ ppm, CDCl ₃) 7.82 (1H, d, J=8.5Hz), 7.51 (1H, d, J=8.1Hz), 7.37 (1H, t, J=7.7Hz), 7.30-7.25 (1H, m), 7.16 (1H, d, J=7.7Hz), 7.06-7.04 (3H, m), 4.56 (1H, q, J=6.6Hz), 4.20 (1H, brs), 3.79 (3H, s), 3.38-2.78 (6H, m), 2.59 (3H, s), 2.16 (3H, s), 1.37 (3H, brs), 1.28-1.26 (6H, brs). MS (ESI, m/z) 506 (M+H) ⁺ .	0.007
1-74		¹ H-NMR (300MHz, δ ppm, DMSO-d ₆) 7.88-7.78 (3H, m), 7.68-7.29 (9H, m), 7.19-7.16 (1H, d, J=7.7Hz), 4.62 (2H, t, J=8.8Hz), 4.51 (1H, q, J=6.2Hz), 3.71 (1H, brs), 3.23 (2H, t, J=8.8Hz), 3.17-3.15 (2H, m), 2.90 (2H, s), 2.83-2.75 (1H, m), 2.64-2.60 (1H, m), 1.27 (3H, d, J=6.2Hz), 1.07 (3H, s), 1.05 (3H, s). MS (ESI, m/z) 540 (M+H) ⁺ .	0.011

Table 28

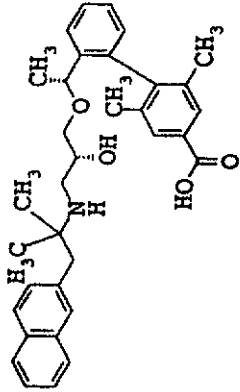
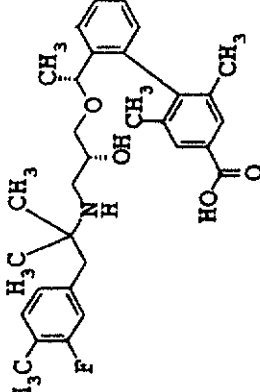
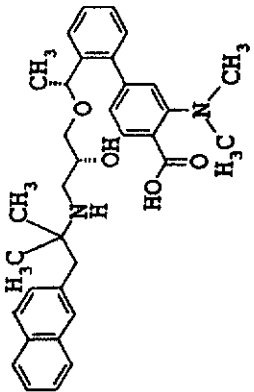
1-75		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.85-7.66 (6H, m), 7.57 (1H, d, J=7.7Hz), 7.47-7.33 (5H, m), 6.97 (1H, d, J=7.4Hz), 3.97 (1H, q, J=6.2Hz), 3.68 (1H, brs), 3.21-3.15 (2H, m), 2.86 (2H, s), 2.81-2.77 (1H, m), 2.64-2.62 (1H, m), 2.01 (3H, s), 1.91 (3H, s), 1.09 (3H, d, J=6.2Hz), 1.04 (3H, s), 1.03 (3H, s). MS (ESI, m/z) 526 (M+H) ⁺ .	0.012
1-76		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.71 (2H, d, J=7.3Hz), 7.56 (1H, d, J=7.7Hz), 7.44-7.30 (2H, m), 7.10 (1H, t, J=8.0Hz), 6.98-6.86 (3H, m), 3.94 (1H, q, J=6.3Hz), 3.63 (1H, brs), 3.17-3.16 (2H, m), 2.75-2.71 (1H, m), 2.65 (2H, brs), 2.57-2.53 (1H, m), 2.17 (3H, s), 2.02 (3H, s), 1.93 (3H, s), 1.11 (3H, d, J=6.3Hz), 0.99 (3H, s), 0.98 (3H, s). MS (ESI, m/z) 508 (M+H) ⁺ .	0.022
1-77		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.98 (1H, d, J=8.1Hz), 7.87-7.76 (2H, m), 7.66 (1H, s), 7.57-7.33 (8H, m), 7.24-7.20 (2H, m), 4.42 (1H, q, J=6.2Hz), 4.06-4.02 (1H, m), 3.68 (2H, brs), 3.16-3.11 (1H, m), 2.83-2.80 (8H, m), 2.73-2.67 (1H, m), 1.28 (3H, d, J=6.2Hz), 1.01 (3H, s), 0.99 (3H, s). MS (ESI, m/z) 541 (M+H) ⁺ .	0.021

Table 29

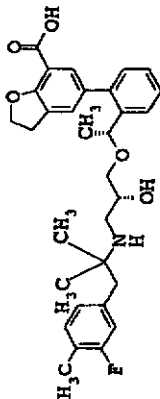
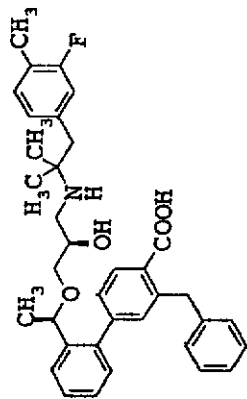
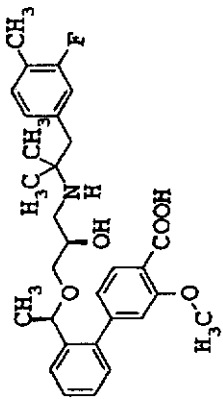
1-78		¹ H-NMR (400MHz, δ ppm, DMSO-d ₆) 7.48-7.46 (1H, d, J=7.7Hz), 7.40-7.25 (4H, m), 7.14-7.09 (2H, m), 6.93-6.85 (2H, m), 4.58 (2H, q, J=8.8Hz), 4.46 (1H, q, J=6.3Hz), 3.65 (1H, brs), 3.20 (2H, t, J=8.8Hz), 3.14-3.09 (2H, m), 2.72-2.67 (3H, m), 2.53-2.51 (1H, m), 2.15 (3H, s), 1.25 (3H, d, J=6.3Hz), 0.98 (3H, s), 0.97 (3H, s). MS (ESI, m/z) 522 (M+H) ⁺ .	0.020
1-79		¹ H-NMR (300MHz, δ ppm, DMSO-d ₆) 7.70 (1H, d, J=7.9Hz), 7.46-7.23 (3H, m), 7.22-7.04 (8H, m), 6.92-6.87 (2H, m), 6.83 (1H, dd, J=7.7, 1.2Hz), 4.44 (1H, d, J=14.4Hz), 4.35 (1H, q, J=6.5Hz), 4.33 (1H, d, J=14.4Hz), 3.63-3.61 (1H, m), 3.04-2.97 (2H, m), 2.71-2.65 (3H, m), 2.51-2.45 (1H, m), 2.15 (3H, s), 1.12 (3H, d, J=6.5Hz), 0.97 (3H, s), 0.96 (3H, s). MS (ESI, m/z) 570 (M+H) ⁺ .	0.004
1-80		¹ H-NMR (300MHz, δ ppm, DMSO-d ₆) 7.63 (1H, d, J=7.9Hz), 7.53-7.41 (2H, m), 7.33 (1H, ddd, J=7.5, 7.5, 1.2Hz), 7.21-7.13 (2H, m), 6.95-6.85 (4H, m), 4.48 (1H, q, J=6.3Hz), 3.79 (3H, s), 3.71-3.70 (1H, m), 3.13-3.11 (2H, m), 2.88-2.86 (1H, m), 2.75 (2H, s), 2.64-2.59 (1H, m), 2.17 (3H, s), 1.29 (3H, d, J=6.3Hz), 1.05 (3H, s), 1.04 (3H, s). MS (ESI, m/z) 494 (M+H) ⁺ .	0.027

Table 30

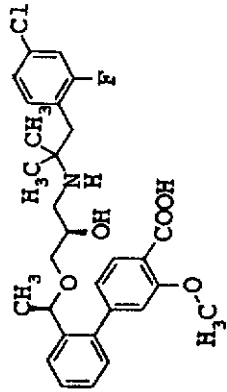
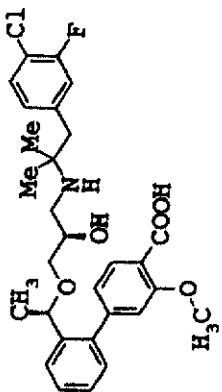
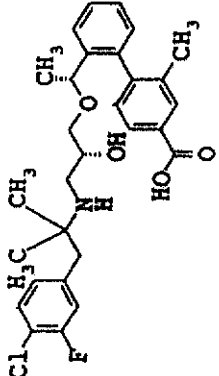
1-81		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.64 (1H, d, J=7.9Hz), 7.52 (1H, d, J=7.9Hz), 7.43-7.16 (6H, m), 6.93 (1H, s), 6.88-6.86 (1H, m), 4.47 (1H, q, J=6.4Hz), 3.79 (3H, s), 3.66-3.64 (1H, m), 3.11-3.10 (2H, m), 2.80-2.74 (2H, m), 2.58-2.53 (1H, m), 1.28 (3H, d, J=6.4Hz), 1.01 (3H, s), 1.00 (3H, s). MS (ESI, m/z) 530 (M+H) ⁺ .	0.026
1-82		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.70 (1H, d, J=8.0Hz), 7.57-7.22 (6H, m), 7.07-6.89 (3H, m), 4.49 (1H, q, J=6.2Hz), 3.83 (3H, s), 3.68-3.67 (1H, m), 3.15-3.13 (2H, m), 2.82-2.77 (3H, m), 2.63-2.57 (1H, m), 1.31 (3H, d, J=6.2Hz), 1.05 (3H, s), 1.04 (3H, s). MS (ESI, m/z) 530 (M+H) ⁺ .	0.027
1-83		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.89 (1H, brs), 7.80 (1H, t, J=8.1Hz), 7.55 (1H, t, J=6.1Hz), 7.44 (1H, t, J=7.5Hz), 7.37-7.24 (3H, m), 7.20-7.06 (3H, m), 4.20 and 4.02 (1H, q, J=6.2Hz), 3.58 (1H, brs), 3.20-3.03 (3H, m), 2.66 (3H, brs), 2.08 and 2.03 (3H, s), 1.19 and 1.13 (3H, d, J=6.2Hz), 0.96 (6H, brs). MS (ESI, m/z) 514 (M+H) ⁺ .	0.016

Table 31

1-84		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.90 (1H, brs), 7.80 (1H, t, J=8.5Hz), 7.55 (1H, t, J=6.3Hz), 7.47-7.32 (3H, m), 7.25-7.02 (4H, m), 4.21 and 4.02 (1H, q, J=6.6Hz), 3.59 (1H, brs), 3.18-3.04 (3H, m), 2.70-2.64 (3H, m), 2.09 and 2.03 (3H, s), 1.19 and 1.13 (3H, d, J=6.6Hz), 0.97 (6H, brs). MS (ESI, m/z) 514 (M+H) ⁺	0.022
1-85		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.88-7.80 (3H, m), 7.69-7.68 (2H, m), 7.53 (1H, dd, J=7.8, 1.3Hz), 7.50-7.26 (7H, m), 7.18 (1H, dd, J=7.5, 1.3Hz), 4.48 (1H, q, J=6.3Hz), 3.78 (1H, m), 3.17 (2H, d, J=5.6Hz), 2.98 (2H, s), 2.91 (1H, dd, J=12, 3.5Hz), 2.69 (1H, dd, J=12, 8.2Hz), 2.56 (3H, s), 1.28 (3H, d, J=6.3Hz), 1.13 (3H, s), 1.12 (3H, s). MS (ESI, m/z) 512 (M+H) ⁺	0.004

1-86		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.66 (1H, d, J=1.9Hz), 7.53 (1H, dd, J=7.7, 1.3Hz), 7.42 (1H, ddd, J=7.6, 7.6, 1.4Hz), 7.35-7.25 (3H, m), 7.18-7.14 (2H, m), 6.95 (1H, dd, J=11.1, 1.2Hz), 6.90 (1H, dd, J=7.7, 1.4Hz), 4.46 (1H, q, J=6.3Hz), 3.74 (1H, m), 3.14 (2H, d, J=5.6Hz), 2.84 (1H, dd, J=12.3, 3.5Hz), 2.77 (2H, s), 2.62 (1H, dd, J=12.8, 1Hz), 2.55 (3H, s), 2.18 (3H, s), 1.28 (3H, d, J=6.3Hz), 1.06 (3H, s), 1.05 (3H, s). MS (ESI, m/z) 494 (M+H) ⁺ .	0.014
1-87		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.85 (1H, d, J=8.4Hz), 7.54 (1H, d, J=7.9Hz), 7.47-7.40 (2H, m), 7.33 (1H, ddd, 7.2, 7.2, 1.2Hz), 7.25 (2H, d, 1.9Hz), 7.20-7.13 (3H, m), 4.47 (1H, q, J=6.5Hz), 3.75-3.60 (1H, m), 3.13 (2H, d, J=5.6Hz), 2.85-2.65 (3H, m), 2.60-2.55 (4H, m), 1.28 (3H, d, J=6.2Hz), 1.03 (3H, s), 1.02 (3H, s). MS (ESI, m/z) 530 (M+H) ⁺ .	0.014

1-88	¹H-NMR (400MHz, δppm, DMSO-d₆) 7.57 (1H, d, J=8.6Hz), 7.49 (1H, d, J=8.1Hz), 7.38 (2H, q, J=7.9Hz), 7.29 (1H, dd, J=7.4, 7.4Hz), 7.20 (1H, d, J=10.7Hz), 7.13 (1H, d, J=7.6Hz), 7.03-6.92 (3H, m), 4.48 (1H, q, J=6.3Hz), 3.57-3.49 (1H, m), 3.08 (2H, d, J=5.6Hz), 2.64-2.54 (3H, m), 2.52-2.37 (4H, m), 1.25 (3H, d, J=6.3Hz), 0.93 (3H, s), 0.91 (3H, s) MS (ESI, m/z) 514 (M+2H-Na)⁺	0.014
1-89	¹H-NMR (400MHz, δppm, DMSO-d₆) 7.74 (1H, d, J=7.9Hz), 7.51 (1H, dd, J=7.9, 1.2Hz), 7.40 (1H, ddd, J=7.9, 7.9, 1.4Hz), 7.31 (1H, ddd, J=7.6, 7.6, 1.2Hz), 7.17-7.04 (6H, m), 4.45 (1H, q, J=6.5Hz), 3.58-3.52 (1H, m), 3.09 (2H, d, J=5.6Hz), 2.64-2.60 (3H, m), 2.52 (3H, s), 2.46-2.40 (1H, m), 1.26 (3H, d, J=6.5Hz), 0.96 (3H, s), 0.94 (3H, s) MS (ESI, m/z) 498 (M+H)⁺	0.271

Table 34

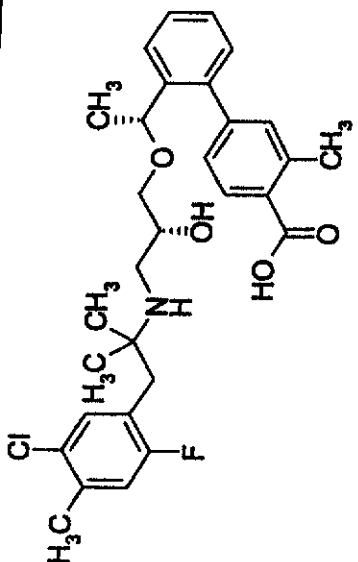
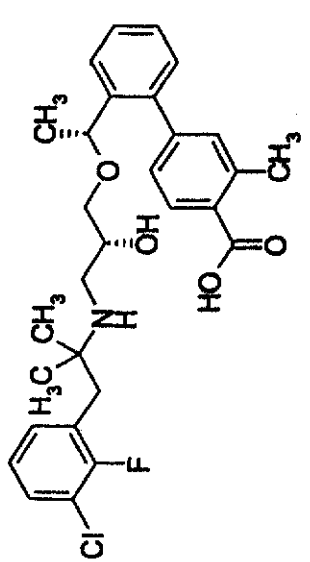
1-90		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.84 (1H, d, J=8.6Hz), 7.54 (1H, d, J=7.0Hz), 7.43 (1H, dd, J=7.7, 1.4Hz), 7.35-7.29 (2H, m), 7.19-7.16 (4H, m), 4.47 (1H, q, J=6.5Hz), 3.65 (1H, m), 3.13 (2H, d, J=5.8Hz), 2.76-2.67 (3H, m), 2.57-2.56 (4H, m), 2.28 (3H, s), 1.27 (3H, d, J=6.5Hz), 1.02 (3H, s), 1.02 (3H, s) MS (ESI, m/z) 528 (M+H) ⁺	0.005
1-91		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.87 (1H, d, J=8.4Hz), 7.57-7.54 (1H, m), 7.47-7.42 (1H, m), 7.38-7.32 (1H, m), 7.27-7.09 (5H, m), 4.46 (1H, q, J=6.2Hz), 3.68-3.64 (1H, m), 3.13 (2H, d, J=5.5Hz), 2.80-2.75 (3H, m), 2.59-2.57 (4H, m), 1.28 (3H, d, J=6.2Hz), 1.04 (3H, s), 1.03 (3H, s) MS (ESI, m/z) 514 (M+H) ⁺	0.028

