Description

VLA-4 INHIBITORS



Technical Field

The present invention relates to novel compounds or salts thereof having inhibitory action on VLA-4 (Very Late Antigen-4), and medicaments having these compounds as an effective ingredient.



Background Art

A main pathological feature of inflammatory and autoimmune diseases resides in accumulation of activated leukocytes on a damaged tissue (inflammated tissue). A process of leukocytes from migration out of the circulatory system to transmigration on the inflammatory site involves four-step cascade reactions which interact each other: (1) adhesion and rolling, (2) activation, (3) firm adhesion and (4) transmigration (Springer, T., *Ann. Rev. Physiol.*, 57: 827(1995)).

First, leukocytes adhere to the vascular endothelium to a slight degree and roll on its surface. Then, activation of cells mediated by soluble chemoattractants occurs, which starts formation of firmer bonding between leukocytes to vascular endothelial cells. This firm bonding successively causes adhesion and transmigration of

leukocytes across the space between the vascular endothelial cells. These steps occur continuously and each step is indispensable for occurrence of leukocyte transmigration. This also suggests that leukocyte transmigration is controlled at each step. This fact provides many interesting themes from the viewpoint of pharmaceutics.

A number of receptors in vivo are known. Among them, receptors taking part in leukocyte transmigration are characterized in that they belong to the cell adhesion molecule family (Carlos and Harlan, *Blood*, 82: 2068(1994)). The initial adhesion and rolling are mediated by an adhesion receptor called "selectin". Firm adhesion is mediated by mutual action between integrins on the leukocyte surface and immunoglobulin superfamily molecules expressed on the vascular endothelial surface. Both of these integrins and immunoglobulin type adhesion molecules mainly participate in leukocyte transmigration. Whether leukocytes pass through the extracellular matrix or stop at the inflammatory site after transmigration depends on integrins.

Integrins are a large family of heterodimeric glycoproteins in each of which two non-equivalent α and β-subunits are associated (Heynes, R., *Cell*, 69: 11(1992)). There exist at least 16 α-subunits (α-1 to α-9, αL, αM,

αD, αX, αE, AIIb, αV) which are different each other and at least 9 β-subunits (β-1 to β9) which are different each other. Integrins are classified into subfamilies based on β-subunits. Leukocytes express many different integrins including α4β1, α5β1, α6β1, α4β7, αLβ2, αXβ2 and αVβ3.

The integrin α4β1 is known as a very late antigen (very late antigen-4; VLA-4) or CD49d/CD29. It is expressed by monocytes, lymphocytes, eosinophils and basocytes and serves as a modification factor to be a key in various inflammatory deficiencies (Helmer, M. *Ann. Rev. Immunol.*, 8: 365(1990)). The integrin α4β1 functions as a receptor for vascular cell adhesion molecule-1 (VCAM-1) and also as a receptor for fibronectin (FN) of extracellular protein (Elices, *et al.*, *Cell*, 60: 577(1990)).

In recent years, it has been proved by the below-described studies that selective inhibition against adhesion mediated by α4β1/VCAM-1 will become a solving means for the treatment of autoimmune and allergic inflammatory diseases.

Described specifically, an in vivo experiment has proved that a monoclonal antibody which blocks the pathway of α4β1/VCAM-1 has anti-inflammatory effects and retards the progress of the diseases (Lobb *et al.*, *J. Clin., Invest.*, 94: 1722-28(1944)). In addition, reported are

suppression, by an anti-α4 antibody, of both antigen-induced airway hypersensitivity and accumulation of leukocytes in airway alveolar secretion in guinea pigs used a pulmonary inflammation model (Pretolani, *et al.*, *J. Exp. Med.*, 180: 795(1994); suppression, by α4 or VCAM-1 antibody, of eosinophil transmigration on the airway of mice used as an antigen-induced model (Nakajima *et al.*, *J. Exp. Med.*, 179: 1145(1994)), retardation or suppression, by α4 or VCAM-1 monoclonal antibody treatment, of onset of delayed dermal hypersensitivity in mice and monkeys (Chisholm *et al.*, *Eur. J. Immunol.*, 179: 1145(1994), Silber *et al.*, *J. Clin., Invest.*, 93: 1554(1993)); a model of cardiac transplantation rejection due to (incidental to) specific immunosuppressive action (Isobe *et al.*, *J. Immunol.*, 153: 5810(1994)); graft versus host disease after bone marrow transplantation in mice (Yang *et al.*, *Proc. Natl. Acad. Sci. USA*, 90; 10494(1993)); and experimental autoimmune encephalomyelitis in rats and mice (Yednock, *et al.*, *Nature.*, 356: 63(1992), Baron, *et al.*, *J. Exp. Med.*, 177: 57(1993)).

In addition, there is a report on significant retardation of the onset of diabetes by administration, to nonobese diabetic mice used as an in vivo model, of soluble VCAM-immunoglobulin (Ig) fusion protein prepared by fusing two human N-terminal regions to the common portion of human

IgG1 in accordance with Rational Drug Design (Significant delays the onset of adoptively transferred autoimmune diabetes in nonobese mice (Jakubowski *et al.*, *J. Immunmol.*, 155: 938(1995)). Another report is that as a result of synthesis of a cyclic peptide antagonist by using the three-dimensional crystal structure of a VCAM-1 fragment for mimicking the binding loop portion of α4 integrin at the domain-1 of VCAM-1, CQIDSPC of the synthesized VCAM-1 peptide succeeded in inhibiting adhesion of VLA-4 expressed cells to purified VCAM-1 (Wang *et al.*, *Proc. Natl. Acad. Sci. USA*, 92: 5714(1995)).

Reported as another strategy are blocking of adhesion of α4β1 to either one of binding sites of its corresponding receptor, that is, fibronectin including connecting segment-1 (CS-1) domain (E.A. Wayner, *J. Cell. Biol.*, 116; 489(1992)); and in vitro inhibition, by synthetic CS-1 tetrapeptide (phenylacetic acid-Leu-Asp-Phe-d-Pro-amide), of leukocyte adhesion mediated by VLA-4 and amelioration of advance of coronary arterial diseases in cardiac transplantation of rabbits (Molossi *et al.*, *J. Clin. Invest.*, 95: 2601(1995)).

In addition, there are several reports on compounds exhibiting in vitro VLA-4 inhibitory activity (U.S. Patent No. 5,821,231, WO96/22966, WO97/03094, WO98/04247 and WO98/04913).

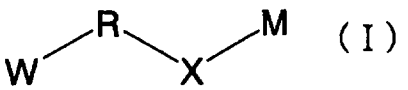
Medicaments exhibiting sufficient effectiveness in oral administration and having clinical utility however have not yet been found.

An object of the present invention is therefore to provide a medicament which serves a selective inhibitor against VLA-4, exhibits effectiveness by oral administration and is administrable for a long period of time.

Disclosure of the Invention

With the foregoing in view, the present inventors have carried out an investigation on low-molecular-weight and non-peptide compounds. As a result, it has been found that compounds represented by the below-described formula (I) selectively inhibit bonding of cell adhesion molecules to VLA-4 and are useful for prevention or treatment of various diseases mediated by migration and adhesion of leukocytes, leading to the completion of the present invention.

In the present invention, there are thus provided a compound represented by the following formula (I):



(I)

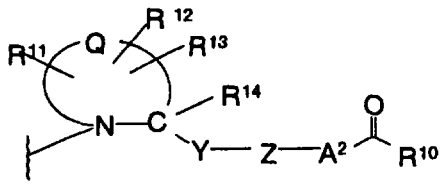
(wherein, W represents W^A-A^1-W^B- (in which, W^A represents a substituted or unsubstituted aryl group or a substituted or unsubstituted monovalent heterocyclic group, A^1 represents

$-NR^1-$, a single bond, $-C(O)-$, $-C(O)NR^1-$, a substituted or unsubstituted vinylene group, an ethynylene group, $-CR^{1a}R^{1b}-O-$, $-CR^{1a}=CR^{1b}-C(O)NR^1-$ or $-CR^{1a}=CR^{1b}-C(O)-$ (in which, R^1 represents a hydrogen atom or a lower alkyl group, and R^{1a} and R^{1b} each independently represents a hydrogen atom or a lower alkyl group), and W^B represents a substituted or unsubstituted arylene group or a substituted or unsubstituted divalent heterocyclic group);

R represents a single bond, $-NH-$, $-OCH_2-$, an alkenylene group or $-(CH_2)_n-$ (in which, n stands for 1 or 2);

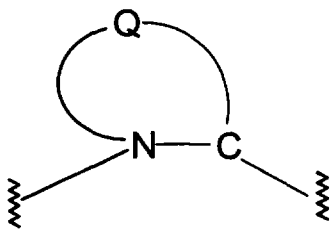
X represents $-C(O)-$, $-CH_2-$ or $-S(O)_2-$, and

M represents the following formula (iii), (iv) or (v):



(iii)

(in which,

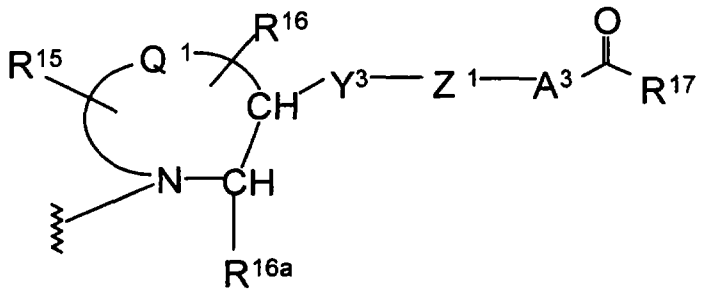


(iii - a)

represents a divalent 4-, 5-, 6- or 7-membered heterocyclic group (in which the nitrogen atom is bonded to X and Q

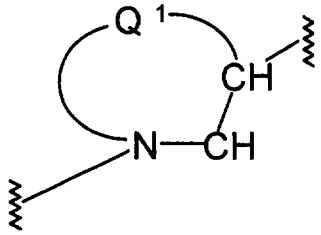
represents a carbon, sulfur, oxygen or nitrogen atom), R^{11}, R^{12} and R^{13} each independently represents a hydrogen atom, a hydroxyl group, an amino group, a halogen atom, a cyano group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a substituted or unsubstituted mono- or dialkylaminocarbonyl group, a substituted or unsubstituted alkyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, a substituted or unsubstituted alkoxy group, a substituted or unsubstituted mono- or dialkylamino group, a substituted or unsubstituted cycloalkylamino group, a substituted or unsubstituted alkylsulfonylamino group, a substituted or unsubstituted arylsulfonylamino group, a substituted or unsubstituted aryloxy group, a substituted or unsubstituted heteroaryloxy group, a substituted or unsubstituted benzyloxy group, a substituted or unsubstituted alkylthio group, a substituted or unsubstituted cycloalkylthio group, a substituted or unsubstituted arylthio group, a substituted or unsubstituted alkylsulfonyl group, a substituted or unsubstituted cycloalkylsulfonyl group, or a substituted or unsubstituted arylsulfonyl group, or R^{11} and R^{12} or R^{12} and R^{13} may be coupled to form, together with the atom constituting the heterocyclic group to which R^{11} to R^{13} are bonded, a 3 to 7-membered cyclic hydrocarbon or heterocycle (the cyclic hydrocarbon and the heterocycle may have thereon 1 to 3 substituents selected from a hydroxyl

group, halogen atoms, an amino group, alkyl groups, alkoxy groups, aryl groups, aryloxy groups, alkylamino groups, a benzyloxy group and heteroaryl groups), R^{14} represents a hydrogen atom or a substituted or unsubstituted lower alkyl group, Y represents a single bond, -C(O)-, -C(O)NH-, or a linear or branched divalent aliphatic C_{1-12} hydrocarbon group which may have a C_{3-6} spiro ring or may have one or more carbon atoms substituted by -O-, -S-, $-S(O)_2-$, -C(O)- or $-NY^1-$ (in which, Y^1 represents a hydrogen atom or a lower alkyl group), Z represents a substituted or unsubstituted arylene group, a substituted or unsubstituted heteroarylene group or a substituted or unsubstituted cycloalkylene group, A^2 represents a single bond, an alkenylene group, an alkynylene group, $-(CH_2)_t-$ or $-O(CH_2)_v-$ (in which, t stands for 1, 2 or 3 and v stands for 0, 1, 2 or 3), and R^{10} represents a hydroxyl or a lower alkoxy group),



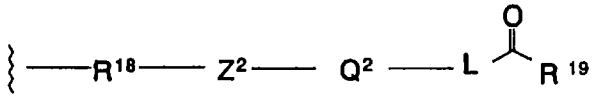
(iv)

(in which,



(iv - a)

represents a divalent 4-, 5-, 6- or 7-membered heterocyclic group (in which the nitrogen atom is bonded to X, and Q^1 represents a carbon, sulfur, oxygen or nitrogen atom), R^{15} and R^{16} each independently represents a hydrogen atom, a hydroxyl group, a halogen atom, a substituted or unsubstituted alkyl group or an alkoxy group, R^{16a} represents a hydrogen atom or a substituted or unsubstituted alkyl group, Y^3 represents -O-, -S-, $-S(O)_2-$, $-(CH_2)_fO-$ or $-NY^4-$ (in which f stands for 1, 2 or 3 and Y^4 represents a hydrogen atom or a lower alkyl group), Z^1 represents a substituted or unsubstituted arylene group, a substituted or unsubstituted heteroarylene group or a substituted or unsubstituted cycloalkylene group, A^3 represents a single bond, an alkenylene group, an alkynylene group or $-(CH_2)_e-$ (in which e stands for 1, 2 or 3), and R^{17} represents a hydroxyl group or a lower alkoxy group),



(v)

(in which, R^{18} represents $-NR^{20}-$ (in which R^{20} represents a

hydrogen atom, a substituted or unsubstituted alkyl group, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted benzyl group, a substituted or unsubstituted lower alkenyl group or a substituted or unsubstituted alkynyl group), Z^2 represents a linear or branched divalent aliphatic C_{1-12} hydrocarbon group which may have a C_{3-6} spiro ring, may have one or more carbon atoms substituted by a divalent C_{3-8} cycloalkylene group or may have one or more carbon atoms substituted by -O-, -S-, $-S(O)_2-$, -C(O)- or $-NR^{21}-$ (in which, R^{21} represents a hydrogen atom or a substituted or unsubstituted lower alkyl group), Q^2 represents a single bond, a substituted or unsubstituted arylene group, a substituted or unsubstituted heteroarylene group or a substituted or unsubstituted cycloalkylene group, L stands for a single bond, a substituted or unsubstituted lower alkylene group or a substituted or unsubstituted lower alkenylene group, or R^{19} represents a hydroxyl or a lower alkoxy group)); or salt thereof; and a medicament containing the same.

In the present invention, there are also provided a medicament and a composition, which comprise a pharmaceutically acceptable carrier and the above-described compound or salt.

In the present invention, there is also provided the use of the above-described compound or salt for the

preparation of a medicament.

In the present invention, there is also provided a treating method of a disease caused by cell adhesion, which comprises administering the above-described compound or salt.

Best Mode for Carrying Out the Invention

The compound of the present invention is represented by the above-described formula (I). The alkyl group in the formula means a linear or branched saturated hydrocarbon group having 1 to 12, preferably 1 to 8 carbon atoms. Examples include methyl, ethyl, propyl, isopropyl, normal butyl, isobutyl, tertiary butyl, pentyl, heptyl and octyl groups.

The lower alkyl group means a linear or branched saturated hydrocarbon group having 1 to 8, preferably 1 to 6 carbon atoms. Examples include methyl, ethyl, propyl, isopropyl, normal butyl, isobutyl, tertiary butyl and pentyl groups.

The alkylene group means a divalent group formed of the above-exemplified alkyl group. Examples include methylene, ethylene, propylene, isopropylene, normal butylene, isobutylene, pentylene, hexylene, heptylene and octylene groups.

The alkenyl group means a linear or branched C_{2-12}, preferably C_{2-8} group formed of an unsaturated hydrocarbon

containing at least one double bond. Examples include vinyl, propenyl, isopropenyl, 1-butenyl, 2-butenyl, 1,3-butadienyl, 1-isobutenyl, 1-pentenyl, 1-heptenyl and 1-octenyl groups.

The alkenylene group means a divalent group formed of the above-exemplified alkenyl group. Examples include vinylene, propenylene, isopropenylene, 1-butenylene, 2-vinylene, 1-isobutenylene, 1-pentenylene, 1-heptenylene and 1-octenylene groups.

The alkynyl group means a linear or branched C_{2-12}, preferably C_{2-8} group formed of an unsaturated hydrocarbon containing one triple bond. Examples include ethynyl, propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 1-heptynyl and 1-octynyl groups.

The alkynylene group means a divalent group formed of the above-exemplified alkynyl group. Examples include ethynylene, propynylene, 1-butynylene, 2-butynylene, 1-pentynylene, 1-heptynylene and 1-octynylene groups.

The cycloalkyl group means a cycloalkyl group having 3 to 10, preferably 3 to 6 carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups.

The cycloalkylene group means a divalent group formed of the above-exemplified cycloalkyl group. The cycloalkyl group in this case is as described above. Examples include cyclopropylene, cyclobutylene, cyclopentylene and cyclohexylene groups.

The aliphatic hydrocarbon group means a linear, branched or cyclic hydrocarbon group having 1 to 18 carbon atoms, preferably 1 to 12 carbon atoms, and it includes alkyl, cycloalkyl, alkenyl, and alkynyl groups and combinations thereof. Examples include ethyl, propyl, propynyl and 2, 4-heptadienyl groups.

The aryl group means an aromatic monocyclic or fused hydrocarbon group having 6 to 18, preferably 6 to 10 carbon atoms and examples include phenyl and naphthyl groups.

The arylene group means a divalent group formed of the above-exemplified aryl group and examples thereof include phenylene and naphthylene groups.

The cyclic hydrocarbon group means a saturated or unsaturated (including aromatic) monocyclic group having 3 to 7 carbon atoms, and examples include cyclopropane, cyclobutane, cyclopentane, cyclopentene, cyclohexane, cyclohexene, cycloheptane and benzene.

The heteroaryl group means a monovalent group formed of a monocyclic or fused aromatic heterocycle having, as the constituent of the ring, 5 to 18 atoms including at least one oxygen, nitrogen and/or sulfur atom, preferably a group formed of an aromatic heterocycle having 5 to 14 atoms. Examples of the monocyclic aromatic heterocycle include pyrrole, 2H-pyrrole, thiophene, furan, imidazole, pyrazole, isoxazole, isothiazole, thiazole, oxazole, oxadiazole, 1,3,4-thiadiazole, triazole, tetrazole,

pyrimidine, pyrazine, pyrimidine, pyridazine, 2H-pyran and 4H-pyran. Among the fused aromatic heterocycles, examples of the bicyclic ones include indole, indolizine, isoindole, 1H-indazole, 2H-indazole, purine, 4H-quinolidine, isoquinoline, quinoline, phthalazine, naphthylidine, quinoxaline, quinazoline, cinnoline, benzopyran, benzo(b)thiophene, 2,3-benzofuran, 3,4-benzofuran, benzoxazole, benzothiazole, benzoisoxazole, benzoisothiazole, benzimidazole, benzotriazole, 1H-pyrrolo(2,3-b)pyridine, 1H-pyrrolo(2,3-c)pyridine, 1H-pyrrolo(3,2-c)pyridine, 1H-pyrrolo(3,2-b)pyridine, 3H-pyrrolo(2,3-b)pyridine, 3H-pyrrolo(2,3-c)pyridine, 3H-pyrrolo(3,2-c)pyridine, 3H-pyrrolo(3,2-b)pyridine, dihydropyrrolo(2,3-b)pyridine, dihydropyrrolo(2,3-c)pyridine, dihydropyrrolo(3,2-c)pyridine, dihydropyrrolo(3,2-b)pyridine, oxazolo(4,5-b)pyridine, oxazolo(4,5-c)pyridine, oxazolo(5,4-c)pyridine, oxazolo(5,4-b)pyridine, thiazolo(4,5-b)pyridine, thiazolo(4,5-c)pyridine, thiazolo(5,4-c)pyridine, thiazolo(5,4-b)pyridine and pyrido(1,2-a)pyrimidine. Examples of the tricyclic aromatic heterocycle include carbazole, carboline, phenoxazine, xanthene, xanthone, dibenzofuran and dibenzothiophene.

The heteroarylene group means a divalent group formed of the above-exemplified heteroaryl group.

The heterocyclic group means a group formed of a

monocyclic or fused aliphatic or aromatic heterocycle having, as a constituent, 5 to 18 atoms, preferably 5 to 14 atoms including at least one oxygen, nitrogen and/or sulfur atom. Examples of the aromatic heterocyclic group are similar to those exemplified above as the heteroaryl group. Examples of the aliphatic heterocyclic group include pyrrolidine, pyrroline, imidazolidine, imidazoline, indoline, tetrahydrofuran, dihydrofuran, tetrahydrothiophene, dihydrothiophene, thiazolidine, thiazoline, oxazoline, oxazolidine, isoxazolidine, isoxazoline, piperidine, morpholine, thiamorpholine, piperazine, tetrahydropyrane, tetrahydrobenzimidazole, tetrahydrobenzofuran, tetrahydrobenzothiophene, tetrahydrobenzothiazole, tetrahydrobenzoxazole, tetrahydroquinoline, tetrahydroisoquinoline and tetrahydroquinazoline.

The halogen atom means a fluorine, chlorine, bromine or iodine atom.

Examples of the alkoxy group include methoxy, ethoxy, propoxy, isopropoxy, normal butoxy, isobutyloxy, tertiarybutoxy, pentyloxy, hexyloxy, heptyloxy and octyloxy groups.

The lower alkoxy group means a linear or branched alkoxy group having 1 to 8, preferably 1 to 6 carbon atoms and examples include methoxy, ethoxy, propoxy, isopropoxy, normal butoxy, isobutyloxy, tertiary butoxy, pentyloxy and

hexyloxy groups.

Examples of the aryloxy group include phenoxy and naphthyloxy groups.

Examples of the heteroaryloxy group include pyridyloxy and indoleoxy groups.

Examples of the alkylthio group include methylthio, ethylthio, propylthio, isopropylthio, normal butylthio, isobutylthio, tertiary butylthio, pentylthio, hexylthio, heptylthio and octylthio groups.

Examples of the cycloalkylthio group include cyclopropylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio and cyclooctylthio groups.

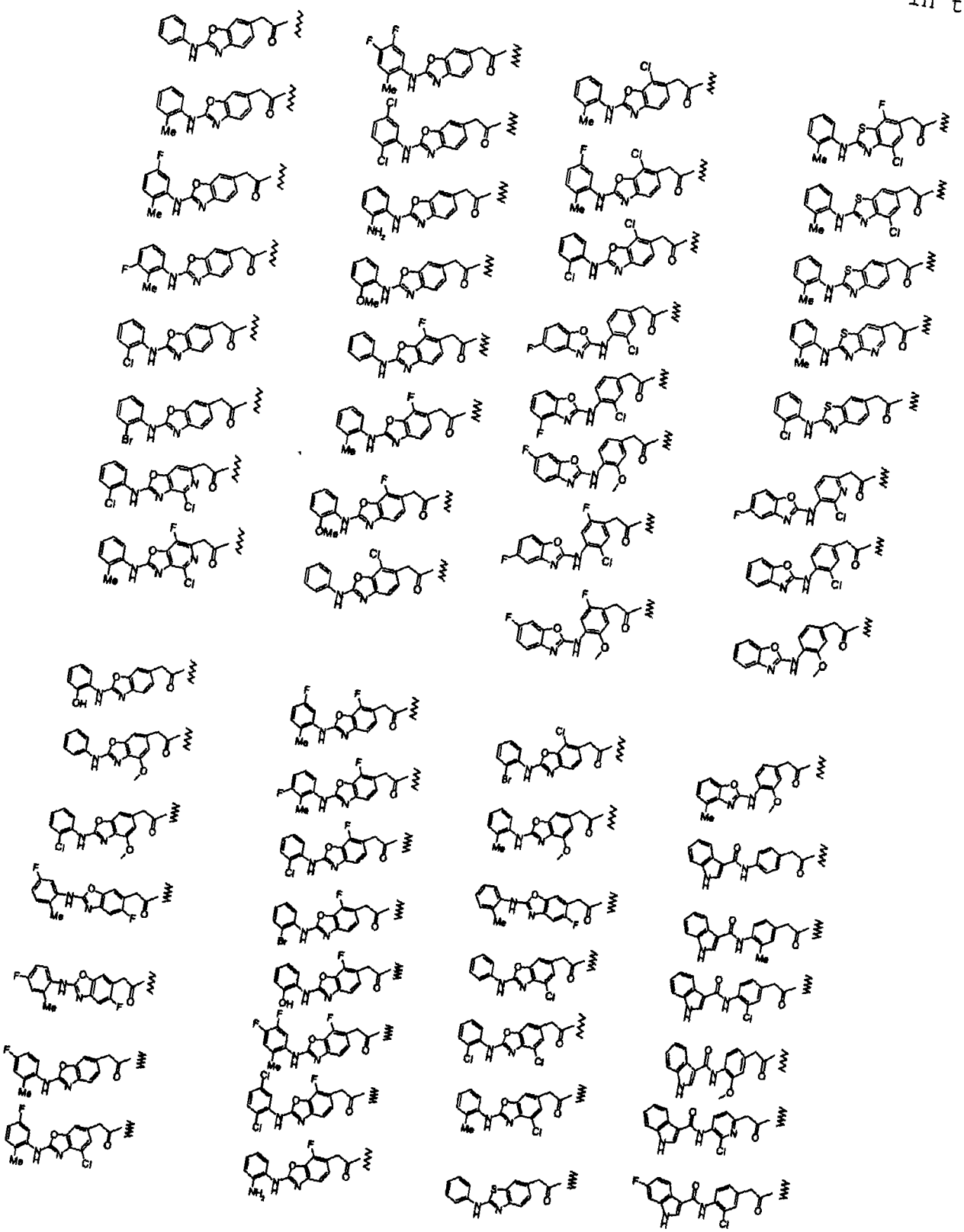
Examples of the arylthio group include phenylthio and naphthylthio groups.

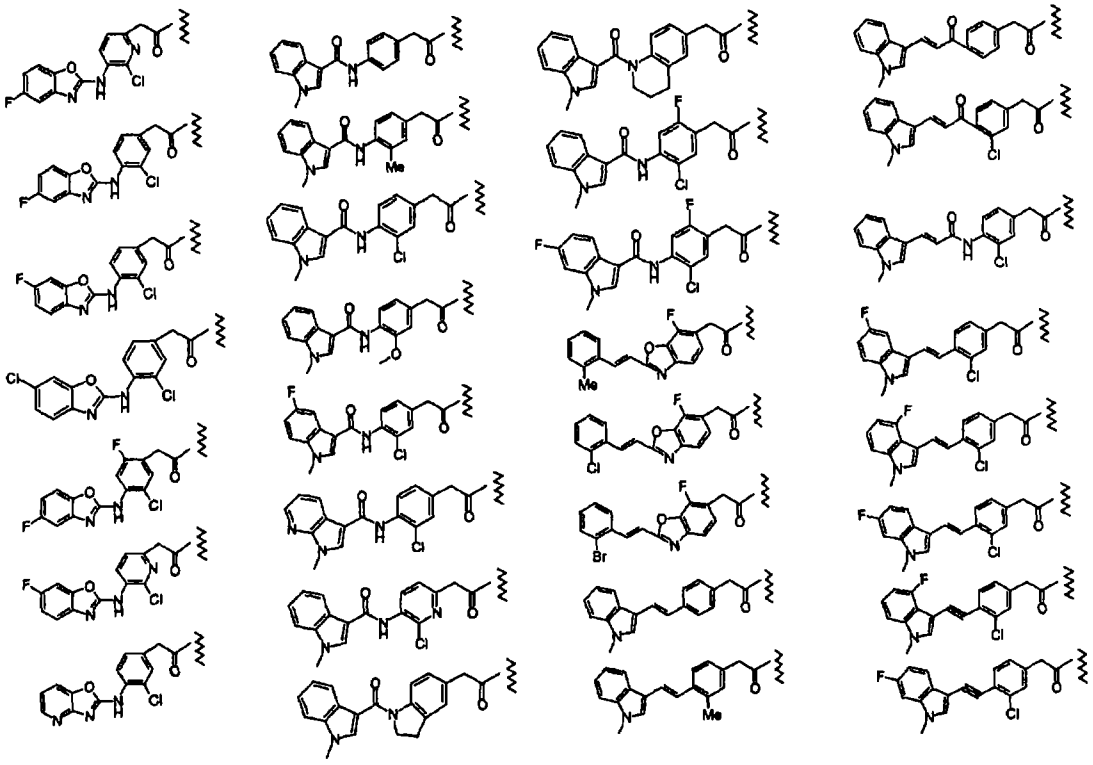
Examples of the alkylsulfonyl group include methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, normal butylsulfonyl, isobutylsulfonyl, tertiary butylsulfonyl, pentylsulfonyl, hexylsulfonyl, heptylsulfonyl and octylsulfonyl groups.

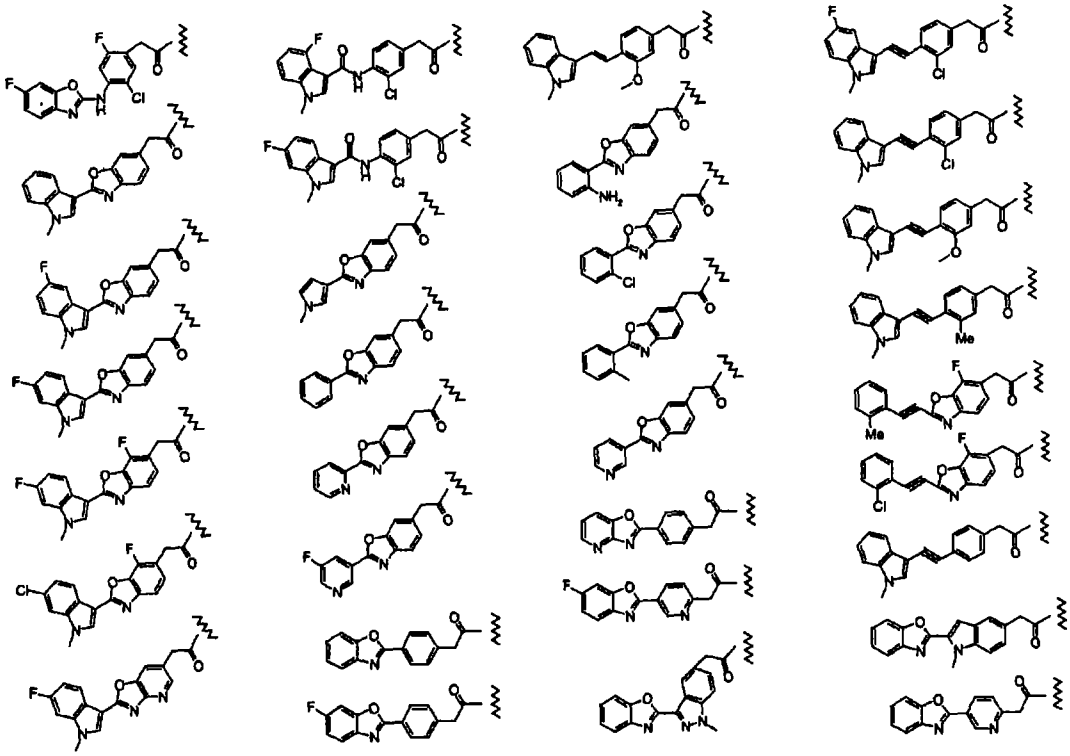
Examples of the cycloalkylsulfonyl group include cyclopropylsulfonyl, cyclobutylsulfonyl, cyclopentylsulfonyl, cyclohexylsulfonyl and cyclooctylsulfonyl groups.

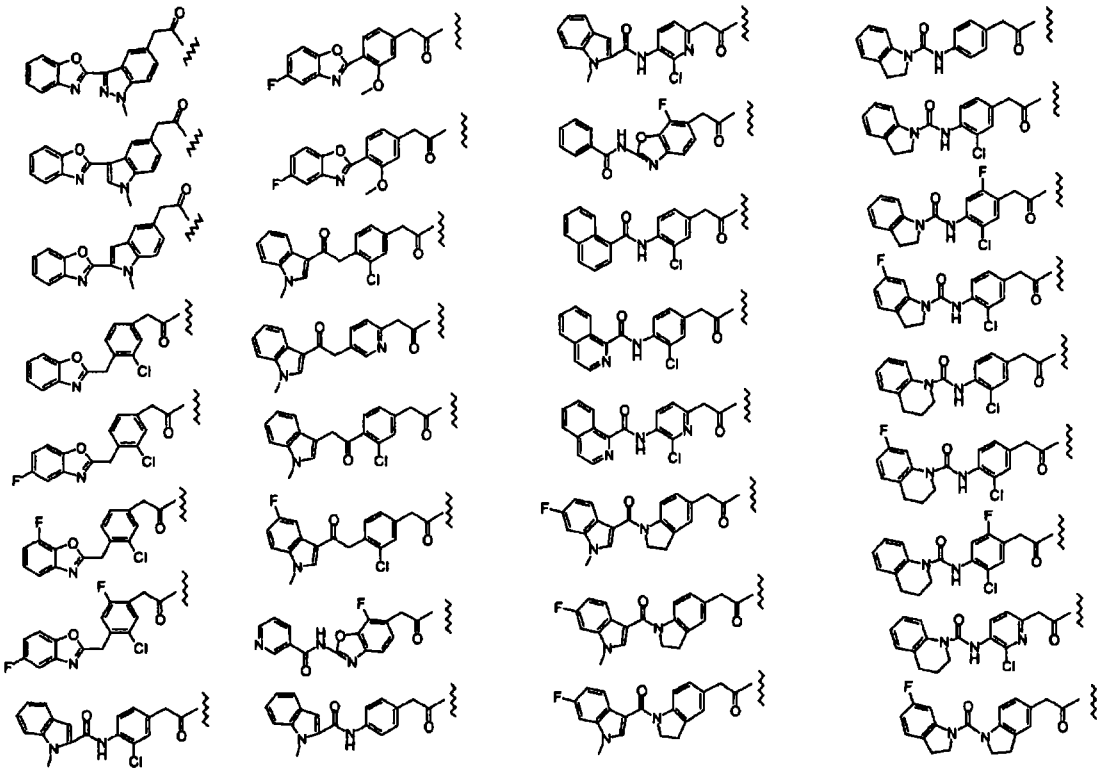
Examples of the arylsulfonyl group include phenylsulfonyl and naphthylsulfonyl groups.