Table 35

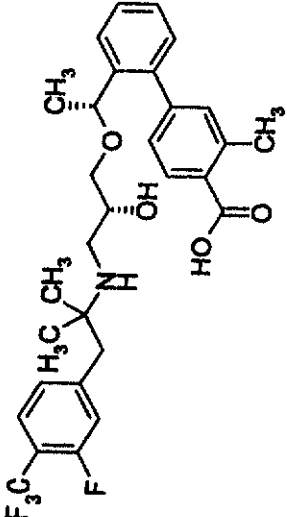
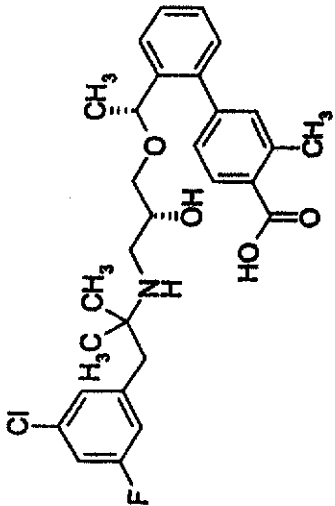
1-92		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.89-7.85 (1H, m), 7.67-7.17 (9H, m), 4.48 (1H, q, J=6.2Hz), 3.64 (1H, m), 3.13 (2H, d, J=4.8Hz), 2.83-2.68 (3H, m), 2.59-2.57 (4H, m), 1.28 (3H, d, J=6.2Hz), 1.04-0.99 (6H, m) MS (ESI, m/z) 548 (M+H) ⁺ .	0.022
1-93		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.89-7.85 (1H, m), 7.56-7.03 (9H, m), 4.48 (1H, q, J=6.2Hz), 3.64 (1H, m), 3.13 (2H, d, J=4.8Hz), 2.75-2.72 (3H, m), 2.57 (3H, s), 1.28 (3H, d, J=6.6Hz), 1.01 (3H, s), 1.00 (3H, s) MS (ESI, m/z) 514 (M+H) ⁺ .	0.027

Table 36

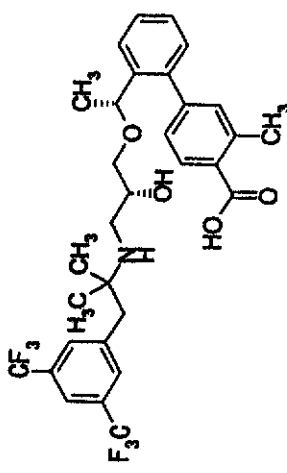
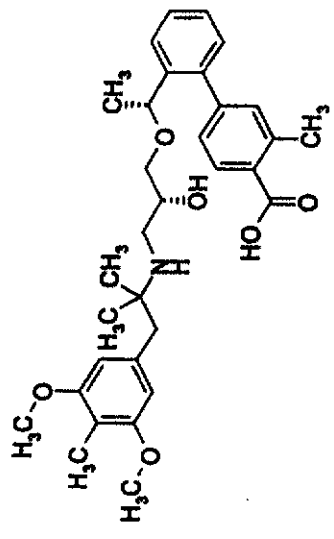
1-94		¹ H-NMR (400MHz, (ppm,DMSO-d6) 7.92-7.85 (4H,m), 7.55-7.31 (3H,m), 7.20-7.16 (3H,m), 4.46 (1H,q,J=6.6Hz), 3.61 (1H,m), 3.12 (2H,d,J=5.1Hz), 2.92-2.68 (3H,m), 2.56 (3H,s), 1.26 (3H,d,J=6.2Hz), 1.02-0.99 (6H,m) MS (ESI, m/z) 598 (M+H) ⁺ .	0.028
1-95		¹ H-NMR (400MHz, (ppm,DMSO-d6) 7.87-7.82 (1H,m), 7.54-7.33 (3H,m), 7.20-7.15 (3H,m), 6.43 (2H,s), 4.48 (1H,q,J=6.6Hz), 3.73 (6H,s), 3.71-3.70 (1H,m), 3.14 (2H,d,J=4.4Hz), 2.91-2.72 (3H,m), 2.57 (3H,s), 1.95 (3H,s), 1.27 (3H,d,J=6.2Hz), 1.12 (3H,s), 1.10 (3H,s) MS (ESI, m/z) 536 (M+H) ⁺ .	

Table 37

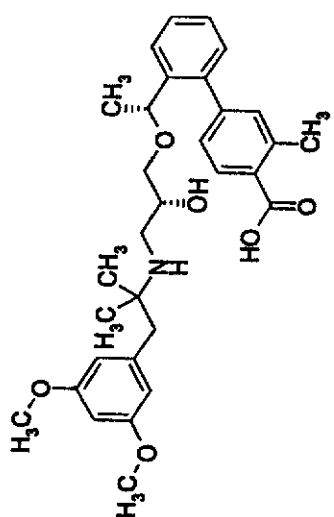
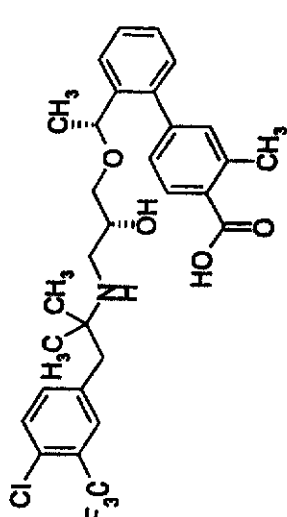
1-96		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.85-7.82 (1H, m), 7.55-7.32 (3H, m), 7.19-7.14 (3H, m), 6.38-6.33 (3H, m), 4.48 (1H, m), 3.70 (6H, s), 3.15-3.12 (2H, m), 2.56-2.654 (3H, m), 1.27 (3H, t, J=6.6Hz) 1.10-1.03 (6H, m) MS (ESI, m/z) 522 (M+H) ⁺ .	
1-97		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.89-7.84 (1H, m), 7.65-7.32 (6H, m), 7.20-7.17 (3H, m), 4.46 (1H, m), 3.64 (1H, m), 3.13 (2H, d, J=5.1Hz), 2.89-2.72 (3H, m), 2.58-2.54 (4H, m), 1.27 (3H, d, J=6.6Hz), 1.04 (3H, s), 1.02 (3H, s) MS (ESI, m/z) 564 (M+H) ⁺ .	0.106

Table 38

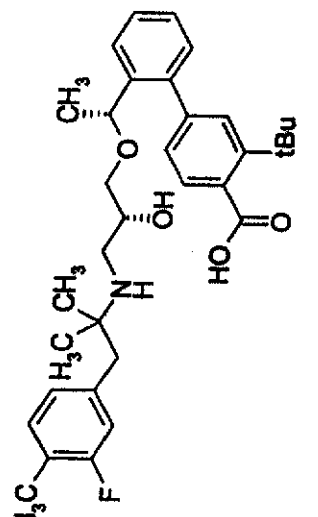
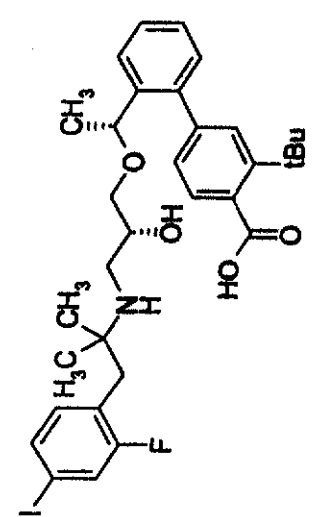
1-98		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.54 (1H, dd, $J=7.7, 1.1$ Hz), 7.47 (1H, d, $J=8.1$ Hz), 7.44-7.31 (2H, m), 7.22-7.13 (4H, m), 6.99-6.91 (2H, m), 4.49 (1H, q, $J=6.3$ Hz), 3.82-3.80 (1H, m), 3.21-3.19 (2H, m), 2.95-2.85 (3H, m), 2.74-2.67 (1H, m), 2.20 (3H, s), 1.43 (9H, s), 1.29 (3H, d, $J=6.3$ Hz), 1.12 (6H, s) MS (ESI, m/z) 536 (M+H) ⁺ .	0.013
1-99		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.55-7.29 (6H, m), 7.22-7.10 (4H, m), 4.48 (1H, q, $J=6.4$ Hz), 3.77-3.75 (1H, m), 3.19-2.65 (6H, m), 1.43 (9H, s), 1.29 (3H, d, $J=6.4$ Hz), 1.08 (6H, s) MS (ESI, m/z) 556 (M+H) ⁺ .	0.023

Table 39

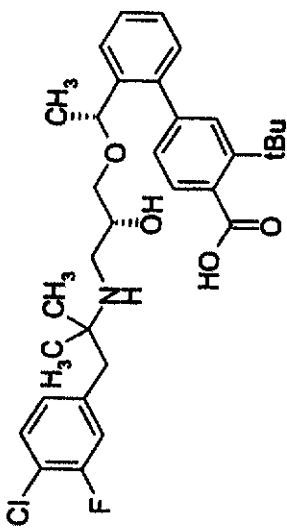
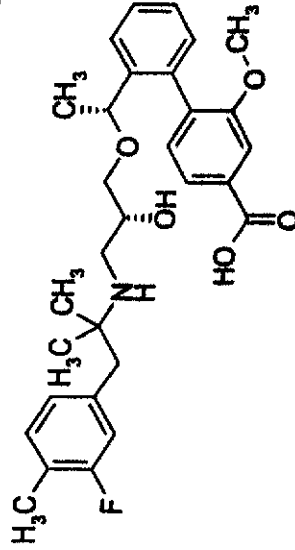
1-100		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.55-7.44 (9H, m), 7.08-7.06 (1H, m), 4.48 (1H, q, J=6.4Hz), 3.76-3.71 (1H, m), 3.19-3.17 (2H, m), 2.87-2.64 (4H, m), 1.43 (9H, s), 1.30 (3H, d, J=6.4Hz), 1.11 (6H, s) MS (ESI, m/z) 556 (M+H) ⁺ .	0.017
1-101		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.65-7.60 (2H, m), 7.53-7.29 (3H, m), 7.24-6.91 (5H, m), 4.19 (1H, q, J=6.6Hz), 3.82-2.57 (10H, m), 2.19 (3H, s), 1.29 (3H, d, J=6.6Hz), 1.13 (3H, s), 1.07 (3H, s) MS (ESI, m/z) 510 (M+H) ⁺ .	0.016

Table 40

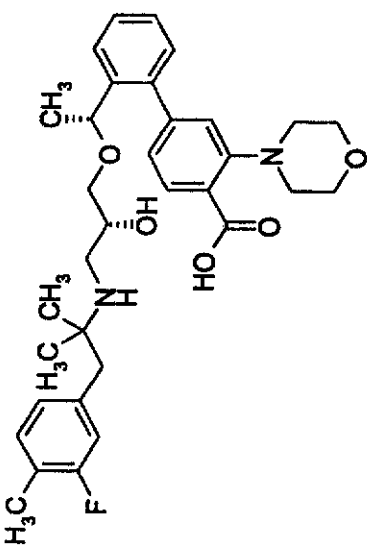
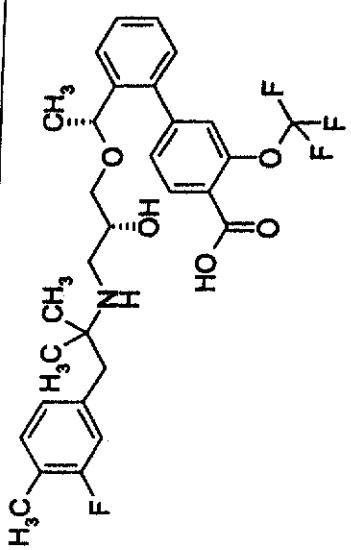
1-102		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.90 (1H, d, J=7.8Hz), 7.55 (1H, dd, J=7.9, 1.1Hz), 7.48-7.31 (3H, m), 7.23-7.12 (3H, m), 6.95-6.87 (2H, m), 4.43 (1H, q, J=6.2Hz), 3.77-3.63 (5H, m), 3.12-3.07 (6H, m), 2.75-2.47 (4H, m), 2.18 (3H, s), 1.30 (3H, d, J=6.2Hz), 1.01 (3H, s), 1.00 (3H, s) MS (ESI, m/z) 565 (M+H) ⁺ .	0.014
1-103		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.84 (1H, d, J=7.9Hz), 7.55-7.32 (4H, m), 7.21-7.15 (3H, m), 6.96-6.89 (2H, m), 4.47 (1H, q, J=5.9Hz), 3.84-3.83 (1H, m), 3.31-2.72 (6H, m), 2.17 (3H, s), 1.26 (3H, d, J=5.9Hz), 1.12 (6H, s) MS (ESI, m/z) 564 (M+H) ⁺ .	0.003

Table 41

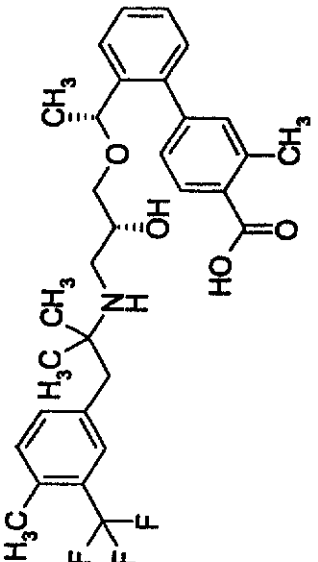
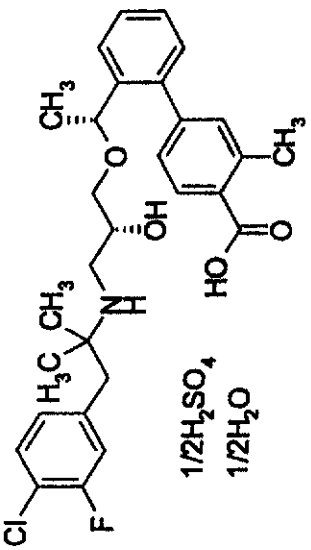
1-104		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.84 (1H, d, J=8.4Hz), 7.54 (1H, d, J=6.9Hz), 7.37-7.28 (3H, m), 7.20-7.12 (3H, m), 4.46 (1H, q, J=6.5Hz), 3.75-3.60 (1H, m), 3.13 (2H, d, J=5.6Hz), 2.85-2.75 (3H, m), 2.65-2.55 (4H, m), 2.34 (3H, s), 1.27 (3H, d, J=6.5Hz), 1.02 (3H, s) MS (ESI, m/z) 544 (M+H) ⁺ .	0.028
1-105	 1/2H ₂ SO ₄ 1/2H ₂ O	¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.87 (1H, d, J=7.9Hz), 7.54 (1H, d, J=7.9Hz), 7.35 (1H, dd, J=7.5, 7.5Hz), 7.25 (1H, d, J=10.5Hz), 7.21-7.14 (3H, m), 7.05 (1H, d, J=8.1Hz), 4.46 (1H, q, J=6.3Hz), 3.80-3.65 (1H, m), 3.13 (2H, d, J=5.4Hz), 2.95-2.75 (3H, m), 2.70-2.55 (4H, m), 1.29 (3H, d, J=6.3Hz), 1.08 (3H, s), 1.07 (3H, s) MS (ESI, m/z) 514 (M+H-1/2H ₂ SO ₄ -1/2H ₂ O) ⁺ .	0.009

Table 42

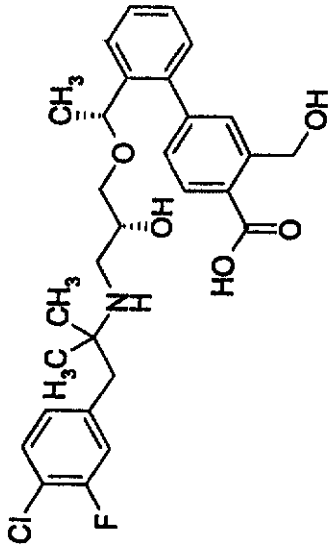
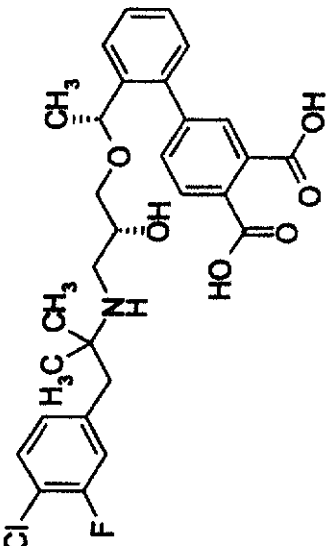
1-106		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.87 (1H, d, J=7.6Hz), 7.54 (1H, d, J=7.7Hz), 7.49-7.37 (3H, m), 7.34 (1H, dd, 7.4, 7.4Hz), 7.25 (1H, d, 10.5Hz), 7.22-7.13 (2H, m), 7.05 (1H, d, J=8.2Hz), 4.73 (2H, s), 4.49 (1H, q, J=6.3Hz), 3.75-3.60 (1H, m), 3.14 (2H, d, J=5.6Hz), 2.90-2.75 (3H, m), 2.66-2.56 (1H, m), 1.28 (3H, d, J=6.3Hz), 1.07 (3H, s), 1.05 (3H, s) MS (ESI, m/z) 530 (M+H) ⁺ .	0.020
1-107		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 8.26 (1H, d, J=7.9Hz), 8.12 (1H, d, J=1.8Hz), 7.60-7.42 (4H, m), 7.38 (1H, dd, J=7.5, 7.5Hz), 7.29 (1H, d, 10.7Hz), 7.23 (1H, d, 7.6Hz), 7.07 (1H, d, J=8.3Hz), 4.45 (1H, q, J=6.3Hz), 3.83-3.73 (1H, m), 3.20-2.71 (6H, m), 1.33 (3H, d, J=6.3Hz), 1.14 (6H, s) MS (ESI, m/z) 544 (M+H) ⁺ .	0.200

Table 43

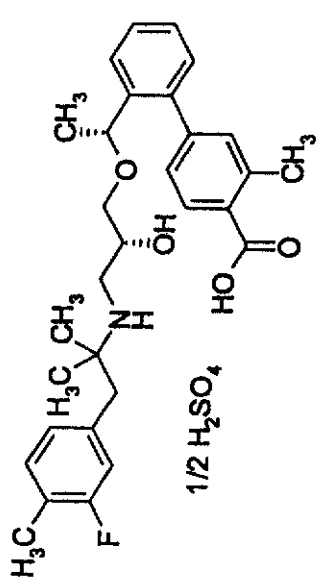
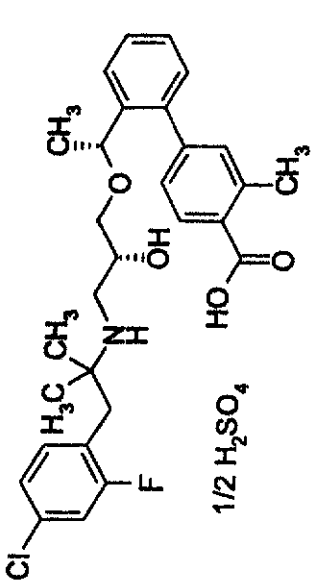
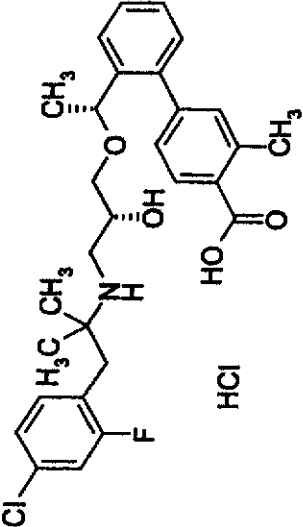
1-108	 1/2 H₂SO₄	¹ H-NMR (400MHz, δ ppm, DMSO-d ₆) 7.85 (1H, d, J=8.6Hz), 7.55 (1H, dd, J=1.1, 7.8Hz), 7.45 (1H, ddd, J=7.4, 7.4, 0.9Hz), 7.35 (1H, ddd, J=7.4, 7.4, 1.4Hz), 7.19-7.16 (4H, m), 6.98-6.90 (2H, m), 4.48 (1H, q, J=6.5Hz), 3.76 (1H, m), 3.14 (2H, d, J=5.8Hz), 2.91-2.88 (1H, m), 2.79 (2H, m), 2.66-2.61 (1H, m), 2.56 (3H, s), 2.19 (s, 3H), 1.28 (3H, d, J=6.3Hz), 1.08 (3H, s), 1.07 (3H, s) MS (ESI, m/z) 494 (M+H-1/2H ₂ SO ₄) ⁺	0.014
1-109	 1/2 H₂SO₄	¹ H-NMR (400MHz, δ ppm, DMSO-d ₆) 7.88 (1H, d, J=8.1Hz), 7.56 (1H, dd, J=7.8, 1.2Hz), 7.46 (1H, ddd, J=7.4, 7.4, 1.2Hz), 7.41-7.29 (4H, m), 7.24-7.18 (3H, m), 4.47 (1H, q, J=6.3Hz), 3.74 (1H, m), 3.13 (2H, d, J=5.3Hz), 2.91-2.84 (3H, m), 2.68-2.61 (1H, m), 2.57 (3H, s), 1.28 (3H, d, J=6.5Hz), 1.08 (6H, s) MS (ESI, m/z) 514 (M+H-1/2H ₂ SO ₄) ⁺	0.015

Table 44

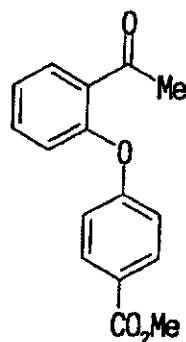
1-110	 HCl	¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 12.89 (1H, s), 8.97 (1H, s), 8.60 (1H, s), 7.91 (1H, d, J=7.6Hz), 7.58 (1H, d, J=7.9Hz), 7.49-7.44 (3H, m), 7.39-7.19 (5H, m), 4.48 (1H, q, J=6.2Hz), 3.92 (1H, m), 3.20-2.97 (5H, m), 2.79 (1H, m), 2.59 (3H, s), 2.50 (3H, s), 1.32 (3H, d, J=6.5Hz), 1.18 (6H, m) MS (ESI, m/z) 514 (M+H-Cl) ⁺ .	0.026
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Example 2-1

4-[2-[(1R)-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]benzoic acid

5 Step 1

methyl 4-(2-acetylphenoxy)benzoate

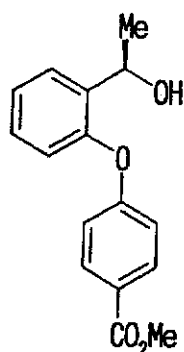


2'-Fluoroacetophenone (10.6 g), methyl 4-hydroxybenzoate (11.7 g) and potassium carbonate (11.2 g) were suspended in dimethylacetamide (70 ml), and the mixture was stirred at 140°C for one day. The reaction mixture was cooled to room temperature and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (n-hexane:ethyl acetate=7:1) to give the title compound (8.62 g).

¹H-NMR (300MHz, δppm, CDCl₃) 8.03 (2H, d, J=6.6Hz), 7.88 (1H, m), 7.50 (1H, m), 7.27 (1H, m), 7.01-6.98 (3H, m), 3.90 (3H, s), 2.57 (3H, s).

Step 2

methyl 4-[2-((1R)-hydroxyethyl)phenoxy]benzoate



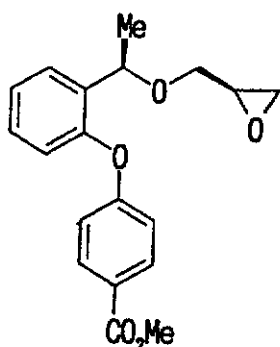
Methyl 4-(2-acetylphenoxy)benzoate (3.0 g) obtained in Step 1, dichloro[(S)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl][(S)-1,1'-bis(p-methoxyphenyl)-2-isopropylethane-
 5 1,2-diamine]ruthenium(II) (68 mg) and potassium-tert-butoxide (301 mg) were suspended in isopropanol (30 ml), and the suspension was hydrogenated (3.0 kgf/cm²) at room temperature for 4.5 hrs at medium pressure. Water (150 ml) was added to the reaction mixture, and the mixture was
 10 extracted with ethyl acetate (150 ml) and washed with brine. The organic layer was dried over sodium sulfate, and concentrated under reduced pressure. The obtained residue was dissolved in tetrahydrofuran (60 ml) and methanol (60 ml) and 4N-lithium hydroxide solution (15 ml) was added. The
 15 mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure and 1N-hydrochloric acid (120 ml) was added. The mixture was extracted with ethyl acetate (150 ml). The organic layer was washed successively with water (50 ml) and brine (50 ml),
 20 dried over sodium sulfate, and concentrated under reduced pressure. The obtained residue was dissolved in methanol (100 ml) and 4-dimethylaminopyridine (142 mg) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (2.49 g) were added. The mixture was stirred for 26 hrs. The
 25 reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column

chromatography (hexane:ethyl acetate=5:1-4:1) to give the title compound (2.63 g).

¹H-NMR(300MHz,δppm,CDCl₃) 8.00(2H,d,J=7.7Hz), 7.59(1H,m),
7.30-7.21(2H,m), 6.97-6.91(3H,m), 5.13(1H,d,J=6.5Hz),
5 3.90(3H,s), 1.48(3H,d,J=6.5Hz).

Step 3

methyl 4-[2-[(1R)-(R)-oxiranylmethoxy]ethyl]phenoxy]benzoate



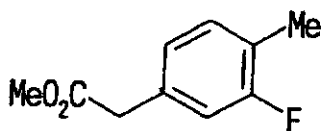
10 Methyl 4-[2-((1R)-hydroxyethyl)phenoxy]benzoate (3.62 g) obtained in Step 2 was dissolved in tetrahydrofuran (15 ml). The mixture was ice-cooled and sodium hydride (471 mg, 60% in oil) was added. The mixture was stirred for 3 min. Then, (R)-glycidyl 3-nitrobenzenesulfonate (3.62 g) and
15 dimethyl sulfoxide (3 ml) were added and the mixture was stirred overnight at room temperature. 10% Aqueous citric acid solution (80 ml) was added to the reaction mixture and the mixture was extracted with ethyl acetate (150 ml). The organic layer was washed successively with water (50 ml) and
20 brine (50 ml), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=4:1-3:1) to give the title compound (315 mg).

25 ¹H-NMR(300MHz,δppm,CDCl₃) 7.99(2H,d,J=6.6Hz), 7.57(1H,m), 7.31-7.23(2H,m), 6.96-6.90(3H,m), 4.80(1H,d,J=6.6Hz),

3.89 (3H,s) , 3.55 (1H,m) , 3.26 (1H,m) , 3.25 (1H,m) , 2.74 (1H,m) ,
2.51 (1H,m) , 1.41 (3H,d,J=6.6Hz) .

Step 4

methyl (3-fluoro-4-methylphenyl)acetate

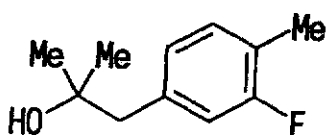


(3-Fluoro-4-methylphenyl)acetic acid (105.3 g) was dissolved in methanol (740 ml). Concentrated sulfuric acid (9.9 ml) was added and the mixture was stirred at 85°C for 1 hr. The reaction mixture was allowed to return to room
10 temperature, and concentrated under reduced pressure. Water was added to the obtained residue and the mixture was extracted with ethyl acetate (1 L). The organic layer was washed successively with water, saturated aqueous sodium hydrogencarbonate solution, water and brine, dried over
15 anhydrous sodium sulfate, and concentrated under reduced pressure to give the title compound (114.2 g).

¹H-NMR(300MHz,δppm,CDCl₃) 7.14-7.10 (1H,m) , 6.96-6.93 (2H,m) , 3.70 (3H,s) , 3.58 (2H,s) , 2.25-2.24 (3H,s) .

Step 5

20 1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-ol



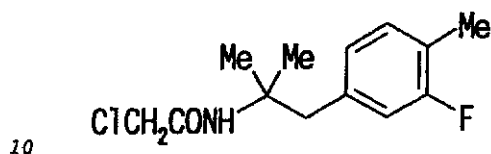
Methyl (3-fluoro-4-methylphenyl)acetate (114.2 g) obtained in Step 4 was dissolved in tetrahydrofuran (800 ml) and 1M-methylmagnesium bromide (1.56 L) was added dropwise
25 under argon streams at 0°C. The mixture was stirred at room temperature for 1 hr. The reaction mixture was ice-cooled, saturated aqueous ammonium chloride solution (155 ml) was

added dropwise and then magnesium sulfate (280 g) was added. The reaction mixture was filtered and the filtrate was dried over magnesium sulfate, and concentrated under reduced pressure to give the title compound (130.1 g).

5 $^1\text{H-NMR}$ (300MHz, δppm , CDCl_3) 7.11-7.08 (1H,m), 6.88-6.86 (2H,m), 2.71 (2H,s), 2.25 (3H,s), 1.22 (6H,s).

Step 6

2-chloro-N-[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]acetamide

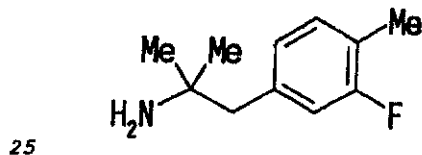


1-(3-Fluoro-4-methylphenyl)-2-methylpropan-2-ol (130.1 g) obtained in Step 5 was dissolved in chloroacetonitrile (139 ml) and acetic acid (115 ml), and concentrated sulfuric acid (33.4 ml) was added dropwise under ice-cooling. The mixture was stirred at room temperature for 2 hrs and 4N-
15 aqueous sodium hydroxide solution (160 ml) was added dropwise under ice-cooling. The mixture was extracted twice with toluene and twice with ethyl acetate. The organic layer was washed twice with 10% brine and concentrated under
20 reduced pressure to give the title compound (131.6 g).

$^1\text{H-NMR}$ (300MHz, δppm , CDCl_3) 7.10-7.06 (1H,m), 6.80-6.76 (2H,m), 6.19 (1H,brs), 3.95 (2H,s), 3.00 (2H,s), 2.24 (3H,s), 1.37 (6H,s).

Step 7

[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amine



2-Chloro-N-[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]acetamide (131.6 g) obtained in Step 6 was dissolved in

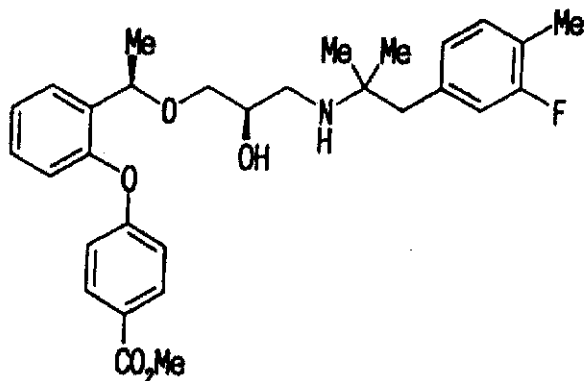
acetic acid (200 ml) and ethanol (1 L), and thiourea (46.6 g) was added. The mixture was stirred overnight at 100°C. The reaction mixture was cooled to room temperature, and the precipitated crystals were filtered. The filtrate was concentrated under reduced pressure, and 4N-sodium hydroxide solution (300 ml) was added to the obtained residue. The mixture was extracted 3 times with toluene. The organic layer was washed with brine, and concentrated under reduced pressure. The obtained residue was dissolved in diethyl ether (1 L) and 4N-hydrochloric acid/ethyl acetate solution (255 ml) was added dropwise under ice-cooling. The mixture was stirred for 1 hr and the precipitated crystals were collected by filtration. The obtained crystals were added to a mixture of toluene and 4N-aqueous sodium hydroxide solution. The toluene layer was separated, washed twice with water, and concentrated under reduced pressure to give the title compound (57.9 g).

$^1\text{H-NMR}$ (300MHz, δ ppm, CDCl_3) 7.11–7.07 (1H, m), 6.85–6.82 (2H, m), 2.61 (2H, s), 2.25 (3H, s), 1.11 (6H, s).

MS (APCI, m/z) 182 (M+H) $^+$.

Step 8

methyl 4-[2-[(1R)-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]benzoate



Methyl 4-[2-[(1R)-((R)-

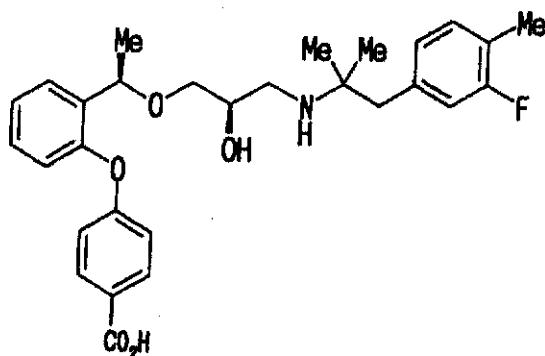
oxiranylmethoxy)ethyl]phenoxy]benzoate (109 mg) obtained in Step 3 was dissolved in toluene (3 ml), and [1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amine (87 mg) obtained in Step 7 and lithium perchlorate (51 mg) were added successively. The mixture was stirred at room temperature for 15 hrs. The reaction mixture was concentrated under reduced pressure and the obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=1:1-chloroform:methanol=10:1) to give the title compound (193 mg).

$^1\text{H-NMR}$ (400MHz, δ ppm, CDCl_3) 7.99 (2H, d, $J=6.9\text{Hz}$), 7.49 (1H, dd, $J=5.4, 2.1\text{Hz}$), 7.35-7.20 (2H, m), 7.15-7.10 (1H, m), 7.00-6.80 (5H, m), 4.72 (1H, q, $J=6.5\text{Hz}$), 4.20-4.10 (1H, m), 3.89 (3H, s), 3.50-3.35 (2H, m), 3.30-3.20 (1H, m), 3.10-2.80 (3H, m), 2.22 (3H, s), 1.40-1.20 (9H, m).

MS (ESI, m/z) 510 ($M+H$) $^+$.

Step 9

4-[2-[(1R)-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]benzoic acid



Methyl 4-[2-[(1R)-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]benzoate (185 mg) obtained in Step 8 was dissolved in methanol (3 ml) and tetrahydrofuran (3 ml), and 2N-sodium hydroxide solution (1.5 ml) was added.

The mixture was stirred at room temperature for 4 hrs. The reaction mixture was concentrated under reduced pressure and the obtained residue was diluted with water. 10% Aqueous citric acid solution was added, and the resulting precipitate was collected by filtration to give the title compound (152 mg).

$^1\text{H-NMR}$ (300MHz, δ ppm, DMSO- d_6) 7.93 (2H, d, $J=8.7\text{Hz}$), 7.55 (1H, d, $J=7.5\text{Hz}$), 7.40-7.25 (2H, m), 7.20-7.10 (1H, m), 7.05-6.85 (5H, m), 4.68 (1H, q, $J=6.3\text{Hz}$), 3.80-3.65 (1H, m), 3.24 (2H, d, $J=5.4\text{Hz}$), 2.85-2.55 (4H, m), 2.19 (3H, s), 1.32 (3H, d, $J=6.3\text{Hz}$), 1.03 (3H, s), 1.02 (3H, s).

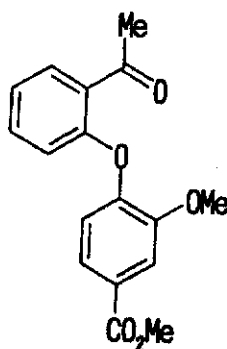
MS (ESI, m/z) 496 ($M+H$) $^+$.