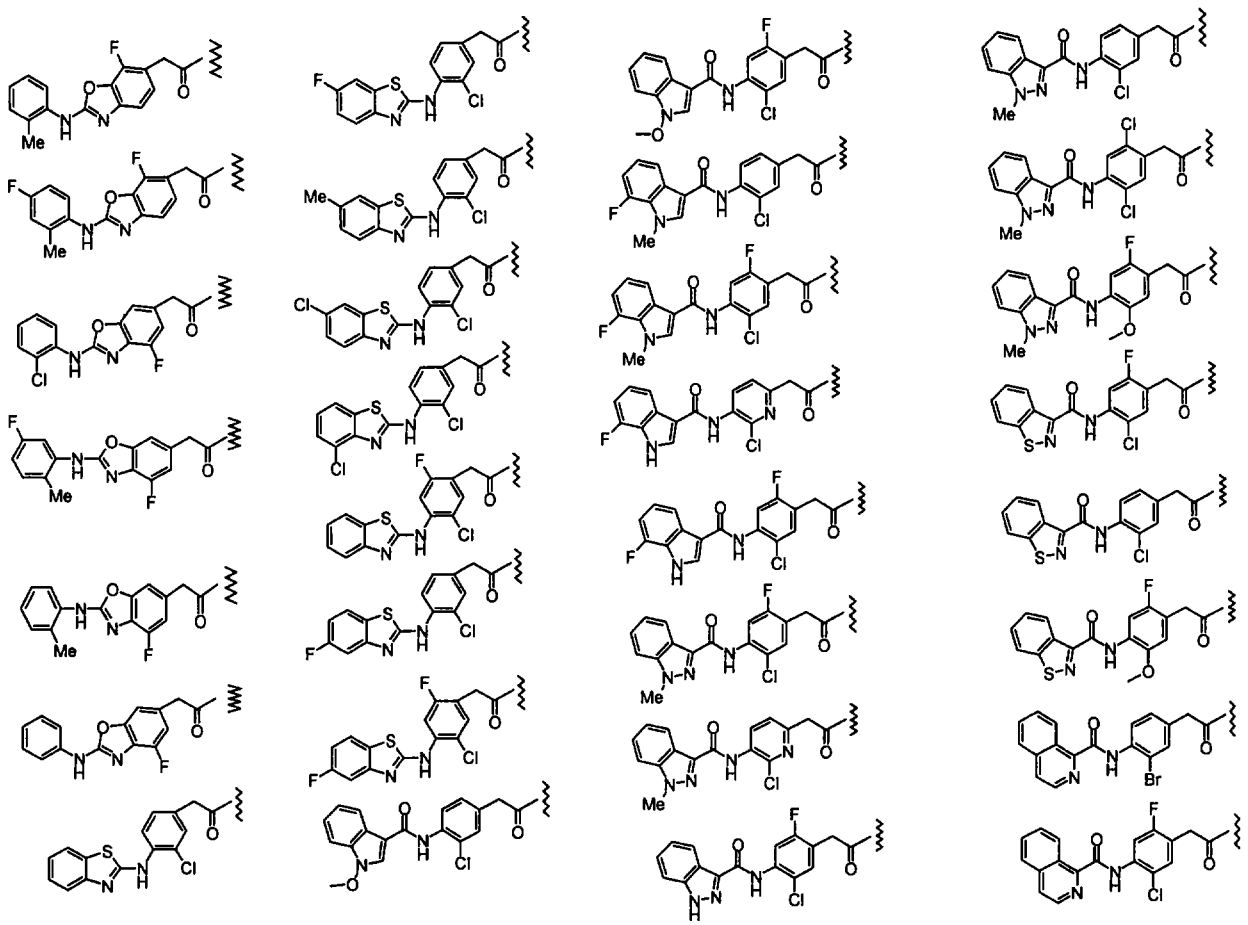
The followings are specific examples of W-R-X- in the formula (I).











In the compound represented by the formula (I), W means the formula: W^A-A^1-W^B.

In the formula, W^A is a substituted or unsubstituted aryl group or a substituted or unsubstituted monovalent heterocyclic group. This aryl group is similar to the above-described one, with a phenyl group being particularly preferred. As the heterocyclic group, preferred is a monovalent group formed, for example, of pyridine, thiazole, pyrimidine, pyrrole, indole, isoquinoline, quinoline, indoline, tetrahydroquinoline, indazole, benzisothiazole, benzisoxazole, benzothiazole or

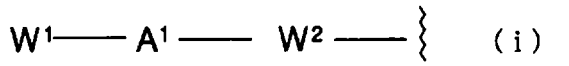
benzoxazole. Examples of the substituent for the aryl group or heterocyclic group include lower alkyl groups, lower alkoxy groups, halogen atoms, amino group and hydroxyl group. The aryl group or heterocyclic group may be substituted with at least one of these substituents.

W^B is a substituted or unsubstituted arylene group or a substituted or unsubstituted divalent heterocyclic group. This arylene group is similar to the above-described one, with a phenylene group being particularly preferred. As the heterocyclic group, preferred is a divalent group formed, for example, of pyridine, thiazole, pyrimidine, pyrrole, indole, isoquinoline, quinoline, indoline, tetrahydroquinoline, benzothiazole or benzoxazole. Examples of the substituent for the arylene group or heterocyclic group include lower alkyl groups, lower alkoxy groups, halogen atoms, amino group and hydroxyl group. The arylene group or heterocyclic group may be substituted with at least one of these substituents.

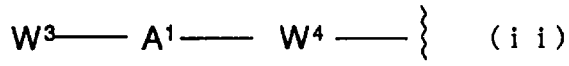
A^1 represents $-NR^1-$, single bond, $-C(O)-$, $-C(O)NR^1-$, a substituted or unsubstituted vinylene group, an ethynylene group, $-CR^{1a}R^{1b}-O-$, $-CR^{1a}=CR^{1b}-C(O)NR^1-$ or $-CR^{1a}=CR^{1b}-C(O)-$ (in which, R^1 represents a hydrogen atom or a lower alkyl group, and R^{1a} and R^{1b} each independently represents a hydrogen atom or a lower alkyl group), of which single bond, $-NH-$ or $-C(O)NH-$ is preferred.

The formula: $W^A-A^1-W^B$ is preferably the following

formula (i) or (ii).



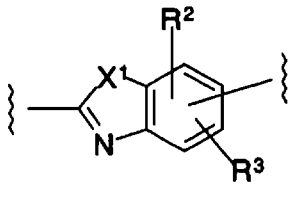
(i)



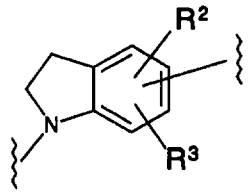
(ii)

In the formula (i), W^1 represents a substituted or unsubstituted aryl group or a substituted or unsubstituted monovalent heterocyclic group and those exemplified above in W^A are preferred. Particularly preferred examples include phenyl, pyridyl, indolyl, isoquinolinyl, indolinyl, tetrahydroquinolinyl, and benzoxazolyl groups, and phenyl, pyridyl, indolyl, isoquinolinyl, indolinyl, tetrahydroquinolinyl, indazolyl, benzisothiazolyl, benzisoxazolyl, benzothiazolyl and benzoxazolyl groups each substituted with a lower alkyl group, a lower alkoxy group or a halogen atom.

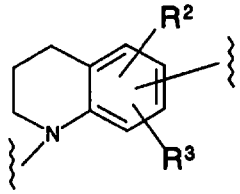
W^2 is a substituted or unsubstituted divalent bicyclic heterocyclic group and particularly preferred is that represented by the following formula (i-a), (i-b) or (i-c).



(i-a)



(i-b)



(i-c)

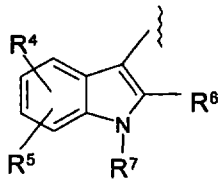
In the above formulas, X^1 represents an oxygen or

sulfur atom, with oxygen atom being particularly preferred.

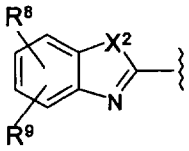
R^2 and R^3 each independently represents a hydrogen atom, a halogen atom, a lower alkyl group, a hydroxyl group, a lower alkoxy group or an amino group, of which a hydrogen atom, a halogen atom, a lower alkyl group or a lower alkoxy group is particularly preferred.

On the right side in the above-described formula (i-a), (i-b) or (i-c), the bonding to R is preferred and said bonding is preferably bonding to R at the para position on the benzene ring relative to the nitrogen atom in the formula (i-a), (i-b) or (i-c).

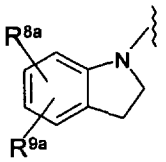
In the formula (ii), W^3 is a substituted or unsubstituted monovalent dicyclic heterocyclic group. Those represented by the following formulas (ii-a) to (ii-j) are preferred as W^3.



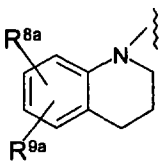
(ii-a)



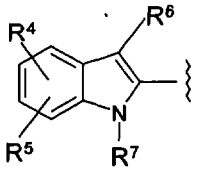
(ii-b)



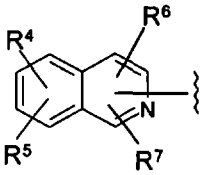
(ii-c)



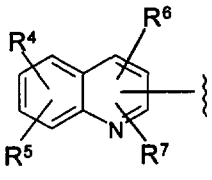
(ii-d)



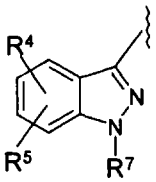
(ii-e)



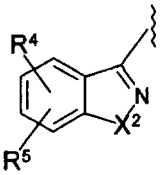
(ii-f)



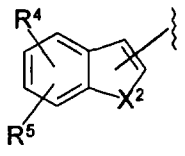
(ii-g)



(ii-h)



(ii-i)



(ii-j)

In the formula, X^2 represents an oxygen or sulfur

atom, with an oxygen atom being particularly preferred.

R^4, R^5, R^8, R^9, R^{8a} and R^{9a} each independently represents a hydrogen atom, a halogen atom, a lower alkyl group, a hydroxyl group, a lower alkoxy group or an amino group, of which a hydrogen atom, a halogen atom, a lower alkyl group or a lower alkoxy group is preferred.

Of these, the formulas (ii-a), (ii-b), (ii-h) and (ii-i) are particularly preferred.

W^4 represents a substituted or unsubstituted arylene group or a substituted or unsubstituted divalent monocyclic heterocyclic group, preferably a phenylene group, a pyridylene group, or a phenylene or pyridylene group substituted with a lower alkyl group, a lower alkoxy group or a halogen atom.

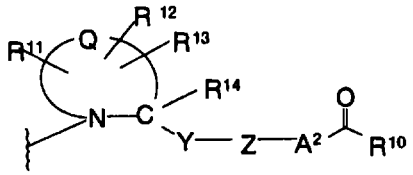
A^1 and R^1 are preferably bonding at para position on the phenylene or pyridylene group.

R is a single bond, -NH-, $-OCH_2-$, an alkenylene group, or $-(CH_2)_n-$ (in which n stands for 1 or 2), of which $-CH_2-$ is particularly preferred.

X is $-C(O)-$, $-CH_2-$ or $-S(O)_2-$, with $-C(O)-$ being particularly preferred.

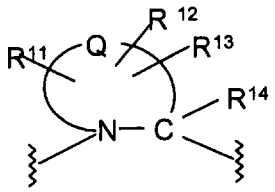
In the compound represented by the formula (I), M represents the below-described formula (iii), (iv) or (v):

Formula (iii):



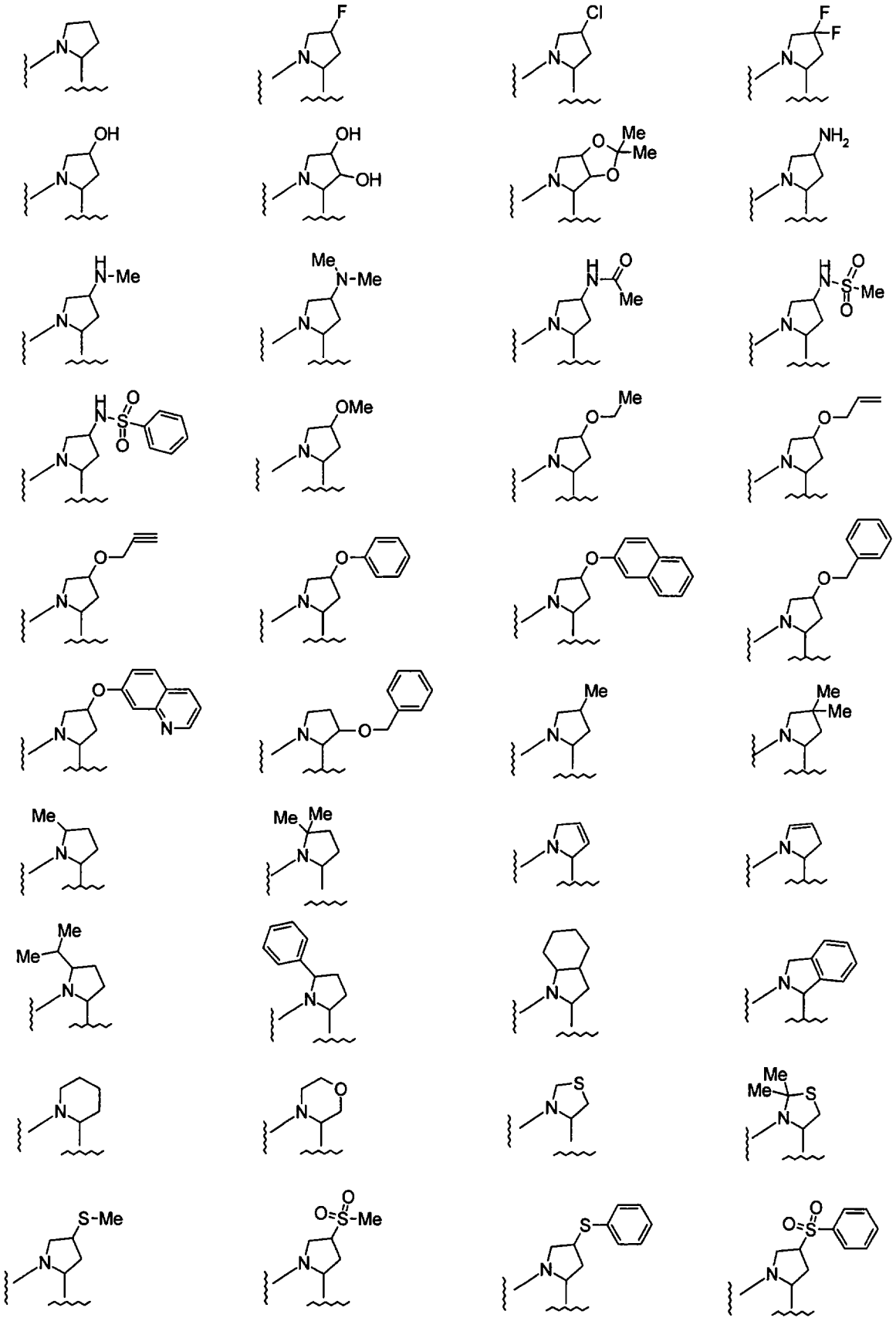
(iii)

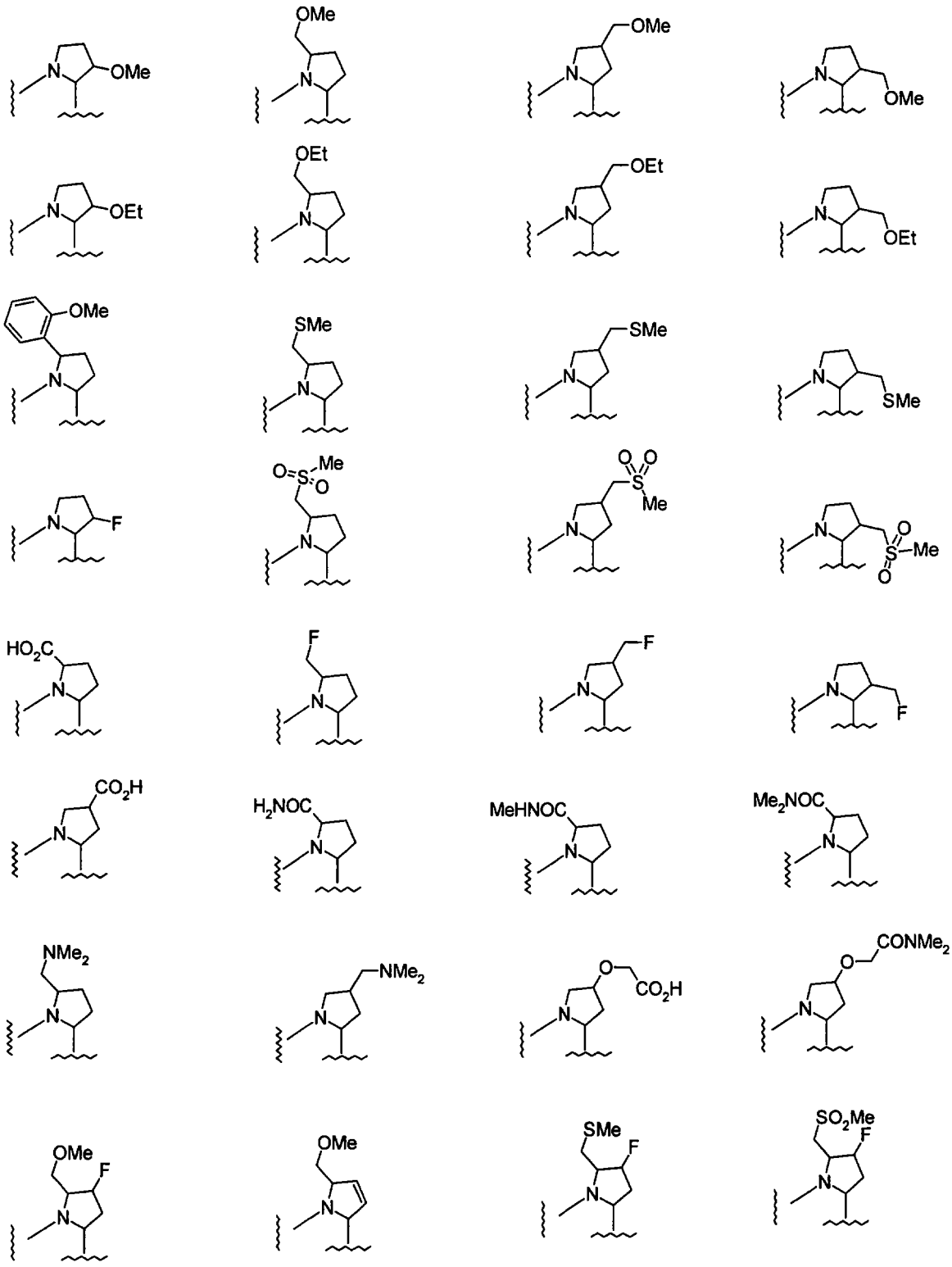
Specific examples of the formula (iii-b):



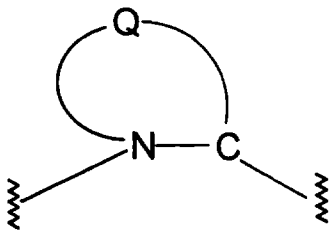
(iii-b)

in the formula (ii) are exemplified below:





In this formula,



(iii - a)

represents a divalent 4-, 5-, 6- or 7-membered heterocyclic group, of which a 5- or 6-membered heterocyclic group having as Q a carbon, oxygen or nitrogen atom is preferred, with a divalent group formed of a pyrrolidine ring being particularly preferred.

Here, when Q is a divalent group formed of a pyrrolidine ring, it is most preferred that the absolute configuration of the 2-position to which a $-Y-Z-A^2-C(O)-R^{10}$ group is bonded is equal to that of the natural L-proline.

R^{11}, R^{12} and R^{13} each independently represents a hydrogen atom, a hydroxyl group, an amino group, a halogen atom, a cyano group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a substituted or unsubstituted mono- or dialkylaminocarbonyl group, a substituted or unsubstituted alkyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, a substituted or unsubstituted alkoxy group, a substituted or unsubstituted mono- or dialkylamino group, a substituted or unsubstituted cycloalkylamino group, a substituted or unsubstituted alkylsulfonylamino group, a substituted or unsubstituted arylsulfonylamino group, a

substituted or unsubstituted aryloxy group, a substituted or unsubstituted heteroaryloxy group, a substituted or unsubstituted benzyloxy group, a substituted or unsubstituted alkylthio group, a substituted or unsubstituted cycloalkylthio group, a substituted or unsubstituted arylthio group, a substituted or unsubstituted alkylsulfonyl group, a substituted or unsubstituted cycloalkylsulfonyl group, or a substituted or unsubstituted arylsulfonyl group, or R^{11} and R^{12}, or R^{12} and R^{13} may be coupled to form, together with the atom constituting the heterocyclic group to which R^{11} to R^{13} are bonded, a 3 to 7-membered cyclic hydrocarbon or heterocycle (the heterocycle may have thereon 1 to 3 substituents selected from a hydroxyl group, halogen atoms, an amino group, alkyl groups, alkoxy groups, aryl groups, aryloxy groups, alkylamino groups, a benzyloxy group and heteroaryl groups).

Examples of the alkyl, aryl, heteroaryl and alkoxy groups are similar to those described above. Examples of the mono- or dialkylamino group include monomethylamino, monoethylamino, isopropylamino, dimethylamino and diethylamino groups. Examples of the cycloalkylamino group include cyclopropylamino, cyclobutylamino and cyclopentylamino groups; those of the alkylsulfonylamino group include methanesulfonylamino, trifluoromethanesulfonylamino and ethanesulfonylamino

groups; and those of the arylsulfonylamino group include benzenesulfonylamino and naphthylsulfonylamino groups. Examples of the substituent for them include halogen atoms, lower alkyl groups, lower alkoxy groups, hydroxyl group, amino group, acylamino groups and alkylamino groups.

In the case where R^{11} and R^{12}, or R^{12} and R^{13} are coupled to form a 3- to 7-membered cyclic hydrocarbon or heterocycle together with the atom constituting the heterocyclic group to which R^{11} to R^{13} are bonded, examples of the thus formed ring include dihydroindole ring, tetrahydroindole ring, isoindoline ring and tetrahydroisoquinoline ring.

It is preferred that any one of R^{11}, R^{12} and R^{13} is a hydroxyl group, substituted or unsubstituted alkoxy group, substituted or unsubstituted alkyl group or halogen atom. Particularly, methoxyl group, methoxymethyl group or fluorine atom is preferred.

R^{14} represents a hydrogen atom, or a substituted or unsubstituted alkyl group, of which a hydrogen atom and methyl group are preferred, particularly hydrogen atom is preferred.

In the formula (iii), Y represent a single bond, -C(O)-, -C(O)NH-, or a linear or branched divalent aliphatic C_{1-12} hydrocarbon group which may have a C_{3-6} spiro ring or may have one or more carbon atoms substituted by -O-, -S-, $-S(O)_2-$, -C(O)- or $-NY^1-$ (in which, Y^1 represents a hydrogen

atom or a lower alkyl group). Examples of the linear or branched divalent aliphatic hydrocarbon group formed of 1 to 12 carbon atoms include methylene, ethylene, propylene, isopropylene, 2,2-dimethylbutylene and 3,3-dimethylpentylene groups. When the aliphatic hydrocarbon group forms a spiro ring formed of 3 to 6 carbon atoms, the resulting ring is, for example, cyclopropane, cyclobutane or cyclohexane.

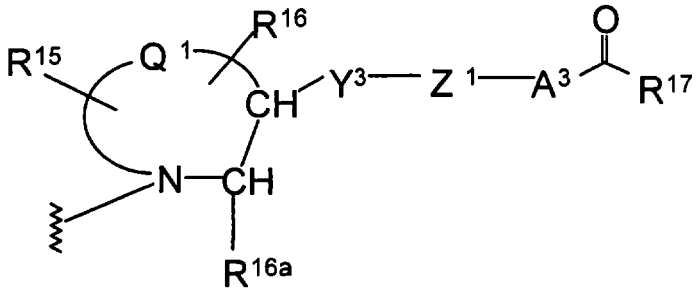
Of these, $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_2-$, $-(CH_2)_2-$, $-CH=CH-$, $-C\equiv C-$ or $-CH_2NY^1-$, particularly $-CH_2O-$ is preferred as Y.

Z represents a substituted or unsubstituted arylene group, a substituted or unsubstituted heteroarylene group or a substituted or unsubstituted cycloalkylene group. These arylene, heteroarylene and cycloalkylene groups are similar to those as exemplified above. Examples of the substituent for them include lower alkyl groups, lower alkoxy groups, halogen atoms, hydroxyl group, amino group and alkylamino groups. As Z, phenylene, pyridylene and cyclohexylene groups are preferred, with cyclohexylene group being particularly preferred. When Z represents a cyclohexylene group, it is most preferred that the relative configuration of the groups -Y- and $-A^2-$ substituted on the cyclohexane ring is 1,4-trans configuration.

A^2 represents a single bond, alkenylene group, alkynylene group, $-(CH_2)_t-$ or $-O(CH_2)_v-$ (in which, t stands

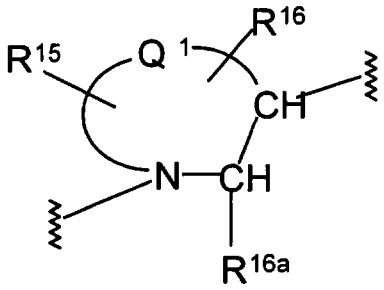
for 1, 2 or 3 and v stands for 0, 1, 2, or 3), of which a single bond is particularly preferred.

Formula (iv):



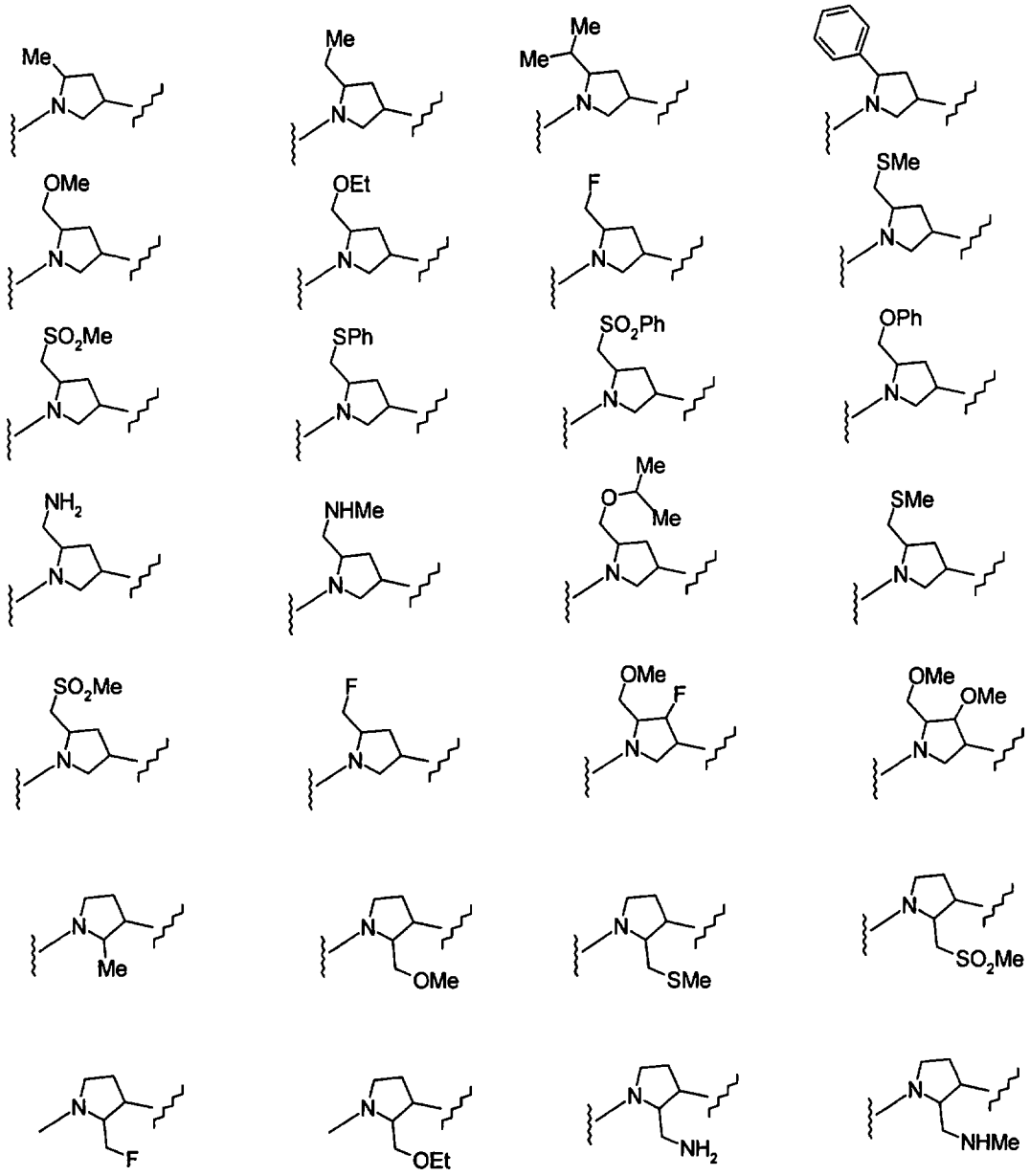
(iv)

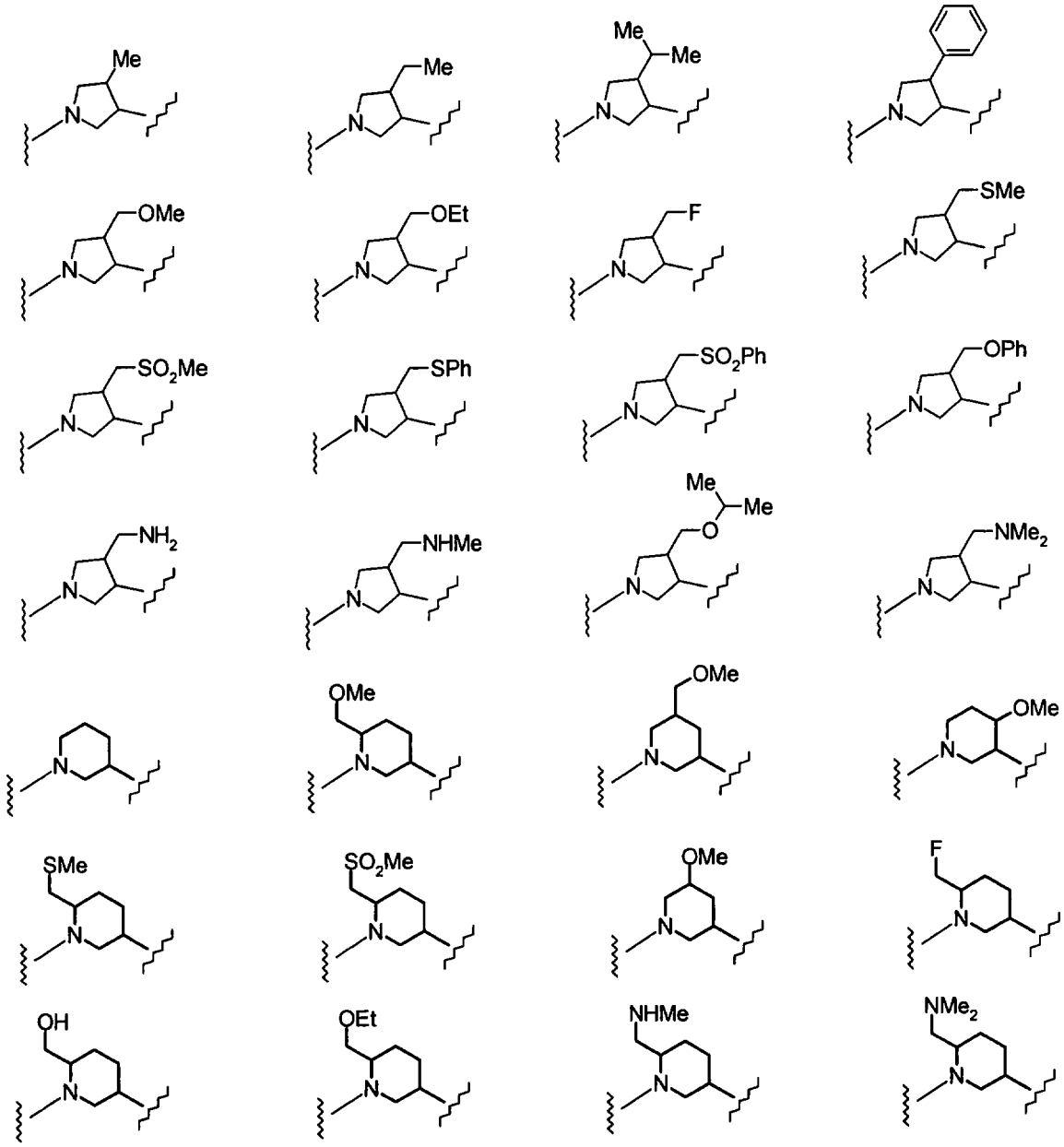
Specific examples of the formula (iv-b)



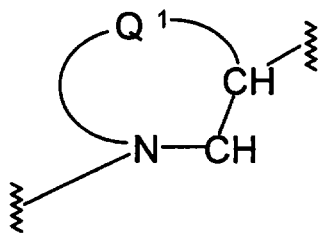
(iv-b)

in the formula (iv) are exemplified below:


Me
Me
Me
Me
OMe
OEt
F
SMe
SO2Me
SPh
SO2Ph
OPh
NH2
NHMe
Me
O
Me
SMe
SO2Me
F
OMe
F
OMe
OMe
N
Me
N
OMe
N
SMe
N
SO2Me
N
F
N
OEt
N
NH2
N
NHMe



In the above formula,



(iv - a)

represents a divalent 4-, 5-, 6- or 7-membered heterocyclic group, of which a 5- or 6-membered heterocyclic group having as Q^1 a carbon, oxygen or nitrogen atom is preferred, with a divalent group formed of a pyrrolidine ring being particularly preferred.