Example 2-2

4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]-3-methoxybenzoic acid

Step 1

methyl 4-(2-acetylphenoxy)-3-methoxybenzoate

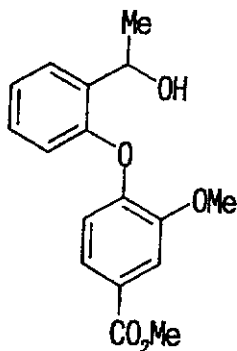


2'-Fluoroacetophenone (1.38 g) and methyl 4-hydroxy-3-methoxybenzoate (1.82 g) were dissolved in dimethylformamide (10 ml), and potassium carbonate (1.45 g) was added. The mixture was stirred at 100°C for 15 hrs. The reaction mixture was cooled to room temperature, and water was added. The mixture was extracted with ethyl acetate. The organic layer was washed successively with water and brine and dried over sodium sulfate. The obtained residue was purified by

silica gel column chromatography (hexane:ethyl acetate=5:1)
to give the title compound (1.25 g).

Step 2

methyl 4-[2-(1-hydroxyethyl)phenoxy]-3-methoxybenzoate

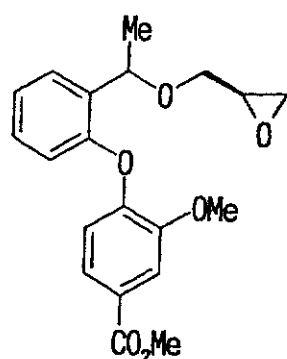


Methyl 4-(2-acetylphenoxy)-3-methoxybenzoate (1.24 g)
obtained in Step 1 was dissolved in methanol (20 ml), and
after ice-cooling, sodium borohydride (312 mg) was added.
The mixture was stirred for 2 hrs. The reaction mixture was
10 concentrated under reduced pressure, and water was added.
The mixture was extracted with ethyl acetate. The organic
layer was washed successively with 5% aqueous citric acid
solution and brine, and dried over sodium sulfate. The
obtained residue was purified by silica gel column
15 chromatography (hexane:ethyl acetate=3:1) to give the title
compound (834 mg).

¹H-NMR(300MHz,δppm,CDCl₃) 7.70-7.50(3H,m), 7.25-7.10(2H,m),
6.90(1H,d,J=8.4Hz), 6.77(1H,dd,J=6.6, 1.5Hz), 5.25-
5.15(1H,m), 3.94(3H,s), 3.93(3H,s), 2.53(1H,d,J=4.2Hz),
20 1.53(3H,d,J=6.6Hz).

Step 3

methyl 3-methoxy-4-[2-[1-((R)-
oxiranylmethoxy)ethyl]phenoxy]benzoate

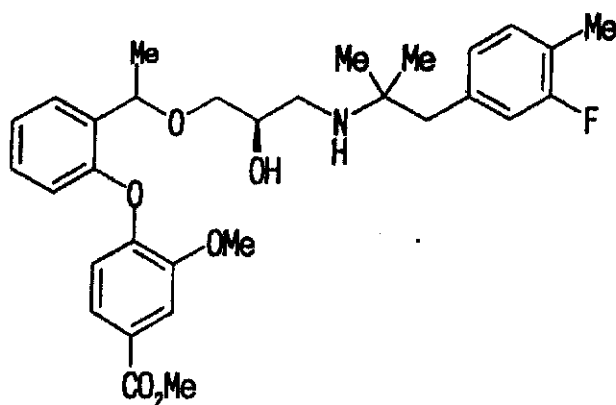


In the same manner as in Step 3 of Example 2-1, the title compound (150 mg) was obtained from methyl 4-[2-(1-hydroxyethyl)phenoxy]-3-methoxybenzoate (660 mg) obtained in
 5 Step 2.

$^1\text{H-NMR}$ (400MHz, δ ppm, CDCl_3) 7.70-7.50 (3H, m), 7.25-7.15 (2H, m), 6.80-6.70 (2H, m), 4.87 (1H, q, $J=6.4\text{Hz}$), 3.91 (6H, s), 3.60-3.50 (1H, m), 3.40-3.25 (1H, m), 3.15-3.10 (1H, m), 2.80-2.70 (1H, m), 2.60-2.50 (1H, m), 1.45-1.40 (3H, m).

10 Step 4

methyl 4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]-3-methoxybenzoate



15 In the same manner as in Step 8 of Example 2-1, the title compound (189 mg) was obtained from methyl 3-methoxy-4-[2-[1-((R)-oxiranylmethoxy)ethyl]phenoxy]benzoate (146 mg) obtained in Step 3 and 1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-ylamine (89 mg) obtained in Step 7 of Example

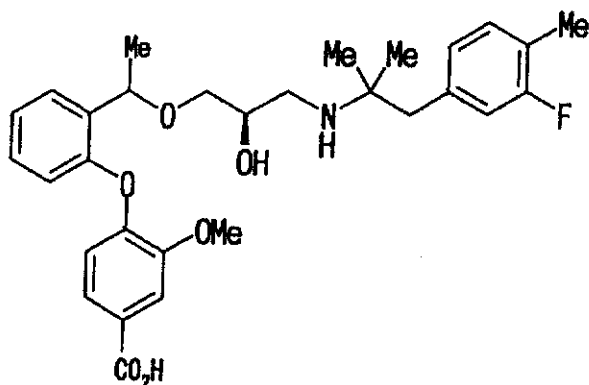
2-1.

$^1\text{H-NMR}$ (400MHz, δppm , CDCl_3) 7.65-7.45 (3H, m), 7.25-7.00 (3H, m),
6.85-6.70 (4H, m), 4.83 (1H, d, $J=6.3\text{Hz}$), 3.90 (6H, s), 3.80-
3.70 (1H, m), 3.40-3.30 (2H, m), 2.85-2.55 (4H, m), 2.23 (3H, s),
5 1.45-1.35 (3H, m), 1.05 (6H, s).

MS (ESI, m/z) 540 ($M+H$) $^+$

Step 5

4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-
methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]-3-
10 methoxybenzoic acid



In the same manner as in Step 9 of Example 2-1, the
title compound (160 mg) was obtained from methyl 4-[2-[1-
[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-
15 yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]-3-methoxybenzoate
(180 mg) obtained in Step 4.

$^1\text{H-NMR}$ (300MHz, δppm , $\text{DMSO}-d_6$) 7.70-7.45 (3H, m), 7.30-7.10 (3H, m),
7.05-6.85 (3H, m), 6.75-6.70 (1H, m), 4.81 (1H, q, $J=6.0\text{Hz}$), 3.90-
3.70 (4H, m), 3.30 (2H, d, $J=5.1\text{Hz}$), 2.95-2.60 (4H, m), 2.19 (3H, s),
20 1.36 (3H, d, $J=6.0\text{Hz}$), 1.05 (6H, s).

MS (ESI, m/z) 496 ($M+H$) $^+$.

Examples 2-3 to 2-36

Examples 2-3 to 2-36 were obtained based on Examples 2-
1 and 2-2. The results are shown in Tables 45-60.

Table 45

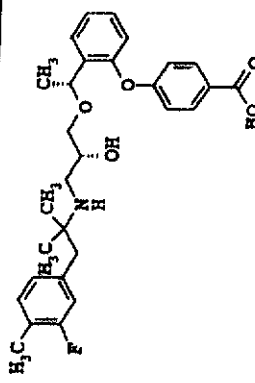
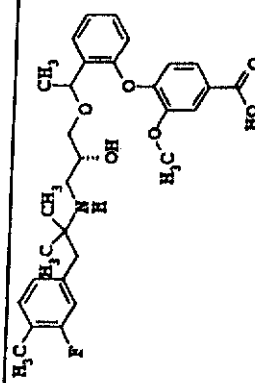
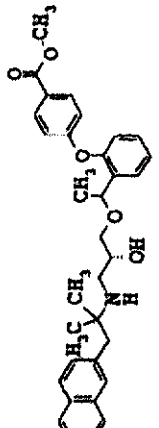
Ex. No.	Structural formula	Property data	Reporter gene assay (μM)
2-1		$^1\text{H-NMR}$ (300MHz, δppm , DMSO-d_6) 7.93 (2H, d, $J=8.7\text{Hz}$), 7.55 (1H, d, $J=7.5\text{Hz}$), 7.20-7.10 (1H, m), 7.05-6.85 (5H, m), 4.68 (1H, q, $J=6.3\text{Hz}$), 3.80-3.65 (1H, m), 3.24 (2H, d, $J=5.4\text{Hz}$), 2.85-2.55 (4H, m), 2.19 (3H, s), 1.32 (3H, d, $J=6.3\text{Hz}$), 1.03 (3H, s), 1.02 (3H, s). MS (ESI, m/z) 496 ($\text{M}+\text{H}$) ⁺ .	0.015
2-2		$^1\text{H-NMR}$ (300MHz, δppm , DMSO-d_6) 7.70-7.45 (3H, m), 7.30-7.10 (3H, m), 7.05-6.85 (3H, m), 6.75-6.70 (1H, m), 4.81 (1H, q, $J=6.0\text{Hz}$), 3.90-3.70 (4H, m), 3.30 (2H, d, $J=5.1\text{Hz}$), 2.95-2.60 (4H, m), 2.19 (3H, s), 1.36 (3H, d, $J=6.0\text{Hz}$), 1.05 (6H, s). MS (ESI, m/z) 496 ($\text{M}+\text{H}$) ⁺ .	0.021
2-3		$^1\text{H-NMR}$ (300MHz, δppm , DMSO-d_6) 8.00-7.75 (5H, m), 7.69 (1H, s), 7.65-7.25 (6H, m), 7.15-6.95 (3H, m), 4.66 (1H, q, $J=6.6\text{Hz}$), 3.81 (3H, s), 3.75-3.65 (1H, brs), 3.30-3.15 (2H, m), 3.00-2.55 (4H, m), 1.40-1.30 (3H, m), 1.07 (6H, s). MS (ESI, m/z) 528 ($\text{M}+\text{H}$) ⁺ .	0.071

Table 46

2-4		¹ H-NMR (300MHz, δ ppm, DMSO-d ₆) 8.00-7.75 (5H, m), 7.70 (1H, s), 7.65-7.20 (6H, m), 7.10-6.85 (3H, m), 4.70 (1H, q, J=6.4Hz), 3.90-3.70 (1H, m), 3.35-3.20 (2H, m), 3.00-2.40 (4H, m), 1.31 (3H, d, J=6.4Hz), 1.10 (6H, s) MS (ESI, m/z) 514 (M+H) ⁺	0.010
2-5		¹ H-NMR (300MHz, δ ppm, DMSO-d ₆) 8.74 (1H, s), 8.12 (1H, s), 8.05-7.80 (4H, m), 7.71 (1H, dd, J=7.6, 7.6Hz), 7.64-7.25 (4H, m), 7.10-6.60 (3H, m), 4.67 (1H, q, J=6.2Hz), 3.80-3.60 (1H, m), 3.55-3.00 (2H, m), 2.95-2.55 (4H, m), 1.40-1.20 (3H, m), 1.20-0.95 (6H, m) MS (ESI, m/z) 515 (M+H) ⁺	0.057
2-6		¹ H-NMR (300MHz, δ ppm, DMSO-d ₆) 7.93 (2H, d, J=8.7Hz), 7.60-7.50 (1H, m), 7.40-7.20 (5H, m), 7.05-6.90 (3H, m), 4.66 (1H, q, J=6.3Hz), 3.75-3.65 (1H, m), 3.30-3.20 (2H, m), 2.80-2.50 (4H, m), 1.31 (3H, d, J=6.3Hz), 1.01 (3H, s), 1.00 (3H, s). MS (ESI, m/z) 516 (M+H) ⁺	0.022
2-7		¹ H-NMR (300MHz, δ ppm, DMSO-d ₆) 7.95 (2H, d, J=8.7Hz), 7.58 (1H, s), 7.55-7.29 (2H, m), 7.21 (1H, m), 7.04-6.93 (5H, m), 4.70 (1H, q, J=6.2Hz), 3.90 (1H, m), 3.30-3.26 (2H, m), 3.00-2.72 (4H, m), 2.20 (3H, s), 1.34 (3H, d, J=6.2Hz), 1.15 (6H, s). MS (ESI, m/z) 496 (M+H) ⁺	0.017

Table 47

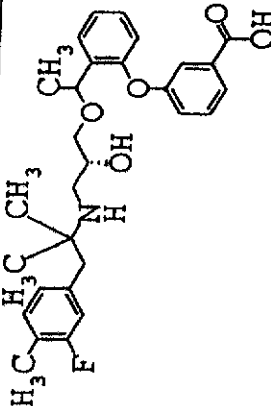
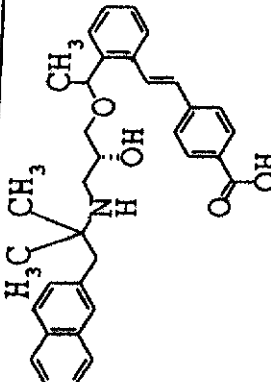
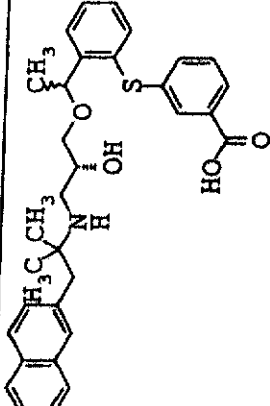
2-8		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.63 (1H, d, J=7.2Hz), 7.53 (1H, m), 7.42 (1H, m), 7.34-7.14 (5H, m), 6.97-6.89 (3H, m), 4.71 (1H, q, J=6.3Hz), 3.76 (1H, m), 3.32-3.21 (2H, m), 2.86-2.62 (2H, m), 2.75 (2H, s), 2.18 (3H, s), 1.32 (3H, d, J=6.3Hz), 1.05 (6H, s). MS (ESI, m/z) 496 (M+H) ⁺ .	0.054
2-9		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.95 (2H, d, J=7.7Hz), 7.85-7.66 (8H, m), 7.46-7.42 (3H, m), 7.35-7.30 (3H, m), 7.17 (1H, d, J=16.2Hz), 4.99 (1H, q, J=6.5Hz), 3.91 (1H, m), 3.45 (1H, m), 3.40 (1H, m), 2.95 (1H, m), 2.93 (2H, s), 2.73 (1H, m), 1.39 (3H, d, J=6.5Hz), 1.08 (6H, s). MS (ESI, m/z) 524 (M+H) ⁺ .	0.016
2-10		¹ H-NMR (500 MHz, δ ppm, CD ₃ OD) 7.92-7.16 (15H, m), 5.07-5.02 (1H, m), 3.96-3.90 (1H, m), 3.40-3.32 (1H, m), 3.28-3.11 (4H, m), 3.04-2.98 (1H, m), 1.42-1.30 (9H, m). MS (ESI, m/z) 530 (M+H) ⁺ .	0.027

Table 48

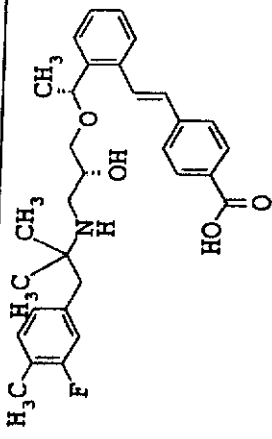
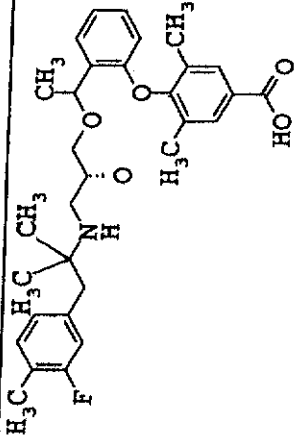
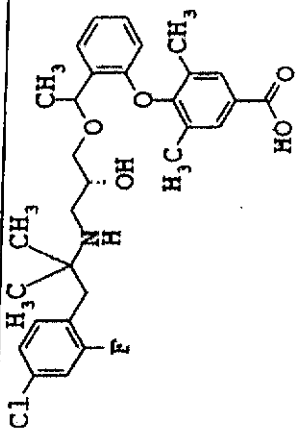
2-11		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.95(2H, d, J=8.0Hz), 7.78-7.69(4H, m), 7.44-7.31(3H, m), 7.20-7.11(2H, m), 6.95-6.86(2H, m), 4.97(1H, q, J=6.6Hz), 3.81(1H, brs), 3.39-3.25(3H, m), 2.83-2.77(1H, m), 2.66(2H, s), 2.61-2.55(1H, m), 2.17(3H, s), 1.38(3H, d, J=6.6Hz), 0.98(6H, brs). MS (ESI, m/z) 506 (M+H) ⁺ .	0.021
2-12		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.74-7.69(2H, m), 7.47-7.42(1H, m), 7.13-6.87(5H, m), 6.15(1H, d, J=8.1Hz), 5.03(1H, q, J=6.3Hz), 3.75(1H, brs), 3.35-3.33(3H, m), 2.78-2.76(1H, m), 2.65-2.51(2H, m), 2.15(3H, s), 2.07(3H, s), 2.02(3H, s), 1.42(3H, d, J=6.3Hz), 0.99(6H, brs). MS (ESI, m/z) 524 (M+H) ⁺ .	0.005
2-13		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.74-7.69(2H, m), 7.48-7.42(1H, m), 7.32-7.26(2H, m), 7.16-7.13(1H, m), 7.09-6.98(2H, m), 6.15(1H, d, J=8.1Hz), 5.03(1H, q, J=6.1Hz), 3.73(1H, brs), 3.38-3.30(3H, m), 2.80-2.55(3H, m), 2.07(3H, s), 2.03(3H, s), 1.43(3H, d, J=6.1Hz), 0.98(6H, brs). MS (ESI, m/z) 544 (M+H) ⁺ .	0.022

Table 49

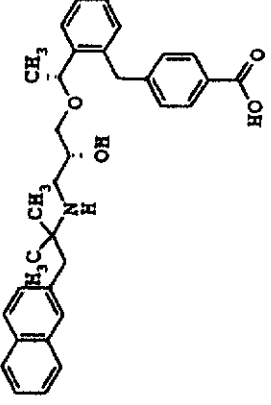
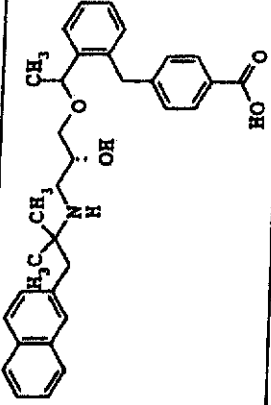
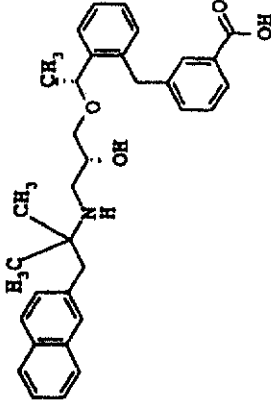
2-14		¹ H-NMR (400MHz, δ ppm, DMSO-d ₆) 7.85-7.76 (5H, m), 7.66 (1H, s), 7.48-7.41 (2H, m), 7.39 (1H, dd, J=7.5, 1.7Hz), 7.33 (1H, dd, J=8.4, 1.6Hz), 7.28-7.15 (5H, m), 4.68 (1H, q, J=6.3Hz), 4.12 (1H, d, J=16Hz), 4.07 (1H, d, J=16Hz), 3.68 (1H, m), 3.09 (2H, d, J=5.6Hz), 2.87 (2H, s), 2.77 (1H, dd, J=11, 3.5Hz), 2.57 (1H, dd, J=11, 7.7Hz), 1.15 (3H, d, J=6.3Hz), 1.05 (3H, s), 1.04 (3H, s). MS (ESI, m/z) 512 (M+H) ⁺	0.053
2-14'		¹ H-NMR (300MHz, δ ppm, DMSO-d ₆) 7.90-7.70 (5H, m), 7.68 (1H, s), 7.55-7.10 (9H, m), 4.68 (1H, q, J=6.2Hz), 4.10 (2H, s), 3.80-3.50 (1H, m), 3.20-2.90 (2H, m), 2.86 (2H, d, J=2.9Hz), 2.80-2.50 (2H, m), 1.15 (3H, d, J=6.3Hz), 1.04 (3H, s), 1.03 (3H, s). MS (ESI, m/z) 512 (M+H) ⁺	0.030
2-15		¹ H-NMR (300MHz, δ ppm, DMSO-d ₆) 7.89-7.70 (6H, m), 7.52-7.34 (6H, m), 7.31-7.17 (3H, m), 4.71 (1H, q, J=6.2Hz), 4.10 (2H, s), 3.75 (1H, m), 3.16-3.07 (2H, m), 2.95 (2H, s), 2.84 (1H, dd, J=12, 2.9Hz), 2.64 (1H, dd, J=12, 7.7Hz), 1.18 (3H, d, J=6.2Hz), 1.10 (3H, s), 1.09 (3H, s). MS (ESI, m/z) 512 (M+H) ⁺	0.016

Table 50

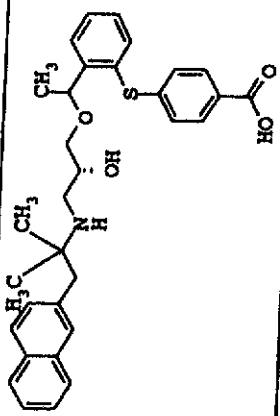
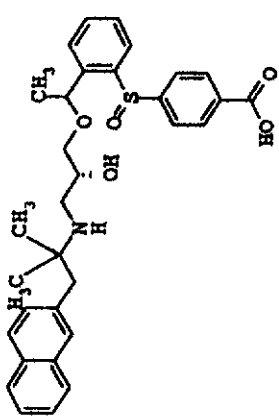
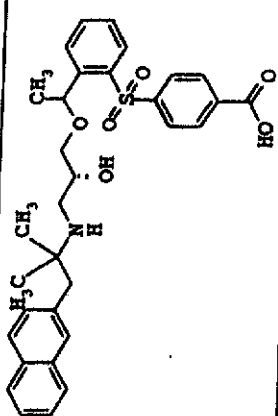
2-16		¹ H-NMR (300MHz, δ ppm, DMSO-d ₆) 7.88-7.80 (5H, m), 7.71 (1H, s), 7.63-7.58 (1H, m), 7.53-7.43 (4H, m), 7.39-7.33 (2H, m), 7.14 (2H, d, J=8.4Hz), 4.93 (1H, q, J=6.6Hz), 3.81 (1H, m), 3.26-3.14 (2H, m), 2.96-2.87 (3H, m), 2.77-2.68 (1H, m), 1.27 (3H, d, J=6.6Hz), 1.11 (6H, s). MS (ESI, m/z) 530 (M+H) ⁺ .	0.014
2-17		¹ H-NMR (400MHz, δ ppm, DMSO-d ₆) 8.12-8.03 (2H, m), 7.89-7.65 (7H, m), 7.58-7.44 (5H, m), 7.39-7.34 (1H, m), 5.21 (0.25H, q, J=6.5Hz), 5.10 (0.25H, q, J=6.5Hz), 4.98-4.93 (0.5H, m), 3.87 (1H, m), 3.25-2.68 (6H, m), 1.37 (1.5H, d, J=6.5Hz), 1.35 (1.5H, d, J=6.5Hz), 1.20-1.15 (6H, m). MS (ESI, m/z) 546 (M+H) ⁺ .	0.148
2-18		¹ H-NMR (400MHz, δ ppm, DMSO-d ₆) 8.16-8.07 (3H, m), 7.90-7.76 (6H, m), 7.73-7.67 (2H, m), 7.65-7.60 (1H, m), 7.50-7.44 (2H, m), 7.38-7.34 (1H, m), 5.16 (0.5H, q, J=6.2Hz), 5.07 (0.5H, q, J=6.2Hz), 3.70 (1H, m), 3.09 (2H, d, J=7.4Hz), 2.97-2.82 (2H, m), 2.74-2.57 (2H, m), 1.26-1.18 (9H, m). MS (ESI, m/z) 562 (M+H) ⁺ .	0.236

Table 51

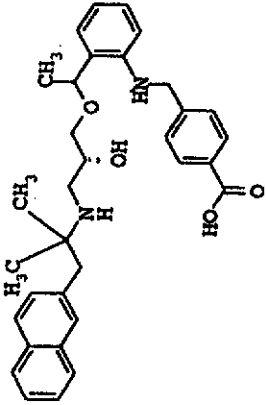
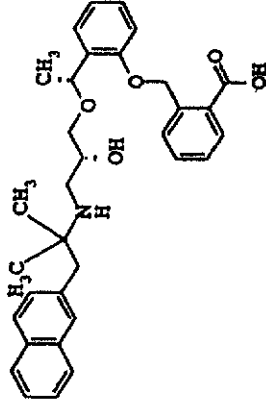
2-19		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.94-7.80 (5H, m), 7.70 (1H, m), 7.51-7.44 (4H, m), 7.38-7.34 (1H, m), 7.07 (1H, d, J=7.4Hz), 6.98 (1H, ddd, J=8.1, 7.0, 1.3Hz), 6.56 (1H, dd, J=7.4, 7.0Hz), 6.43 (1H, d, J=8.1Hz), 6.12-6.03 (1H, m), 4.67 (0.5H, q, J=6.6Hz), 4.65 (0.5H, q, J=6.6Hz), 4.41 (2H, m), 3.91 (1H, m), 3.42-3.30 (2H, m), 3.00-2.90 (3H, m), 2.82-2.73 (1H, m), 1.46 (1.5H, d, J=6.6Hz), 1.45 (1.5H, d, J=6.6Hz), 1.12-1.10 (6H, m). MS (ESI, m/z) 527 (M+H) ⁺ .	0.029
2-20		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.89-7.83 (3H, m), 7.77-7.73 (2H, m), 7.49-7.45 (3H, m), 7.38-7.32 (4H, m), 7.22 (1H, ddd, J=8.4, 7.4, 1.8Hz), 7.09 (1H, d, J=8.4Hz), 6.96 (1H, dd, J=7.4, 7.4Hz), 5.58 (1H, d, J=11Hz), 5.19 (1H, d, J=11Hz), 4.99 (1H, q, J=6.3Hz), 4.01 (1H, m), 3.43 (1H, dd, J=11, 6.8Hz), 3.33 (1H, dd, J=11, 6.1Hz), 3.12-3.07 (3H, m), 2.83 (1H, dd, J=12, 6.5Hz), 1.26 (3H, d, J=6.3Hz), 1.20 (6H, s). MS (ESI, m/z) 528 (M+H) ⁺ .	0.020

Table 52

2-20'	Chemical structure of compound 2-20': A 1,2,3,4-tetrahydronaphthalene derivative with a methyl group at C1, a methyl group on the nitrogen, and a 2-(4-(benzyloxymethyl)phenyl)ethoxy group at C2. The benzyloxymethyl group is attached to a benzene ring which also has a carboxylic acid group at the para position.	¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 8.00-7.65 (5H, m), 7.60-7.30 (7H, m), 7.23 (1H, dd, J=7.4, 7.4, Hz), 7.10 (1H, d, J=8.4Hz), 6.97 (1H, dd, J=7.4, 7.4Hz), 5.68 (0.5H, d, J=10Hz), 5.59 (0.5H, d, J=10Hz), 5.25-4.90 (2H, m), 4.25-3.95 (1H, m), 3.50-3.20 (2H, m), 3.15-2.95 (2H, m), 2.90-2.65 (1H, m), 1.35-1.00 (9H, m), MS (ESI, m/z) 528 (M+H) ⁺ .	0.021
2-21	Chemical structure of compound 2-21: A 1,2,3,4-tetrahydronaphthalene derivative with a methyl group at C1, a methyl group on the nitrogen, and a 2-(4-(benzyloxymethyl)phenyl)ethoxy group at C2. The benzyloxymethyl group is attached to a benzene ring which also has a carboxylic acid group at the para position.	¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 8.06 (1H, s), 7.88-7.81 (4H, m), 7.72 (1H, s), 7.54-7.34 (6H, m), 7.20 (1H, ddd, J=8.4, 7.4, 1.8Hz), 7.05 (1H, d, J=8.4Hz), 6.95 (1H, dd, J=7.4, 7.4Hz), 5.27 (1H, d, J=13Hz), 5.22 (1H, d, J=13Hz), 4.97 (1H, q, J=6.2Hz), 3.98 (1H, m), 3.40 (1H, dd, J=10, 6.1Hz), 3.33 (1H, dd, J=10, 5.3Hz), 3.08 (2H, s), 3.00 (1H, dd, J=12, 3.5Hz), 2.78 (1H, dd, J=12, 7.6Hz), 1.34 (3H, d, J=6.2Hz), 1.18 (3H, s), 1.17 (3H, s). MS (ESI, m/z) 528 (M+H) ⁺ .	0.017

Table 53

2-21'	Chemical structure of compound 2-21': A naphthalene ring system with a methyl group at position 1 and a side chain at position 2. The side chain consists of a methylene group, a nitrogen atom (labeled H), a chiral center (labeled CH₃ and OH), and a methoxy group. The methoxy group is connected to a benzene ring, which is further connected to a carboxylic acid group (HO-C=O).	¹ H-NMR (300MHz, δ ppm, DMSO-d ₆) 8.06 (1H, s), 7.89-7.81 (4H, m), 7.72 (1H, s), 7.54-7.34 (6H, m), 7.24-7.16 (1H, m), 7.06 (1H, d, J=8.4Hz), 6.96 (1H, m), 5.33-5.21 (2H, m), 5.00 (1H, m), 3.99 (1H, m), 3.42-3.28 (2H, m), 3.08 (2H, s), 3.05 (1H, s), 2.98-2.71 (2H, m), 1.34 (1.5H, d, J=6.2Hz), 1.33 (1.5H, d, J=6.2Hz), 1.15 (6H, s). MS (ESI, m/z) 528 (M+H) ⁺ .	0.026
2-22	Chemical structure of compound 2-22: A naphthalene ring system with a methyl group at position 1 and a side chain at position 2. The side chain consists of a methylene group, a nitrogen atom (labeled H), a chiral center (labeled CH₃ and OH), and a methoxy group. The methoxy group is connected to a benzene ring, which is further connected to a carboxylic acid group (HO-C=O).	¹ H-NMR (400MHz, δ ppm, DMSO-d ₆) 7.97 (2H, d, J=8.3Hz), 7.86-7.78 (3H, m), 7.69 (1H, s), 7.52 (2H, d, J=8.3Hz), 7.48-7.43 (2H, m), 7.37-7.34 (2H, m), 7.22 (1H, ddd, J=8.3, 7.4, 1.7Hz), 7.06 (1H, d, J=8.3Hz), 6.97 (1H, dd, J=7.4, 7.4Hz), 5.20 (2H, s), 4.91 (1H, q, J=6.3Hz), 3.84 (1H, m), 3.30 (2H, m), 2.94-2.90 (3H, m), 2.70 (1H, dd, J=12, 7.9Hz), 1.33 (3H, d, J=6.3Hz), 1.10 (3H, s), 1.09 (3H, s). MS (ESI, m/z) 528 (M+H) ⁺ .	0.017

Table 54

2-22'	Chemical structure of compound 2-22': A 1,2,3,4-tetrahydronaphthalene derivative with a methyl group at position 1, a 2-methyl-2-phenylpropyl group at position 2, and a 1-hydroxy-2-(4-(benzyloxy)phenyl)ethyl group at position 3.	¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.98 (2H, d, J=8.3Hz), 7.87-7.78 (3H, m), 7.70 (1H, s), 7.53 (2H, d, J=8.3Hz), 7.49-7.35 (4H, m), 7.23 (1H, m), 7.06 (1H, d, J=8.3Hz), 6.98 (1H, dd, J=7.4, 7.4Hz), 5.21 (2H, s), 4.91 (1H, q, J=6.3Hz), 3.82 (1H, m), 3.31 (2H, m), 2.91-2.86 (3H, m), 2.77-2.64 (1H, m), 1.32 (3H, d, J=6.3Hz), 1.08 (6H, s). MS (ESI, m/z) 528 (M+H) ⁺ .	0.023
2-23	Chemical structure of compound 2-23: A 1,2,3,4-tetrahydronaphthalene derivative with a methyl group at position 1, a 2-methyl-2-(4-fluorophenyl)propyl group at position 2, and a 1-hydroxy-2-(4-(benzyloxy)phenyl)ethyl group at position 3.	¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 8.03 (1H, s), 7.81 (1H, d, J=7.7Hz), 7.51 (1H, d, J=7.7Hz), 7.39 (1H, dd, J=7.7, 7.7Hz), 7.34 (1H, dd, J=7.7, 1.6Hz), 7.21-7.15 (2H, m), 7.04 (1H, d, J=7.7Hz), 7.00-6.92 (3H, m), 5.27 (1H, d, J=13Hz), 5.22 (1H, d, J=13Hz), 4.96 (1H, q, J=6.4Hz), 3.93 (1H, m), 3.38 (1H, dd, J=10, 6.3Hz), 3.30 (1H, dd, J=10, 5.4Hz), 2.93-2.83 (3H, m), 2.69 (1H, dd, J=12, 7.3Hz), 2.18 (3H, s), 1.33 (3H, d, J=6.4Hz), 1.10 (6H, s). MS (ESI, m/z) 510 (M+H) ⁺ .	0.027

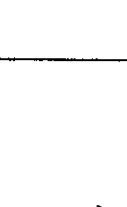
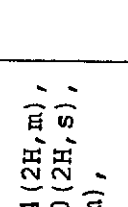
2-24 	¹H-NMR (400MHz, δppm, DMSO-d₆) 7.96 (2H, d, J=8.4Hz), 7.51 (2H, d, J=8.4Hz), 7.36 (1H, dd, J=7.6, 1.6Hz), 7.22 (1H, ddd, J=7.6, 7.6, 1.6Hz), 7.15 (1H, dd, J=8.1, 8.1Hz), 7.05 (1H, d, J=8.1Hz), 6.99-6.94 (2H, m), 6.90 (1H, dd, J=7.6, 1.4Hz), 5.20 (2H, s), 4.90 (1H, q, J=6.4Hz), 3.80 (1H, m), 3.31-3.24 (2H, m), 2.86 (1H, dd, J=12, 3.2Hz), 2.73 (2H, s), 2.63 (1H, dd, J=12, 8.1Hz), 2.17 (3H, s), 1.33 (3H, d, J=6.4Hz), 1.04 (3H, s), 1.03 (3H, s). MS (ESI, m/z) 510 (M+H)⁺.	0.057
2-25 	¹H-NMR (300MHz, δppm, DMSO-d₆) 7.89 (1H, dd, J=8.1, 1.5Hz), 7.65 (1H, dd, J=11, 1.5Hz), 7.59 (1H, dd, J=7.7, 7.7Hz), 7.37 (1H, dd, J=7.7, 1.8Hz), 7.29-7.12 (3H, m), 7.03-6.91 (3H, m), 5.20 (2H, s), 4.86 (1H, q, J=6.2Hz), 3.90 (1H, m), 3.30-3.22 (2H, m), 2.98 (1H, dd, J=12, 2.7Hz), 2.83 (2H, s), 2.72 (1H, dd, J=12, 8.8Hz), 2.18 (3H, s), 1.30 (3H, d, J=6.2Hz), 1.11 (6H, s). MS (ESI, m/z) 528 (M+H)⁺.	0.065