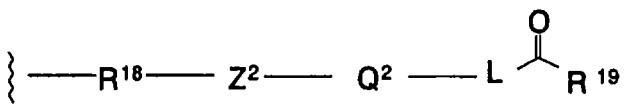
R^{15} and R^{16} each independently represents a hydrogen atom, a hydroxyl group, a halogen atom, a substituted or unsubstituted alkyl group or an alkoxy group, of which halogen atom, substituted or unsubstituted alkyl group or alkoxy group is preferred, with fluorine atom, methoxyl group or methoxymethyl group being particularly preferred.

Y^3 represents -O-, -S-, $-S(O_2)-$, $-(CH_2)_fO-$ or $-NY^4-$ (in which f stands for 1, 2 or 3 and Y^4 represents a hydrogen atom or a lower alkyl group), with -O- or $-CH_2O-$ being particularly preferred.

Z^1 represents a substituted or unsubstituted arylene group, a substituted or unsubstituted heteroarylene group or a substituted or unsubstituted cycloalkylene group. Those exemplified above in Z are preferred.

A^3 represents a single bond, alkenylene group, alkynylene group or $-(CH_2)_e-$ (in which, e stands for 1, 2 or 3), of which single bond is particularly preferred.

The formula (v):



(v)

In the formula (v), R^{18} represents $-NR^{20}-$, and R^{20} represents a hydrogen atom, a substituted or unsubstituted alkyl group, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted benzyl group, a substituted or unsubstituted lower alkenyl group or a substituted or unsubstituted alkynyl group. These alkyl, cycloalkyl, aryl, lower alkenyl and alkynyl groups are similar to those exemplified above. Substituents for them include alkoxy groups, alkyl groups, halogen atoms and hydroxyl group.

As R^{20}, preferred are substituted or unsubstituted alkyl groups, substituted or unsubstituted alkenyl groups and substituted or unsubstituted alkynyl groups, with methyl group, 2-fluoromethyl group, allyl group and propargyl group being particularly preferred.

Z^2 represents a linear or branched divalent aliphatic C_{1-12} hydrocarbon group which may have a C_{3-6} spiro ring, may have one or more carbon atoms substituted by a divalent C_{3-8} cycloalkylene group, or may have one or more carbon atoms substituted by $-O-$, $-S-$, $-S(O)_2-$, $-C(O)-$ or $-NR^{21}$ (in which, R^{21} represents a hydrogen atom or a substituted or unsubstituted lower alkyl group). As Z^2, those exemplified above in Y of the formula (iii) are preferred.

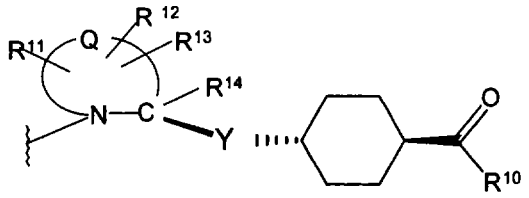
Q^2 represents a single bond, a substituted or unsubstituted arylene group, a substituted or unsubstituted heteroarylene group or a substituted or unsubstituted

cycloalkylene group. As Q^2, those exemplified above in Z are preferred.

L represents a single bond, a substituted or unsubstituted lower alkylene group or a substituted or unsubstituted lower alkenylene group. The lower alkylene and lower alkenylene group are similar to those as described above and substituents for them include lower alkyl groups and halogen atoms. As L, preferred are a single bond and a lower alkenylene group.

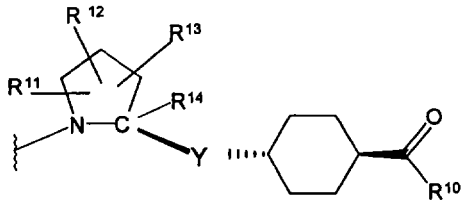
As M, the formula (iii) or (iv) is preferred.

In the case where Z is a cyclohexylene group and A^2 is a single bond in the formula (iii), the formula (iii-c) is preferred.



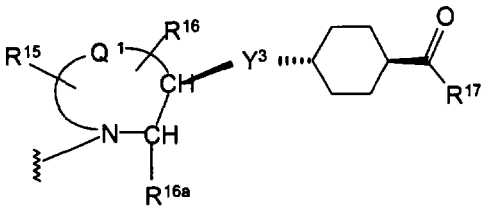
(iii-c)

Particularly, the formula (iii-d) is preferred.



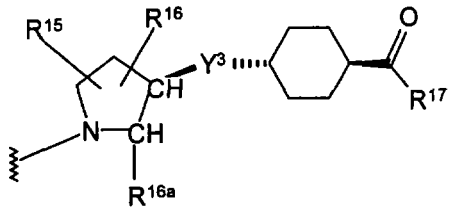
(iii-d)

In the case where Z^1 is a cyclohexylene group and A^3 is a single bond in the formula (iv), the formula (iv-c) is preferred.



(iv-c)

Particularly, the formula (iv-d) is preferred.



(iv-d)

As M, the formula (iii) is particularly preferred.

The invention compounds (I) can be converted into physiologically acceptable salts thereof as desired by using an inorganic acid such as hydrochloric acid, sulfuric acid or phosphoric acid, or an organic acid such as formic acid, acetic acid or methanesulfonic acid. When the invention compounds (I) have an acidic group such as carboxyl group, base addition salts can usually be formed. As physiologically acceptable salts, either organic salts or inorganic salts are possible. Preferred examples include alkali metal salts such as lithium salt, sodium salt and potassium salt, alkaline earth metal salts such as magnesium salt and calcium salt, ammonium salt, triethylamine salt, N-methylglucamine salt and tris(hydroxymethyl)aminomethane salt.

The invention compounds in the free form or salt form

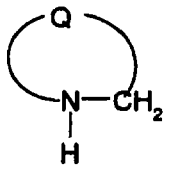
may exist as a solvate.

No particular limitation is imposed on the solvate insofar as it is a pharmaceutically acceptable one. Specific examples include hydrates and ethanolates. When the invention compounds (I) contain a nitrogen atom, they may exist as their N-oxides forms. These solvates and N-oxide forms are also embraced in the present invention.

Depending on the kind or combination of substituents, the invention compounds (I) or salts thereof have a variety of isomers, for example, geometrical isomers such as cis isomers and trans isomers, and optical isomers such as d-isomers and l- isomers. The present invention embraces all of these steric isomers and mixtures thereof at any ratio.

The invention compounds can be synthesized, for example, in accordance with any one of the below-described (Scheme 1) to (Scheme 18).

The compound of the formula (I) wherein X represents -C(O)- can be prepared by the coupling reaction of a carboxylic acid (1) and a cyclic amine (2), (3) or salt thereof, or a chain amine (4) or salt thereof (in the scheme,

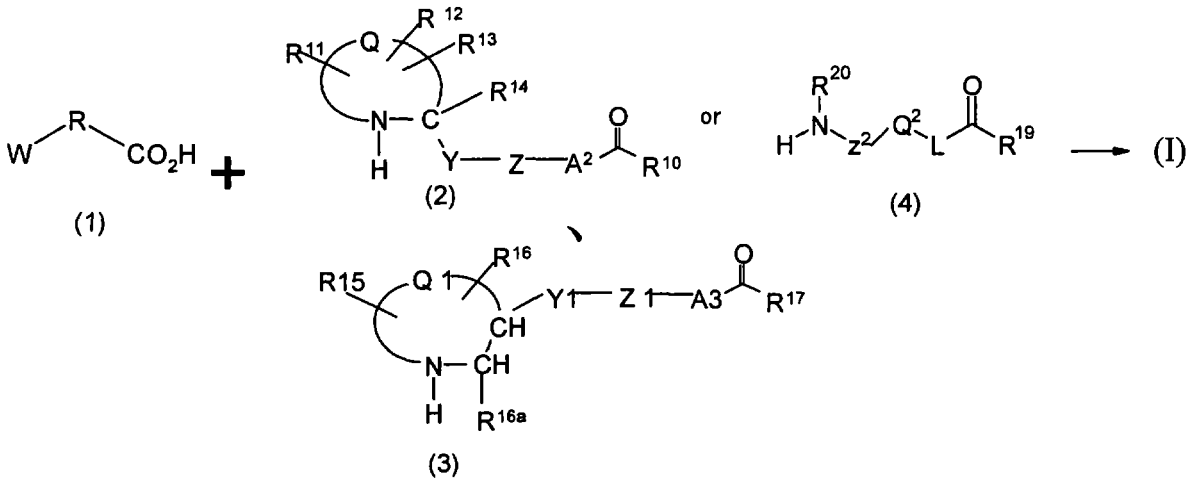


represents a 4-, 5-, 6- or 7-membered cyclic amine, and W,

R, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{16a}, Y, Y^1, Z, Z^1, A^2, A^3, R^{10}, R^{17}, R^{20}, Z^2, Q^2, L and R^{19} have the same meanings as described above).

When in the compound of the formula (2), (3) or (4), R^{10}, R^{17} or R^{19} is a lower alkoxy group, the compounds obtained by the above-described coupling reaction can be converted into the corresponding free carboxylic acid type compound by alkaline hydrolysis.

(Scheme 1)



The compound (I) in (Scheme 1) can be prepared in a known manner. The compound of the formula (I) can be prepared by reacting a carboxylic acid (1) with a cyclic amine (2) or (3), or a chain amine (4) in accordance with a known condensing method by using a condensing agent such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, N,N-dicyclohexylcarbodiimide or N,N-carbonyldiimidazole or an analogue thereto in an inert halogenated hydrocarbon solvent such as methylene chloride,

an inert hydrocarbon solvent such as toluene, an inert ether solvent such as tetrahydrofuran or an inert polar solvent such as N,N-dimethylformamide at a temperature range of from -20°C to the boiling point of the solvent, preferably 0°C to room temperature. This reaction can also be conducted in the presence of an organic amine base such as triethylamine or 4-dimethylaminopyridine, or an organic amine base and 1-hydroxybenzotriazole.

In the below-described (Scheme 1A) to (Scheme 4), a synthesizing process of the carboxylic acid (1) used as a raw material for the above-described reaction will be indicated (in the schemes, X^1, R, R^4, R^5, W^1, W^2, W^3 and W^4 have the same meanings as described above, R^{23}s each independently represents a hydrogen atom, a halogen atom, a lower alkyl group, a hydroxyl group, a substituted or unsubstituted lower alkoxy group or an amino group, R^{22} represents a lower alkyl or benzyl group, and R^{24} represents a lower alkyl group).

In the below-described (Scheme 1A) and (Scheme 1B), a process for preparing a compound of the formula (I) wherein A^1 is a single bond is indicated.

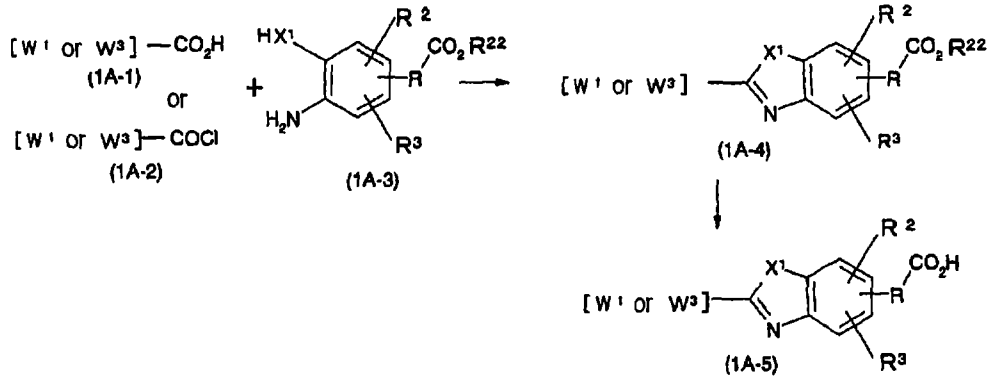
Compounds of the formulas (1A-5) and (1B-5) can be prepared in a known manner. Compound (1A-4) is available, for example, by heating and refluxing - in the presence of an acid such as boric acid in an inert hydrocarbon solvent such as xylene - a compound of the formula (1A-1) which is

commercially available or can be readily prepared in a known manner, preferably a compound of the formula (1A-2) which has been prepared by acting an acid halide such as oxalyl chloride, thionyl chloride, phosphorous trichloride or phosphorous pentachloride, preferably oxalyl chloride or thionyl chloride and a catalytic amount of N,N-dimethylformamide on the compound (1A-1) in an inert halogenated hydrocarbon solvent such as methylene chloride, an inert hydrocarbon solvent such as toluene or an inert ether solvent such as tetrahydrofuran at a temperature range of from -20°C to the boiling point of the solvent, together with the compound of the formula (1A-3) (M.Terashima *et al.*, *Synthesis*, 484 (1982)). And compound (1A-4) is also available, when carboxylic acid radical of the formula (1A-4) is formyl radical, via cyclization reaction using $Ph\text{-}I(OAc)_2$ (M.H.Jung *et al.*, *J. Med. Chem.*, 9, 56(1999)). The carboxylic acid (1A-5) is then available by alkaline hydrolysis of the ester portion of the resulting compound in a known manner. In the case of a benzyl ester, the target product is available by, instead of the above-described alkaline hydrolysis, catalytic hydrogenation to remove the benzyl portion.

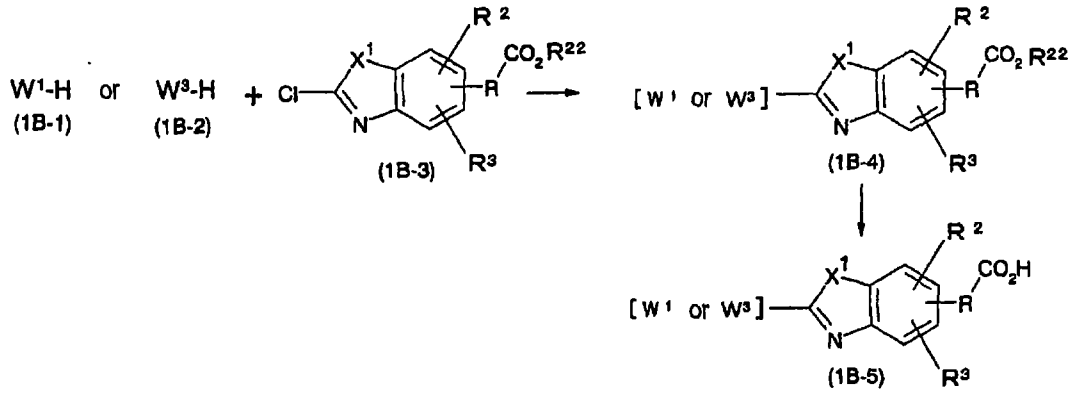
A compound of the formula (1B-4) can be prepared by effecting nucleophilic displacement reaction of a compound of the formula (1B-1) or (1B-2) (wherein, -H is bonded to the nitrogen atom of a nitrogen-containing heterocycle) and

a compound of the formula (1B-3) in an inert hydrocarbon solvent such as xylene at a temperature range of from room temperature to the boiling point of the solvent. This reaction can be conducted in the presence of an organic base such as triethylamine or an inorganic base such as potassium carbonate. The reaction may be effected in a solventless manner at a temperature range of from room temperature to 200°C. By subjecting the resulting compound of the formula (1B-4) to hydrolysis or catalytic hydrogenation as indicated in (Scheme 1A), the compound of the formula (1B-5) can be prepared.

[Scheme 1A]



[Scheme 1B]

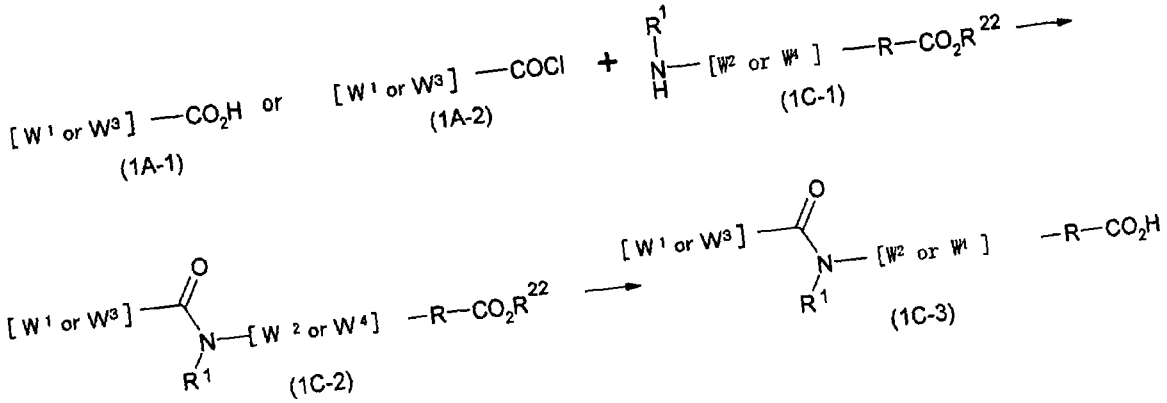


The below-described (Scheme 1C) is a process for preparing a compound of the formula (I) wherein A^1 is -C(O)NR^1-.

A compound of the formula (1C-3) can be prepared in a known manner. For example, a compound of the formula (1C-2) can be prepared by reacting the compound (1A-2) as indicated in the above-described (Scheme 1A) with a compound of the formula (1C-1) in an inert halogenated hydrocarbon solvent such as methylene chloride, an inert

hydrocarbon solvent such as toluene or an inert ether solvent such as tetrahydrofuran at a temperature range of from -20°C to the boiling point of the solvent, preferably from room temperature to the boiling point of the solvent in the presence of an organic base such as triethylamine. Alternatively, the compound of the formula (1C-2) can be prepared by reacting the compound (1A-1) indicated in the above-described (Scheme 1A) with the compound of the formula (1C-1) by using a condensing agent such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, N,N-dicyclohexylcarbodiimide or N,N-carbonyldiimidazole or an analogue thereto in an inert halogenated hydrocarbon solvent such as methylene chloride, an inert hydrocarbon solvent such as toluene, an inert ether solvent such as tetrahydrofuran, or an inert polar solvent such as N,N-dimethylformamide at a temperature range of from -20°C to the boiling point of the solvent. This reaction may be effected in the presence of an organic amine base such as triethylamine or 4-dimethylaminopyridine, or an inorganic base and 1-hydroxybenzotriazole. By subjecting the resulting compound of the formula (1C-2) to hydrolysis or catalytic hydrogenation as indicated in (Scheme 1A), the compound of the formula (1C-3) is available.

(Scheme 1C)

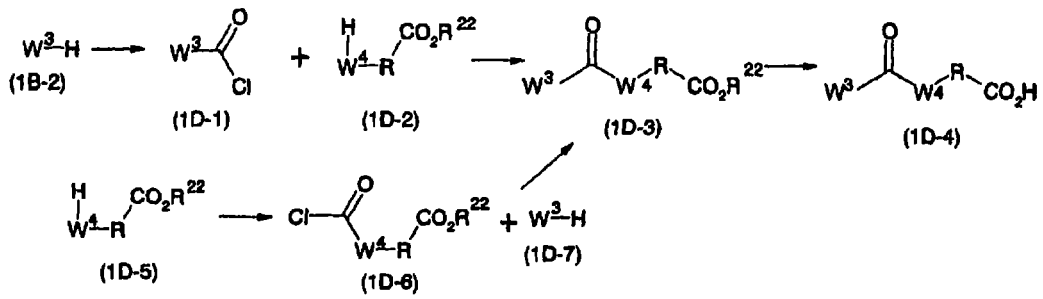


The below-described (Scheme 1D) is a preparation process of a compound of the formula (I) wherein A^1 represents -C(O)- (in the scheme, -H of each of the compounds (1D-2), (1D-5) and (1D-7) is bonded to the nitrogen atom of the nitrogen-containing heterocycle).

A compound of the formula (1D-4) can be prepared in a known manner. For example, a compound of the formula (1D-1) is prepared by acting phosgene or a phosgene equivalent such as triphosgene on the compound (1B-2) shown in (Scheme 1B) in an inert halogenated hydrocarbon solvent such as methylene chloride, an inert hydrocarbon solvent such as toluene or an inert ether solvent such as tetrahydrofuran at a temperature range of from -20°C to the boiling point of the solvent, preferably from -20°C to room temperature. Then, a compound of the formula (1D-2) is acted on the compound (1D-1), whereby a compound of the formula (1D-3) can be obtained. The compound of the formula (1D-3) is available in a similar manner by preparing a compound of the formula (1D-6) from a compound of the formula (1D-5)

and then reacting the resulting compound with a compound of the formula (1D-7). The compound (1D-3) is also available by acting N,N-carbonyldiimidazole on the compound of the formula (1B-2) or (1D-5) in an inert polar solvent such as N,N-dimethylformamide at a temperature range of from -20°C to the boiling point of the solvent, followed by the addition of the compound (1D-2) in the case of the compound of (1B-2) or the compound (1D-7) in the case of the compound (1D-5) to cause reaction. The compound of the formula (1D-3) is then subjected to hydrolysis or catalytic hydrogenation as shown in (Scheme 1A), whereby the compound of the formula (1D-4) can be prepared.

[Scheme 1D]

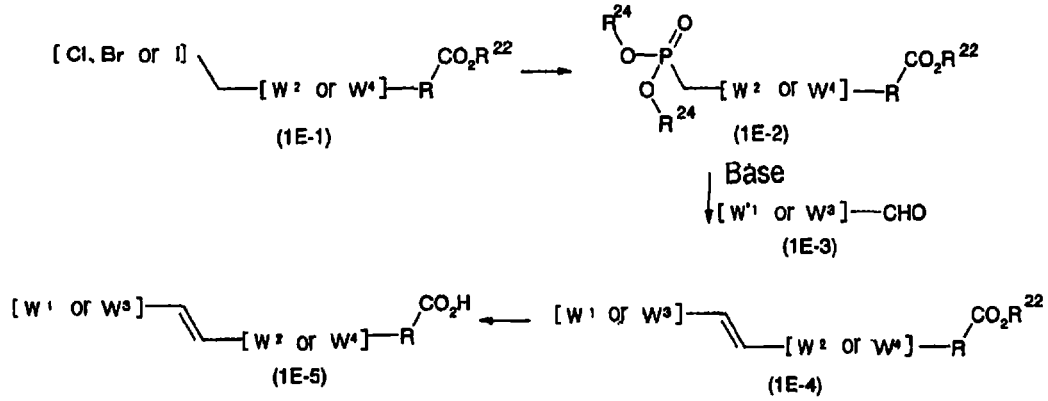


In the below-described (Scheme 1E), a compound of the formula (I) wherein A^1 represents vinylene is indicated.

A compound of the formula (1E-4) in (Scheme 1E) can be prepared by Wittig-Horner reaction. For example, the compound of the formula (1E- 4) can be prepared by acting a trialkyl phosphite ester on a compound of the formula (1E-1), which is commercially available or can easily be

prepared in a known manner, in a solventless manner at a temperature range of from room temperature to 200°C to prepare the corresponding alkyl phosphite diester (1E-2); acting thereon a base such as sodium hydride, lithium hexamethyl disilazane or sodium methoxide in an inert alcohol solvent such as ethanol, an inert hydrocarbon solvent such as toluene, an inert ether solvent such as tetrahydrofuran or inert polar solvent such as dimethylsulfoxide at a temperature range of from -78°C to the boiling point of the solvent, preferably from -20°C to room temperature, to generate a carbanion; and acting a compound of the formula (1E-3), which is commercially available or can easily prepared in a known manner, on the carbanion. By subjecting the resulting compound o f the formula (1E-4) to alkaline hydrolysis, a compound of the formula (1E-5) is available.

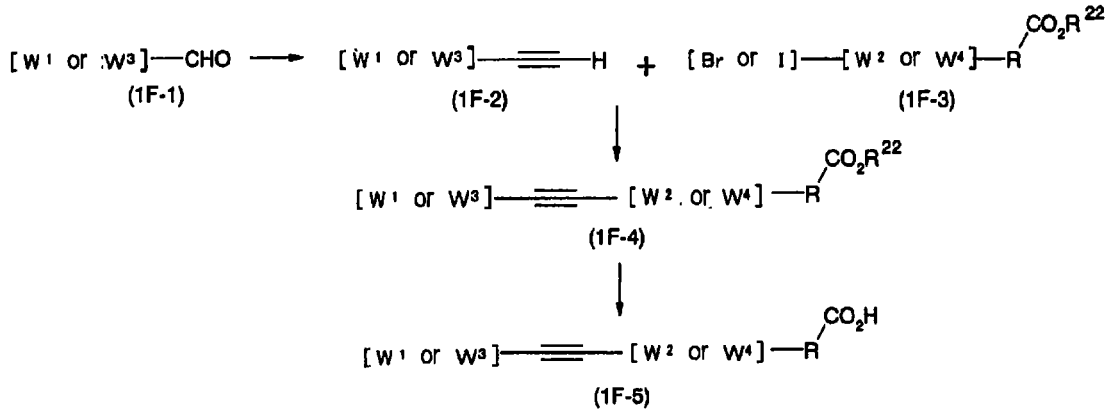
[Scheme 1E]



In the below-described (Scheme 1F), a compound of the formula (I) wherein A represents ethynylene is indicated.

A compound of the formula (IF-4) can be prepared in a known manner. For example, a compound of the formula (1F-1) which is commercially available or can be prepared readily in a known manner is introduced into the corresponding dihalogeno-olefin in accordance with the Corey method and then, an organolithium such as butyl lithium is acted on the resulting compound, whereby a compound of the formula (1F-2) can be obtained. Alternatively, the compound of the formula (1F-2) can be prepared by reacting the compound (1F-1) with a carbanion easily available from trimethylsilyldiazomethane and an organolithium, followed by rearrangement (Y.Ito *et al.*, *Synlett*, 1163 (1997)). Then, Heck type carbon-carbon coupling reaction is conducted with a compound of the formula (1F-3), whereby the compound of the formula (1F-4) can be obtained (T.Eckert *et al.*, *Synth. Commun.*, 28, 327 (1998)). By subjecting the resulting compound of the formula (1F-4) to alkaline hydrolysis, a compound of the formula (1F-5) is available.

[Scheme 1F]

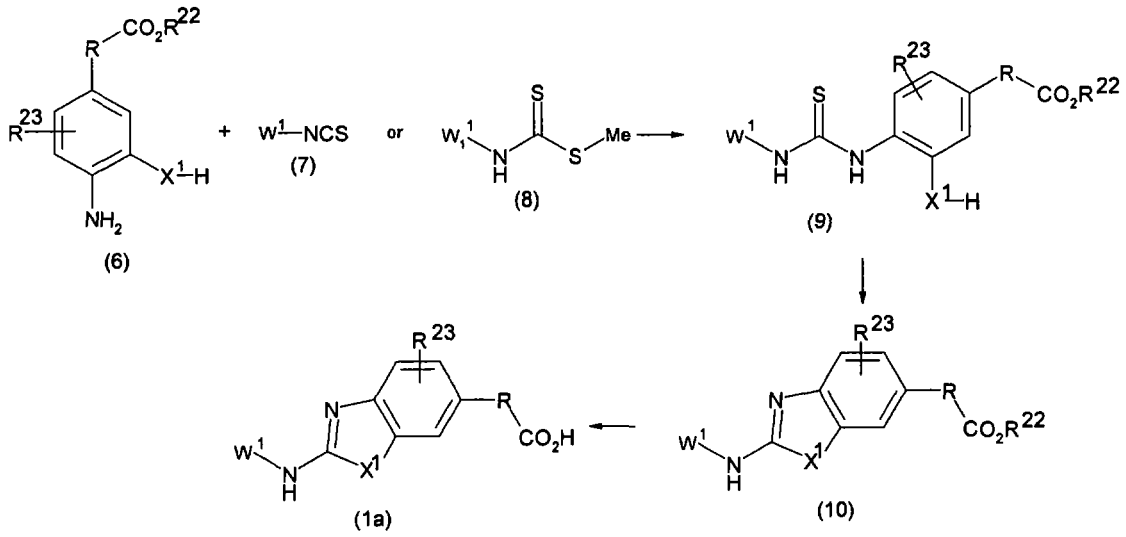


In the below-described (Scheme 2) to (Scheme 4), a compound of the formula (I) wherein A^1 represents $-NR^1$ is indicated.

A compound of the formula (1a) in the below-described (Scheme 2) can be prepared in a known manner. For example, an aniline derivative (6) which is known by itself or can be prepared in a known manner, and a thioisocyanate derivative (7) which is commercially available or can be prepared in a known manner or a xanthate derivative (8) which can be prepared in a known manner are treated in an inert halogenated hydrocarbon solvent such as methylene chloride, an inert hydrocarbon solvent such as toluene, an inert ether solvent such as tetrahydrofuran or an inert alcohol solvent such as ethanol at a temperature range of from -20°C to the boiling point of the solvent, preferably from 0°C to room temperature, whereby the corresponding thiourea derivative (9) can be prepared. In a known

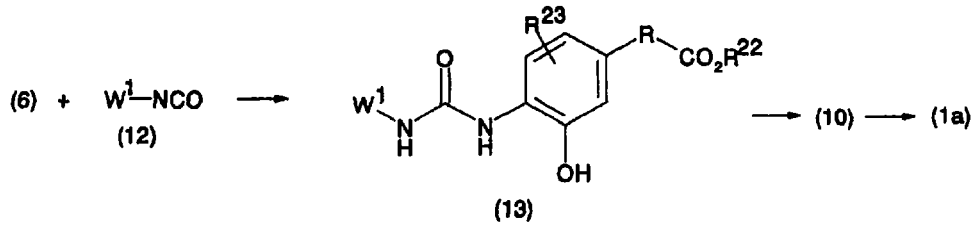
manner, the resulting compound is then treated with KO_2 or Ni_2O_3, preferably mercuric oxide (yellow), each commercially available, in an inert hydrocarbon solvent such as toluene, inert ether solvent such as tetrahydrofuran or inert polar solvent such as N,N-dimethylformamide at a temperature range of from -20°C to the boiling point of the solvent, preferably from room temperature to the boiling point of the solvent, whereby the corresponding ring-closed compound (10) can be obtained (A. Koshiro *et al.*, *Chem.Pharm.Bull.*, 7, 725 (1959); H.Ogura et al., ibid., 29, 1518 (1981); H.S.Chan et al., *Chem.Lett.*, 1291 (1986)). The resulting compound is then subjected to hydrolysis, or catalytic hydrogenation method as described in (Scheme 1), whereby the carboxylic acid (1a) can be obtained.

(Scheme 2)



In the below-described (Scheme 3), another process for preparing the compound of the formula (10) is indicated. An urea derivative (13) is available by reacting the aniline derivative (6) with an isocyanate (12) which is commercially available or can be prepared in a known manner in an inert halogenated hydrocarbon solvent such as methylene chloride, an inert hydrocarbon solvent such as toluene or an inert ether solvent such as tetrahydrofuran at a temperature range of from -20°C to the boiling point of the solvent, preferably from 0°C to the boiling point of the solvent. Then, for example, by treating the compound (13) with an organic acid such as pyridinium para-toluenesulfonate in an inert halogenated hydrocarbon solvent such as methylene chloride at a temperature range from room temperature to the boiling point of the solvent, the ring closed compound (10) is available (M.J.Suto *et al., Tetrahedron Lett.*, 36, 7213 (1995)).