Table 56

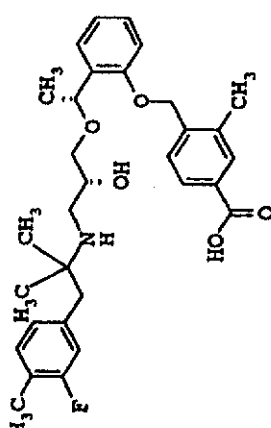
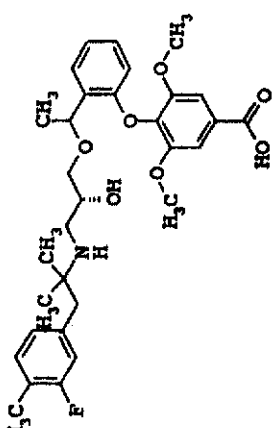
2-26		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.78-7.76 (2H, m), 7.51 (1H, d, J=7.4Hz), 7.36 (1H, m), 7.26-7.22 (1H, m), 7.16-7.11 (2H, m), 7.00-6.88 (3H, m), 5.16 (1H, d, J=13Hz), 5.14 (1H, d, J=13Hz), 4.83 (1H, m), 3.76 (1H, m), 3.26 (2H, m), 2.83 (1H, m), 2.70 (2H, s), 2.60 (1H, m), 2.37 (3H, s), 2.17 (3H, s), 1.30 (3H, d, J=6.2Hz), 1.02 (6H, s). MS (ESI, m/z) 524 (M+H) ⁺ .	0.024
2-27		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.40-7.30 (1H, m), 7.29 (2H, s), 7.12 (1H, dd, J=7.9, 7.9Hz), 7.03 (1H, dd, J=7.9, 7.9Hz), 6.97-6.88 (3H, m), 6.31 (1H, d, J=7.9Hz), 5.05-4.95 (1H, m), 3.81-3.71 (7H, m), 3.37-3.31 (2H, m), 2.85-2.77 (1H, m), 2.70-2.55 (3H, m), 2.15 (3H, s), 1.40 (3H, d, J=6.3Hz), 1.01 (3H, s), 1.00 (3H, s). MS (ESI, m/z) 496 (M+H) ⁺ .	0.027

Table 57

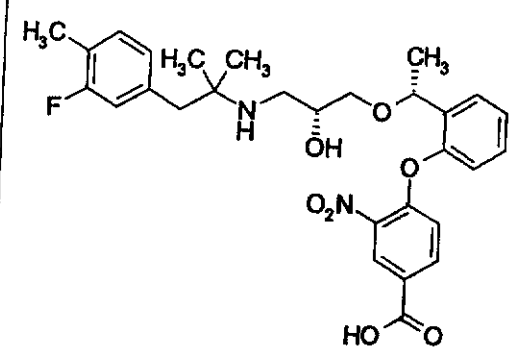
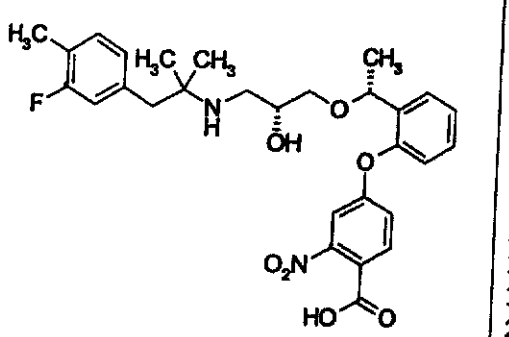
2-28		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 8.42 (1H, d, $J=1.9$ Hz) , 8.08 (1H, dd, $J=8.5$, 1.8Hz), 7.56 (1H, dd, $J=7.2$, 2.0Hz), 7.36- 7.27 (2H, m), 7.17 (1H, t, $J=8.1$ Hz) , 7.01-6.90 (4H, m), 4.73 (1H, q, $J=6.3$ Hz) , 3.85-3.75 (1H, m), 3.26 (2H, d, $J=5.5$ Hz) , 2.90-2.63 (7H, m), 2.17 (3H, s), 1.35 (3H, d, $J=6.2$ Hz) , 1.08 (3H, s), 1.08 (3H, s) MS (ESI, m/z) 541 (M+H) ⁺ .	0.003
2-29		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.70 (1H, d, $J=1.9$ Hz) , 7.56 (1H, dd, $J=7.6$, 2.1Hz), 7.41-7.29 (2H, m), 7.23-7.18 (2H, m), 7.08-6.94 (4H, m), 4.72 (1H, q, $J=6.6$ Hz) , 3.90-3.74 (1H, m), 3.27-3.23 (2H, m), 3.05-2.71 (7H, m), 2.20 (3H, s), 1.35 (3H, d, $J=6.2$ Hz) , 1.12 (3H, s), 1.12 (3H, s) MS (ESI, m/z) 541 (M+H) ⁺ .	0.011

Table 58

2-30		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 8.00 (1H, d, J=1.9Hz), 7.81 (1H, dd, J=8.5, 1.8Hz), 7.54 (1H, dd, J=7.3, 1.8Hz), 7.35-7.23 (2H, m), 7.16 (1H, t, J=7.9Hz), 6.98-6.85 (4H, m), 4.74 (1H, q, J=6.2Hz), 3.83-3.73 (1H, m), 3.27 (2H, d, J=5.5Hz), 2.89-2.62 (7H, m), 2.18 (3H, s), 1.36 (3H, d, J=6.6Hz), 1.06 (3H, s), 1.05 (3H, s) MS (ESI, m/z) 530 (M+H) ⁺ .	0.003
2-31		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.59 (1H, d, J=8.8Hz), 7.54 (1H, dd, J=5.5, 1.8Hz), 7.39-7.26 (2H, m), 7.18 (1H, t, J=8.3Hz), 7.03 (1H, dd, 6.6, 1.5Hz), 6.98-6.88 (3H, m), 6.81 (1H, dd, J=8.5, 2.6Hz), 4.68 (1H, q, J=6.6Hz), 3.74-3.62 (1H, m), 3.28-3.16 (2H, m), 2.87-2.64 (7H, m), 2.19 (3H, s), 1.34 (3H, d, J=6.2Hz), 1.08 (3H, s), 1.08 (3H, s) MS (ESI, m/z) 530 (M+H) ⁺ .	0.016

Table 59

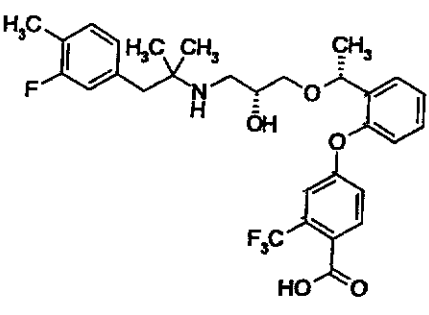
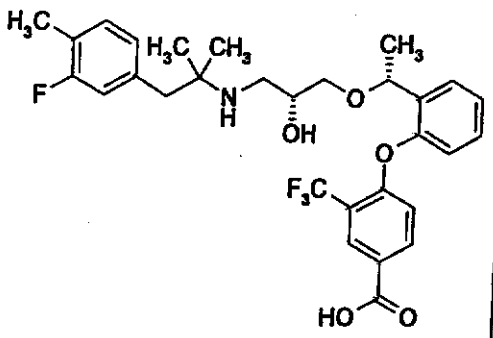
2-32		¹ H-NMR (300MHz, δ ppm, DMS O-d ₆) 7.57 (2H, t, J=8.8Hz) , 7.40-7.28 (2H, m) , 7.22-7.13 (2H, m) , 7.09-7.02 (2H, m) , 6.98-6.91 (2H, m) , 4.71 (1H, q, J=6.4Hz) , 3.81-3.71 (1H, m) , 3.29-3.17 (2H, m) , 2.96-2.67 (7H, m) , 2.19 (3H, s) , 1.35 (3H, d, J=6.6Hz) , 1.12 (3H, s) , 1.12 (3H, s) MS (ESI, m/z) 564 (M+H) ⁺ .	0.014
2-33		¹ H-NMR (300MHz, δ ppm, DMS O-d ₆) 8.22 (1H, d, J=2.2Hz) , 8.09 (1H, dd, J=8.5, 1.8Hz) , 7.58 (1H, dd, J=7.4, 2.2Hz) , 7.41-7.30 (2H, m) , 7.16 (1H, t, J=8.0Hz) , 7.03-6.90 (3H, m) , 6.83 (1H, d, J=8.4Hz) , 4.65 (1H, q, J=6.2Hz) , 3.84-3.71 (1H, m) , 3.29-3.20 (2H, m) , 2.91-2.63 (7H, m) , 2.17 (3H, s) , 1.33 (3H, d, J=6.6Hz) , 1.07 (3H, s) , 1.06 (3H, s) MS (ESI, m/z) 564 (M+H) ⁺ .	0.002

Table 60

2-34		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.79 (1H, d, J=1.8Hz), 7.71 (1H, d, J=8.5Hz), 7.53 (1H, dd, J=7.4, 2.2Hz), 7.34-7.22 (2H, m), 7.16 (1H, t, J=7.9Hz), 6.98-6.87 (4H, m), 4.80 (1H, q, J=6.6Hz), 3.81-3.71 (1H, m), 3.28 (2H, d, J=5.5Hz), 2.85-2.58 (7H, m), 2.18 (3H, s), 1.36 (3H, d, J=6.6Hz), 1.04 (3H, s), 1.03 (3H, s) MS (ESI, m/z) 514 (M+H) ⁺ .	0.006
2-35		¹ H-NMR (400MHz, δ ppm, DMSO- d_6) 7.90 (2H, m), 7.60-7.20 (5H, m), 7.05-6.90 (4H, m), 4.66 (1H, q, J=6.4Hz), 3.70-3.60 (1H, m), 3.25-3.15 (2H, m), 2.80-2.70 (2H, m), 2.60-2.50 (2H, m), 1.35-1.30 (3H, m), 1.05-0.95 (6H, m) MS (ESI, m/z) 516 (M+H) ⁺ .	0.011
2-36		¹ H-NMR (300MHz, δ ppm, DMSO- d_6) 7.88 (1H, s), 7.80-7.20 (6H, m), 7.03 (1H, d, J=7.8Hz), 6.87 (1H, d, J=6.6Hz), 6.67 (1H, d, J=9.0Hz), 4.68 (1H, q, J=6.6Hz), 3.70-3.60 (1H, m), 3.30-3.15 (2H, m), 2.70-2.50 (4H, m), 2.31 (3H, s), 1.40-1.20 (3H, m), 1.00-0.90 (6H, m) MS (ESI, m/z) 530 (M+H) ⁺ .	0.013

Experimental Examples

The bioactivity of the compound of the present invention was examined by tests.

Experimental Example 1

- 5 Evaluation of antagonistic action on calcium receptor using reporter gene

Luciferase cDNA and human calcium receptor cDNA were introduced into a cell strain derived from rat adrenal to transform the cells, and the transformed cells were cultured
10 in a medium (80 μ l, F12 medium containing 0.5% dialyzed horse serum and 0.25% dialyzed bovine fetal serum). A dimethyl sulfoxide solution containing a test compound at 0.1 - 10000 μ M was diluted 100-fold with the medium and added to the test compound group at 10 μ l per well (final concentration of
15 dimethyl sulfoxide is 0.1%). In the same manner as in test compound group, dimethyl sulfoxide diluted 100-fold with medium was added to a control group and a blank group. Then, 50 mM calcium chloride-containing medium was added to every well except the blank group at 10 μ l per well (final
20 concentration 5 mM). A medium alone was added to the blank group. After cultureing for 4 hrs, luciferase substrate was added and the luciferase activity was measured with a photoluminometer. The inhibitory rate (%) was calculated from the obtained measured values according to the following
25 formula.

$$\text{Inhibitory rate (\%)} = 100 - \frac{\begin{array}{c} \text{measured value} \\ \text{of compound} \\ \text{group} \end{array} - \begin{array}{c} \text{measured value} \\ \text{of blank} \\ \text{group} \end{array}}{\begin{array}{c} \text{measured value} \\ \text{of control} \\ \text{group} \end{array} - \begin{array}{c} \text{measured value} \\ \text{of blank} \\ \text{group} \end{array}} \times 100$$

Based on the results, the concentration (IC_{50}) showing 50% inhibitory rate was determined. The results are shown in
30 the aforementioned Tables 1 to 60.

Experimental Example 2

PTH secretion action

The test compound was orally administered to 5 to 9-week-old male SD rats (Charles River Japan, Inc.) fasted for 20 hr, using a solvent (0.5% methyl cellulose solution) at a dose of 1 mg/5 ml/kg. A solvent alone was orally administered to the control group at a dose of 5 ml/kg. The blood was drawn from the tail vein, at 15 min, 30 min, 60 min and 120 min after the administration of the test compound, and serum was obtained. The serum PTH concentration was measured using rat PTH ELISA kit (Amersham Biosciences). The results are shown in Table 61.

As a comparative example, moreover, the following compound was used at a dose of 30 mg/5 ml/kg in a similar test, but a PTH secretion enhancing effect was not observed:

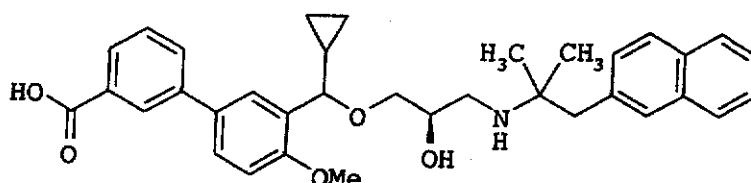


Table 61

Test compound	Serum PTH concentration (pg/ml)			
	15 min later	30 min later	60 min later	120 min later
	Control group			
	Test compound administration group			
1-1	13.2±2.6	18.0±1.5	14.6±3.6	15.9±2.7
	43.9±2.0	25.0±3.2	17.9±2.0	14.8±1.6
1-2	8.8±1.3	12.5±0.6	13.4±2.7	13.0±1.8
	28.5±5.3	27.1±2.3	10.5±1.3	12.4±1.6
1-3	8.8±1.3	12.5±0.6	13.4±2.7	13.0±1.8
	23.8±1.6	25.1±3.9	9.5±0.5	11.6±0.9
1-6	11.9±2.4	15.9±1.0	8.7±1.2	9.4±2.1
	28.9±6.9	19.2±3.1	10.0±1.7	8.3±0.6
1-30	14.9±1.3	14.5±2.7	12.9±2.1	11.1±2.2
	26.1±2.3	24.2±3.3	18.2±1.3	13.8±0.6

Experimental Example 3**5 PTH secretion action**

The test compound was orally administered to 5 to 9-week-old male SD rats (Charles River Japan, Inc.) fasted for 20 hrs, using a solvent (0.5% methyl cellulose solution) at a dose of 1 mg/5 ml/kg. A solvent alone was orally

10 administered to the control group at a dose of 5 ml/kg. The blood was drawn from the tail vein at 15 min, 30 min after administration of the test compound, and serum was obtained. The serum PTH concentration was measured using rat PTH ELISA kit (Amersham Biosciences). The results are shown in Table

15 62.

Table 62

Test compound	Serum PTH concentration (pg/ml)	
	15 min later	30 min later
	Control group	
	Test compound administration group	
2-1	13.7±2.3	17.6±3.1
	25.1±2.3	19.1±0.9

Experimental Example 4

5 Metabolic enzyme CYP2D6 inhibitory activity

Using a metabolic enzyme CYP2D6 inhibition measurement kit (BD Bioscience) and following the manual of the kit, the inhibitory activity of the test compound was measured. As the enzyme activity showing 100% at the test compound-free, the concentration showing 50% inhibition (IC₅₀) was determined. The results are shown in Table 63 and Table 64, wherein ">10" means over 10 μ M.

Table 63

Test compound	IC ₅₀ (μ M)
1-57	>10
1-59	>10
1-26	>10
1-27	>10
1-32	10.0
1-33	>10
1-34	>10
1-35	>10
1-73	>10
1-39	>10
1-48	>10
1-80	>10

Table 64

Test compound	IC ₅₀ (μM)
2-5	>10
2-20'	>10

Experimental Example 5

Effect of concomitant administration of test compound and
5 estrogen on bone resorption and PTH secretion

The 13-week-old ovariectomized rats were divided into 4
groups of a control group (Group A), an estrogen
administration group (Group B), a test compound
administration group (Group C), and a test compound and
10 estrogen concomitant administration group (Group D). One
sham control group (E group) subjected to a sham surgery was
also established. Estradiol was dissolved in 5% benzyl
alcohol-corn oil and subcutaneously administered to an
estrogen administration groups (Group B and Group D) at the
15 dose of 10 μg/kg. 5% Benzyl alcohol-corn oil was
subcutaneously administered to groups (Group A and Group C)
free from administration of estrogen. The compound of
Example 1-1 was suspended in 0.5% methyl cellulose solution
and orally administered to groups (Group C and Group D) to
20 be administered with the test compound at the dose of 3 .
mg/kg. As regards the groups (Group A and Group B) free from
administration of the test compound, 0.5% methyl cellulose
solution was orally administered.

On day 13 from the start of the administration, the
25 blood was drawn in each group from the tail vein, and serum
was obtained. ICTP, which is a blood bone resorption marker,
was measured using a commercially available ELISA kit
("RatLaps ELISA kit", Nordic Bioscience Diagnostics).

In addition, blood was drawn with time for the
30 measurement of blood PTH at day 16 of administration. The

blood was drawn in each group from the tail vein just before oral administration and 0.25, 0.5, 1, 2 and 4 hr later, and serum was obtained. For serum PTH measurement, a commercially available ELISA kit ("rat intact PTH ELISA kit", 5 Immutopics) was used.