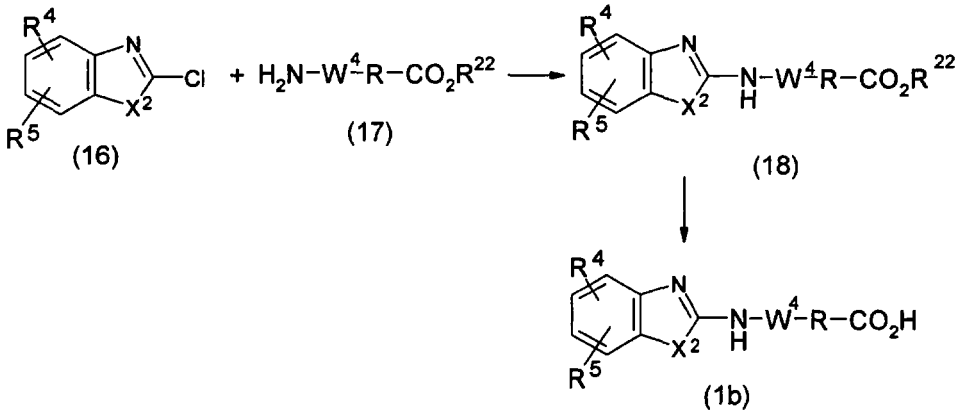
[Scheme 3]



In the below-described (Scheme 4), a compound of the formula (1b) can be prepared in the following manner. A 2-benzazole chloride derivative (16) and an amine derivative (17) each available commercially or readily in a known

manner are treated in an inert polar solvent such as N,N-dimethylformamide or an inert hydrocarbon solvent such as xylene at a temperature range of from room temperature to the boiling point of the solvent, preferably from 100°C to the boiling point of the solvent or treated in a solventless manner at a temperature range of from room temperature to 200°C, preferably from 100 to 200°C, whereby a compound of the formula (18) can be obtained. This reaction may be effected in the presence of an organic amine base such as triethylamine or an inorganic base such as potassium carbonate. Then, by hydrolysis or hydrogenolysis of an ester portion in accordance with the hydrolysis or catalytic hydrogenation method as shown in (Scheme 1A), the carboxylic acid (1b) can be obtained.

(Scheme 4)



In the below-described (Scheme 5) to (Scheme 9), a preparation process of a compound of the formula (2) or (3) to be used in the above-described reaction as a raw

material will be indicated (in the scheme, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, A^2, A^3, Z, Z^1, R^{10} and R^{17} have the same meanings as described above, X^4 represents a carbon or nitrogen atom, Z^3 represents a substituted or unsubstituted arylene group or a substituted or unsubstituted heteroarylene group, Z^4 represents a substituted or unsubstituted cycloalkylene group or a substituted or unsubstituted hetero cycloalkylene group, Z^5 represents a substituted or unsubstituted arylene group or a substituted or unsubstituted heteroarylene group, R^{30} represents a lower alkyl group, E represents a protecting group (*Protective Groups in Organic Synthesis*, eds. by T.W.Greene and P.G.Wuts, John Wiley & Sons, Inc., New York, 1991) of a primary or secondary amine and n^1 stands for 0, 1 or 2).

In the below-described (Scheme 5), indicated is a process for preparing compounds of the formulas (2a) and (2b) including a step of forming an ether bond portion. An ester derivative (20) available commercially or in a known manner can be converted into the corresponding alcohol derivative (22) by known reduction. For example, the alcohol derivative (22) can be prepared by, after acidic or alkaline hydrolysis of the ester derivative (20) into the corresponding carboxylic acid (21), treating the resulting compound with borane or a reducing agent of such a kind in an inert halogenated hydrocarbon solvent such as methylene chloride, an inert hydrocarbon solvent such as toluene or

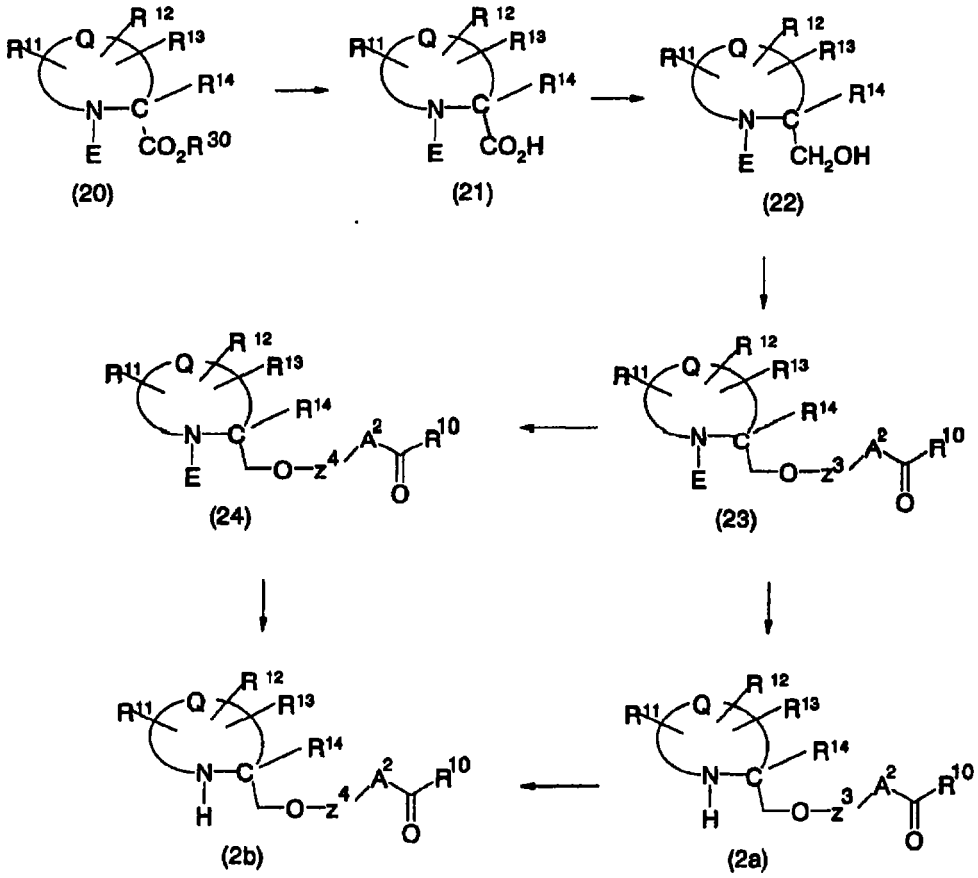
an inert ether solvent such as tetrahydrofuran at a temperature range of from -20°C to the boiling point of the solvent, preferably from 0°C to the boiling point of the solvent. In this reduction, a preferable protecting group must be introduced as E of the ester derivative (20) and a tertiary butyloxycarbonyl group is preferred as it. Alternatively, the alcohol derivative (22) can be prepared not via the carboxylic acid (21) but directly from the ester derivative (20). For example, the alcohol derivative (22) can be prepared by treating the ester derivative (20) with a reducing agent such as diisobutyl aluminum hydride in an inert ether solvent such as tetrahydrofuran, preferably in an inert hydrocarbon solvent such as toluene or an inert halogenated hydrocarbon solvent such as methylene chloride at a temperature range of from -78°C to the boiling point of the solvent, preferably from 0°C to room temperature. Also in this case, a preferable protecting group must be introduced as E of the ester derivative (20) and, as it, a tertiary butyloxycarbonyl group is preferred. After formation of an ether bond by the Mitsunobu reaction with a phenol such as methyl 4-hydroxybenzoate and introduction of an aryl group or a heteroaryl group are conducted simultaneously, the protecting group E is removed. When E is a tertiary butyloxycarbonyl group, deprotection is performed by treating with trifluoroacetic acid in a solventless manner

or in an inert halogenated hydrocarbon solvent such as methylene chloride, whereby the compound of the formula (2a) can be prepared. The ether bond formation of the compound (23) from the compound (22) can be conducted, instead of the above-described Mitsunobu reaction, by converting the primary hydroxy group of the compound (22) into an eliminating group such as mesyloxy group and then treating the resulting compound with a phenol such as methyl 4-hydroxybenzoate in an inert polar solvent such N,N-dimethylformamide at a temperature range from 0°C to 90°C in the presence of an inorganic base such as sodium hydride or potassium carbonate. In this case, a preferable protecting group E, for example, is a benzyloxycarbonyl group.

When Z_3 of the compound (23) is an phenylene group, a cyclohexane derivative (24) can be prepared by nuclear reduction of the benzene ring in a known manner. For example, a reduced derivative (24) can be prepared by catalytic hydrogenation of a compound of the formula (23) in an inert alcohol solvent such as methanol in the presence of a catalyst such as palladium, platinum oxide, preferably rhodium at 1 to 1000 atm, preferably 1 to 100 atm under a hydrogen atmosphere (R.A.Finnegan *et al.*, *J. Org. Chem.*, 30, 4145 (1965); A.I.Meyers *et al.*, *Org. Synth.*, 51, 103 (1971)). The above-described reduction is preferably conducted in the presence of acetic acid or

trifluoroacetic acid. The protecting group E is then removed, for example, by treating, when E is a tertiary butyloxycarbonyl group, with trifluoroacetic acid in a solventless manner or an inert halogenated hydrocarbon solvent such as methylene chloride, whereby a compound of the compound (2b) can be prepared. The compound (2b) is also available by deprotection of E from the compound (23), followed by the above-described reduction.

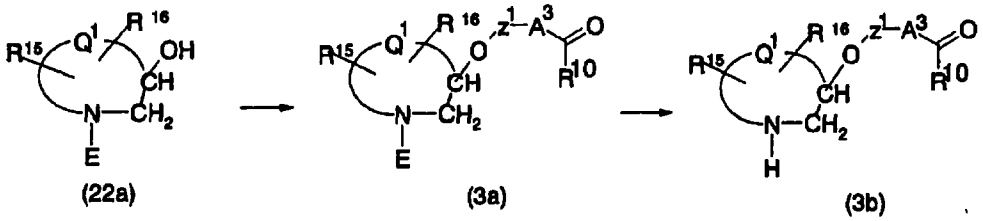
[Scheme 5]



In the below-described (Scheme 5a), shown is a process permitting preparation of compounds of the formulas (3a) and (3b) in accordance with the preparation process of

(Scheme 5) by using, as a raw material, a compound of the formula (22a) which is available commercially or in a known manner. Or, a primary alcohol derivative can be prepared in a known manner, for example, by converting the secondary hydroxy group of the compound (3a) into an eliminating group such as mesyloxy group, converting it into a cyano group by acting a cyanation agent such as potassium cyanide, then converting it into a formyl group by using diisopropyl aluminum hydride, and effecting reduction by sodium borohydride. An compound which is extended by one carbon between oxygen atom and ring in the compound (3b) can be prepared by using the resulting primary alcohol derivative as a raw material in accordance with the above-described ether bond formation method (A.Tarnowsky *et al.*, *Bioorg. Med. Chem. Lett.*, 7, 573 (1997)).

[Scheme 5a]



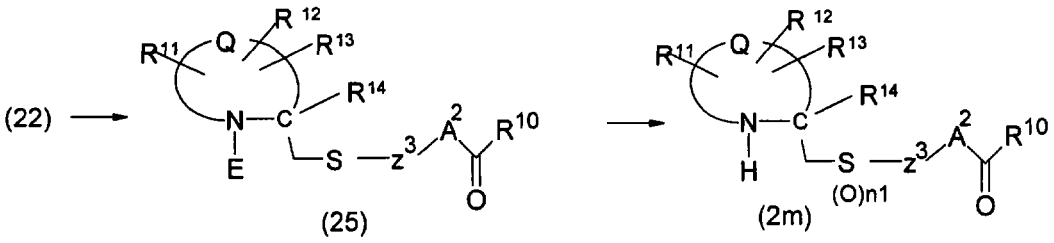
In the below-described (Scheme 6), indicated is a process for preparing a sulfide, sulfoxide or sulfone derivative (2m) in a known manner by using the alcohol derivative (22) as a starting material.

For example, a compound of the formula (25) can be

prepared by converting a primary hydroxyl group of the alcohol derivative (22) into an eliminating group such as mesyloxy group and then treating the resulting compound with a thiol, which is available commercially or in a known manner, in an inert ether solvent such as tetrahydrofuran, an inert halogenated hydrocarbon solvent such as methylene chloride, preferably in an inert polar solvent such as N,N-dimethylformamide at a temperature range of from -20°C to the boiling point of the solvent, preferably from room temperature to the boiling point of the solvent in the presence of a base such as potassium carbonate or sodium hydride. By subjecting the resulting compound to known oxidation reaction, its sulfide portion can be converted into a sulfoxide or sulfone group.

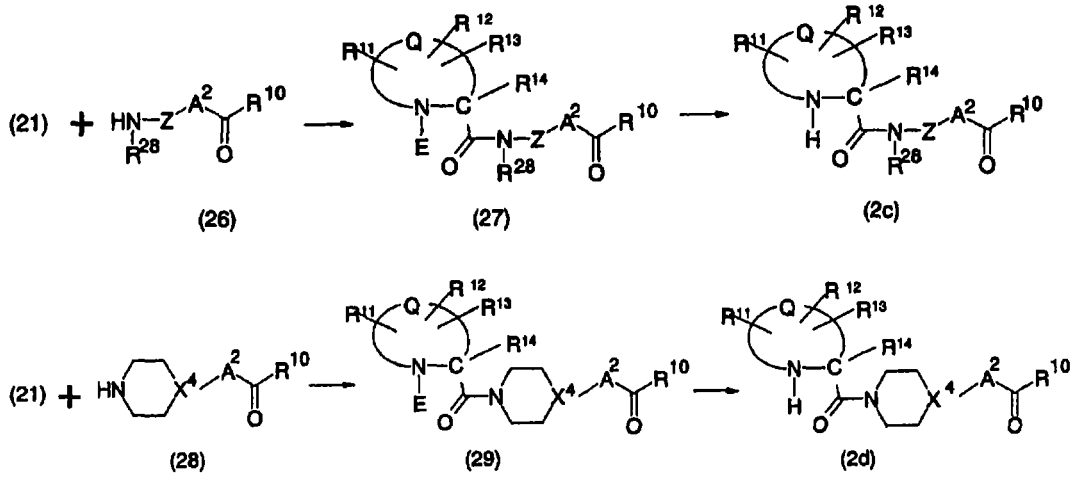
For example, the compound (25) can be converted into the corresponding sulfoxide or sulfone derivative by treating it with commercially available 3-chloroperbenzoic acid or peroxide such as hydrogen peroxide in an inert halogenated hydrocarbon solvent such as methylene chloride at a temperature range of from -78°C to the boiling point of the solvent, preferably from -20°C to room temperature. The protecting group E is then removed from the compound (25), or sulfoxide or sulfone derivative thereof, whereby a compound (2m) can be prepared.

(Scheme 6)



In the below-described (Scheme 7), a process for preparing compounds of the formulas (2c) and (2d) including a step of forming an amide bond is indicated. An amide derivative (27) or (29) can be prepared by reacting the carboxylic acid derivative (21) and a chain amine (26) or cyclic amine (28), which is available commercially or in a known manner, by using a condensing agent such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, N,N-dicyclohexylcarbodiimide or N,N-carbonyldiimidazole or an analogue thereto in an inert halogenated hydrocarbon solvent such as methylene chloride, an inert hydrocarbon solvent such as toluene, an inert ether solvent such as tetrahydrofuran or an inert polar solvent such as N,N-dimethylformamide at a temperature range of from -20°C to the boiling point of the solvent, preferably from 0°C to room temperature. This reaction can also be conducted in the presence of an organic amine base such as triethylamine or N,N-dimethylaminopyridine, or the organic amine base and 1-hydroxybenzotriazole. By deprotection of E, the compound of the formula (2c) or (2d) can be prepared.

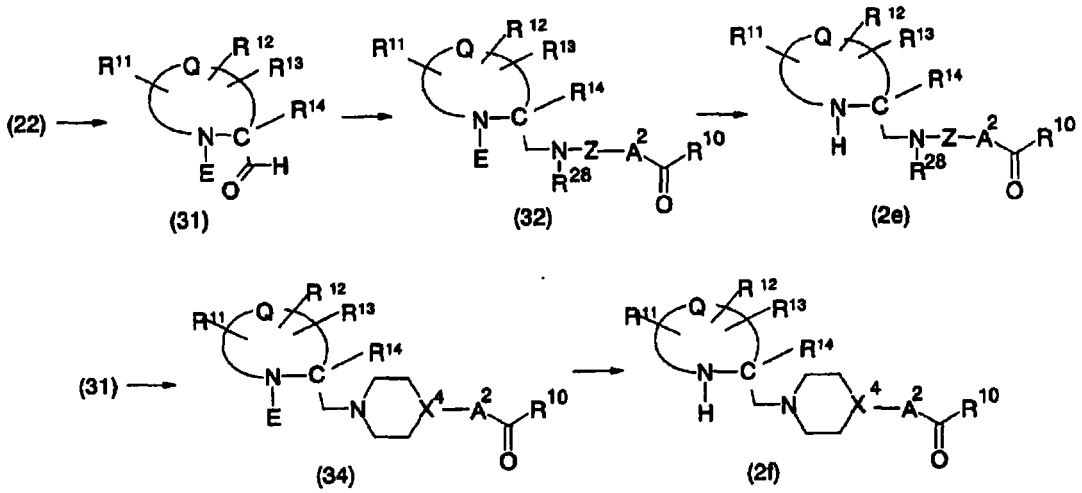
[. Scheme 7]



In the below-described (Scheme 8), a preparation process of a compound of the formula (2e) or (2f) including an N-alkylating step is indicated. The alcohol derivative (22) in (Scheme 5) can be converted into the corresponding aldehyde derivative (31) by oxidizing a primary hydroxyl group into an aldehyde in a known manner. For example, oxidation using a chromic acid, or oxidation using dimethylsulfoxide, for example, Swern oxidation is usable for conversion. The resulting aldehyde derivative (31) is then subjected to reductive N-alkylation reaction with the above-described amine derivative (26) or (28) in a known manner. This reducing reaction can be conducted using a reducing agent such as sodium cyanoborohydride or triacetoxy sodium borohydride in an inert alcohol solvent such as methanol or an inert ether solvent such as tetrahydrofuran. When sodium cyanoborohydride is used, reaction is preferably conducted under acidic conditions,

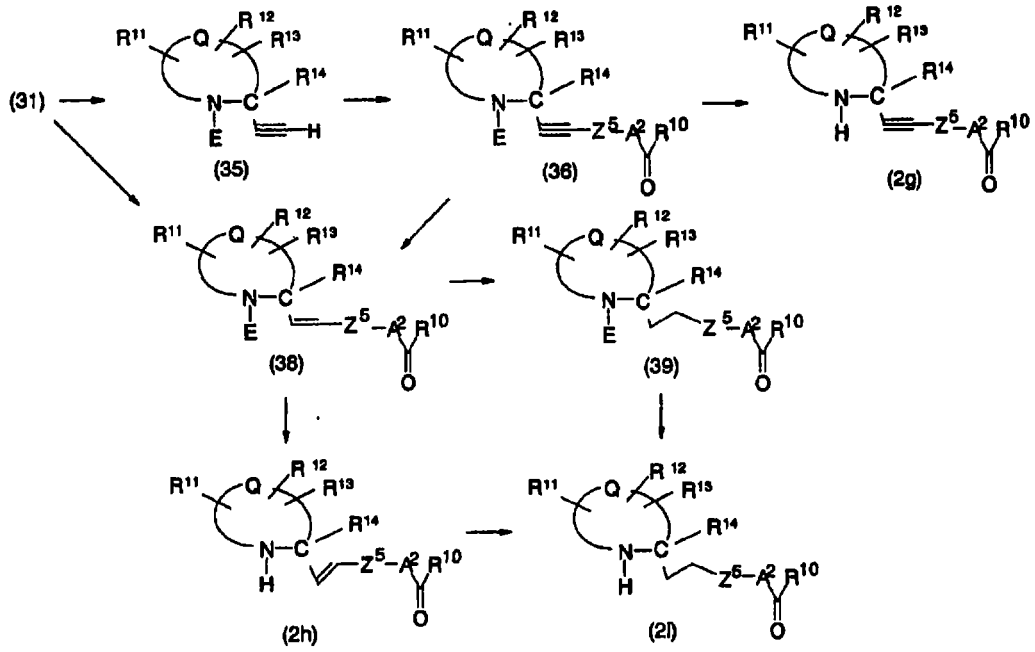
for example, in the presence of acetic acid. The N-alkylation reaction can also be conducted by catalytic hydrogenation using a commercially available catalyst such as palladium-carbon. By the deprotection of protecting group E from the reduced derivative (32) or (34), a compound of the formula (2e) or (2f) can be prepared.

[Scheme 8]



In the below-described (Scheme 9), indicated is a preparation process of the compounds of the formulas (2g), (2h) and (2i) which are compounds of the formula (2) wherein Ys are a carbon-carbon triple bond (ethynyl group), a carbon-carbon double bond (vinyl group) and a carbon-carbon single bond (ethyl group), respectively.

[Scheme 9]



An acetylene derivative (35) can be prepared from the compound (31) in accordance with a known triple bond forming reaction, for example, by reacting trimethylsilyldiazomethane with a base such as lithium diisopropylamide in an inert ether solvent such as tetrahydrofuran at a temperature range of from -78°C to the boiling point of the solvent and then reacting the resulting compound with the above-described aldehyde derivative (31) (Y.Ito *et al.*, *Synlett*, 1163 (1997)). The acetylene derivative thus obtained is then reacted, in a known manner, with an aryl halide derivative or trifluoromethylsulfonyloxyaryl derivative, which is available commercially or in a known manner, in the presence of a palladium catalyst such as

tetrakistriphenylphosphine palladium or palladium acetate and an organic base such as diisopropylamine or an inorganic base such as potassium carbonate in an inert polar solvent such as N,N-dimethylformamide at a temperature range of from -20°C to the boiling point of the solvent, preferably from 0°C to the boiling point, whereby the corresponding ethynyl derivative (36) can be prepared (T.Eckert *et al.*, *Synth.Commun.*, 28, 327 (1998)). By deprotection of E from the resulting derivative, a compound of the formula (2g) can be prepared. As the preferable protecting group E, a tert-butoxycarbonyl group can be exemplified.

A vinyl derivative (38) is available in a known manner by using the above-described aldehyde derivative (31) as a raw material. The compound of the formula (38) can be prepared by reacting a Wittig-Horner reagent, which is available commercially or in a known manner, with a base such as lithium hexamethyldisilazane in an inert ether solvent such as tetrahydrofuran at a temperature range of from -78°C to the boiling point of the solvent, preferably from -78°C to room temperature and then reacting the resulting compound with the aldehyde derivative (31). Then, by deprotection of E, the compound of the formula (2h) can be prepared. Alternatively, the vinyl derivative (38) is available by subjecting the above-described ethynyl derivative (36) used as a raw material to known reducing

reaction. For example, the ethynyl derivative (36) is subjected to catalytic hydrogenation in an inert alcohol solvent such as ethanol in the presence of a Lindlar catalyst and an organic amine base, such as quinoline, serving as a catalytic poison, whereby the vinyl derivative (38) can be prepared. Also upon preparation of the vinyl derivative, a preferable protecting group E must be used and as it, a tertiary butoxycarbonyl group is preferred.

An ethyl derivative (39) is available by catalytic hydrogenation of the ethynyl derivative (36) or vinyl derivative (38) used as a raw material. Then, the protecting group E is removed, whereby the compound of the formula (2i) can be prepared. Alternatively, the compound of the formula (2i) can be obtained by catalytic hydrogenation of the ethynyl derivative (2g) or vinyl derivative (2h).

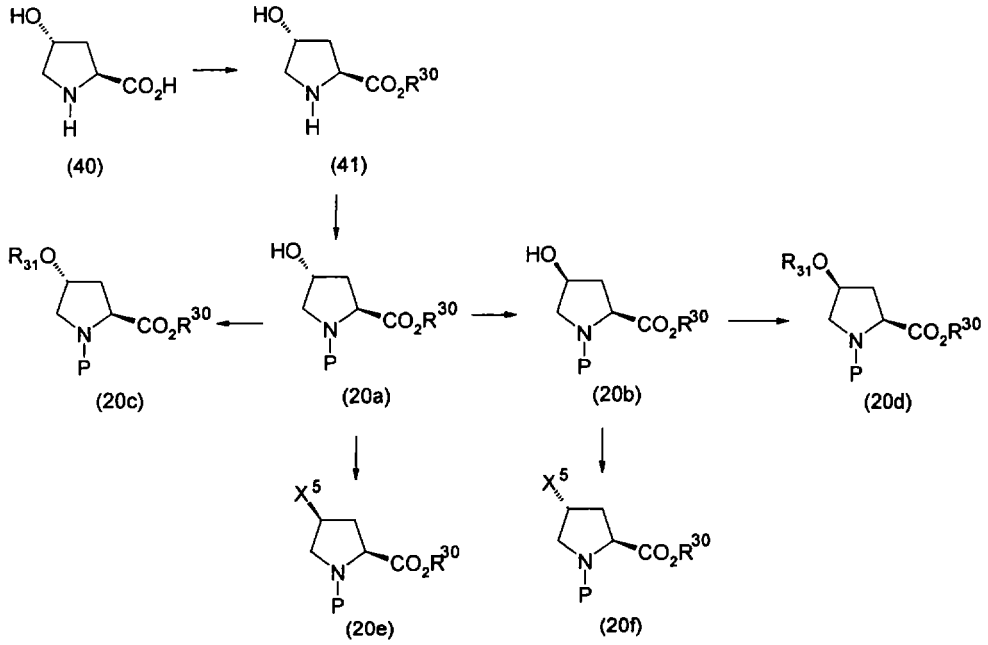
In the below-described (Scheme 10) to (Scheme 13), a preparation process of a pyrrolidine is shown as a specific example of a preparation process of the compound of the formula (20) used as a raw material in (Scheme 5) (in the schemes, R^{30} represents a lower alkyl group, R^{31}, R^{33}, R^{36} and R^{34} each independently represents a substituted or unsubstituted alkyl group, a substituted or unsubstituted aryl group or a substituted or unsubstituted heteroaryl group, X^5 represents a cyano group, an amino group, an azide group, a halogen atom, a substituted or unsubstituted

monoalkylamino group, a substituted or unsubstituted dialkylamino group, a substituted or unsubstituted cycloalkylamino group, a substituted or unsubstituted alkylsulfonylamino group, a substituted or unsubstituted allyloxy group, a substituted or unsubstituted alkylthio group, a substituted or unsubstituted alkylsulfoxide group or a substituted or unsubstituted alkylsulfone group and E has the same meaning as described above).

In the below-described (Scheme 10), shown is a preparation process of a compound having a substituent introduced into the 4-position of pyrrolidine. An ester derivative (41) can be prepared by reacting commercially available 4-hydroxy-L-proline (40) with methanol hydrochloride, for example, at a temperature range of from room temperature to the boiling point of the solvent. The resulting ester derivative is then treated in an inert polar solvent mixture such as water and acetonitrile in the presence of an acid anhydride such as di-tert-butyl dicarbonate, an acyl-halide such as benzyloxycarbonyl chloride, an organic amine base such as triethylamine or an inorganic base such as potassium carbonate, whereby a compound of the formula (20a) can be prepared. The secondary hydroxyl group of the alcohol derivative (20a) can be converted into a secondary hydroxyl group having a contrary steric configuration by the Mitsunobu reaction. For example, the alcohol derivative (20a) and formic acid

are subjected to the Mitsunobu reaction to introduce a formyloxy group into the secondary hydroxyl group portion, followed by alkaline hydrolysis by using an inorganic base such as potassium carbonate, preferably sodium bicarbonate, whereby the compound (20b) can be prepared.

(Scheme 10)



Alkoxy derivatives (20c) and (20d) can be prepared by treating the secondary hydroxyl group portion of the alcohol derivatives (20a) and (20b) in a known manner or while maintaining the steric structure in a known manner. For example, the alkoxy compounds (20c) and (20d) can be prepared by treating the alcohol compounds (20a) and (20b) in an inert ether solvent such as tetrahydrofuran or an inert polar solvent such as N,N-dimethylformamide at a

temperature range of from -20°C to the boiling point of the solvent, preferably from -20°C to room temperature in the presence of an alkyl halide such as methyl iodide or benzyl bromide and an inorganic base such as sodium hydride. When the corresponding benzyloxy derivative is prepared by the above-described alkylation, it is preferred to add an inorganic base to the reaction mixture in the final stage of reaction at a temperature range of from -20°C to room temperature. A compound of the formula (I) having a hydroxy group at 4-position of the pyrrolidine ring can be prepared, for example, by protecting the 4-hydroxyl group of the pyrrolidine ring of the compound (20a) or (20b) with a tertiary butyldimethylsilyl group and then using the resulting compound as a raw material.

By known S_N2 type nucleophilic displacement reaction of the secondary hydroxyl groups of the compounds (20a) and (20b), these compounds can be converted into the compounds (20e) and (20f), respectively. For example, a fluorine atom can be introduced by treating, for example, the compound (20a) with a fluorinating agent such as diethylaminosulfur trifluoride in an inert halogenated hydrocarbon solvent such as methylene chloride at a temperature range of from -78°C to the boiling point of the solvent, preferably from 0°C to room temperature (L.Demange *et al., Tetrahedron Lett.*, 39, 1169 (1998)). Alternatively, a fluorine atom can be introduced by

converting the secondary hydroxyl groups of the compounds (20a) and (20b) into an eliminating group such as alkyl or arylsulfonyloxy group, e.g., mesyloxy group and then treating the resulting compound with a fluoride of an alkali metal such as potassium fluoride or a fluoride of an alkaline earth metal such as cesium fluoride in an inert polar solvent such as N,N-dimethylformamide or ethylene glycol (G.Giardina *et al.*, *Synlett*, 1, 57 (1995)). A cyano group can be introduced into the mesyloxy derivative by acting thereon a cyanation agent such as potassium cyanide. The secondary hydroxyl group of each of the compounds (20a) and (20b) can be converted into a chlorine atom by reacting it with triphenylphosphine in a carbon tetrachloride solvent at a temperature range of from -20°C to the boiling point of the solvent, preferably from room temperature to the boiling point of the solvent (T.R.Webb *et al.*, *J. Org. Chem.*, 56, 3009 (1991)). It can also be converted into a phenoxy or phthaloyl group by the Mitsunobu reaction. This phthaloyl group can be converted into an amino group in a known manner by treating it with a commercially available hydrazine hydrate in an inert alcohol solvent such as ethanol. Furthermore, this amino group can be converted into a monoalkylamino or dialkylamino group by the above-described reductive amination reaction or treatment with a carbon halide such as iodomethane in the presence of an organic amine base such as triethylamine or an inorganic

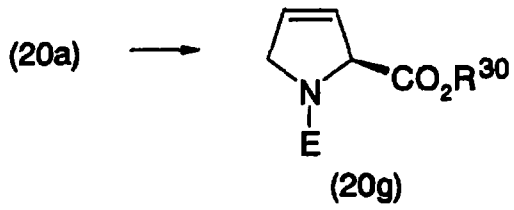
base such as potassium carbonate.

The above-described conversion into an amino group can be conducted by an alternative process. For example, after conversion of the secondary hydroxyl group of each of the compounds (20a) and (20b) into an eliminating group such as mesyloxy group, the compound is treated with lithium azide or sodium azide in an inert polar solvent such as N,N-dimethylformamide or inert ether solvent such as tetrahydrofuran at a temperature range of from -20°C to the boiling point of the solvent, whereby the corresponding azide derivative can be obtained. It is then treated with triphenylphosphine and water in a known reducing method in an inert ether solvent such as tetrahydrofuran at a temperature range of from -20°C to the boiling point of the solvent, preferably from room temperature to the boiling point of the solvent, or is subjected to catalytic hydrogenation or reduction with a reducing agent such as sodium borohydride in a known manner to convert the group into an amino group. An introduction of substituent at the 3-position of pyrrolidine ring can also be conducted by using commercially available trans-3-hydroxy-L-proline as a raw material in accordance with the manner described in (Scheme 10).

In the below-described (Scheme 11), a process for preparing dehydropyrrolidine (20g) in a known manner is indicated. For example, a 3,4-dihydropyrrolidine

derivative (20g) can be prepared by converting the secondary hydroxyl group of the derivative (20a) into an eliminating group such as a mesyloxy group or bromine atom, preferably iodine atom, and then treating the resulting compound with an organic amine base such as 1,8-diazabicyclo(5,4,0)-7-undecene. Alternatively, the 3,4-dihydropyrrolidine derivative (20g) can be prepared by converting the secondary hydroxyl group of the derivative (20a) into the above-described eliminating group, treating with phenylselenyl sodium, which has been prepared from diphenyl diselenide and sodium borohydride, in methanol and then treating with a peroxide such as hydrogen peroxide in methylene chloride in the presence of pyridine (H.Rueger *et al., Can.J.Chem.*, 60, 2918 (1982)).

[Scheme 11]



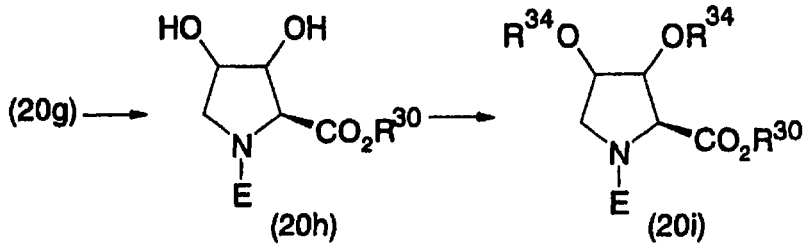
(20g)

In the below-described (Scheme 12), a process for preparing a 3,4-dihydroxy derivative (20h) and a 3,4-dialkoxy derivative (20i) in a known manner by using, as a raw material, the compound (20g) shown in (Scheme 11) is specifically indicated.

The compound (20g) can be converted into its

corresponding 3,4-dihydroxy derivative (20h) by treating it with a commercially available oxidizing agent such as 4-methylmorpholin-4-oxide derivative and osmium tetraoxide in a mixture of an inert polar solvent such as acetone with water or an inert ether solvent such as tetrahydrofuran with water, at a temperature range of from -20°C to the boiling point of the solvent, preferably from 0°C to room temperature. Then, the resulting compound can be converted into a dialkoxy derivative (20i) by treating with an alkyl halide such as methyl iodide or benzyl bromide in the presence of an inorganic base such as sodium hydride in an inert polar solvent such as N,N-dimethylformamide. Or, a derivative (20i) having a cyclic acetal or cyclic ketal introduced therein can be prepared by treating with a commercially available ketalization agent or acetalization agent in an inert polar solvent such as N,N-dimethylformamide or an inert halogenated hydrocarbon solvent such as methylene chloride in the presence of an organic acid such as tosylic acid (J.E.Baldwin *et al.*, *Tetrahedron Lett.*, 35, 4649 (1994); D.M.Goli *et al.*, *Carbohydr.Res.*, 259, 219 (1994)). The above-described ketal or acetal is usable as a protecting group for the secondary hydroxyl group at the 3,4-position. The ketal or acetal derivative can be used as a raw material for the preparation of a compound of the formula (I) having 3,4-dihydroxypyrrolidine.

[Scheme 12]

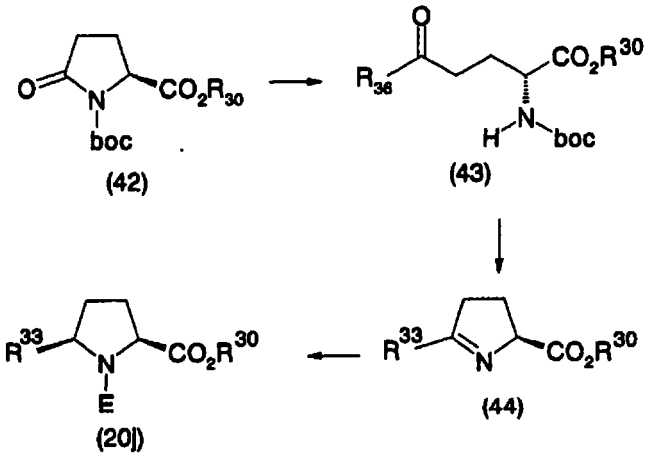


In the below-described (Scheme 13), a process for preparing a derivative (20j) having a substituent introduced at the 5-position of pyrrolidine in a known manner is indicated. For example, a commercially available N-(tertiary butyloxycarbonyl)-L-pyroglutamate ester (42) can be converted into the corresponding ring-opened derivative (43) by treating with an organolithium reagent such as phenyl lithium or a Grignard reagent such as methyl magnesium bromide in an inert ether solvent such as tetrahydrofuran at a temperature range of from -20°C to the boiling point of the solvent, preferably from -20°C to room temperature.

Then the resulting derivative can be converted into the corresponding cyclic imine derivative (44) by treating under acidic conditions, preferably, with trifluoroacetic acid to remove the tertiary butoxycarbonyl group. By catalytic hydrogenation of the resulting compound, the corresponding pyrrolidine derivative (20j) having a 2,5-cis configuration can be prepared (J.V.Betsbrugge *et al.*,

Tetrahedron, 54, 1753 (1998)). It can also be prepared by, instead of catalytic hydrogenation, reduction of imine with a reducing agent such as sodium cyanoborohydride. A pyrrolidine derivative having a 2,5-trans configuration can be prepared, for example, by using commercially available benzyl glycidyl ether as a starting material in accordance with Takano's procedure (S.Takano *et al.*, *Tetrahedron Lett.*, 30, 3805 (1989)).

[Scheme 13]

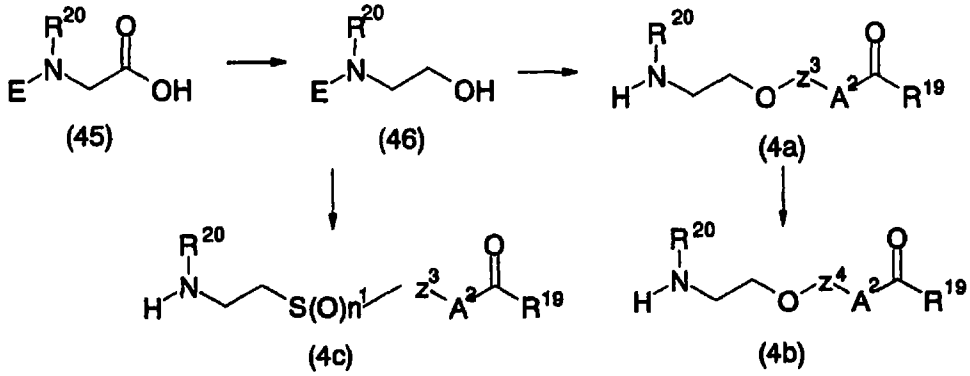


In the below-described (Scheme 14) to (Scheme 18), a process for preparing the compound of the formula (4) serving as a raw material in (Scheme 1) from commercially available amino acid, for example, glycine, is shown (in these schemes, E, R^{20}, R^{10}, R^{28}, R^{20}, Z, Z^3, Z^4, A^2, X^4, n^1 and R^{19} have the same meanings as described above).

The below-described (Scheme 14) indicates that compounds of the formulas (4a), (4b) and (4c) can be synthesized in accordance with the preparation process as

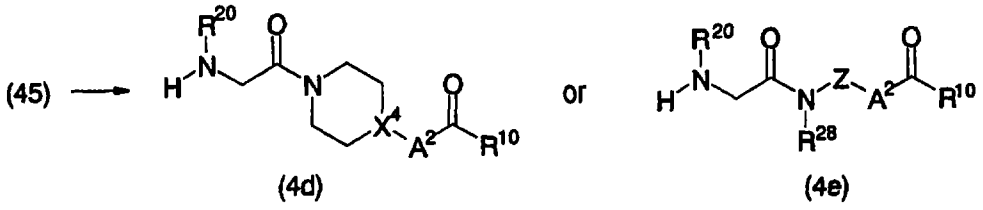
shown above in (Scheme 5) and (Scheme 6) by using as a raw material a glycine derivative (45) which can be prepared in a known manner.

[Scheme 14]



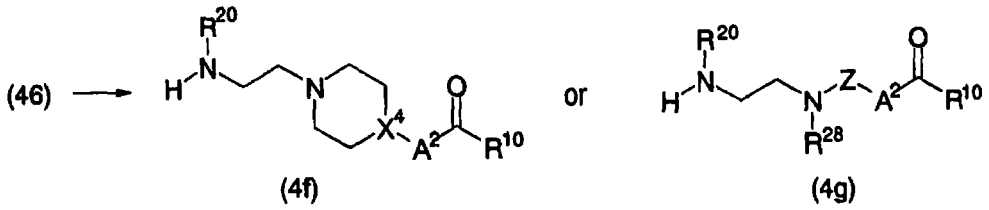
The below-described (Scheme 15) indicates that compounds of the formulas (4d) and (4e) can be prepared in accordance with a preparation process shown in (Scheme 7) by using the above-described glycine derivative (45) as a raw material.

[Scheme 15]



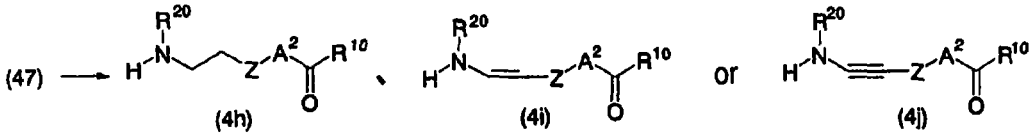
The below-described (Scheme 16) indicates that compounds of the formulas (4f) and (4g) can be prepared in accordance with a preparation process as shown in (Scheme 8) by using the above-described alcoholic derivative (46) as a raw material.

[Scheme 16]



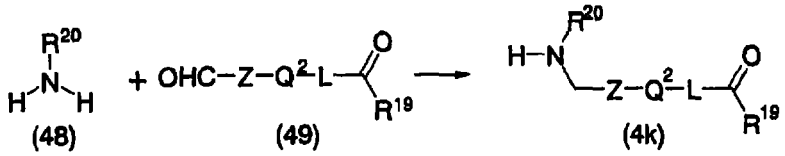
The below-described (Scheme 17) indicates that compounds of the formulas (4h), (4i) and (4j) can be prepared in accordance with a preparation process as shown in (Scheme 9) by using the above-described alcohol derivative (46) as a raw material.

[Scheme 17]



The below-described (Scheme 18) indicates that a primary amine (48) which is available commercially or in a known manner can be converted into a compound of the formula (4k) in accordance with the reductive N-alkylating reaction as shown in (Scheme 8) by reacting the primary amine with an aldehyde derivative (49) which is available commercially or in a known manner.

[Scheme 18]



As described later in Tests, the invention compounds

or salts thereof thus obtained selectively inhibit the binding of cell adhesion molecules to VLA-4 and at the same time, exhibits high oral absorption. Accordingly, the invention compounds are useful as a preventive or remedy of diseases caused by VLA-4-related cell adhesion, that is, various diseases mediated by migration and adhesion of leukocytes, such as inflammatory diseases, autoimmune diseases, metastasis, bronchial asthma, rhinostenosis, diabetes, arthritis, psoriasis, multiple sclerosis, inflammatory intestinal diseases and rejection upon transplantation.

The medicament of the present invention can be administered through various administration routes including oral administration.

As an injection, they can be administered by any one of intravenous injection, intramuscular injection or subcutaneous administration.

Such formulations can be prepared by selecting a proper form depending on the administration route and adopting a usually employed method for it.

Examples of orally administrable formulations include tablets, powders, granules, capsules, solutions, syrups, elixirs, and oily or aqueous suspensions. Injections sometimes contain a stabilizer, antiseptic, solubilizing aid or the like. It is possible that after an injection solution which may contain such an aid is encapsulated in a

container, it may be lyophilized into a solid formulation and reconstituted upon use if desired. Liquid formulations include solutions, suspensions and emulsions. Upon preparation of them, a suspending agent or emulsifying agent can be added as an additive.

The medicament containing the invention compound is preferably administered to adult by repeating once/day administration at proper intervals. Dosage falls within a range of 0.01 mg to 2000 mg, preferably 0.1 mg to 1000 mg.

To the medicament of the present invention, it is possible to use, in combination, an anti-inflammatory, anti-arthritic, adrenocortical steroid (corticosteroid), immunosuppressant, antipsoriatic, bronchodilator, a drug for bronchial asthma or antidiabetic as needed within an extent not damaging the effect of the invention.

Examples

The present invention will hereinafter be described in detail by Examples.

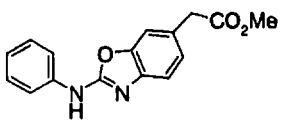
In Examples, "IR", "NMR" and "MS" mean "infrared absorption spectrum", "nuclear magnetic resonance spectrum" and "mass spectrometry", respectively. A ratio of an eluting solvent used for separation and purification by chromatography means a volumetric ratio. "IR" means the measurement by the KBr tablet method or ATR method. In the parentheses of "NMR" mean a measuring solvent with TMS

(tetramethylsilane) used as an internal standard substance. "Anal. Calcd for rational formula" means a calculated value of elemental analysis, while a measured value is indicated after "Found". "HPLC" is an abbreviation of High Performance Liquid Chromatography and indicated in the parentheses are column and eluting solvent.

Example 1

4-((4S)-Fluoro-1-(2-phenylamino-6-benzoxazolylacetyl-(2S)-pyrrolidinylmethoxy)benzoic acid:

(Step 1) Synthesis of methyl 2-phenylaminobenzoxazol-6-acetate

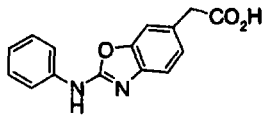


In ethanol (10 ml) was dissolved methyl 3-hydroxy-4-nitrophenylacetate (592 mg, 2.81 mmol), followed by the addition of 5% palladium/carbon (194 mg). The resulting mixture was subjected to catalytic hydrogenation overnight under stirring at room temperature and normal pressure. After removal the catalyst from the reaction mixture by filtration through Celite under reduced pressure, the filtrated cake was washed with ethanol (30 ml). The filtrate was stirred at room temperature. After addition of phenyl isothiocyanate (370 µl, 3.09 mmol) and stirring at room temperature for one hour, mercuric oxide (yellow)

(1.1 g, 5.07 mmol) was added. The reaction mixture was heated under reflux for 3 hours. The mixture was then cooled and the insoluble matter was filtered out under reduced pressure. The filtrate was distilled under reduced pressure. The residue was purified by chromatography on a silica gel column, whereby methyl 2-phenylaminobenzoxazol-6-acetate (480 mg, 61%) was obtained as a white solid from chloroform-ethyl acetate (10:1, v/v) eluate fractions.

^{1}H-NMR ($CDCl_3$) δ: 3.69 (s, 2H), 3.70 (s, 3H), 7.11 (m, 2H), 7.24 (m, 1H), 7.30 (s, 1H), 7.50-7.38 (m, 3H), 7.59 (d, J=1.2Hz, 2H).

(Step 2) Synthesis of 2-phenylaminobenzoxazol-6-acetic acid

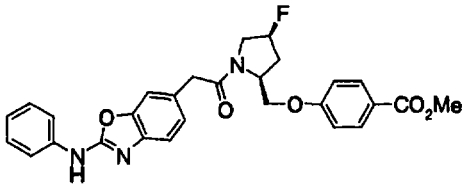


In tetrahydrofuran (which will hereinafter be abbreviated as "THF") (2 ml) and methanol (2 ml) was dissolved methyl 2-phenylaminobenzoxazol-6-acetate (460 mg, 1.63 mmol), followed by the addition of 1N NaOH (3.3 ml) under stirring at room temperature. After further stirring overnight at room temperature, the reaction mixture was concentrated into a small volume. The concentrate was acidified with acetic acid. The crystals thus obtained were collected by filtration, washed with water and then

dried, whereby 2-phenylaminobenzoxazol-6-acetic acid (348 mg, 80%) was obtained as a pale yellow solid.

^{1}H-NMR (DMSO-d_6) δ: 3.64 (s, 2H), 7.03 (t, J=7.6Hz, 1H), 7.11 (dd, J=1.2,8.0Hz, 1H), 7.35-7.40 (m, 4H), 7.76 (d, J=8.8Hz, 2H), 10.60 (brs, 1H), 12.4 (br, 1H).

(Step 3) Synthesis of methyl 4-((4S)-fluoro-1-(2-phenylamino-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)benzoate

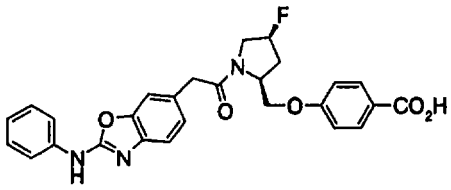


In N,N-dimethylformamide (which will hereinafter be abbreviated as "DMF") (12 ml) were dissolved 2-phenylaminobenzoxazol-6-acetic acid (309 mg, 1.15 mmol) and methyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)benzoate (292 mg, 1.15 mmol), followed by the addition of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (which will hereinafter be abbreviated as "EDC·HCl") (331 mg, 1.73 mmol), 1-hydroxybenzotriazole (which will hereinafter be abbreviated as "HOBt") and 4-dimethylaminopyridine (which will hereinafter be abbreviated as "DMAP") under stirring at room temperature. The reaction mixture was further stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate. The diluted

mixture was then washed with saturated brine, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (10:1, v/v) eluate fractions, methyl 4-((4S)-fluoro-1-(2-phenylamino-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)benzoate (560 mg, 96%) was obtained as a pale brown powder.

^{1}H-NMR ($CDCl_3$) δ: 1.20-1.25 (m, 1H), 2.02-2.22 (m, 1H), 2.32-2.56 (series of dd, J=15.0,19.6Hz, total 1H), 3.63-4.13 (m, total 4H), 3.85 (s, 3H), 4.51 (dd, J=4.4,8.8Hz, 1H), 4.62 (dt, J=4.4,8.8Hz, 1H), 5.29 (ABq, 1H), 6.84 (t, J=8.8Hz, 1H), 6.95 (d, J=9.2Hz, 2H), 7.08 (t, J=6.3Hz, 2H), 7.31-7.42 (m, 3H), 7.60 (t, J=6.8Hz, 2H), 7.90-8.00 (m, 2H).

(Step 4) Synthesis of 4-((4S)-fluoro-1-(2-phenylamino-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)benzoic acid



In THF (8 ml) and methanol (2 ml) was dissolved methyl 4-((4S)-fluoro-1-(2-phenylamino-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)benzoate (383 mg, 0.76 mmol). After addition of 0.25N NaOH (2 eq), the mixture was stirred overnight at room temperature. The reaction mixture was

diluted with chloroform-methanol (5:1, v/v). The diluted mixture was washed with 1N HCl, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (5:1, v/v) eluate fractions, 4-((4S)-fluoro-1-(2-phenylamino-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)benzoic acid (210 mg, 56%) was obtained as a pale brown powder.

IR (KBr) 2977, 1683, 1643, 1604 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.09 (t, J=7.0Hz, 1H), 2.24-2.31 (m, 2H), 3.75-4.42 (m, total 7H), 5.44 (m, total 1H), 7.00-7.12 (m, 4H), 7.37 (m, 4H), 7.75 (d, J=8.4Hz, 2H), 8.87 (d, J=8.4Hz, 2H).

MS (FAB) m/z 490 (M^++1);

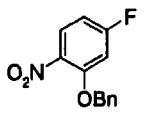
Anal. Calcd for $C_{27}H_{24}FN_3O_5 \cdot 2.75H_2O$: C, 60.16; H, 5.52; N, 7.80.

Found: C, 60.46; H, 5.19; N, 7.24.

Example 2

4-((4S)-Fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)benzoic acid

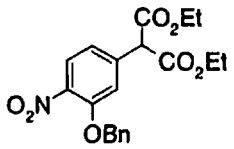
(Step 1) Synthesis of benzyl 5-fluoro-2-nitrophenyl ether



In DMF (300 ml), 5-fluoro-2-nitrophenol (10.0 g, 63.7 mmol), benzyl bromide (10.9 g, 63.7 mmol) and potassium carbonate (13.2 g, 95.6 mmol) were stirred at 80°C for 4 hours. After cooling, the reaction mixture was poured in water (200 ml), followed by extraction with ether (2 × 200 ml). The extract was washed with saturated brine (200 ml), dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (4:1) eluate fractions, the title compound (14.3 g, 91.3%) was obtained as a pale yellow amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 5.22 (s, 2H), 6.71-6.75 (m, 1H), 6.83 (dd, J=10.3,2.5Hz, 1H), 7.33-7.47 (m, 5H), 7.96 (dd, J=9.1,5.4Hz, 1H).

(Step 2) Synthesis of diethyl 3-benzyloxy-4-nitrophenylmalonate

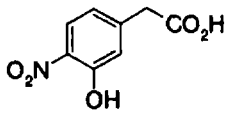


In DMF (100 ml) was suspended sodium hydride (4.63 g, 115.7 mmol). Under cooling at 0°C and stirring, diethyl malonate (18.5 g, 115.7 mmol) was added dropwise. After vigorous evolution of a hydrogen gas stopped, a solution of

benzyl 5-fluoro-2-nitrophenyl ether (14.3 g, 57.8 mmol) in DMF (100 ml) was added to the reaction mixture at 0°C. The reaction mixture was stirred for 15 hours at room temperature. Water (500 ml) was poured and the mixture was extracted with ethyl acetate (300 ml). The extract was washed with saturated brine (200 ml), dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (3:1) eluate fractions, the title compound (22.0 g, 100%) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.24-1.28 (m, 6H), 4.18-4.29 (m, 4H), 4.62 (s, 1H), 5.25 (s, 2H), 7.05 (dd, J=8.3,1.7Hz, 1H), 7.29-7.48 (m, 6H), 7.85 (d, J=8.3Hz, 1H).

(Step 3) Synthesis of 3-hydroxy-4-nitrophenylacetic acid

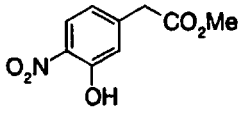


A mixture of diethyl 3-benzyloxy-4-nitrophenylmalonate (22.0 g, 57.8 mmol), acetic acid (200 ml) and concentrated hydrochloric acid (100 ml) was heated under reflux for 15 hours under stirring. After the reaction mixture was cooled to room temperature, the solvent was distilled off from the reaction mixture under reduced pressure. The solid thus obtained was collected by filtration under

reduced pressure, followed by drying under reduced pressure, whereby the title compound (5.45 g, 48%) was obtained as a pale yellow amorphous substance.

^{1}H-NMR (DMSO-d_6) δ: 3.64 (s, 2H), 6.88 (dd, J=8.3,1.6Hz), 7.05 (s, 1H), 7.85 (d, J=8.3Hz, 1H), 10.90 (s, 1H), 12.55 (br s, 1H).

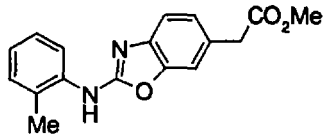
(Step 4) Synthesis of methyl 3-hydroxy-4-nitrophenylacetate



To 3-hydroxy-4-nitrophenylacetic acid (5.45 g, 27.6 mol) and methanol (100 ml) was added concentrated sulfuric acid (0.5 ml). The mixture was then heated under reflux for 4 hours under stirring. After cooling to room temperature, the reaction mixture was distilled under reduced pressure to remove the solvent. Water (100 ml) was added to the residue, followed by extraction with ether (300 ml). The extract was washed successively with a saturated aqueous solution (100 ml) of sodium bicarbonate and saturated brine (100 ml), dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent, whereby the title compound (4.90 g, 84%) was obtained as a yellow crystalline powder.

^{1}H-NMR ($CDCl_3$) δ: 3.67 (s, 2H), 3.73 (s, 3H), 6.91 (d, J=8.3Hz, 1H), 7.08 (s, 1H), 8.06 (d, J=8.3Hz, 1H), 10.59 (s, 1H).

(Step 5) Synthesis of methyl 2-(2-methylphenylamino)-6-benzoxazolylacetate

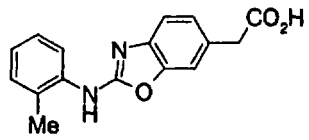


In ethanol (20 ml) was dissolved methyl 3-hydroxy-4-nitrophenylacetate (1.00 g, 4.74 mmol), followed by the addition of 5% palladium/carbon (500 mg). Under stirring at room temperature, the mixture was subjected to catalytic hydrogenation for 15 hours. After filtration of the reaction mixture through Celite to remove the insoluble matter, 2-tolyl isothiocyanate (765 µl, 5.69 mmol) was added to the filtrate while stirring at room temperature. The reaction mixture was stirred for 15 hours. After addition of mercuric oxide (yellow) (1.72 g, 7.94 mmol), the mixture was heated under reflux for 5 hours under stirring. The reaction mixture was then cooled to room temperature. After filtration of the reaction mixture through Celite under reduced pressure, the solvent was distilled off under reduced pressure from the filtrate. The residue was purified by chromatography on a silica gel column, whereby from chloroform-ethyl acetate (10:1) eluate

fractions, the title compound (1.18 g, 84%) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 2.35 (s, 3H), 3.69 (s, 2H), 3.70 (s, 3H), 7.07 (t, J=8.1Hz, 1H), 7.12 (dd, J=8.1,1.5Hz, 1H), 7.22-7.33 (m, 3H), 7.40 (d, J=8.1Hz, 1H), 8.06 (d, J=8.1Hz, 1H).

(Step 6) Synthesis of 2-(2-methylphenylamino)-6-benzoxazolylacetic acid

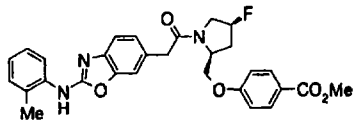


THF (30 ml) and 0.25N NaOH (32 ml, 8.00 mmol) were added to methyl 2-(2-methylphenylamino)-6-benzoxazolylacetate (1.18 g, 3.98 mmol), followed by stirring at room temperature for 5 hours. The reaction mixture was poured in 1N HCl (50 ml), followed by extraction with a chloroform-methanol (5:1, 2 × 200 ml) mixture. The extract was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent, whereby the title compound (867 mg, 77%) was obtained as a pale yellow amorphous substance.

^{1}H-NMR (DMSO-d_6) δ: 2.31 (s, 3H), 3.64 (s, 2H), 7.09-7.13 (m, 2H), 7.24-7.30 (m, 3H), 7.39 (d, J=1.0Hz, 1H), 7.80 (dd, J=7.3,1.5Hz, 1H).

MS (ESI) m/z, 283 (M^++1).

(Step 7) Synthesis of methyl 4-((4S)-fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)benzoate

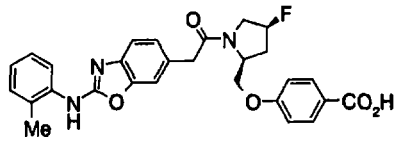


In DMF (10 ml) were dissolved 2-(2-methylphenylamino)-6-benzoxazolylacetic acid (300 mg, 1.06 mmol) and 4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)benzoate (269 mg, 1.06 mmol). After addition of EDC·HCl (305 mg, 1.59 mmol), HOBt (cat.) and DMAP (cat.) under stirring at room temperature, the mixture was stirred at room temperature for 15 hours. Water (200 ml) was added and the mixture was extracted with ethyl acetate (200 ml). The extract was washed with saturated brine (2 × 200 ml), dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-ethyl acetate (9:1) eluate fractions, the title compound (573 mg, 100%) was obtained as a yellow foam.

^{1}H-NMR ($CDCl_3$) δ: 2.06-2.59 (series of m, 5H), 3.68-4.15 (series of m, 8H), 4.52-4.65 (m, 2H), 5.24 and 5.37 (m, each, total 1H), 6.86-7.42 (series of m, 9H), 7.94-8.07 (m, 3H).

MS (ESI) m/z, 518 (M^++1).

(Step 8) Synthesis of 4-((4S)-fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)benzoic acid



In THF (10 ml) was dissolved methyl 4-((4S)-fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)benzoate (573 mg, 1.11 mmol). After addition of 0.25N NaOH (8.8 ml, 2.2 mmol) under stirring at room temperature, the mixture was stirred at room temperature for 15 hours. The reaction mixture was poured in 1N HCl (50 ml), followed by extraction with a chloroform-methanol (5:1, 2 × 200 ml). The extract was washed with anhydrous magnesium sulfate and then distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (20:1 to 10:1) eluate fractions, the title compound (365 mg, 65%) was obtained as a colorless crystalline solid.

^{1}H-NMR (DMSO-d_6) δ: 2.25-2.51 (series of m, total 5H, including s, 3H, at d 2.30), 3.70-4.67 (series of m, 7H), 5.30-5.50 (m, total 1H), 7.03-7.09 (m, 4H), 7.24-7.34 (m, 4H), 7.81-7.91 (m, 3H), 9.61 (br s, 1H).

MS (ESI) m/z, 504 (M^++1);

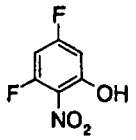
Anal. Calcd for $C_{28}H_{26}FN_3O_5 \cdot 0.5H_2O$: C, 65.62; H, 5.31; N, 8.20.

Found: C, 65.97; H, 5.61; N, 7.73.

Example 3

4-((4S)-Fluoro-1-(4-methoxy-2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)benzoic acid

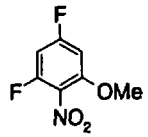
(Step 1) Synthesis of 3,5-difluoro-2-nitrophenol



Dimethylsulfoxide (which will hereinafter be abbreviated as "DMSO") (50 ml) and 10N NaOH (12 ml, 120 mmol) were added to 1,3,5-trifluoro-2-nitrobenzene (10.0 g, 56.5 mmol). The mixture was stirred at room temperature for 15 hours. Water (100 ml) and ether (200 ml) were added to separate the reaction mixture into layers. The water layer thus obtained was acidified with 1N HCl, followed by extraction with ether (2 × 200 ml). The extract was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-ethyl acetate (10:1) eluate fractions, the title compound (7.97 g, 81%) was obtained as a yellow crystalline powder.

^{1}H-NMR ($CDCl_3$) δ: 6.53-6.59 (m, 1H), 6.66-6.70 (m, 1H), 10.87 (d, J=1.2Hz, 1H).

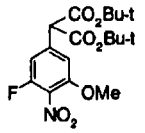
(Step 2) Synthesis of 3,5-difluoro-2-nitroanisole



In DMF (50 ml) was dissolved 3,5-difluoro-2-nitrophenol. Potassium carbonate (10.4 g, 75.5 mmol) and methyl iodide (6.3 ml, 100.6 mmol) were added and the mixture was stirred for 15 hours at room temperature. Water (300 ml) was added, followed by extraction with ether (500 ml). The extract was washed with saturated brine (2 × 200 ml), dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent, whereby the title compound (8.29 g, 87%) was obtained as a yellow crystalline powder.

^{1}H-NMR ($DMSO-d_6$) δ: 3.97 (s, 3H), 7.21-7.27 (m, 2H).

(Step 3) Synthesis of di-tert-butyl 3-fluoro-5-methoxy-4-nitrophenylmalonate

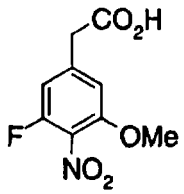


In DMF (60 ml) was suspended sodium hydride (2.75 g, 68.7 mmol). Under stirring at 0°C, di-tert-butyl malonate

(14.9 g, 68.7 mmol) was added dropwise. After vigorous emission of a hydrogen gas stopped, a solution of 3,5-difluoro-2-nitroanisole (5.20 g, 27.5 mmol) in DMF (40 ml) was added. The reaction mixture was stirred at 80°C for 4 hours. After cooling the reaction mixture to room temperature, water (200 ml) was added to terminate the reaction, followed by extraction with ether (300 ml). The extract was washed with saturated brine (200 ml), dried over anhydrous magnesium sulfate and distilled reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby hexane-ethyl acetate (10:1) eluate fractions, the title compound (6.56 g, 62%) was obtained as an yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.48 (s, 18H), 3.94 (s, 3H), 4.41 (s, 1H), 6.92 (m, 2H).

(Step 4) Synthesis of 3-fluoro-5-methoxy-4-nitrophenylacetic acid

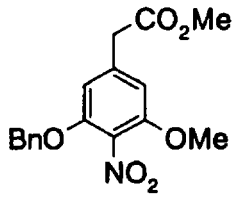


Acetic acid (7 ml) and concentrated hydrochloric acid (7 ml) were added to di-tert-butyl 3-fluoro-5-methoxy-4-nitrophenylmalonate (4.88 g, 12.7 mmol). The mixture was heated under reflux for 15 hours under stirring. After

cooling, the reaction mixture was distilled under reduced pressure to remove the solvent. To the residue were added 1N NaOH (200 ml) and ether (200 ml) to separate it into layers. The water layer thus obtained was acidified with 1N HCl, followed by extraction with ether (200 ml). The extract was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent, whereby the title compound (2.83 g, 97%) was obtained as a pale brown solid.

^{1}H-NMR ($CDCl_3$) δ: 3.68 (s, 2H), 3.93 (s, 3H), 6.78 (m, 2H), 9.31 (br s, 1H).

(Step 5) Methyl 3-benzyloxy-5-methoxy-4-nitrophenylacetate

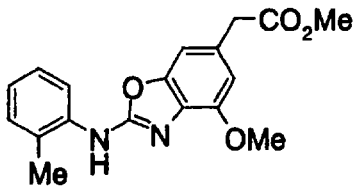


Sodium hydride (918 mg, 23.0 mmol) was added to benzyl alcohol (30 ml) in portions. After vigorous evolution of a hydrogen gas stopped, a solution of 3-fluoro-5-methoxy-4-nitrophenylacetic acid (2.63 g, 11.5 mmol) in benzyl alcohol (20 ml) was added to the reaction mixture. After stirring at 50°C for 15 hours, the reaction mixture was cooled. To the mixture was added 1N NaOH (100 ml), followed by extraction with ether (200 ml). After addition of 1N HCl to the water layer, the mixture was extracted

with ether (2 × 200 ml). The extract was dried over anhydrous magnesium sulfate and then, distilled under reduced pressure to remove the solvent, whereby a pale yellow oil was obtained. Methanol (50 ml) and concentrated sulfuric acid (0.5 ml) were added to the resulting oil and the mixture was heated and refluxed for 4 hours under stirring. The reaction mixture was then cooled to room temperature. After addition of a saturated aqueous solution of sodium bicarbonate for neutralization, the mixture was extracted with chloroform (2 × 250 ml). The extract was dried over anhydrous magnesium sulfate and then distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform eluate solutions, the title compound (2.77 g, 61%) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 3.58 (s, 2H), 3.69 (s, 3H), 3.88 (s, 3H), 5.15 (s, 2H), 6.55 (s, 1H), 6.60 (d, J=1.2Hz, 1H), 7.36 (m, 5H).