The measurement results of blood ICTP are shown in Table 65 and the blood PTH measurement results are shown in Table 66.

10

Table 65

	Blood I CTP concentration (ng/ml)
Group A	29.21±5.14
Group B	20.93±3.18
Group C	26.10±3.45
Group D	21.77±3.34
Group E	18.84±2.356

mean±S.D., n=5

Table 66

	PTH(1-84) concentration (pg/ml)					
	0 hr	0.25 hr	0.5 hr	1 hr	2 hr	4 hr
Group A	29.45±8.67	26.74±6.49	48.15±10.13	33.93±7.09	37.29±14.84	55.83±18.16
Group B	36.83±14.45	53.65±56.31	56.55±21.71	35.70±21.30	41.94±20.85	46.84±14.62
Group C	31.19±16.28	371.21±77.74	370.78±98.28	177.39±96.06	117.51±123.12	56.50±12.29
Group D	27.12±4.58	407.35±134.53	418.87±154.78	279.76±117.98	115.50±74.98	58.84±16.75

mean±S.D., n=5

When osteoporosis is to be treated by increasing the blood PTH concentration based on inhibition of the action of calcium receptor, the compound to be used for this end should have at least the following properties.

- 5 (i) The compound has a sufficient antagonistic action on calcium receptors. In other words, the compound has a sufficiently low IC_{50} value. In the specification of WO99/51241, it is described, "In general, a compound showing a low IC_{50} value in the assay of calcium receptor inhibitor
10 is a more superior compound. A compound showing an IC_{50} value of not lower than 50 μM is considered to be inactive. A preferable compound shows an IC_{50} value of not more than 10 μM , more preferably 1 μM , and most preferably not more than 0.1 μM ."
- 15 (ii) Administration of the compound results in a sufficient increase in the blood PTH concentration.
- (iii) The time-course concentrations in blood after administration of the compound are not sustainable. Desirably, the PTH concentration returns to the level before
20 administration in 3-4 hr after administration of the compound.

Moreover, it is preferable to satisfy the following two aspects;

(1) Administration of the compound does not inhibit the
25 action of bone resorption suppressants such as estrogen and the like.

(2) The PTH secretion action of the compound is not inhibited by bone resorption suppressants such as estrogen and the like.

30 By the result of the test showing above, it is obvious that the compound of the present invention has above mentioned properties.

As regards (i); as shown in Tables 1 to 60, the IC_{50}

value of the compound of the present invention is not more than 1 μ M, and the compound has a sufficient antagonistic action on calcium receptors. The compound of the present invention is considered to be preferable in view of the IC₅₀ value.

As regards (ii); as shown in Tables 61 and 62, the serum PTH concentration 15 min later was 1.8-3.3 times higher (compound wherein n=0) and 1.8 times higher (compound wherein n=1) than control, and the compound of the present invention has been confirmed to have a superior PTH secretion promoting action.

As regards (iii); as shown in Table 62, PTH secretion by the compound of the present invention reached a peak at 15 min after administration, sharply decreased thereafter and returned to the blood PTH concentration of before administration in about 1 - 2 hr. It is clear from this aspect that the compound of the present invention is superior. In contrast, as a result of the reproductive test of NPS-2143 of the reference, the sustained secretion promoting action of NPS-2143 was confirmed.

As regards (1); as shown in Table 65, comparison of the sham control group subjected to a sham surgery and the control group reveals an increase in ICTP due to ovary enucleation, thereby confirming promoted bone resorption. This increase was suppressed by an exclusive administration of estrogen, and concomitant administration of Example 1-1 did not show changes in the ability to suppress of estrogen.

As regards (2); as shown in Table 66, there was no difference found in blood PTH value before administration between each group. By examination of the changes with time, increase in blood PTH was not observed by estrogen exclusive administration, but a transitional increase was observed in both the Example 1-1 exclusive group and Example 1-1 and

estrogen concomitant administration group.

Industrial Applicability

As is clear from the above-mentioned Experimental
5 Example 1, the compound of the formula (1) of the present
invention has a superior calcium receptor antagonistic
action. Accordingly, the compound is expected to be useful
as a therapeutic drug for diseases accompanied by abnormal
calcium homeostasis, such as osteoporosis, hypoparathyreosis,
10 osteosarcoma, periodontal disease, bone fracture,
osteoarthritis, chronic rheumatoid arthritis, Paget's
disease, humoral hypercalcemia, autosomal dominant
hypocalcemia, Parkinson's disease, dementia and the like. As
is clear from Experimental Examples 2 and 3, the compound of
15 the present invention has a temporary PTH secretion
promoting action, and as is clear from Experimental Example
4, it has weak metabolic enzyme CYP2D6 inhibitory activity.
Accordingly, the compound is particularly useful as a
therapeutic agent for osteoporosis.

20

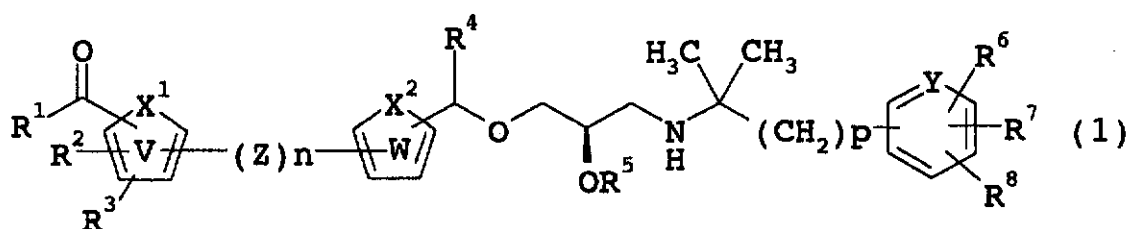
As is clear from Experimental Example 5, moreover, the
compound of the present invention does not inhibit the
action of bone resorption suppressants such as estrogen and
the like, and the PTH secretion action of the compound of
25 the present invention is not inhibited by bone resorption
suppressants such as estrogen and the like. Therefore, use
of the compound of the present invention and bone resorption
suppressants such as estrogen and the like in combination is
considered to be extremely effective for osteoporosis.

30

This application is based on a patent application No.
119131/2003 filed in Japan, the contents of which are
hereby incorporated by reference.

CLAIMS

1. A compound represented by the following formula (1):



wherein

n is 1,

p is an integer of 1 to 3,

R¹ is a hydroxyl group, a C₁₋₆ alkoxy group or R^A,

wherein R^A is R^C-OC(=O)O-C₁₋₄ alkylene-O- or OH-NH-,

wherein R^C is a C₁₋₆ alkyl group or a C₃₋₆ cycloalkyl group,

R² and R³ are the same or different and each is a hydrogen atom, a hydroxyl group, a halogen atom, an amino group, a C₁₋₇ acylamino group, a halo C₁₋₆ alkyl group, a carboxyl group, a C₁₋₆ alkoxy-carbonyl group, a C₁₋₆ alkoxy group, a halo C₁₋₆ alkoxy group, a C₁₋₆ alkyl group, a hydroxy-C₁₋₆ alkyl group, a C₁₋₇ acylamino-C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, an aralkyl group, a phenyl group, a C₁₋₆ alkylamino group, a di(C₁₋₆ alkyl)amino group, a C₁₋₆ alkoxy-C₁₋₆ alkyl group, a mercapto group, a cyano group, a nitro group, a morpholino group, a piperidino group or a pyrrolidino group, or R² and R³ are joined to form an ethyleneoxy group,

X¹ is -C=C-, -C=N-, an oxygen atom or a sulfur atom,

Z is -S-, -SO-, -SO₂-, -(CH₂)_{m1}-O-, -O-(CH₂)_{m1}-, -(CH₂)_{m2}-NH-, -NH-(CH₂)_{m2}-, -(CH₂)_{m3}-N(CH₃)-, -N(CH₃)-(CH₂)_{m3}-, a C₁₋₄ alkylene group, -SO₂-N(CH₃)-, -N(CH₃)-SO₂-, -NHCO-, -CONH- or a C₂₋₄ alkenylene group,

wherein m₁, m₂ and m₃ are each an integer of 0 to 2,

X² is -C=C-, an oxygen atom or a sulfur atom,

R⁴ is a C₁₋₆ alkyl group or a C₃₋₆ cycloalkyl group,

R⁵ is a hydrogen atom or R^B,

wherein R^B is a C₁₋₇ acyl group optionally substituted by a carboxyl group,

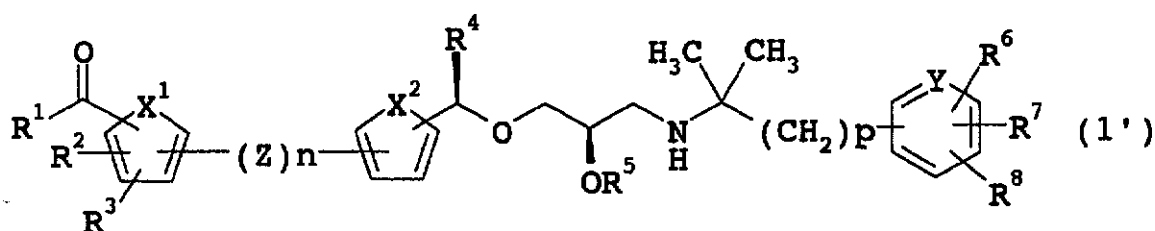
Y is a carbon atom or a nitrogen atom, and

R⁶, R⁷ and R⁸ are the same or different and each is a hydrogen atom, a halogen atom, a C₁₋₆ alkyl group, a C₁₋₆ alkoxy group, a halo C₁₋₆ alkyl group, a halo C₁₋₆ alkoxy group, a carboxyl group, a hydroxyl group, a cyano group, a nitro group, a phenyl group, a C₃₋₆ cycloalkyl group, a di(C₁₋₆ alkyl)aminocarbonyl group or a hydroxy-C₁₋₆ alkyl group, or adjacent R⁶ and R⁷ are joined to form -CH=CH-CH=CH-, -C(OH)=CH-CH=CH-, -CH=C(OH)-CH=CH-, -O-(CH₂)_{k1}-O-, -O-(CH₂)_{k2}- or -(CH₂)_{k3}-,

wherein k₁ is an integer of 1 to 4, k₂ is an integer of 2 to 5, k₃ is an integer of 3 to 6,

provided that when R² and R³ are both hydrogen atoms and n is 1, then Z should be a group other than -SO₂-N(CH₃)- wherein sulfur atom is bonded to ring V and a nitrogen atom is bonded to ring W, a pharmaceutically acceptable salt thereof or an optically active form thereof.

2. The compound of claim 1, which has a configuration represented by the following formula (1')



wherein each symbol is as defined in claim 1, or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1 or 2, wherein

p is 1,

R¹ is a hydroxyl group or a C₁₋₆ alkoxy group,

R² and R³ are the same or different and each is a hydrogen atom, a hydroxyl group, a halogen atom, an amino group, a C₁₋₇ acylamino group, a trifluoromethyl group, a C₁₋₆ alkoxy-carbonyl group, a C₁₋₆ alkoxy group, a C₁₋₆ alkyl group, a hydroxy-C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a phenyl group, a benzyl group, a di(C₁₋₆ alkyl)amino group or a nitro group, or R² and R³ are joined to form an ethyleneoxy group,

X¹ is -C=C- or -C=N-,

X² is -C=C-,

Z is -S-, -SO-, -SO₂-, -(CH₂)_{m1}-O-, -O-(CH₂)_{m1}-, -(CH₂)_{m2}-NH-, -NH-(CH₂)_{m2}-, -(CH₂)_{m3}-N(CH₃)-, -N(CH₃)-(CH₂)_{m3}-, a C₁₋₄ alkylene group or a C₂₋₄ alkenylene group,

wherein m₁, m₂ and m₃ are each an integer of 0 to 2,

R⁴ is a C₁₋₆ alkyl group or a C₃₋₆ cycloalkyl group,

R⁵ is a hydrogen atom,

Y is a carbon atom or a nitrogen atom, and

R⁶, R⁷ and R⁸ are the same or different and each is a hydrogen atom, a halogen atom, a C₁₋₆ alkyl group or a C₁₋₆ alkoxy group, or adjacent R⁶ and R⁷ are joined to form -CH=CH-CH=CH-, a pharmaceutically acceptable salt thereof or an optically active form thereof.

4. The compound of claim 3, wherein

p is 1,

R¹ is a hydroxyl group or a C₁₋₆ alkoxy group,

R² and R³ are the same or different and each is a hydrogen atom, a halogen atom, a C₁₋₆ alkoxy group or a C₁₋₆ alkyl group,

X¹ is -C=C-,

Z is -S-, -SO-, -SO₂-, -(CH₂)_{m1}-O-, -O-(CH₂)_{m1}-, -CH₂-NH-, -NH-CH₂-, -N(CH₃)-, methylene or vinylene,

wherein m₁ is 0 or 1,

X² is -C=C-,

R⁴ is a methyl group or a cyclopropyl group,

R⁵ is a hydrogen atom,

Y is a carbon atom or a nitrogen atom, and
R⁶, R⁷ and R⁸ are the same or different and each is a hydrogen atom, a halogen atom or a C₁₋₆ alkyl group, or adjacent R⁶ and R⁷ are joined to form -CH=CH-CH=CH-,
a pharmaceutically acceptable salt thereof or an optically active form thereof.

5. The compound of claim 1 or 2, which is selected from the group consisting of

4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]benzoic acid,

4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]-3-methoxybenzoic acid,

methyl 4-[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]benzoate,

4-[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]benzoic acid,

4-[2-[1-[(2R)-3-[[1-(quinolin-3-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]benzoic acid,

4-[2-[1-[(2R)-3-[[1-(4-chloro-2-fluorophenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]benzoic acid,

4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]benzoic acid,

3-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenoxy]benzoic acid,

4-[2-[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenyl]vinyl]benzoic acid,

3-[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-yl]amino]-2-hydroxypropoxy]ethyl]phenylthio]benzoic acid,

4-[2-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-2-yl]amino]-2-

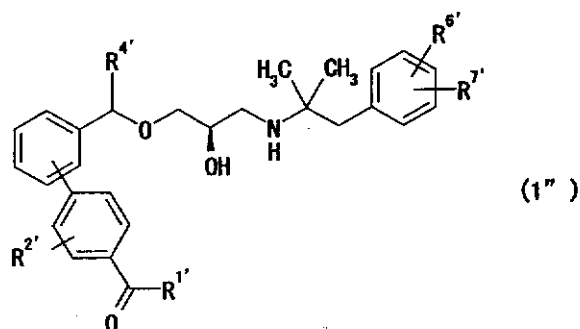
hydroxypropoxy]ethyl]phenyl]vinyl]benzoic acid,

4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-

2-yl] amino] -2-hydroxypropoxy] ethyl] phenoxy] -3,5-
 dimethylbenzoic acid,
 4-[2-[1-[(2R)-3-[[1-(4-chloro-2-fluorophenyl)-2-methylpropan-
 2-yl] amino] -2-hydroxypropoxy] ethyl] phenoxy] -3,5-
 dimethylbenzoic acid,
 4-[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-
 yl] amino] -2-hydroxypropoxy] ethyl] benzyl] benzoic acid,
 3-[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-
 yl] amino] -2-hydroxypropoxy] ethyl] benzyl] benzoic acid,
 4-[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-
 yl] amino] -2-hydroxypropoxy] ethyl] phenylthio] benzoic acid,
 4-[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-
 yl] amino] -2-hydroxypropoxy] ethyl] phenylsulfinyl] benzoic acid,
 4-[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-
 yl] amino] -2-hydroxypropoxy] ethyl] phenylsulfonyl] benzoic acid,
 4-[[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-
 yl] amino] -2-hydroxypropoxy] ethyl] phenylamino] methyl] benzoic
 acid,
 2-[[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-
 yl] amino] -2-hydroxypropoxy] ethyl] phenoxy] methyl] benzoic acid,
 3-[[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-
 yl] amino] -2-hydroxypropoxy] ethyl] phenoxy] methyl] benzoic acid,
 4-[[2-[1-[(2R)-3-[[1-(naphthalen-2-yl)-2-methylpropan-2-
 yl] amino] -2-hydroxypropoxy] ethyl] phenoxy] methyl] benzoic acid,
 3-[[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-
 methylpropan-2-yl] amino] -2-
 hydroxypropoxy] ethyl] phenoxy] methyl] benzoic acid,
 4-[[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-
 methylpropan-2-yl] amino] -2-
 hydroxypropoxy] ethyl] phenoxy] methyl] benzoic acid,
 3-fluoro-4-[[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-
 methylpropan-2-yl] amino] -2-
 hydroxypropoxy] ethyl] phenoxy] methyl] benzoic acid,
 4-[[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-

methylpropan-2-yl] amino] -2-
 hydroxypropoxy] ethyl] phenoxy] methyl] -3-methylbenzoic acid,
 4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-
 2-yl] amino] -2-hydroxypropoxy] ethyl] phenoxy] -3,5-
 dimethoxybenzoic acid,
 4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-
 2-yl] amino] -2-hydroxypropoxy] ethyl] phenoxy] -3-nitrobenzoic
 acid,
 4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-
 2-yl] amino] -2-hydroxypropoxy] ethyl] phenoxy] -2-nitrobenzoic
 acid,
 4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-
 2-yl] amino] -2-hydroxypropoxy] ethyl] phenoxy] -3-chlorobenzoic
 acid,
 4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-
 2-yl] amino] -2-hydroxypropoxy] ethyl] phenoxy] -2-chlorobenzoic
 acid,
 4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-
 2-yl] amino] -2-hydroxypropoxy] ethyl] phenoxy] -2-
 trifluoromethylbenzoic acid,
 4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-
 2-yl] amino] -2-hydroxypropoxy] ethyl] phenoxy] -3-
 trifluoromethylbenzoic acid,
 4-[2-[1-[(2R)-3-[[1-(3-fluoro-4-methylphenyl)-2-methylpropan-
 2-yl] amino] -2-hydroxypropoxy] ethyl] phenoxy] -3-fluorobenzoic
 acid,
 4-[2-[1-[(2R)-3-[[1-(4-chloro-3-fluorophenyl)-2-methylpropan-
 2-yl] amino] -2-hydroxypropoxy] ethyl] phenoxy] benzoic acid, and
 4-[2-[1-[(2R)-3-[[1-(4-chloro-3-fluorophenyl)-2-methylpropan-
 2-yl] amino] -2-hydroxypropoxy] ethyl] phenoxy] -5-methylbenzoic
 acid,
 a pharmaceutically acceptable salt thereof or an optically
 active form thereof.