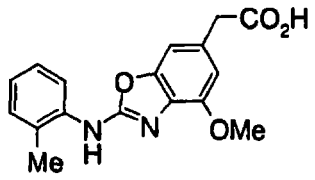
(Step 6) Synthesis of methyl 4-methoxy-2-(2-methylphenylamino)-6-benzoxazolylacetate



In ethanol (100 ml) was dissolved methyl 3-benzyloxy-5-methoxy-4-nitrophenylacetate (2.77 g, 8.36 mmol), followed by the addition of 5% palladium/carbon (1 g). Under stirring at room temperature, the resulting mixture was subjected to catalytic hydrogenation for 15 hours. The reaction mixture was filtered through Celite under reduced pressure to remove the insoluble matter. To the filtrate was added 2-tolyl thioisocyanate (1.35 ml, 10.0 mmol) under stirring at room temperature. The mixture was stirred at room temperature for 15 hours. Mercuric oxide (yellow) (3.08 g, 14.2 mmol) was added and the mixture was heated and refluxed for 4 hours under stirring. After the reaction mixture was cooled to room temperature, the insoluble matter was filtered off through Celite. The residue obtained by distilling off the solvent from the filtrate was purified by chromatography on a silica gel column, whereby from chloroform-ethyl acetate (4:1) eluate fractions, the title compound (1.30 g, 48%) was obtained as a brown oil.

^{1}H-NMR ($CDCl_3$) δ: 2.33 (s, 3H), 3.66 (s, 2H), 3.71 (d, J=0.49Hz, 3H), 3.96 (s, 3H), 6.67 (s, 1H), 6.93 (d, J=0.49Hz, 1H), 7.05 (t, J=7.3Hz, 1H), 7.20 (d, J=7.3Hz, 1H), 7.28 (m, 1H), 8.06 (d, J=8.1Hz, 1H).

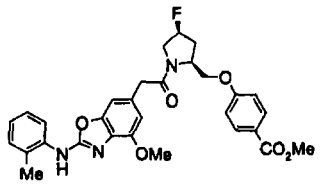
(Step 7) Synthesis of 4-methoxy-2-(2-methylphenylamino)-6-benzoxazolylacetic acid



In THF (30 ml) was dissolved methyl 4-methoxy-2-(2-methylphenylamino)-6-benzoxazolylacetate (1.30 g, 3.98 mmol), followed by the addition of 0.25N NaOH (32 ml, 8.00 mmol). The mixture was stirred at room temperature for 15 hours. The reaction mixture was poured in 1N HCl (100 ml), followed by extraction with a chloroform-methanol (4:1, 2 × 200 ml) mixture. The extract was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent, whereby the title compound (1.24 g, 100%) was obtained as a brown amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 2.30 (s, 3H), 3.75 (m, 2H), 3.93 (s, 3H), 6.70 (s, 1H), 6.93 (s, 1H), 7.05 (s, 1H), 7.17-7.21 (m, 2H), 7.74 (d, J=7.1Hz, 1H).

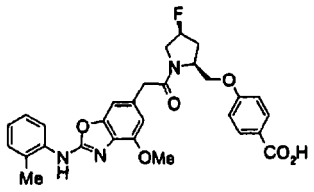
(Step 8) Synthesis of methyl 4-((4S)-fluoro-1-(4-methoxy-2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)benzoate



In DMF (10 ml) were dissolved 4-methoxy-2-(2-methylphenylamino)-6-benzoxazolylacetic acid (200 mg, 0.640 mmol) and methyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)benzoate. EDC·HCl (184 mg, 0.960 mmol), HOBt (cat.) and DMAP (cat.) were added under stirring at room temperature and stirring was conducted for 15 hours. Water (200 ml) was added to the reaction mixture, followed by extraction with ethyl acetate (300 ml). The extract was washed with saturated brine (2 × 200 ml), dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (20:1) eluate fractions, the title compound (312 mg, 89%) was obtained as a yellow viscous oil.

^{1}H-NMR ($CDCl_3$) δ: 2.04-2.57 (series of m, 5H), 3.61-4.14 (series of m, 11H), 4.48-4.65 (m, 2H), 5.22 and 5.36 (m, each, total 1H), 6.66 (d, J=8.8Hz, 2H), 7.03-7.08 (m, 1H), 7.20-7.29 (m, 2H), 7.51 (br s, 1H), 7.95-8.03 (m, 2H).

(Step 9) Synthesis of 4-((4S)-fluoro-1-(4-methoxy-2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)benzoic acid



In THF (5 ml) was dissolved methyl 4-((4S)-fluoro-1-(4-methoxy-2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)benzoate (312 mg, 0.570 mmol), followed by the addition of 0.25N NaOH (4.6 ml, 1.15 mmol). The resulting mixture was heated and refluxed for 4 hours under stirring. After the reaction mixture was cooled to room temperature, 1N HCl (100 ml) was poured therein. The crystals thus obtained were collected by filtration under reduced pressure, washed with water and dried under reduced pressure, whereby the title compound (100 mg, 33%) was obtained as a pale yellow amorphous substance.

^{1}H-NMR (DMSO-d_6) δ: 2.17-2.51 (series of m, total 5H, including s, 3H, at d 2.30), 3.35-4.66 (series of m, total 10H, including s, 3H, at d 3.89), 5.32-5.51 (m, 1H), 6.68 and 6.99 (s, each, total 1H), 7.03-7.09 (m, 3H), 7.23-7.27 (m, 2H), 7.85-7.92 (m, 3H).

MS (FAB) m/z, 534 (M^++1);

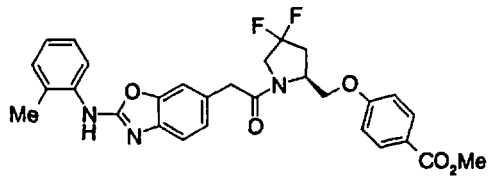
Anal. Calcd for $C_{29}H_{28}FN_3O_6 \cdot 0.25H_2O$: C, 64.74; H, 5.34; N, 7.81.

Found: C, 64.68; H, 5.49; N, 7.67.

Example 4

4-(4,4-Difluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-2S-pyrrolidinylmethoxy)benzoic acid:

(Step 1) Synthesis of methyl 4-(4,4-difluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)benzoate

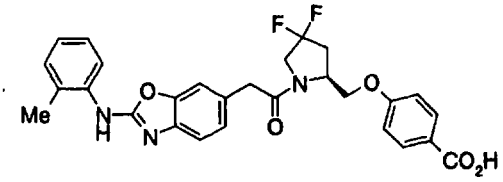


In DMF (6.6 ml) were dissolved methyl 4-(4,4-difluoro-(2S)-pyrrolidinylmethoxy)benzoate (160.2 mg, 0.591 mmol), 2-(2-methylphenylamino)-6-benzoxazolylacetic acid (166.7 mg, 0.591 mmol) and HOBt (16.0 mg, 0.118 mmol). To the resulting solution was added EDC·HCl (169.8 mg, 0.886 mmol) at room temperature. The resulting mixture was stirred overnight at room temperature. After the reaction mixture was diluted with ethyl acetate, the diluted mixture was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (1:1, v/v) eluate fractions, the title compound (324.3 mg, 100%) was obtained as a light orange amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 2.37 (3H, s), 2.47-2.70 (2H, m), 3.67 (1H, d, J=15.2Hz), 3.72 (1H, d, J=15.2Hz), 3.74-4.02 (total

5H, m, including 3H, s at (3.84), 4.19 (1H, m), 4.38 (1H, m), 4.70 (1H, m), 6.80-7.43 (9H, series of m), 7.95 (2H, m), 8.08 (1H, d, J=8.0Hz).

(Step 2) Synthesis of 4-(4,4-difluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-2S-pyrrolidinylmethoxy)benzoic acid



In THF (6.5 ml) was dissolved methyl 4-(4,4-difluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)benzoate (324.3 mg, 0.606 mmol). To the resulting solution was added 0.25N NaOH (6.5 ml) at 0°C. After stirring overnight at room temperature, the reaction mixture was further stirred overnight at 50°C. The reaction mixture was concentrated, followed by neutralization with 1N HCl. The crystals thus obtained were collected by filtration, washed with water and dried at 50°C, whereby the title compound (271.9 mg, 88% for 2 steps) was obtained as a pale brown solid.

IR (KBr) 3440, 1685, 1641, 1604, 1577 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 2.28 (3H, s), 2.38-2.86 (2H, m), 3.65-4.27 (6H, m), 4.54 (1H, m), 6.95-7.38 (8H, series of m),

7.79 (1H, d, J=8.0Hz), 7.82-7.93 (3H, m), 9.62 (1H, broad s).

MS (ESI) m/z 522 (M^++1).

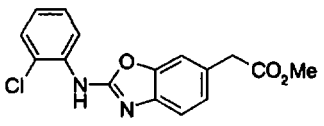
Anal. Calcd for $C_{28}H_{25}F_2N_3O_5 \cdot 0.75H_2O$: C, 62.86; H, 4.99; N, 7.85; F, 7.10.

Found: C, 63.09; H, 5.04; N, 7.66; F, 6.83.

Example 5

4-((2S,4S)-1-(2-(2-Chlorophenylamino)-6-benzoxazolylacetyl)-4-fluoro-2-pyrrolidinylmethoxy)benzoic acid:

(Step 1) Synthesis of methyl 2-(2-chlorophenylamino)-6-benzoxazolylacetate

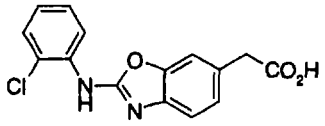


In methanol (50 ml) was dissolved methyl 4-amino-3-hydroxyphenylacetate (2.30 g, 12.7 mmol). After addition of 2-methylphenyl thioisocyanate (1.99 ml, 15.2 mmol) at room temperature, the mixture was stirred at room temperature for 3 hours. Mercuric oxide (yellow) (2.75 g, 15.2 mmol) was added to the reaction mixture. The mixture was then stirred at 50°C for 50 minutes. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue thus obtained was purified by chromatography on a silica gel column (silica

gel: 100 g), whereby from chloroform/ethyl acetate (10/1) eluate fractions, the title compound (3.35 g, 83%) was obtained as a pale yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 3.71 (s, 5H), 7.03 (dt, J=7.6,1.5Hz, 1H), 7.16 (dd, J=8.1,1.7Hz, 1H), 7.33 (d, J=1.0Hz, 1H), 7.36-7.43 (m, 3H), 7.46 (d, J=8.1Hz, 1H), 7.52 (br, 1H), 8.55 (dd, J=8.3,1.7Hz, 1H).

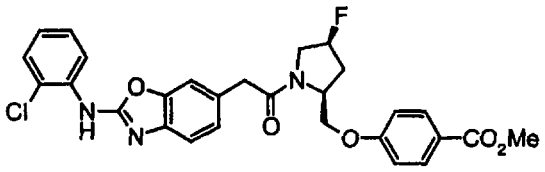
(Step 2) Synthesis of 2-(2-chlorophenylamino)-6-benzoxazolylacetic acid



In THF (200 ml) was dissolved methyl 2-(2-chlorophenylamino)-6-benzoxazolylacetate (3.35 g, 10.6 mmol). After addition of 0.25N NaOH (200 ml), the mixture was stirred at room temperature for 16 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue was acidified with 1N HCl, followed by extraction with a chloroform/methanol (10/1) mixture. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent, whereby the title compound (2.94 g, 92%) was obtained as a pale brown solid.

^{1}H-NMR (DMSO-d_6) δ: 3.62 (s, 2H), 7.09 (d, J=7.8Hz, 1H), 7.19 (t, J=7.1Hz, 1H), 7.31 (d, J=8.1Hz, 1H), 7.39 (s, 1H), 7.41 (d, J=7.6Hz, 1H), 7.52 (d, J=7.3Hz, 1H), 8.08 (d, J=6.8Hz, 1H), 9.99 (br, 1H).

(Step 3) Synthesis of methyl 4-((2S,4S)-1-(2-(2-chlorophenylamino)-6-benzoxazolylacetyl)-4-fluoro-2-pyrrolidinylmethoxy)benzoate

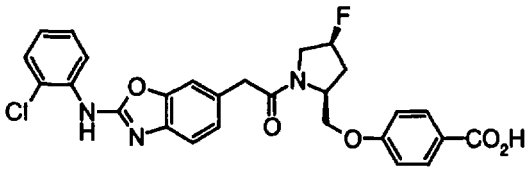


In DMF (5 ml), 2-(2-chlorophenylamino)-6-benzoxazolylacetic acid (303 mg, 1.0 mmol), methyl 4-((2S,4S)-4-fluoro-2-pyrrolidinylmethoxy)benzoate (253 mg, 1.0 mmol), EDC·HCl (288 mg, 1.5 mmol), HOBt (203 mg, 1.5 mmol) and triethylamine (0.70 ml, 5.0 mmol) were stirred at room temperature for 14 hours. The reaction mixture was poured in ice water (30 ml), followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica gel: 50 g), whereby from chloroform/acetone (10/1) eluate fractions, the title compound (360 mg, 67%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 2.05-2.30 (m, 1H), 2.35-2.60 (m, 1H), 3.75 (d, J=4.6Hz, 2H), 3.868 and 3.870 (each s, total 3H, amide isomers), 3.88-4.09 (m, 3H), 4.54-4.63 (m, 2H), 5.32 (dt, J=52.8,3.9Hz, 1H), 6.87 and 6.99 (each d, J=8.8 and 9.0Hz respectively, total 2H, amide isomers), 7.04 (t, J=6.4Hz, 1H), 7.14 (d, J=8.1Hz, 1H), 7.33 (s, 1H), 7.36-7.53 (m, 4H), 7.96 and 7.99 (each d, each J=9.0Hz, total 2H, amide isomers), 8.54 (dd, J=8.3,1.2Hz, 1H).

MS (ESI) m/z 538 (M^++1), 540 (M^++3).

(Step 4) Synthesis of 4-((2S,4S)-1-(2-(2-chlorophenylamino)-6-benzoxazolylacetyl)-4-fluoro-2-pyrrolidinylmethoxy)benzoic acid



In THF (20 ml) was dissolved methyl 4-((2S,4S)-1-(2-(2-chlorophenylamino)-6-benzoxazolylacetyl)-4-fluoro-2-pyrrolidinylmethoxy)benzoate (360 mg, 0.669 mmol), followed by the addition of 0.25N NaOH (20 ml). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue was then acidified with 1N HCl, followed by extraction with a chloroform/methanol (10/1) mixture. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled

under reduced pressure to remove the solvent. The residue was purified by thin-layer silica gel chromatography and separated using (chloroform/methanol (20/1)), whereby the title compound (273 mg, 78%) was obtained as a colorless amorphous substance.

IR (KBr) 3396, 2978, 2941, 1701, 1637, 1603, 1572 cm^{-1};

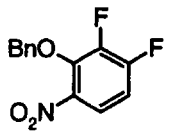
^{1}H-NMR (DMSO-d_6) δ: 2.23-2.37 (m, 2H), 3.32 (br, 2H), 3.76-4.72 (m, 7H), 5.31-5.57 (m, 1H), 7.02-7.11 (m, 3H), 7.18 (t, J=6.1Hz, 1H), 7.28-7.35 (m, 1H), 7.37 (s, 1H), 7.41 (dt, J=8.0,1.5Hz, 1H), 7.52 (dd, J=8.0,1.2Hz, 1H), 7.86 and 7.89 (each d, J=8.8 and 10.9Hz respectively, total 2H, amide isomers), 8.09 (d, J=7.3Hz, 1H), 8.31 (s, 1H).

MS (ESI) m/z 524 (M^++1), 526 (M^++3).

Example 6

4-((2S,4S)-1-(7-Fluoro-2-(2-methylphenylamino)-6-benzoxazolylacetyl)-4-fluoro-2-pyrrolidinylmethoxy)benzoic acid:

(Step 1) Synthesis of 1-benzyloxy-2,3-difluoro-6-nitrobenzene

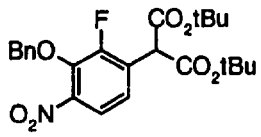


In THF (200 ml) was dissolved 2,3-difluoro-6-nitrophenol (10.0 g, 57.1 mmol), followed by the addition of potassium carbonate (15.8 g, 114.2 mmol) and benzyl

bromide (7.47 ml, 62.8 mmol) at room temperature. The reaction mixture was stirred at 60°C for 6 hours. DMF (100 ml) was added to the reaction mixture and the mixture was stirred at 60°C for 24 hours. After cooling to room temperature, the reaction mixture was distilled under reduced pressure to remove the solvent. The residue was diluted with ether (100 ml), washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica gel: 100 g), whereby from the hexane/ethyl acetate (4/1) eluate fractions, the title compound (4.17 g, 28%) was obtained as a yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 5.29 (s, 2H), 7.00 (m, 1H), 7.38 (m, 3H), 7.46 (m, 2H), 7.66 (m, 1H).

(Step 2) Synthesis of di-tert-butyl (3-benzyloxy-2-fluoro-4-nitrophenyl)malonate

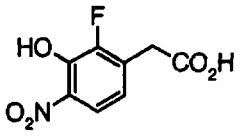


In THF (100 ml) were dissolved 1-benzyloxy-2,3-difluoro-6-nitrobenzene (4.17 g, 15.7 mmol) and di-tert-butyl malonate (3.52 ml, 15.7 mmol). To the resulting solution was added sodium hydride (60% in oil, 1.26 g, 31.4 mmol) in portions under stirring at 0°C. The reaction

mixture was stirred at 0°C for 30 minutes and then at 80°C for 9 hours. Di-tert-butyl malonate (7.04 ml, 31.4 mmol) and sodium hydride (60%; 2.52 g, 52.8 mmol) were added and the mixture was stirred at 80°C for 2 days. After cooling to room temperature, the reaction mixture was poured in ice water (100 ml), followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica gel: 200 g), whereby from hexane/ethyl acetate (8/1) eluate fractions, the title compound (6.87 g, 95%) was obtained as an orange solid.

^{1}H-NMR ($CDCl_3$) δ: 1.47 (s, 9H), 1.49 (s, 9H), 4.83 (s, 1H), 5.28 (s, 2H), 7.33-7.41 (m, 4H), 7.61 (d, J=8.5Hz, 1H).

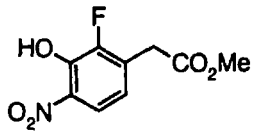
(Step 3) Synthesis of 2-fluoro-3-hydroxy-4-nitrophenylacetic acid



Di-tert-butyl (3-benzyloxy-2-fluoro-4-nitrophenyl)malonate (6.87 g, 14.9 mmol), acetic acid (200 ml) and concentrated hydrochloric acid (35 ml) were stirred at 120°C for 6 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced

pressure, whereby the title compound was obtained as a brown oil (this compound was provided for the subsequent reaction without further purification).

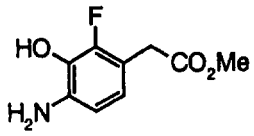
(Step 4) Synthesis of methyl 2-fluoro-3-hydroxy-4-nitrophenylacetate



In methanol (300 ml), the above-described 1-benzyloxy-2-fluoro-6-nitrophenylacetic acid (14.9 mmol) and concentrated sulfuric acid (2 ml) were stirred at 70°C for 4 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was neutralized with a saturated aqueous solution of sodium bicarbonate, followed by extraction with chloroform. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica gel: 200 g), whereby from the hexane/ethyl acetate (4/1) eluate fractions, the title compound (5.22 g, 100% (2 steps)) was obtained as a brown solid.

^{1}H-NMR ($CDCl_3$) δ: 3.74 (s, 3H), 3.76 (d, J=1.2Hz, 2H), 6.90 (dd, J=9.0,6.3Hz, 1H), 7.88 (dd, J=9.0,2.0Hz, 1H), 10.51 (s, 1H).

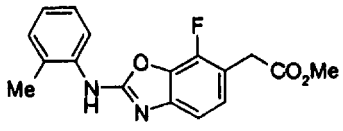
(Step 5) Synthesis of methyl 4-amino-3-hydroxy-2-fluorophenylacetate



Methyl 2-fluoro-3-hydroxy-4-nitrophenylacetate (5.22 g, 14.9 mmol), reduced iron powder (2.66 g, 47.7 mmol), sodium acetate·trihydrate (2.03 g, 14.9 mmol) and acetic acid (5.54 ml) were heated and refluxed at 110°C for 4 hours in methanol:water (1:4, 300 ml). After cooling to room temperature, the reaction mixture was filtered through Celite under reduced pressure to remove the insoluble matter. The filtrate was then concentrated, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica gel: 50 g), whereby from hexane/ethyl acetate (2/1) eluate fractions, the title compound (1.29 g, 44%) was obtained as a brown oil.

^{1}H-NMR ($CDCl_3$) δ: 3.54 (s, 2H), 3.68 (s, 3H), 4.99 (s, 2H), 6.42 (d, J=7.6Hz, 1H), 6.53 (d, J=7.1Hz, 1H).

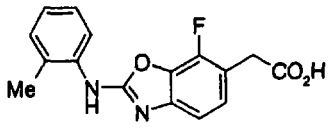
(Step 6) Synthesis of methyl 7-fluoro-2-(2-methylphenylamino)-6-benzoxazolylacetate



Methyl 4-amino-3-hydroxy-2-fluorophenylacetate (1.29 g, 6.48 mmol) was dissolved in methanol (20 ml). At room temperature, o-tolyl thioisocyanate (1.05 ml, 7.78 mmol) was added and the mixture was stirred for 5 hours. Mercuric oxide (yellow) (1.68 g, 7.77 mmol) was added to the reaction mixture, followed by stirring at 80°C for further 3 hours. After the reaction mixture was cooled to room temperature, the solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (silica gel: 100 g), whereby chloroform/ethyl acetate (10/1) eluate fractions, the title compound (1.31 g, 64% (2 steps)) was obtained as a pale brown solid.

^{1}H-NMR ($CDCl_3$) δ: 2.34 (s, 3H), 3.72 (s, 3H), 3.74 (s, 2H), 7.05-7.10 (m, 2H), 7.15 (d, J=7.8Hz, 1H), 7.21 (d, J=8.6Hz, 1H), 7.29 (t, J=7.8Hz, 1H), 7.32 (br, 1H), 8.01 (d, J=8.1Hz, 1H).

(Step 7) Synthesis of 7-fluoro-2-(2-methylphenylamino)-6-benzoxazolylacetic acid

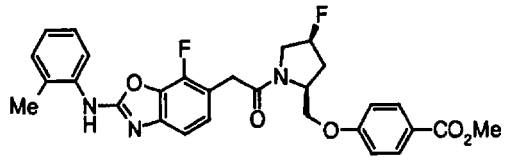


Methyl 7-fluoro-2-(2-methylphenylamino)-6-benzoxazolylacetate (1.31 g, 4.17 mmol) was dissolved in THF (30 ml), followed by the addition of 0.25N NaOH (30 ml). The resulting mixture was stirred at room temperature for 20 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue was acidified with 1N HCl, followed by extraction with a chloroform/methanol (10/1) mixture. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent, whereby the title compound (1.08 g, 86%) was obtained as a pale brown solid.

^{1}H-NMR (DMSO-d_6) δ: 2.30 (s, 3H), 3.68 (s, 2H), 7.09-7.18 (m, 3H), 7.25 (d, J=6.9Hz, 2H), 7.80 (d, J=8.1Hz, 1H), 8.30 (s, 1H), 12.46 (br, 1H).

MS (ESI) m/z 301 (M^++1).

(Step 8) Synthesis of methyl 4-((2S,4S)-1-(7-fluoro-2-(2-methylphenylamino)-6-benzoxazolylacetyl)-4-fluoro-2-pyrrolidinylmethoxy)benzoate

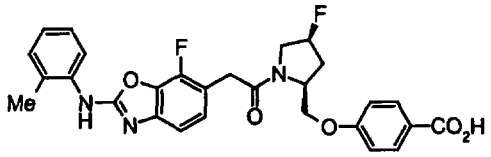


In DMF (5 ml), 7-fluoro-2-(2-methylphenylamino)-6-benzoxazolylacetic acid (300 mg, 1.0 mmol), methyl 4-((2S,4S)-4-fluoro-2-pyrrolidinylmethoxy)benzoate (253 mg, 1.0 mmol), EDC·HCl (288 mg, 1.5 mmol), HOBt (203 mg, 1.5 mmol) and triethylamine (0.70 ml, 5.0 mmol) were stirred at room temperature for 14 hours. After the reaction mixture was poured in ice water (20 ml), the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica gel: 50 g), whereby from chloroform/acetone (10/1) eluate fractions, the title compound (490 mg, 92%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 2.10-2.30 (m, 1H), 2.35 (s, 3H), 2.58 (dd, J=19.8,15.2Hz, 1H), 3.74 (s, 2H), 3.86 (s, 3H), 3.87-4.22 (m, 3H), 4.54-4.63 (m, 2H), 5.30-5.43 (m, 1H), 6.90 and 6.98 (each d, each J=9.1Hz, total 2H, amide isomers), 7.04-7.13 (m, 3H), 7.21 (d, J=7.8Hz, 2H), 7.30 (t, J=8.1Hz, 1H), 7.94 (d, J=9.1Hz, 2H), 8.05 (d, J=8.3Hz, 1H).

MS (ESI) m/z 536 (M^++1).

(Step 9) Synthesis of 4-((2S,4S)-1-(7-fluoro-2-(2-methylphenylamino)-6-benzoxazolylacetyl)-4-fluoro-2-pyrrolidinylmethoxy)benzoic acid



Methyl 4-((2S,4S)-1-(7-fluoro-2-(2-methylphenylamino)-6-benzoxazolylacetyl)-4-fluoro-2-pyrrolidinylmethoxy)benzoate (490 mg, 0.915 mmol) was dissolved in THF (40 ml). To the resulting solution was added 0.25N NaOH (40 ml), followed by stirring at room temperature for 14 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue was acidified with 1N HCl, followed by extraction with a chloroform/methanol (10/1) mixture. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica gel: 50 g), whereby from chloroform/methanol (20/1) eluate fractions, the title compound (394 mg, 83%) was obtained as a colorless amorphous substance.

IR (KBr) 3249, 3051, 2978, 1685, 1641, 1579, 1510 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 2.20-2.26 (m, 2H), 2.31 (s, 3H), 3.74-4.80 (m, 7H), 5.35-5.55 (m, 1H), 7.03-7.14 (m, 5H), 7.25

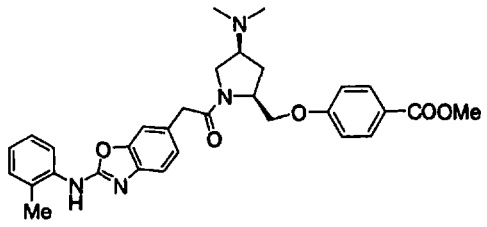
(t, J=6.6Hz, 2H), 7.80 (d, J=8.0Hz, 1H), 7.86 and 7.90 (each d, J=8.8 and 9.0Hz respectively, total 2H, amide isomers), 9.89 (br, 1H), 12.62 (br, 1H).

MS (ESI) m/z 522 (M^++1).

Example 7

4-((4S)-Dimethylamino-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)benzoic acid

(Step 1) Synthesis of methyl 4-((4S)-dimethylamino-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)benzoate

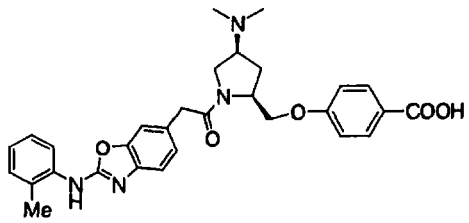


In methylene chloride (15 ml), EDC(HCl (144 mg, 0.5 mmol) was added to methyl 4-((4S)-dimethylamino-(2S)-pyrrolidinylmethoxy)benzoate (140 mg, 0.5 mmol), 2-(2-methylphenylamino)-6-benzoxazolylacetic acid (141 mg, 0.5 mmol), HOBt (68 mg, 0.5 mmol) and triethylamine (208 µl, 1.5 mmol) under stirring at 0°C. The reaction mixture was stirred at room temperature for 16 hours. Then, the solvent was distilled off under reduced pressure. Water (30 ml) was added to the residue and the mixture was extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium bicarbonate, dried

over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue thus obtained was purified by thin-layer silica gel chromatography, whereby from methanol-methylene chloride (5:95, v/v) eluate fractions, the title compound (230 mg, 85%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 2.24-2.61 (m, 11H), 3.17-3.22 (m, 1H), 3.71-3.87 (m, 5H), 4.11-4.21 (m, 1H), 4.42-4.52 (m, 1H), 6.86-7.37 (m, 9H), 7.94 (d, J=7.6Hz, 2H), 8.10 (d, J=8.0Hz, 1H).

(Step 2) Synthesis of 4-((4S)-dimethylamino-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)benzoic acid



In THF (6.0 ml) and methanol (3.0 ml) was dissolved methyl 4-((4S)-dimethylamino-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)benzoate (230 mg, 0.42 mmol), followed by the addition of 1N NaOH (1.5 ml, 1.5 mmol). The resulting mixture was stirred at 70°C for 4 hours. The reaction mixture was concentrated under reduced pressure and the residue was acidified with water and 1N HCl. The crystals thus obtained were collected by

filtration under reduced pressure, washed with water and dried under reduced pressure, whereby the title compound (130 mg, 59%) was obtained as a white crystalline substance.

IR (KBr) 2950, 1639, 1573, 1438, 1245, 1166;

^{1}H-NMR (DMSO-d_6) δ: 1.80-2.50 (m, 11H), 3.50-4.30 (m, 8H), 6.98-7.35 (m, 8H), 7.80-7.87 (m, 3H).

MS (FAB) m/z 529 $(M+H)^+$;

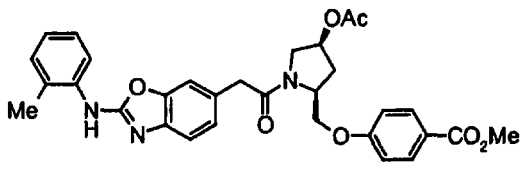
Anal. Calcd for $C_{30}H_{32}N_4O_5 \cdot 1.3H_2O$: C, 65.27; H, 6.32; N, 10.15.

Found: C, 65.48; H, 6.21; N, 9.88.

Example 8

4-((2S,4S)-4-Hydroxy-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-2-pyrrolidinylmethoxy)benzoic acid:

(Step 1) Synthesis of methyl 4-((2S,4S)-4-acetoxy-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-2-pyrrolidinylmethoxy)benzoate



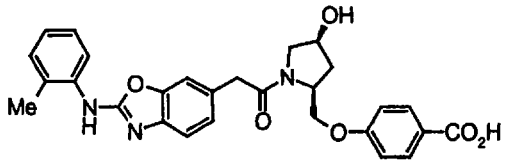
In DMF (10 ml), a mixture of 2-(2-methylphenylamino)-6-benzoxazolylacetic acid (318 mg, 1.13 mmol), 4-((2S,4S)-4-acetoxy-2-pyrrolidinylmethoxy)benzoate (330 mg, 1.13 mmol), EDC·HCl (325 mg, 1.70 mmol), HOBt (230 mg, 1.70

mmol) and triethylamine (1.18 ml, 8.50 mmol) was stirred at room temperature for 21 hours. The reaction mixture was poured in ice water (30 ml), followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica gel: 40 g), whereby from chloroform/acetone (20/1) eluate fractions, the title compound (610 mg, 97%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 2.03 (s, 3H), 2.30 (d, J=2.9Hz, 2H), 2.36 (s, 3H), 3.56 and 3.59 (each s, total 1H, amide isomers), 3.70 (s, 2H), 3.86 (s, 3H), 3.88 (m, 1H), 3.99-4.13 (m, 1H), 4.46-4.60 (m, 2H), 5.29-5.40 (m, 1H), 6.68 and 6.97 (each dd, each J=8.8 and 2.2Hz respectively, total 2H, amide isomers), 7.08 (t, J=7.1Hz, 2H), 7.22 and 7.24 (each s, total 2H, amide isomers), 7.27 and 7.30 (each s, total 2H, amide isomers), 7.36 (dd, JJ=7.8,2.7Hz, 1H), 7.96 (dd, J=9.0,2.4Hz, 2H), 8.01 and 8.04 (each s, total 1H, amide isomers).

MS (ESI) m/z 558 (M^++1).

(Step 2) Synthesis of 4-((2S,4S)-4-hydroxy-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-2-pyrrolidinylmethoxy)benzoic acid



To a solution of methyl 4-((2S,4S)-4-acetoxy-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-2-pyrrolidinylmethoxy)benzoate (610 mg, 1.09 mmol) in THF (40 ml) was added 0.25N NaOH (40 ml). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was concentrated under reduced pressure. The residue was acidified with 1N HCl, followed by extraction with a chloroform-methanol (10/1) mixture. The extract was washed with water and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to remove the solvent, whereby the title compound (500 mg, 92%) was obtained as a pale pink amorphous substance.

IR (ATR) 3211, 2941, 2877, 1682, 1639, 1604, 1576, 1439 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.91-2.20 (m, 2H), 2.30 (s, 3H), 3.21 (d, J=13.2Hz, 1H), 3.42 (d, J=11.3Hz, 1H), 3.71 and 3.73 (each d, J=4.7 and 6.1Hz respectively, total 1H, amide isomers), 4.18-4.59 (m, 4H), 5.16 and 5.18 (each d, each J=2.9Hz, total 1H, amide isomers), 7.01 and 7.08 (each d, J=9.1 and 8.3Hz, total 1H, amide isomers), 7.05 (d, J=9.1Hz, 2H), 7.20-7.32 (m, 4H), 7.81 (d, J=7.8Hz, 1H),

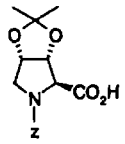
7.86 and 7.89 (each d, J=8.8 and 9.1Hz, total 2H, amide isomers), 9.61 (br, 1H), 12.56 (br, 1H).

MS (ESI) m/z 502 (M^++1).

Example 9

4-((3R,4S)-Isopropylidenedioxy-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2R)-pyrrolidinylmethoxy)benzoic acid:

(Step 1) Synthesis of 1-benzyloxycarbonyl-(3R,4S)-isopropylidenedioxy-(2S)-pyrrolidinylcarboxylic acid

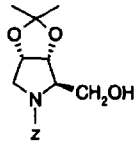


To a solution of methyl 1-benzyloxycarbonyl-(3R,4S)-isopropylidenedioxy-2-pyrrolidinylcarboxylate in THF (250 ml) was added 0.25N NaOH (255 ml). The resulting mixture was stirred overnight at room temperature. The reaction mixture was acidified with 1N HCl, followed by extraction with ethyl acetate. The extract was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent, whereby the title compound (9.87 g, 96%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.32 (s, 3H), 1.46 (d, J=2.7Hz, 3H), 3.61 (m, 1H), 3.82 and 3.92 (each d, each J=12.7Hz, total 1H, amide isomers), 4.58 and 4.64 (each s, total 1H, amide

isomers), 4.77 (t, J=5.1Hz, 1H), 4.83 and 4.89 (each d, each J=5.9Hz, total 1H, amide isomers), 5.15 and 5.19 (d and s, J=2.4Hz, total 2H, amide isomers), 7.31-7.37 (m, 5H).

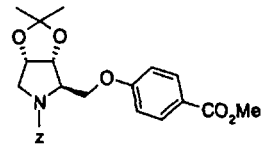
(Step 2) Synthesis of 1-benzyloxycarbonyl-(3R,4S)-isopropylidenedioxy-(2R)-pyrrolidinylmethanol



To a solution of 1-benzyloxycarbonyl-(3R,4S)-isopropylidenedioxy-(2S)-pyrrolidinylcarboxylic acid (9.87 g, 30.7 mmol) in THF (200 ml) was added a borane dimethyl sulfide solution (6.14 ml, 61.4 mmol) at 0°C. After stirring at room temperature for 2 hours, the reaction mixture was heated and refluxed for further 2 hours. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure. Water (10 ml) was then added to the residue. The mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica gel: 200 g), whereby from chloroform/methanol (20/1) eluate fractions, the title compound (10.1 g, 100%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.31 (s, 3H), 1.45 (s, 3H), 3.56-4.74 (m, 7H), 5.14 (s, 2H), 7.34 (m, 5H).

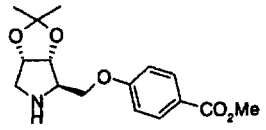
(Step 3) Synthesis of methyl 4-(1-benzyloxycarbonyl-(3R,4S)-isopropylidenedioxy-(2R)-pyrrolidinylmethoxy)benzoate



DIAD (138 ml, 0.70 mmol) was added dropwise to a solution of 1-benzyloxycarbonyl-(3R,4S)-isopropylidenedioxy-(2R)-pyrrolidinylmethanol (312 mg, 0.64 mmol), methyl 4-hydroxybenzoate (67 ml, 0.70 mmol) and triphenylphosphine (184 mg, 0.70 mmol) in THF (7 ml) under stirring at 0°C in a nitrogen gas stream. The reaction mixture was stirred at room temperature for 3 hours. The residue obtained by concentration of the reaction mixture under reduced pressure was purified by chromatography on a silica gel column (silica gel: 10 g), whereby from hexane/ethyl acetate (4/1) eluate fractions, the title compound (321 mg, 83%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.01 (s, 6H), 1.03 (s, 3H), 2.23 (m, 1H), 2.63 (m, 1H), 3.61 (d, J=12.5Hz, 1H), 3.80-4.27 (m, 4H), 4.84 (br, 1H), 5.01 and 5.08 (ABq, each J=12.2Hz, total 1H, amide isomers), 6.75-6.87 (m, 3H), 7.19-7.63 (m, 15H).

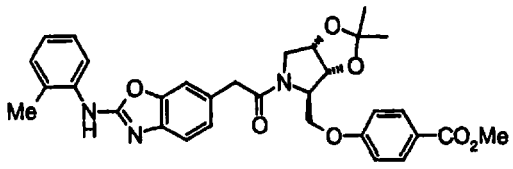
(Step 4) Synthesis of methyl 4-((3R,4S)-isopropylidenedioxy-(2R)-pyrrolidinylmethoxy)benzoate



In ethanol (170 ml) were suspended methyl 4-(1-benzyloxycarbonyl-(3R,4S)-isopropylidenedioxy-(2R)-pyrrolidinylmethoxy)benzoate (2.37 g, 5.76 mmol) and 10% palladium/carbon (240 mg), followed by catalytic hydrogenation for one day under stirring at room temperature and normal pressure. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue thus obtained was purified by chromatography on a silica gel column (silica gel: 100 g), whereby from chloroform/acetone (20/1) eluate fractions, the title compound (930 mg, 53%) was obtained as a brown oil.

^{1}H-NMR ($CDCl_3$) δ: 1.35 (s, 3H), 1.50 (s, 3H), 3.02 (dd, J=13.7,4.1Hz, 1H), 3.13 (d, J=13.7Hz, 1H), 3.58 (t, J=6.3Hz, 1H), 3.88 (s, 3H), 3.90 (dd, J=9.3,6.6Hz, 1H), 4.02 (dd, J=9.5,3.9Hz, 1H), 4.74 (d, J=5.6Hz, 1H), 4.79 (m, 1H), 6.90 (d, J=9.0Hz, 2H), 7.98 (d, J=9.0Hz, 2H).

(Step 5) Synthesis of methyl 4-((3R,4S)-isopropylidenedioxy-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2R)-pyrrolidinylmethoxy)benzoate

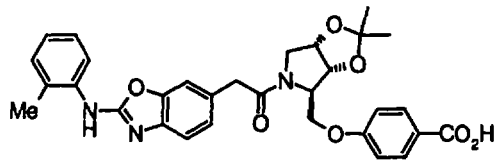


In DMF (10 ml), a mixture of 2-(2-methylphenylamino)-6-benzoxazolylacetic acid (184 mg, 0.651 mmol), methyl 4-((3R,4S)-isopropylidenedioxy-(2R)-pyrrolidinylmethoxy)benzoate (200 mg, 0.651 mmol), EDC·HCl (187 mg, 0.977 mmol), 1-hydroxybenzotriazole (132 mg, 0.977 mmol) and triethylamine (0.45 ml, 3.26 mmol) was stirred at room temperature for 22 hours. The reaction mixture was poured in ice water (30 ml) and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue thus obtained was separated and purified by thin-layer silica gel chromatography with (chloroform/acetone (5/1)), whereby the title compound (389 mg, 100%) was obtained as a colorless amorphous substance. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (s, 3H), 1.40 (s, 3H), 2.35 (s, 3H), 3.67-3.78 (m, 4H), 3.79 (s, 3H), 4.13 (dd, J=9.8,1.9Hz, 1H), 4.43 (dd, J=9.8,3.4Hz, 1H), 4.68 (s, 1H), 4.80 (d,

J=6.1Hz, 1H), 4.89 (t, J=5.4Hz, 1H), 6.76 (d, J=8.8Hz, 2H), 7.03 (d, J=8.1Hz, 1H), 7.07 (d, J=7.3Hz, 1H), 7.13 (s, 2H), 7.21 (d, J=7.3Hz, 1H), 7.29-7.38 (m, 2H), 7.93 (dd, J=7.1,1.7Hz, 2H), 8.05 (d, J=8.1Hz, 1H).

MS (ESI) m/z 572 (M^++1).

(Step 6) Synthesis of 4-((3R,4S)3,4-isopropylidenedioxy-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2R)-pyrrolidinylmethoxy)benzoic acid



To a solution of methyl 4-((3R,4S)-isopropylidenedioxy-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2R)-pyrrolidinylmethoxy)benzoate (188 mg, 0.329 mmol) in THF (15 ml) was added 0.25 NaOH (15 ml). The resulting mixture was stirred at room temperature for 17 hours. The reaction mixture was then concentrated under reduced pressure. The residue thus obtained was acidified with 1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure, whereby the title compound (149 mg, 81%) was obtained as a colorless solid.

IR (ATR) 2989, 2939, 1685, 1639, 1604, 1576, 1510 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.18, 1.23, 1.25 and 1.30 (each s, total 6H, amide isomers), 2.39 (s, 3H), 3.65 and 3.69 (each d, J=6.1 and 5.4Hz respectively, total 1H, amide isomers), 3.74 and 3.78 (each s, total 1H, amide isomers), 3.82 and 3.85 (each s, total 1H, amide isomers), 3.92 and 3.95 (each d, J=7.8 and 6.1Hz respectively, total 1H, amide isomers), 4.11-4.20 (m, 2H), 4.43 and 4.54 (m and t, J=4.4Hz, total 1H, amide isomers), 4.74 (dd, J=6.1,2.4Hz, 1H), 4.84 and 4.92 (each t, J=4.4 and 3.9Hz respectively, total 1H, amide isomers), 7.00 (s, 1H), 7.02 (s, 1H), 7.02 (s, 1H), 7.04 (s, 1H), 7.08 (d, J=7.1Hz, 1H), 7.19-7.25 (m, 3H), 7.31 and 7.33 (each s, total 1H, amide isomers), 7.79 (d, J=7.8Hz, 1H), 7.86 and 7.89 (each dd, each J=9.1,2.2Hz, total 2H, amide isomers), 9.61 (br, 1H);

MS (ESI) m/z 558 (M^++1);

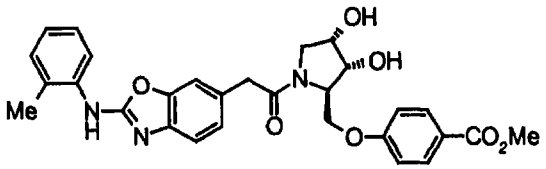
Anal. Calcd for $C_{31}H_{31}N_3O_7 \cdot 0.7H_2O$: C, 65.30; H, 5.73; N, 7.37.

Found: C, 65.46; H, 5.67; N, 7.04.

Example 10

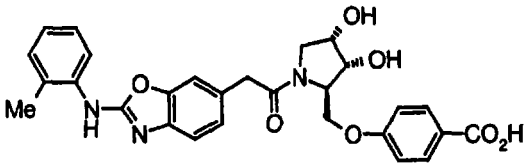
4-((3R,4S)-Dihydroxy-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2R)-pyrrolidinylmethoxy)benzoic acid:

(Step 1) Synthesis of methyl 4-((3R,4S)-dihydroxy-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2R)-pyrrolidinylmethoxy)benzoate



A mixture of methyl 4-((3R,4S)-isopropylidenedioxy-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2R)-pyrrolidinylmethoxy)benzoate (201 mg, 0.352 mmol) and an HCl-gas-introduced methanol (20 ml) was stirred at room temperature for 16 hours. The reaction mixture was concentrated under reduced pressure. Water (30 ml) was added to the residue and the mixture was extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium bicarbonate and saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent, whereby the title compound (144 mg, 77%) was obtained as an amorphous substance (this compound was provided for the subsequent reaction without further purification).

(Step 2) Synthesis of 4-((3R,4S)-dihydroxy-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2R)-pyrrolidinylmethoxy)benzoic acid



To a solution of methyl 4-((3R,4S)-dihydroxy-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2R)-pyrrolidinylmethoxy)benzoate (144 mg, 0.271 mmol) in THF (4 ml) was added 0.25N NaOH (4 ml). The resulting mixture was stirred at room temperature for 21 hours. The reaction mixture was concentrated under reduced pressure. After 1N HCl was added to the residue to acidify the same, the mixture was extracted with a chloroform/methanol (10/1) mixture. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue thus obtained was purified by chromatography on a thin-layer silica gel column with (chloroform/methanol (10/1)), whereby the title compound (24 mg, 17%) was obtained as a colorless amorphous substance.

IR (ATR) 3205, 3060, 2937, 1687, 1639, 1604, 1576, 1512, 1487, 1439 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 2.30 (s, 3H), 3.39 (m, 1H), 3.65-3.80 (m, 3H), 4.00 (d, J=2.9Hz, 1H), 4.04 (s, 1H), 4.15-4.23 (m, 2H), 4.30 (d, J=3.9Hz, 1H), 5.08 (br, 2H), 7.02 (d, J=8.8Hz, 3H), 7.07 (t, J=7.3Hz, 1H), 7.23 (d, J=7.6Hz, 3H),

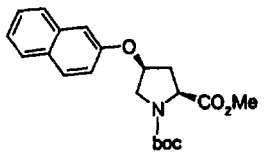
7.30 (s, 2H), 7.80 (d, J=8.1Hz, 1H), 7.86 (d, J=8.8Hz, 2H), 9.60 (br, 1H).

MS (ESI) m/z 518 (M^++1).

Example 11

4-((2S,4S)-1-(2-(2-Methylphenylamino)-6-benzoxazolylacetyl)-4-(2-naphthyloxy)-2-pyrrolidinylmethoxy)benzoic acid:

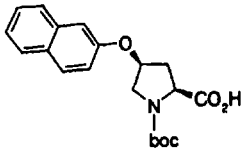
(Step 1) Synthesis of methyl (2S,4S)-1-tert-butoxycarbonyl-4-(2-naphthyloxy)-2-pyrrolidinylcarboxylate



DIAD (3.72 ml, 18.9 mmol) was added to a solution of methyl (2S,4S)-1-tert-butoxycarbonyl-4-hydroxy-2-pyrrolidinylcarboxylate (4.22 g, 17.2 mmol), 2-naphthol (2.73 g, 18.9 mmol) and triphenylphosphine (4.96 g, 18.9 mmol) in THF (80 ml) under stirring at room temperature in a nitrogen gas stream. The mixture was stirred overnight at room temperature. The residue, which had been obtained by concentrating the reaction mixture under reduced pressure, was purified by chromatography on a silica gel column (silica gel: 600 g), whereby from chloroform/ethyl acetate (10/1) eluate fractions, the title compound (5.37 g) was obtained as an amorphous substance (this compound

was provided for the subsequent reaction without further purification).

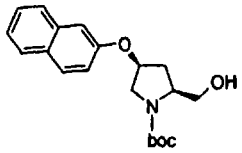
(Step 2) Synthesis of (2S,4S)-1-tert-butoxycarbonyl-4-(2-naphthyloxy)-2-pyrrolidinylcarboxylic acid



To a solution of methyl (2S,4S)-1-tert-butoxycarbonyl-4-(2-naphthyloxy)-2-pyrrolidinylcarboxylate (5.37 g) in THF (116 ml) was added 0.25N NaOH (116 ml, 29.0 mmol). The resulting mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure. The residue was acidified with 1N HCl, followed by extraction with chloroform. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue thus obtained was recrystallized from hexane-chloroform, whereby the title compound (4.44 g, 85% (2 steps)) was obtained as white crystalline powder.

^{1}H-NMR (DMSO-d_6) δ: 1.37 and 1.41 (each s, total 9H, amide isomers), 2.26 (d, J=13.9Hz, 1H), 2.65 (m, 1H), 3.47 (d, J=11.5Hz, 1H), 3.81 (m, 1H), 4.30 (m, 1H), 5.14 (m, 1H), 7.02-7.86 (m, 7H).

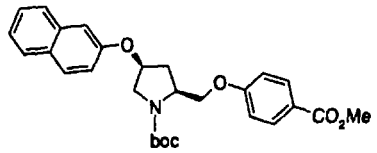
(Step 3) (2S,4S)-1-tert-Butoxycarbonyl-4-(2-naphthyloxy)-2-pyrrolidinylmethanol



Borane-dimethyl sulfide (0.63 ml, 6.3 mmol) was added to a solution of (2S,4S)-1-tert-butoxycarbonyl-4-(2-naphthyloxy)-2-pyrrolidinylcarboxylic acid (1.12 g, 3.13 mmol) in THF (30 ml) under stirring at 0°C. The reaction mixture was stirred at 50°C for 1.5 hours. After the reaction mixture was cooled to 0°C, water (20 ml) was added thereto. The mixture was then extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica gel: 50 g), whereby from chloroform/methanol (50/1) eluate fractions, the title compound (1.10 g, 100%) was obtained as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.48 (s, 9H), 2.45 (m, 1H), 3.58-4.80 (m, 4H), 5.01 (br, 1H), 7.04-7.99 (m, 7H).

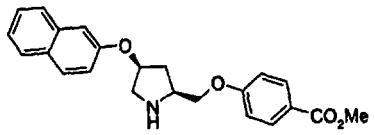
(Step 4) Synthesis of methyl 4-((2S,4S)-1-tert-butoxycarbonyl-4-(2-naphthyloxy)-2-pyrrolidinylmethoxy)benzoate



DIAD (0.37 ml, 1.86 mmol) was added to a solution of (2S,4S)-1-tert-butoxycarbonyl-4-(2-naphthyloxy)-2-pyrrolidinylmethanol (640 mg, 1.86 mmol), methyl 4-hydroxybenzoate (283 mg, 1.86 mmol) and triphenylphosphine (488 mg, 1.86 mmol) in THF (18 ml) under stirring at room temperature in a nitrogen gas stream. The reaction mixture was stirred overnight at room temperature. The residue obtained by concentrating the reaction mixture under reduced pressure was purified by chromatography on a silica gel column (silica gel: 100 g), whereby from hexane/ethyl acetate (2/1) eluate fractions, the title compound (830 mg, 93%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.49 and 1.51 (each s, total 9H, amide isomers), 2.34 (m, 1H), 2.53 (d, J=14.2Hz, 1H), 3.72-3.85 (m, 1H), 3.86 and 3.87 (each s, total 3H, amide isomers), 4.17 (m, 1H), 4.26-4.52 (m, 2H), 5.06 (br, 1H), 6.87 (d, J=8.8Hz, 1H), 6.94 (d, J=8.8Hz, 2H), 7.04 (br, 2H), 7.33 (t, J=7.3Hz, 1H), 7.42 (t, J=7.3Hz, 1H), 7.64-8.02 (m, 5H).

(Step 5) Synthesis of methyl 4-((2S,4S)-4-(2-naphthyloxy)-2-pyrrolidinylmethoxy)benzoate

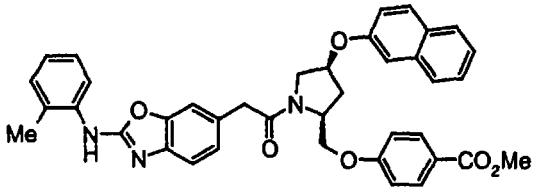


Trifluoroacetic acid (6 ml) was added to a solution of methyl 4-((2S,4S)-1-tert-butoxycarbonyl-4-(2-naphthyloxy)-2-pyrrolidinylmethoxy)benzoate (870 mg, 1.74 mmol) in methylene chloride (24 ml). The resulting mixture was stirred overnight at room temperature. To the residue obtained by concentrating the reaction mixture under reduced pressure was added 1N NaOH under ice cooling to make the residue alkaline, followed by extraction with methylene chloride. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica gel: 100 g), whereby from hexane/ethyl acetate (2/1) eluate fractions, the title compound (750 mg, 100%) was obtained as a black oil.

^{1}H-NMR ($CDCl_3$) δ: 1.99 (dd, J=14.2,5.6Hz, 1H), 2.48 (m, 1H), 3.22 (dd, J=12.2,4.6Hz, 1H), 3.43 (d, J=12.5Hz, 1H), 3.67 (m, 1H), 3.86 and 3.87 (each s, total 3H, amide isomers), 4.11 (m, 2H), 5.04 (m, 1H), 6.83 (d, J=8.5Hz, 1H), 6.89 (d, J=8.8Hz, 2H), 7.07 (d, J=2.0Hz, 1H), 7.12 (d, J=9.0Hz, 1H), 7.33 (dt, J=8.1,1.2Hz, 1H), 7.44 (dt,

J=6.8,1.2Hz, 1H), 7.70 (d, J=8.1Hz, 1H), 7.75 (dd, J=9.0,5.1Hz, 2H), 7.90 (d, J=8.5Hz, 1H), 7.96 (dd, J=6.8,2.0Hz, 2H).

(Step 6) Synthesis of methyl 4-((2S,4S)-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-4-(2-naphthyloxy)-2-pyrrolidinylmethoxy)benzoate

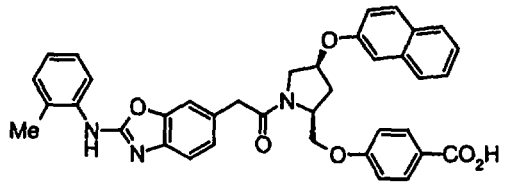


In DMF (10 ml), a mixture of 2-(2-methylphenylamino)-6-benzoxazolylacetic acid (141 mg, 0.50 mmol), methyl 4-((2S,4S)-4-(2-naphthyloxy)-2-pyrrolidinylmethoxy)benzoate (189 mg, 0.50 mmol), EDC·HCl (144 mg, 0.75 mmol), HOBt (101 mg, 0.75 mmol) and triethylamine was stirred at room temperature for 16 hours. The reaction mixture was poured in ice water (30 ml), followed by extraction with ethyl acetate. The extract was washed with ice water and saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was separated and purified by chromatography on a thin-layer silica gel column with (chloroform/acetone (5/1)), whereby the title compound (312 mg, 97%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 2.35 and 2.36 (each s, total 3H, amide isomers), 2.38 and 2.57 (m and d, J=14.5Hz, total 1H, amide isomers), 3.74 (s, 2H), 3.86 (s, 3H), 3.88 and 3.94 (m and dd, J=12.7,5.2Hz, total 1H, amide isomers), 4.17-4.31 (m, 2H), 4.56 (dd, J=9.3,3.7Hz, 1H), 4.65 (m, 1H), 5.12 (br, 1H), 6.83 and 6.86 (br and d, J=8.8Hz respectively, total 1H, amide isomers), 6.97 (d, J=8.8Hz, 1H), 7.04-7.13 (m, 4H), 7.22 (d, J=7.3Hz, 1H), 7.26-7.33 (m, 2H), 7.35 (d, J=8.0Hz, 1H), 8.39 (t, J=8.1Hz, 1H), 7.44 (t, J=6.9Hz, 1H), 7.67 (d, J=8.1Hz, 1H), 7.74 (t, J=10.3Hz, 2H), 7.94 and 7.98 (each d, each J=8.6Hz, total 2H, amide isomers), 8.08 (d, J=8.6Hz, 1H).

MS (ESI) m/z 642 (M^++1).

(Step 7) Synthesis of 4-((2S,4S)-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-4-(2-naphthyloxy)-2-pyrrolidinylmethoxy)benzoic acid



To a solution of methyl 4-((2S,4S)-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-4-(2-naphthyloxy)-2-pyrrolidinylmethoxy)benzoate (312 mg, 0.486 mmol) in THF (20 ml) was added 0.25N NaOH (20 ml). The resulting mixture was stirred at room temperature for 15 hours. The

reaction mixture was then concentrated under reduced pressure. The residue was acidified with 1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure, whereby the title compound (253 mg, 83%) was obtained as a pale pink solid.

IR (ATR) 3060, 2941, 2879, 1682, 1639, 1603, 1576, 1510, 1439 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 2.30 (s, 3H), 2.31-2.44 (m, 1H), 3.78 (s, 2H), 3.86 and 3.89 (each s, total 1H, amide isomers), 3.99-4.78 (m, 5H), 5.25 and 5.32 (each m, total 1H, amide isomers), 7.02-7.10 (m, 4H), 7.16 (dd, J=9.2,2.2Hz, 1H), 7.24 (m, 1H), 7.25 (s, 1H), 7.27 (m, 1H), 7.33-7.38 (m, 3H), 7.46 (t, J=7.1Hz, 1H), 7.77-7.89 (m, 7H), 9.62 (br, 1H).

MS (ESI) m/z 470 (M^++1);

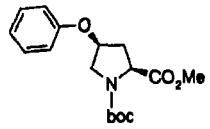
Anal. Calcd for $C_{38}H_{33}N_3O_6 \cdot 1.0H_2O$: C, 70.68; H, 5.46; N, 6.51.

Found: C, 70.51; H, 5.41; N, 6.27.

Example 12

4-((2S,4S)-1-(2-(2-Methylphenylamino)-6-benzoxazolylacetyl)-4-phenoxy-2-pyrrolidinylmethoxy)benzoic acid

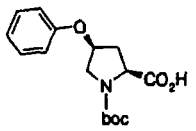
(Step 1) Synthesis of methyl (2S,4S)-1-tert-butoxycarbonyl-4-phenoxy-2-pyrrolidinylcarboxylate



DIAD (4.13 ml, 21.0 mmol) was added to a solution of methyl (2S,4S)-1-tert-butoxycarbonyl-4-hydroxy-2-pyrrolidinylcarboxylate (4.69 g, 19.1 mmol), phenol (1.98 g, 21.0 mmol) and triphenylphosphine (5.51 g, 21.0 mmol) in THF (80 ml) under stirring at room temperature in a nitrogen gas stream. The reaction mixture was stirred overnight at room temperature. The residue obtained by concentrating the reaction mixture under reduced pressure was purified by chromatography on a silica gel column (silica gel: 700 g), whereby from chloroform/ethyl acetate (10/1) eluate fractions, the title compound (5.31 mg, 86%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.43 and 1.48 (each br, total 9H, amide isomers), 2.48 (m, 1H), 3.75 (br, 3H), 4.42-4.96 (m, 2H), 6.88-7.35 (m, 5H).

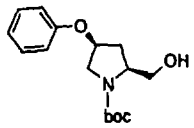
(Step 2) Synthesis of (2S,4S)-1-tert-butoxycarbonyl-4-phenoxy-2-pyrrolidinylcarboxylic acid



To a solution of methyl (2S,4S)-1-tert-butoxycarbonyl-4-phenoxy-2-pyrrolidinylcarboxylate (5.31 g, 16.5 mmol) in THF (132 ml) was added 0.25N NaOH (132 ml, 33.0 mmol). The reaction mixture was stirred overnight at room temperature. The residue obtained by concentrating the reaction mixture under reduced pressure was acidified with 1N HCl, followed by extraction with chloroform. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The crude crystals thus obtained were recrystallized from hexane-chloroform, whereby the title compound (2.96 g, 58%) was obtained as a white crystalline powder.

^{1}H-NMR (DMSO-d_6) δ: 1.36 (s, 9H), 2.16 (d, J=13.2Hz, 1H), 2.56 (m, 1H), 3.46 (m, 1H), 3.71 (dt, J=12.0,5.4Hz, 1H), 4.26 (dt, J=9.5,7.1Hz, 1H), 4.99 (m, 1H), 6.85 (m, 2H), 6.94 (t, J=7.3Hz, 1H), 7.28 (t, J=7.3Hz, 1H).

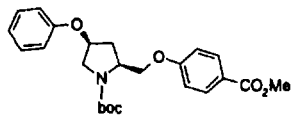
(Step 3) Synthesis of (2S,4S)-1-tert-butoxycarbonyl-4-phenoxy-2-pyrrolidinylmethanol



Borane-dimethyl sulfide (1.55 ml, 15.5 mmol) was added to a solution of (2S,4S)-1-tert-butoxycarbonyl-4-phenoxy-2-pyrrolidinylcarboxylic acid (2.39 g, 7.76 mmol) in THF (50 ml) under stirring at 0°C. The reaction mixture was stirred at the same temperature for 10 minutes and then at 50°C for 2 hours. After cooling the reaction mixture to 0°C, water (30 ml) was added thereto, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica gel: 60 g), whereby from chloroform/methanol (50/1) eluate fractions, the title compound (2.83 g, 100%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.47 (s, 9H), 1.95 (br, 1H), 2.36 (m, 1H), 3.56-3.74 (m, 3H), 3.89-4.52 (m, 3H), 4.85 (br, 1H), 6.84 (dd, J=8.8,1.2Hz, 2H), 6.97 (t, J=7.2Hz, 1H), 7.29 (t, 2H, J=7.8Hz).

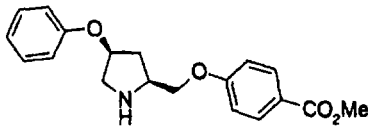
(Step 4) Synthesis of methyl 4-((2S,4S)-1-tert-butoxycarbonyl-4-phenoxy-2-pyrrolidinylmethoxy)benzoate



DIAD (0.64 ml, 3.25 mmol) was added dropwise while stirring a mixture of (2S,4S)-1-tert-butoxycarbonyl-4-phenoxy-2-pyrrolidinylmethanol (1.16 g, 3.25 mmol), methyl 4-hydoxybenzoate (494 mg, 3.25 mmol) and triphenylphosphine (852 mg, 3.25 mmol) in THF (30 ml) at room temperature in a nitrogen gas stream. After completion of the dropwise addition, the reaction mixture was stirred at room temperature for 20 minutes and at 80°C for 8 hours. After cooling, the reaction mixture was concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (silica gel: 200 g), whereby from chloroform/acetone (20/1) eluate fractions, the title compound (2.07 g, 100%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.56 (s, 9H), 2.30 (m, 1H), 2.47 and 2.49 (each br, total 1H, amide isomers), 3.69-3.80 (m, 3H), 3.88 (s, 3H), 4.08-4.49 (m, 2H), 4.94 (t, J=4.9Hz, 1H), 6.82 (d, J=8.1Hz, 2H), 6.96 (m, 3H), 7.27 (m, 2H), 7.96 (d, J=8.1Hz, 2H).

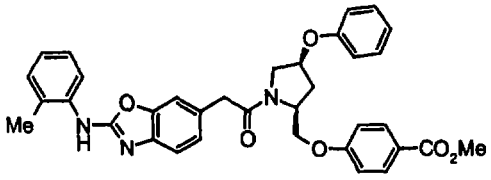
(Step 5) Synthesis of methyl 4-((2S,4S)-4-phenoxy-2-pyrrolidinylmethoxy)benzoate



Trifluoroacetic acid (20 ml) was added to a solution of methyl 4-((2S,4S)-1-tert-butoxycarbonyl-4-phenoxy-2-pyrrolidinylmethoxy)benzoate (2.02 g, 3.25 mmol) in methylene chloride (100 ml). The resulting mixture was stirred at room temperature for 5 hours. The reaction mixture was then concentrated under reduced pressure. The residue was diluted with methylene chloride (50 ml), followed by washing with 1N NaOH. The organic layer was fractionated, followed by washing with saturated brine, drying over anhydrous sodium sulfate and distillation under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica gel: 70 g), whereby from chloroform/acetone (10/1) - chloroform/methanol (10/1) eluate fractions, the title compound (970 mg, 91%) was obtained as a brown oil.

^{1}H-NMR ($CDCl_3$) δ: 1.88 (dd, J=12.9,4.3Hz, 1H), 2.39 (qq, J=6.8,6.8Hz, 1H), 2.83 (br, 1H), 3.19 (dd, J=12.0,5.1Hz, 1H), 3.33 (d, J=12.0Hz, 1H), 3.64 (m, 1H), 3.87 (s, 3H), 4.07 (m, 2H), 4.88 (m, 1H), 6.86 (d, J=8.5Hz, 2H), 6.90 (d, J=7.1Hz, 2H), 6.94 (d, J=7.3Hz, 1H), 7.26 (d, J=7.3Hz, 2H), 7.96 (d, J=9.0Hz, 2H).

(Step 6) Synthesis of methyl 4-((2S,4S)-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-4-phenoxy-2-pyrrolidinylmethoxy)benzoate



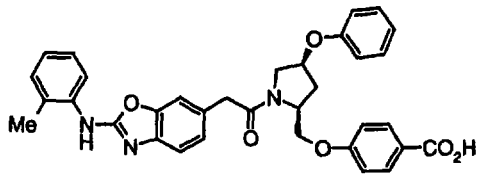
In DMF (10 ml), a mixture of 2-(2-methylphenylamino)-6-benzoxazolylacetic acid (351 mg, 1.07 mmol), methyl 4-((2S,4S)-4-phenoxy-2-pyrrolidinylmethoxy)benzoate (303 mg, 1.07 mmol), EDC·HCl (308 mg, 1.61 mmol), HOBt (218 mg, 1.61 mmol) and triethylamine (0.74 ml, 5.35 mmol) was stirred at room temperature for 21 hours. The reaction mixture was poured in ice water (30 ml), followed by extraction with ethyl acetate. The extract was washed with ice water and saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica gel: 40 g), whereby from chloroform/acetone (10/1) eluate fractions, the title compound (640 mg, 100%) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 2.17-2.52 (m, 5H), 3.68-3.80 (m, 3H), 3.86 (s, 3H), 3.88 (m, 1H), 4.12-4.29 (m, 1H), 4.53 (dd, J=13.0,3.9Hz, 1H), 4.62 (m, 1H), 4.97 (m, 1H), 6.80 (d, J=7.8Hz, 2H), 6.86 (d, J=9.1Hz, 1H), 6.95-6.99 (m, 2H), 7.07 (t, J=8.1Hz, 2H), 7.21-7.33 (m, 5H), 7.39 (d, J=8.1Hz,

1H), 7.94-7.99 (m, 2H), 8.01 (s, 1H), 8.08 (d, J=8.3Hz, 1H).

MS (ESI) m/z 592 (M^++1).

(Step 7) Synthesis of 4-((2S,4S)-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-4-phenoxy-2-pyrrolidinylmethoxy)benzoic acid



To a solution of methyl 4-((2S,4S)-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-4-phenoxy-2-pyrrolidinylmethoxy)benzoate (640 mg, 1.07 mmol) in THF (30 ml) was added 0.25N NaOH (30 ml). The resulting mixture was stirred at room temperature for 14 hours. The reaction mixture was then concentrated under reduced pressure. After addition of 1N HCl to the residue, the crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure, whereby the title compound (366 mg, 60%) was obtained as a pale pink solid.