6. A compound represented by the following formula (1''), a pharmaceutically acceptable salt thereof or an optically active form thereof:



wherein

R^{1'} is a hydroxyl group or a C₁₋₆ alkoxy group,

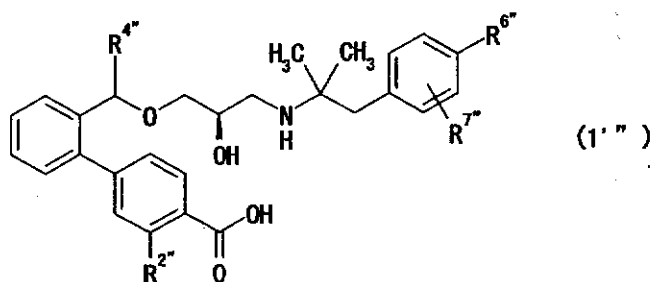
R^{2'} is a hydroxyl group, a halogen atom, an amino group, a C₁₋₇ acylamino group, a halo C₁₋₆ alkyl group, a C₁₋₆ alkoxy-carbonyl group, a C₁₋₆ alkoxy group, a halo C₁₋₆ alkoxy group, a C₁₋₆ alkyl group, a hydroxy-C₁₋₆ alkyl group, a di(C₁₋₆ alkyl)amino group or a nitro group,

R^{4'} is a C₁₋₆ alkyl group or a C₃₋₆ cycloalkyl group,

R^{6'} is a halogen atom, a C₁₋₆ alkyl group, a C₁₋₆ alkoxy group or a halo C₁₋₆ alkyl group, or when R^{7'} is adjacent, R^{6'} and R^{7'} are linked to form -CH=CH-CH=CH-, and

R^{7'} is a hydrogen atom, a halogen atom, a C₁₋₆ alkyl group, a C₁₋₆ alkoxy group or a halo C₁₋₆ alkyl group.

7. A compound represented by the following formula (1''), a pharmaceutically acceptable salt thereof or an optically active form thereof:



wherein

R^{2''} is a C₁₋₆ alkyl group,

R^{4''} is a methyl group or a cyclopropyl group,

R^{6''} is a halogen atom or a C₁₋₆ alkyl group, and

R^{7''} is a hydrogen atom, a halogen atom, a C₁₋₆ alkyl group, a C₁₋₆ alkoxy group or a halo C₁₋₆ alkyl group.

8. The compound of claim 6 or 7, which is selected from the group consisting of

2' - [1 - [(2R) - 3 - [[1 - (3-fluoro-4-methylphenyl) - 2-methylpropan-2-yl]amino] - 2-hydroxypropoxy]ethyl] - 3-methylbiphenyl-4-carboxylic acid,

2' - [1 - [(2R) - 3 - [[1 - (4-chloro-3-fluorophenyl) - 2-methylpropan-2-yl]amino] - 2-hydroxypropoxy]ethyl] - 3-methylbiphenyl-4-carboxylic acid,

2' - [1 - [(2R) - 3 - [[1 - (3-chloro-4-methylphenyl) - 2-methylpropan-2-yl]amino] - 2-hydroxypropoxy]ethyl] - 3-methylbiphenyl-4-carboxylic acid,

2' - [1 - [(2R) - 3 - [[1 - (4-chloro-3-methylphenyl) - 2-methylpropan-2-yl]amino] - 2-hydroxypropoxy]ethyl] - 3-methylbiphenyl-4-carboxylic acid,

2' - [1 - [(2R) - 3 - [[1 - (4-chloro-2-fluorophenyl) - 2-methylpropan-2-yl]amino] - 2-hydroxypropoxy]ethyl] - 3-methylbiphenyl-4-carboxylic acid,

2' - [1 - [(2R) - 3 - [[1 - (2-fluoro-4-methylphenyl) - 2-methylpropan-2-yl]amino] - 2-hydroxypropoxy]ethyl] - 3-methylbiphenyl-4-carboxylic acid,

2' - [1 - [(2R) - 3 - [[1 - (4-ethyl-3-fluorophenyl) - 2-methylpropan-2-yl]amino] - 2-hydroxypropoxy]ethyl] - 3-methylbiphenyl-4-carboxylic acid,

2' - [1 - [(2R) - 3 - [[1 - (3-fluoro-4-methylphenyl) - 2-methylpropan-2-yl]amino] - 2-hydroxypropoxy]ethyl] - 3-methylbiphenyl-4-carboxylic acid,

2' - [(cyclopropyl) [(2R) - 3 - [[1 - (4-chloro-2-fluorophenyl) - 2-

methylpropan-2-yl] amino] -2-hydroxypropoxy] methyl] -3-
 methylbiphenyl-4-carboxylic acid,
 2' - [(cyclopropyl) [(2R) -3- [[1- (4-chloro-3-fluorophenyl) -2-
 methylpropan-2-yl] amino] -2-hydroxypropoxy] methyl] -3-
 methylbiphenyl-4-carboxylic acid,
 3-methyl-2' - [1- [(2R) -3- [[1- (3,4-dimethylphenyl) -2-
 methylpropan-2-yl] amino] -2-hydroxypropoxy] ethyl] biphenyl-4-
 carboxylic acid,
 2' - [1- [(2R) -3- [[1- (4-methylphenyl) -2-methylpropan-2-
 yl] amino] -2-hydroxypropoxy] ethyl] -3-methylbiphenyl-4-
 carboxylic acid,
 2' - [1- [(2R) -3- [[1- (4-chloro-3-methoxyphenyl) -2-methylpropan-
 2-yl] amino] -2-hydroxypropoxy] ethyl] -3-methylbiphenyl-4-
 carboxylic acid,
 2' - [1- [(2R) -3- [[1- (4-ethylphenyl) -2-methylpropan-2-yl] amino] -
 2-hydroxypropoxy] ethyl] -3-methylbiphenyl-4-carboxylic acid,
 3-ethyl-2' - [1- [(2R) -3- [[1- (3-fluoro-4-methylphenyl) -2-
 methylpropan-2-yl] amino] -2-hydroxypropoxy] ethyl] biphenyl-4-
 carboxylic acid,
 2' - [1- [(2R) -3- [[1- (3-fluoro-4-methylphenyl) -2-methylpropan-2-
 yl] amino] -2-hydroxypropoxy] ethyl] -3-isopropylbiphenyl-4-
 carboxylic acid,
 2' - [1- [(2R) -3- [[1- (3-fluoro-4-methylphenyl) -2-methylpropan-2-
 yl] amino] -2-hydroxypropoxy] ethyl] -3-propylbiphenyl-4-
 carboxylic acid,
 2' - [1- [(2R) -3- [[1- (3-fluoro-4-methylphenyl) -2-methylpropan-2-
 yl] amino] -2-hydroxypropoxy] ethyl] -3-isobutylbiphenyl-4-
 carboxylic acid,
 3-ethyl-2' - [1- [(2R) -3- [[1- (4-chloro-3-fluorophenyl) -2-
 methylpropan-2-yl] amino] -2-hydroxypropoxy] ethyl] biphenyl-4-
 carboxylic acid,
 2' - [1- [(2R) -3- [[1- (4-chloro-3-fluorophenyl) -2-methylpropan-2-
 yl] amino] -2-hydroxypropoxy] ethyl] -3-isopropylbiphenyl-4-
 carboxylic acid,

2' - [1 - [(2R) - 3 - [[1 - (3-fluoro-4-methylphenyl) - 2-methylpropan-2-yl] amino] - 2-hydroxypropoxy] ethyl] - 3 - (1-methylpropyl) biphenyl-4-carboxylic acid,

2' - [1 - [(2R) - 3 - [[1 - (3-chlorophenyl) - 2-methylpropan-2-yl] amino] - 2-hydroxypropoxy] ethyl] - 3-methylbiphenyl-4-carboxylic acid,

2' - [1 - [(2R) - 3 - [[1 - (3,4-dichlorophenyl) - 2-methylpropan-2-yl] amino] - 2-hydroxypropoxy] ethyl] - 3-methylbiphenyl-4-carboxylic acid,

2' - [1 - [(2R) - 3 - [[1 - (3-methoxy-4-methylphenyl) - 2-methylpropan-2-yl] amino] - 2-hydroxypropoxy] ethyl] - 3-methylbiphenyl-4-carboxylic acid,

2' - [1 - [(2R) - 3 - [[1 - (3,5-dichlorophenyl) - 2-methylpropan-2-yl] amino] - 2-hydroxypropoxy] ethyl] - 3-methylbiphenyl-4-carboxylic acid,

2' - [1 - [(2R) - 3 - [[1 - (4-chloro-3-trifluoromethylphenyl) - 2-methylpropan-2-yl] amino] - 2-hydroxypropoxy] ethyl] - 3-methylbiphenyl-4-carboxylic acid,

2' - [1 - [(2R) - 3 - [[1 - (3-fluoro-4-methylphenyl) - 2-methylpropan-2-yl] amino] - 2-hydroxypropoxy] ethyl] - 3-t-butylbiphenyl-4-carboxylic acid,

2' - [1 - [(2R) - 3 - [[1 - (4-chloro-2-fluorophenyl) - 2-methylpropan-2-yl] amino] - 2-hydroxypropoxy] ethyl] - 3-t-butylbiphenyl-4-carboxylic acid,

2' - [1 - [(2R) - 3 - [[1 - (4-chloro-3-fluorophenyl) - 2-methylpropan-2-yl] amino] - 2-hydroxypropoxy] ethyl] - 3-t-butylbiphenyl-4-carboxylic acid and

2' - [1 - [(2R) - 3 - [[1 - (3-trifluoromethyl-4-methylphenyl) - 2-methylpropan-2-yl] amino] - 2-hydroxypropoxy] ethyl] - 3-methylbiphenyl-4-carboxylic acid

a pharmaceutically acceptable salt thereof or an optically active form thereof.

9. The compound of claim 8, which is selected from the group

consisting of

2' - [1 - [(2R) - 3 - [[1 - (3-fluoro-4-methylphenyl) - 2-methylpropan-2-yl] amino] - 2-hydroxypropoxy] ethyl] - 3-methylbiphenyl-4-carboxylic acid,

2' - [1 - [(2R) - 3 - [[1 - (4-chloro-3-fluorophenyl) - 2-methylpropan-2-yl] amino] - 2-hydroxypropoxy] ethyl] - 3-methylbiphenyl-4-carboxylic acid,

2' - [1 - [(2R) - 3 - [[1 - (3-chloro-4-methylphenyl) - 2-methylpropan-2-yl] amino] - 2-hydroxypropoxy] ethyl] - 3-methylbiphenyl-4-carboxylic acid and

2' - [1 - [(2R) - 3 - [[1 - (4-chloro-2-fluorophenyl) - 2-methylpropan-2-yl] amino] - 2-hydroxypropoxy] ethyl] - 3-methylbiphenyl-4-carboxylic acid,

a pharmaceutically acceptable salt thereof or an optically active form thereof.

10. 2' - [1 - [(2R) - 3 - [[1 - (3-Fluoro-4-methylphenyl) - 2-methylpropan-2-yl] amino] - 2-hydroxypropoxy] ethyl] - 3-methylbiphenyl-4-carboxylic acid, a pharmaceutically acceptable salt thereof or an optically active form thereof.

11. 2' - [1 - [(2R) - 3 - [[1 - (4-Chloro-3-fluorophenyl) - 2-methylpropan-2-yl] amino] - 2-hydroxypropoxy] ethyl] - 3-methylbiphenyl-4-carboxylic acid, a pharmaceutically acceptable salt thereof or an optically active form thereof.

12. 2' - [1 - [(2R) - 3 - [[1 - (3-Chloro-4-methylphenyl) - 2-methylpropan-2-yl] amino] - 2-hydroxypropoxy] ethyl] - 3-methylbiphenyl-4-carboxylic acid, a pharmaceutically acceptable salt thereof or an optically active form thereof.

13. 2' - [1 - [(2R) - 3 - [[1 - (4-Chloro-2-fluorophenyl) - 2-methylpropan-2-yl] amino] - 2-hydroxypropoxy] ethyl] - 3-methylbiphenyl-4-carboxylic acid, a pharmaceutically

acceptable salt thereof or an optically active form thereof.

14. A pharmaceutical composition comprising a pharmaceutically acceptable carrier, and a compound of any one of claims 1 to 13, a pharmaceutically acceptable salt thereof or an optically active form thereof as an active ingredient.

15. The pharmaceutical composition of claim 14, wherein the active ingredient is a compound of any one of claims 1 to 5, a pharmaceutically acceptable salt thereof or an optically active form thereof.

16. The pharmaceutical composition of claim 14, wherein the active ingredient is a compound of any one of claims 6 to 13, a pharmaceutically acceptable salt thereof or an optically active form thereof.

17. A therapeutic drug for osteoporosis, which comprises a pharmaceutically acceptable carrier, and a compound of any one of claims 1 to 13, a pharmaceutically acceptable salt thereof or an optically active form thereof, as an active ingredient.

18. The therapeutic drug for osteoporosis of claim 17, wherein the active ingredient is a compound of any one of claims 1 to 5, a pharmaceutically acceptable salt thereof or an optically active form thereof.

19. The therapeutic drug for osteoporosis of claim 17, wherein the active ingredient is a compound of any one of claims 6 to 13, a pharmaceutically acceptable salt thereof or an optically active form thereof.

20. The therapeutic drug for osteoporosis of any one of claims 17 to 19, further containing a different therapeutic drug for osteoporosis.

21. The therapeutic drug for osteoporosis of claim 20, wherein the different therapeutic drug for osteoporosis is selected from the group consisting of a calcium agent, a vitamin D preparation, a vitamin K preparation, a female hormone preparation, an estrogen antagonist preparation, an anabolic steroid preparation, a parathyroid hormone preparation, a calcitonin preparation, a bisphosphonate preparation and an ipriflavone preparation.

22. A pharmaceutical composition for antagonizing calcium receptor comprising a pharmaceutically acceptable carrier, and a compound of any one of claims 1 to 13, a pharmaceutically acceptable salt thereof or an optically active form thereof as an active ingredient.

23. The pharmaceutical composition of claim 22, wherein the active ingredient is a compound of any one of claims 1 to 5, a pharmaceutically acceptable salt thereof or an optically active form thereof.

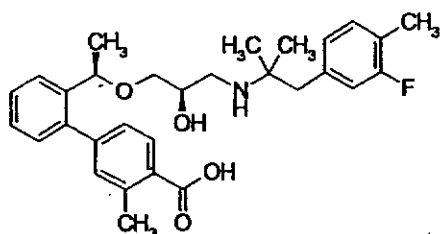
24. The pharmaceutical composition of claim 22, wherein the active ingredient is a compound of any one of claims 6 to 13, a pharmaceutically acceptable salt thereof or an optically active form thereof.

25. A pharmaceutical composition for PTH secretion comprising a pharmaceutical acceptable carrier and a compound of any one of claims 1 to 13, a pharmaceutically acceptable salt thereof or an optically active form thereof as an active ingredient.

26. The pharmaceutical composition of claim 25, wherein the active ingredient is a compound of any one of claims 1 to 5, a pharmaceutically acceptable salt thereof or an optically active form thereof.

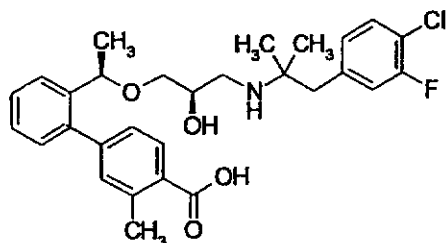
27. The pharmaceutical composition of claim 25, wherein the active ingredient is a compound of any one of claims 11 to 13, a pharmaceutically acceptable salt thereof or an optically active form thereof.

28. The compound of claim 10 which is



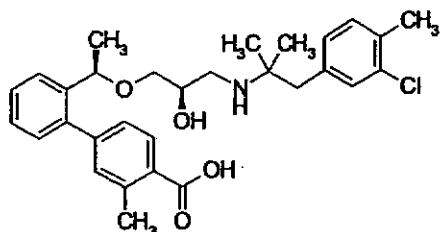
or pharmaceutically acceptable salt thereof.

29. The compound of claim 11 which is



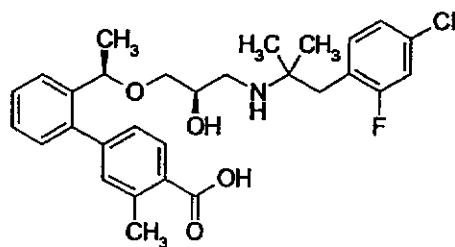
or pharmaceutically acceptable salt thereof.

30. The compound of claim 12 which is



or pharmaceutically acceptable salt thereof.

31. The compound of claim 13 which is



or pharmaceutically acceptable salt thereof.