IR (ATR) 3060, 2985, 2941, 1687, 1639, 1603, 1576, 1489, 1439 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 2.17-2.25 (m, 2H), 2.30 (s, 3H), 3.39-4.27 (m, 7H), 5.09-5.20 (m, 1H), 6.93 (d, J=7.8Hz, 2H),

7.01-7.10 (m, 5H), 7.25-7.33 (m, 7H), 7.80-7.89 (m, 3H), 9.64 (br, 1H).

MS (ESI) m/z 470 (M^++1);

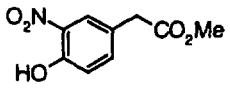
Anal. Calcd for $C_{34}H_{31}N_3O_6 \cdot 1.0H_2O$: C, 68.56; H, 5.58; N, 7.05.

Found: C, 68.77; H, 5.61; N, 7.00.

Example 13

4-((2S,4S)-4-Fluoro-1-(2-(2-methylphenylamino)-5-benzoxazolylacetyl)-2-pyrrolidinylmethoxy)benzoic acid

(Step 1) Synthesis of methyl 4-hydroxy-3-nitrophenylacetate

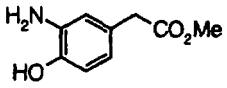


In methanol/toluene (1:10, 55 ml) was dissolved 4-hydroxy-3-nitrophenylacetic acid (2.0 g, 10.1 mmol). Trimethylsilyldiazomethane (2.0M hexane solution, 5.0 ml) was added dropwise to the resulting solution. After stirring at room temperature for 50 minutes, the reaction mixture was distilled under reduced pressure to remove the solvent. The residue was diluted with ethyl acetate. The ethyl acetate extract was then washed with a saturated aqueous solution of sodium bicarbonate and saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent, whereby the title compound (2.15 g, 100%) was obtained as a yellow solid

(this compound was provided for the subsequent reaction without further purification).

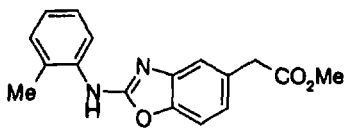
^{1}H-NMR ($CDCl_3$) δ: 3.63 (s, 2H), 3.72 (s, 3H), 7.13 (d, J=8.5Hz, 1H), 7.52 (dd, J=8.8,2.2Hz, 1H), 10.53 (s, 1H).

(Step 2) Synthesis of methyl 3-amino-4-hydroxyphenylacetate



Methyl 4-hydroxy-3-nitrophenylacetate (2.15 g, 10.1 mmol) and 5% palladium/carbon (2.15 g) were suspended in methanol (100 ml). The resulting suspension was subjected to catalytic hydrogenation for 20 hours under stirring at room temperature and normal pressure. The catalyst was then filtered off from the reaction mixture. The filtrate was distilled under reduced pressure to remove the solvent, whereby the title compound (1.72 g, 93%) was obtained as a brown solid (this compound was provided for the subsequent reaction without further purification).

(Step 3) Synthesis of methyl 2-(2-methylphenylamino)-5-benzoxazolylacetate

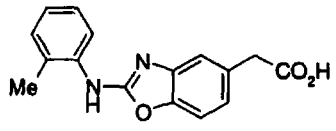


Methyl 3-amino-4-hydroxyphenylacetate (1.72 g, 9.49

mmol) was dissolved in methanol (100 ml). Under stirring at room temperature, o-tolyl thioisocyanate (1.91 ml, 14.3 mmol) was added, followed by stirring at room temperature for 24 hours. Mercuric oxide (yellow) (3.49 g, 16.1 mmol) was added to the reaction mixture. The reaction mixture was then stirred at room temperature for 2.5 hours. After cooling to room temperature, the reaction mixture was distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica gel: 100 g), whereby from hexane/ethyl acetate (2/1) eluate fractions, the title compound (2.33 g, 83% (2 steps)) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 2.35(s, 3H), 3.686(s, 2H), 3.692(s, 3H), 6.93(br, 1H), 7.02(dd, J=8.3,1.7Hz, 1H), 7.07(t, J=7.3Hz, 1H), 7.22(d, J=7.6Hz, 1H), 7.25(d, J=3.2Hz, 1H), 7.30(dt, J=8.6,0.5Hz, 1H), 7.38(d, J=1.5Hz, 1H), 8.05(d, J=8.1Hz, 1H).

(Step 4) Synthesis of 2-(2-methylphenylamino)-5-benzoxazolylacetic acid

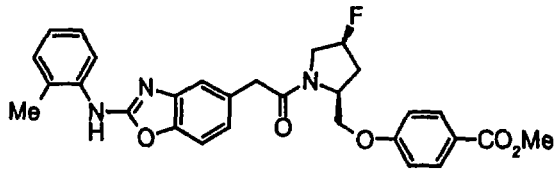


Methyl 2-(2-methylphenylamino)-5-benzoxazolylacetate (2.32 g, 7.86 mmol) was dissolved in THF (40 ml). After addition of 0.25N NaOH (40 ml) under stirring at room

temperature, the mixture was stirred for 15 hours. The residue, which had been obtained by distilling the reaction mixture under reduced pressure to remove the solvent, was acidified with 1N HCl. The crystals thus obtained were collected by filtration under reduced pressure, washed with water, dried under reduced pressure, whereby the title compound (894 mg) was obtained as a pale black crystalline powder. The water layer was extracted with a chloroform/methanol (10/1) mixture. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent, whereby the title compound (1.03 g) was obtained as a colorless solid (total yield: 88%).

^{1}H-NMR ($CDCl_3$) δ: 2.29 (s, 3H), 3.50 (s, 2H), 6.96 (dd, J=8.1,1.7Hz, 1H), 7.09 (t, J=7.6Hz, 1H), 7.23 (m, 3H), 7.36 (d, J=8.1Hz, 1H), 9.46 (br, 1H), 12.28 (br, 1H).

(Step 5) Synthesis of methyl 4-((2S,4S)-4-fluoro-1-(2-(2-methylphenylamino)-5-benzoxazolylacetyl)-2-pyrrolidinylmethoxy)benzoate



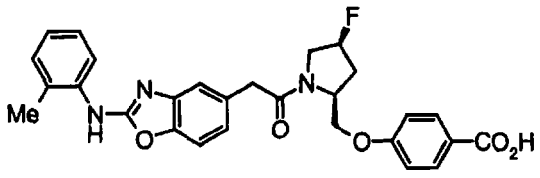
In DMF (5 ml), 2-(2-methylphenylamino)-5-benzoxazolylacetic acid (282 mg, 1.0 mmol), methyl 4-((2S,4S)-4-fluoro-1-2-pyrrolidinylmethoxy)benzoate (253 mg,

1.0 mmol), EDC·HCl (288 mg, 1.5 mmol), HOBT (203 mg, 1.5 mmol) and triethylamine (0.70 ml, 5.0 mmol) were stirred at room temperature for 18 hours. The reaction mixture was poured in water, followed by extraction with ethyl acetate. The extract was washed with ice water and saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica gel: 50 g), whereby from chloroform/acetone (10/1) eluate fractions, the title compound (405 mg, 78%) was obtained as a pale brown amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 2.03-2.26 (m, 1H), 2.49 (s, 3H), 2.53 (dd, J=19.5,15.1Hz, 1H), 3.63-3.82 (m, 3H), 3.87 (s, 3H), 3.92 (d, J=9.5Hz, 1H), 4.02-4.15 (m, 1H), 4.50-4.64 (m, 2H), 5.29 (d, J=52.7Hz, 1H), 6.86 and 7.03 (each d, J=8.8 and 8.3Hz respectively, total 1H, amide isomers), 7.99 (d, J=8.8Hz, 2H), 7.08 (t, J=7.6Hz, 1H), 7.21-7.34 (m, 5H), 7.96 (d, J=9.0Hz, 2H), 8.01 (t, J=8.1Hz, 1H).

MS (ESI) m/z 518 (M^++1).

(Step 6) Synthesis of 4-((2S,4S)-4-fluoro-1-(2-(2-methylphenylamino)-5-benzoxazolylacetyl)-2-pyrrolidinylmethoxy)benzoic acid



Methyl 4-((2S,4S)-4-fluoro-1-(2-(2-methylphenylamino)-5-benzoxazolylacetyl)-2-pyrrolidinylmethoxy)benzoate (405 mg, 0.783 mmol) was dissolved in THF (20 ml). To the resulting solution was added 0.25N NaOH (20 ml), followed by stirring at room temperature for 18 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue was acidified with 1N HCl. The crystals thus obtained were collected by filtration under reduced pressure, washed with water and dried under reduced pressure, whereby the title compound (200 mg, 81%) was obtained as a colorless crystalline powder.

IR (KBr) 3423, 3251, 2973, 2941, 1685, 1643, 1579 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 2.18-2.24 (m, 2H), 2.30 (s, 3H), 3.58-4.72 (m, 7H), 5.38 and 5.44 (each m, total 1H, amide isomers), 6.98 (d, J=8.3Hz, 1H), 7.02-7.13 (m, 4H), 7.19-7.28 (m, 3H), 7.37 (m, 1H), 7.78 (d, J=8.8Hz, 2H), 7.87 (d, J=8.8Hz, 2H), 9.72 (br, 1H).

MS (ESI) m/z 470 (M^++1);

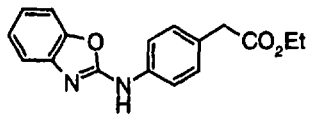
Anal. Calcd for $C_{28}H_{26}FN_3O_5 \cdot 1.1H_2O$: C, 64.26; H, 5.43; F, 3.63; N, 8.03.

Found: C, 64.07; H, 5.34; F, 3.66; N, 8.01.

Example 14

4-((2S,4S)-1-(4-(2-Benzoxazolylamino)phenylacetyl)-4-fluoro-2-pyrrolidinylmethoxy)benzoic acid:

(Step 1) Synthesis of ethyl 4-(2-benzoxazolylamino)phenylacetate

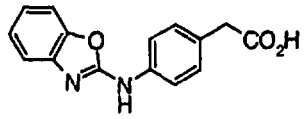


In xylene (10 mL), 2-chlorobenzoxazole (1.00 g, 6.51 mmol) and ethyl 4-aminophenylacetate (1.67 g, 6.51 mmol) were heated and refluxed for 10 hours. After cooling, water was added to the reaction mixture, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (3:1, v/v) eluate fractions, ethyl 4-(2-benzoxazolylamino)phenylacetate (2.08 g, 99%) was obtained as a yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 1.26 (t, J=7.1Hz, 3H), 3.61 (2H, s), 4.16 (q, J=7.1Hz, 2H), 7.13 (td, J=7.8,1.2Hz, 1H), 7.24 (td, J=7.8,1.2Hz, 1H), 7.31 (d, J=8.5Hz, 2H), 7.34 (dd, J=7.8,1.2Hz, 1H), 7.49 (dd, J=7.8,1.2Hz, 1H), 7.57 (d, J=8.5Hz, 2H), 7.67 (1H, broad s).

MS (ESI) m/z 297 (M^++1).

(Step 2) Synthesis of 4-(2-benzoxazolylamino)phenylacetic acid

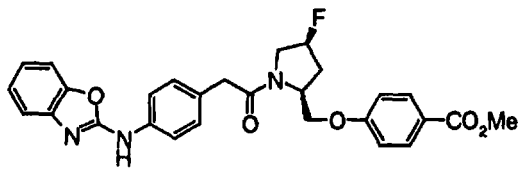


In THF (70 mL) was dissolved ethyl 4-(2-benzoxazolylamino)phenylacetate (2.08 g, 7.02 mmol), followed by the addition of 0.25N NaOH (42.0 mL, 10.5 mmol) at room temperature. After stirring for 24 hours, the reaction mixture was poured in 1N HCl (50 ml) at 0°C. The crystals thus precipitated were collected by filtration, whereby 4-(2-benzoxazolylamino)phenylacetic acid (1.85 g, 98%) was obtained as a solid.

^{1}H-NMR (DMSO-d_6) δ: 3.53 (2H, s), 7.12 (t, 1H, J=7.8Hz, 1H), 7.21 (t, J=7.8Hz, 1H), 7.25 (d, J=8.5Hz, 2H), 7.44 (d, J=7.8Hz, 1H), 7.47 (d, J=7.8Hz, 1H), 7.68 (d, J=8.5Hz, 2H), 10.56 (1H, s), 12.27 (1H, broad s).

MS (ESI) m/z 269 (M^++1).

(Step 3) Synthesis of methyl 4-((2S,4S)-1-(4-(2-benzoxazolylamino)phenylacetyl)-4-fluoro-2-pyrrolidinylmethoxy)benzoate



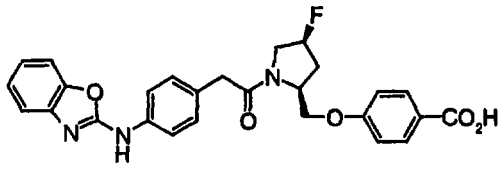
In DMF (8.8 mL) were dissolved 4-(2-benzoxazolylamino)phenylacetic acid (235 mg, 0.88 mmol), methyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)benzoate (222 mg, 0.88 mmol), HOBt (24.0 mg, 0.18 mmol) and triethylamine (0.18 mL, 1.31 mmol). EDC·HCl (252 mg, 1.31 mmol) was then added to the resulting solution. After the resulting mixture was stirred for 3 hours, water (30 ml) was added thereto, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (1:2, v/v) eluate fractions, methyl 4-((2S,4S)-1-(4-(2-benzoxazolylamino)phenylacetyl)-4-fluoro-2-pyrrolidinylmethoxy)benzoate (440 mg, 99%) was obtained as a pale yellow amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 2.14 (1H, m), 2.56 (1H, m), 3.63 (d, J=15.1Hz, 1H), 3.80 (d, J=15.1Hz, 1H), 3.87 (3H, s), 3.76-4.07 (3H, m), 4.55 (1H, m), 4.64 (1H, m), 5.31 (1H, m), 6.99 (d, J=8.8Hz, 2H), 7.12 (t, J=7.6Hz, 1H), 7.23 (t, J=7.6Hz, 1H), 7.27 (d, J=8.6Hz, 2H), 7.33 (d, J=7.6Hz, 1H), 7.48 (d, J=7.6Hz, 1H), 7.58 (d, J=8.6Hz, 2H), 7.96 (d, J=8.8Hz, 2H).

MS (ESI) m/z 504 (M^++1).

(Step 4) Synthesis of 4-((2S,4S)-1-(4-(2-

benzoxazolylamino)phenylacetyl)-4-fluoro-2-pyrrolidinylmethoxy)benzoic acid



In THF (10 mL) was dissolved methyl 4-((2S,4S)-1-(4-(2-benzoxazolylamino)phenylacetyl)-4-fluoro-2-pyrrolidinylmethoxy)benzoate (440 mg, 0.87 mmol). At room temperature, 0.25N NaOH (5.24 ml, 1.31 mmol) was added to the resulting solution. After stirring at room temperature for 24 hours, the reaction mixture was poured in 1N HCl (30 ml) at 0°C and the crystals thus obtained were collected by filtration. The crystals were dissolved in chloroform. The resulting solution was washed with saturated brine and then distilled under reduced pressure to remove the solvent. The crude crystals thus obtained were recrystallized from chloroform-hexane, whereby the title compound (388 mg, 91%) was obtained as a colorless amorphous substance.

IR (KBr) 3417, 3278, 3058, 2958, 1681, 1644, 1604, 1573, 1513, 1459, 1432 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 2.24-2.31 (2H, m), 3.63 (d, J=15.6Hz, 1H), 3.68 (d, J=15.6Hz, 1H), 3.77-3.92 (3H, m), 4.38-4.43 (2H, m), 5.44 (1H, m), 7.08 (d, J=8.5Hz, 2H), 7.12(t,

J=8.1Hz, 1H), 7.22 (t, J=8.1Hz, 1H), 7.25 (d, J=8.5Hz, 2H), 7.44 (d, J=8.1Hz, 1H), 7.48 (d, J=8.1Hz, 1H), 7.70 (d, J=8.5Hz, 2H), 7.88 (d, J=8.5Hz, 2H), 10.57 (1H, broad s), 12.63 (1H, s; broad s).

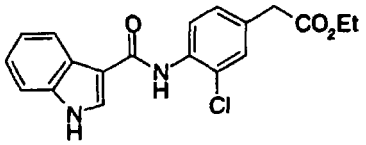
MS (ESI) m/z 504 (M^++1);

Anal. Calcd for $C_{27}H_{24}FN_3O_5 \cdot H_2O$: C, 63.90; H, 5.16; N, 8.28. Found C, 63.96; H, 5.48; N, 7.86.

Example 15

4-(1-(3-Chloro-4-(3-indolylcarbonylamino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)benzoic acid

(Step 1) Synthesis of ethyl 3-chloro-4-(3-indolylcarbonylamino)phenylacetate

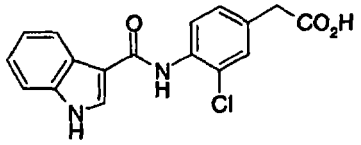


EDC·HCl (1.78 g, 9.28 mmol) was added to a solution of indole-3-carboxylic acid (1.00 g, 6.21 mmol), ethyl 4-amino-3-chlorophenylacetate (1.33 g, 6.22 mmol) and triethylamine (1.80 mL, 12.9 mmol). The mixture was stirred at 70°C for 24 hours. After cooling to room temperature, the reaction mixture was added with water (30 ml), followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified

by chromatography on a silica gel column, whereby from hexane-ethyl acetate (1:1, v/v) eluate fractions, ethyl 3-chloro-4-(3-indolylcarbonylamino)phenylacetate (1.25 g, 56%) was obtained as a pale yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 1.27 (t, J=7.1Hz, 3H), 3.59 (s, 2H), 4.17 (q, J=7.1Hz, 2H), 7.23 (m, 1H), 7.30-7.34 (m, 2H), 7.37 (d, J=2.0Hz, 1H), 7.47 (m, 1H), 7.91 (d, J=2.9Hz, 1H), 8.16 (m, 1H), 8.32 (broad s, 1H), 8.58 (d, J=8.5Hz, 1H), 8.82 (broad s, 1H).

(Step 2) Synthesis of 3-chloro-4-(3-indolylcarbonylamino)phenylacetic acid

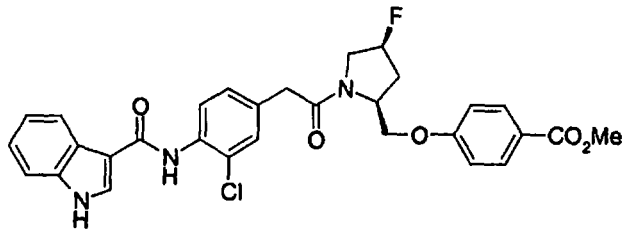


To a solution of ethyl 3-chloro-4-(3-indolylcarbonylamino)phenylacetate (1.25 g, 3.50 mmol) in THF (35 mL) was added 0.25N NaOH (21 mL, 5.23 mmol) under stirring. The reaction mixture was then stirred at room temperature for 24 hours. The reaction mixture was poured in 1N HCl (30 ml) under stirring at 0°C. The crystals thus precipitated were collected by filtration, whereby 3-chloro-4-(N-(3-indolylcarbonyl)amino)phenylacetic acid (1.05 g, 91%) was obtained as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 3.61 (s, 2H), 7.12-7.20 (m, 2H), 7.24

(d, J=8.3Hz, 1H), 7.44 (s, 1H), 7.47 (d, J=7.3Hz, 1H), 7.67 (d, J=8.3Hz, 1H), 8.14 (d, J=7.3Hz, 1H), 8.29 (s, 1H), 9.32 (s, 1H), 11.75 (broads, 1H).

(Step 3) Synthesis of methyl 4-(1-(3-chloro-4-(3-indolylcarbonylamino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)benzoate

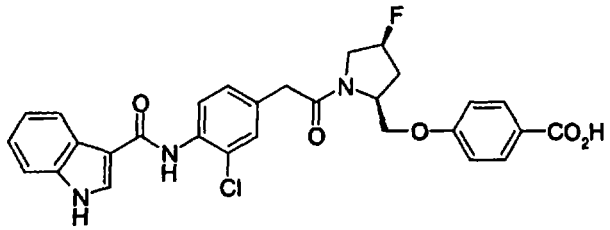


EDC·HCl (0.92 g, 4.79 mmol) was added to a solution of 3-chloro-4-(3-indolylcarbonylamino)phenylacetic acid (1.05 g, 3.19 mmol), methyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)benzoate (0.81 g, 3.19 mmol), HOBt (86.3 mg, 0.64 mmol) and triethylamine (0.68 mL, 4.79 mmol) in DMF (30 mL). The mixture was then stirred at 60°C for 10 hours. After cooling to room temperature, the reaction mixture was poured in water (30 ml), followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The crystals thus precipitated were collected by filtration, washed with water and dried under reduced pressure, whereby methyl 4-(1-(3-chloro-4-(3-indolylcarbonylamino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)benzoate (0.73 g, 40%) was

obtained as a brown solid.

^{1}H-NMR (DMSO-d_6) δ: 2.22-2.36 (m, 2H), 3.70 (d, J=16.1Hz, 1H), 3.76 (d, J=16.1Hz, 1H), 3.80 (s, 3H), 3.82-3.97 (m, 3H), 4.39-4.44 (m, 2H), 5.47 (m, 1H), 7.10 (d, J=8.8Hz, 2H), 7.14-7.25 (m, 2H), 7.42 (d, J=1.5Hz, 1H), 7.47 (d, J=7.8Hz, 1H), 7.66 (d, J=8.1Hz, 1H), 7.90 (d, J=8.8Hz, 2H), 8.14 (d, J=7.8Hz, 1H), 8.29 (s, 1H), 9.33 (s, 1H), 11.76 (broad s, 1H).

(Step 4) Synthesis of 4-(1-(3-chloro-4-(3-indolylcarbonylamino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)benzoic acid



To a solution of methyl 4-(1-(3-chloro-4-(3-indolylcarbonylamino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)benzoate (725 mg, 1.32 mmol) in THF-methanol (60 mL, 5:1, v/v) was added 0.25N NaOH (15.0 ml, 3.75 mmol). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was poured in 1N HCl (20 ml) at 0°C. The crystals thus precipitated were collected by filtration, washed with water and dried under reduced pressure, whereby 4-(1-(3-chloro-4-(N-(3-indolylcarbonylamino)phenylacetyl)-4-fluoro-2-

pyrrolidinylmethoxy)benzoic acid (399 mg, 55%) was obtained as a colorless solid.

IR (KBr) 3220, 2975, 1637, 1604, 1513, 14245, 1403 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 2.27-2.33 (m, 2H), 3.60 (d, J=15.9Hz, 1H), 3.76 (d, J=15.9Hz, 1H), 3.81-4.05 (m, 3H), 4.40-4.49 (m, 2H), 5.47 (m, 1H), 7.06 (d, J=8.6Hz, 2H), 7.15-7.21 (m, 2H), 7.24 (d, J=8.2Hz, 1H), 7.43 (s, 1H), 7.48 (d, J=7.8Hz, 1H), 7.68 (d, J=8.2Hz, 1H), 7.90 (d, J=8.6Hz, 2H), 8.14 (d, J=7.8Hz, 1H), 8.30 (s, 1H), 9.35 (s, 1H), 11.81 (broad s, 1H).

FAB-MS m/z 550 (M^++1);

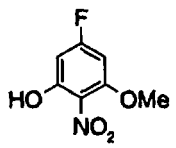
Anal. Calcd for $C_{29}H_{25}ClFN_3O_5 \cdot 3.25H_2O$: C, 57.24; H, 5.22; N, 6.91.

Found: C, 57.29; H, 5.55; N, 6.50.

Example 16

4-((4S)-Fluoro-1-(4-methoxy-2-(2-methylphenylamino)-6-benzoxazolyl)oxyacetyl-(2S)-pyrrolidinylmethoxy)benzoic acid:

(Step 1) Synthesis of 5-fluoro-3-methoxy-2-nitrophenol

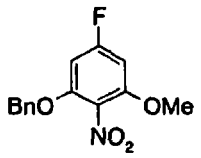


In 10N NaOH (13.1 ml, 131 mmol) and DMSO (25 ml), 3,5-difluoro-2-nitroanisole (8.29 g, 43.8 mmol) was stirred at

50°C for 5 hours. After cooling, the reaction mixture was poured in 1N HCl (200 ml), followed by extraction with ethyl acetate (300 ml). The extract was washed with saturated brine (2 × 100 ml), dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (4:1) eluate fractions, the title compound (4.14 g, 51%) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 3.94 (s, 3H), 6.28 (dd, J=10.5,2.7Hz, 1H), 6.41 (dd, J=9.8,2.7Hz, 1H), 10.92 (s, 1H).

(Step 2) Synthesis of benzyl 5-fluoro-3-methoxy-2-nitrophenyl ether

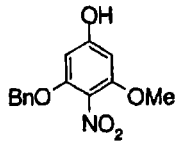


In DMF (20 ml), 5-fluoro-3-methoxy-2-nitrophenol (4.14 g, 22.1 mmol), benzyl bromide (3.2 ml, 26.5 mmol) and potassium carbonate (4.58 g, 33.2 mmol) were stirred at 70°C for 5 hours. The reaction mixture was poured in water (200 ml), followed by extraction with ethyl acetate (300 ml). The extract was washed with saturated brine (200 ml), dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was

purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (4:1) eluate fractions, the title compound (6.13 g, 100%) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 3.86 (s, 3H), 5.13 (s, 2H), 6.35 (dd, J=10.3,2.2Hz, 1H), 6.38 (dd, J=10.3,2.2Hz, 1H), 7.33-7.38 (m, 5H).

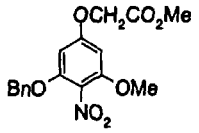
(Step 3) Synthesis of 3-benzyloxy-5-methoxy-4-nitrophenol



In 10N NaOH (5.8 ml, 58.0 mmol) and DMSO (20 ml), benzyl 5-fluoro-3-methoxy-2-nitrophenyl ether (5.35 g, 19.3 mmol) was stirred for 15 hours. The reaction mixture was poured in 1N HCl (100 ml), followed by extraction with ether (300 ml). The extract was washed with saturated brine (2 × 100 ml), dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-ethyl acetate (4:1) eluate fractions, the title compound (1.43 g, 27%) was obtained as a brown oil.

^{1}H-NMR ($CDCl_3$) δ: 3.81 (s, 3H), 5.08 (s, 2H), 6.10 (dd, J=10.8,2.2Hz, 2H), 6.37 (s, 1H), 7.34 (m, 5H).

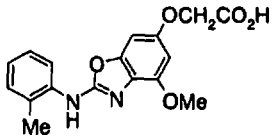
(Step 4) Synthesis of methyl 3-benzyloxy-5-methoxy-4-nitrophenoxyacetate



In DMF (10 ml), 3-benzyloxy-5-methoxy-4-nitrophenol (1.43 g, 5.20 mmol), potassium carbonate (1.08 g, 7.79 mmol) and methyl bromoacetate (591 µl, 6.24 mmol) were stirred at room temperature for 2 days. The reaction mixture was poured in water (200 ml), followed by extraction with ether (200 ml). The extract was washed with saturated brine (200 ml), dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-ethyl acetate (20:1) eluate fractions, the title compound (1.53 g, 85%) was obtained as a yellow crystalline solid.

^{1}H-NMR ($CDCl_3$) δ: 3.79 (s, 3H), 3.84 (s, 3H), 4.59 (s, 2H), 5.12 (s, 2H), 6.15 (s, 2H), 7.35 (m, 5H).

(Step 5) Synthesis of 3-benzyloxy-5-methoxy-4-nitrophenoxyacetic acid

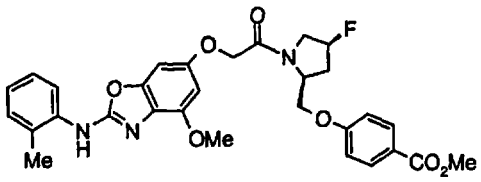


In ethanol (50 ml) was dissolved methyl 3-benzyloxy-5-

methoxy-4-nitrophenoxyacetate (1.53 g, 4.41 mmol), followed by the addition of 5% palladium/carbon (1 g). At room temperature and normal pressure, the mixture was subjected to catalytic hydrogenation for 15 hours. The reaction mixture was filtered through Celite under reduced pressure to remove the insoluble matter. The filtrate was stirred at room temperature. To the filtrate was added 2-tolyl isothiocyanate (711 µl, 5.29 mmol). After stirring at room temperature for 15 hours, mercuric oxide (yellow) (1.62 g, 7.50 mmol) was added and the mixture was heated and refluxed for 4 hours. After cooling to room temperature, the reaction mixture was filtered through Celite under reduced pressure to remove the insoluble matter. The filtrate was then distilled under reduced pressure to remove the solvent. The resulting oily residue was dissolved in THF (35 ml). To the solution was added 0.25N NaOH (35 ml, 8.75 mmol) and the mixture was stirred at room temperature for 15 hours. The reaction mixture was poured in 1N HCl (100 ml), followed by extraction with a chloroform-methanol (4:1, 2 × 200 ml) mixture. The extract was dried over anhydrous magnesium sulfate and then distilled under reduced pressure to remove the solvent. Chloroform-hexane was added to the residue to crystallize the same, whereby the title compound (487 mg, 34%) was obtained as a pale yellow amorphous substance.

^{1}H-NMR (DMSO-d_6) δ: 2.29 (s, 3H), 3.89 (s, 3H), 4.70 (s, 2H), 6.48 (d, J=7.3Hz, 1H), 6.78 (d, J=2.0Hz, 1H), 7.06 (t, J=7.3Hz, 1H), 7.22-7.24 (m, 2H), 7.85 (d, J=8.3Hz, 1H).

(Step 6) Synthesis of methyl 4-((4S)-fluoro-1-(4-methoxy-2-(2-methylphenylamino)-6-benzoxazolyl)oxyacetyl-(2S)-pyrrolidinylmethoxy)benzoate



In DMF (4 ml) was dissolved (4-methoxy-2-(2-methylphenylamino)-6-benzoxazolyl)oxyacetic acid (160 mg, 0.49 mmol) and methyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)benzoate (125 mg, 0.49 mmol). EDC·HCl (144 mg, 0.75 mmol), HOBt and DMAP were added to the resulting solution. The mixture was stirred overnight at room temperature. The reaction mixture was then diluted with ethyl acetate. The diluted mixture was washed with saturated brine, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column and chloroform/methanol (20:1, v/v) eluate fractions were collected. They were purified further by thin-layer silica gel column chromatography (TLC) with chloroform-methanol (20:1, v/v), whereby methyl 4-((4S)-fluoro-1-(4-methoxy-2-(2-methylphenylamino)-6-benzoxazolyl)oxyacetyl-

(2S)-pyrrolidinylmethoxy)benzoate (228 mg, 83%) was obtained as a pale brown solid.

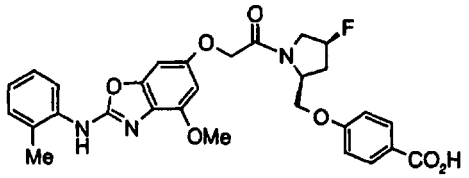
IR (KBr) 2950, 1714, 1645, 1591 cm^{-1};

^{1}H-NMR ($CDCl_3$) δ: 2.06 (m, 2H), 2.23 (s, 3H), 2.42 (dd, J=15.1,19.6Hz, 1H), 3.74 (s, 3H), 3.80 (s, 3H), 3.86 (m, 1H), 3.94 (m, 1H), 4.39 (dd, J=4.0,9.2Hz, 1H), 4.51 (br, 1H), 4.55 (m, 1H), 5.13-5.30 (series of m, total 1H), 6.37 (d, J=2.4Hz, 1H), 6.47 (d, J=2.4Hz, 1H), 6.86 (d, J=8.8Hz, 2H), 6.94 (m, 1H), 7.08 (m, 2H), 7.15 (m, 1H), 7.35 (br, 1H), 7.87 (t, J=8.8Hz, 2H), 7.94 (d, J=8.0Hz, 1H).

MS (ESI) m/z 564 $(M+H)^+$;

Anal. Calced for $C_{30}H_{30}FN_3O_7 \cdot H_2O$: C, 61.96; H, 5.55; N, 7.22. Found: C, 61.77; H, 5.55; N, 6.97.

(Step 7) Synthesis of 4-((4S)-fluoro-1-(4-methoxy-2-(2-methylphenylamino)-6-benzoxazolyl)oxyacetyl-(2S)-pyrrolidinylmethoxy)benzoic acid



Methyl 4-((4S)-fluoro-1-(4-methoxy-2-(2-methylphenylamino)-6-benzoxazolyl)oxyacetyl-(2S)-pyrrolidinylmethoxy)benzoate (225 mg, 0.40 mmol) was dissolved in THF 4 ml) and methanol (1 ml), followed by the addition of 0.25N NaOH (two equivalents). The resulting mixture was stirred overnight at room temperature. The

reaction mixture was diluted with chloroform-methanol (5:1, v/v). The diluted mixture was washed with 1N HCl, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column. Chloroform-methanol (20:1, v/v) eluate fractions were collected and they were purified further by a thin-layer silica gel column chromatography (TLC) with chloroform-methanol (20:1, v/v), whereby 4-((4S)-fluoro-1-(4-methoxy-2-(2-methylphenylamino)-6-benzoxazolyl)oxyacetyl-(2S)-pyrrolidinylmethoxy)benzoic acid (161 mg, 73%) was obtained as white powder.

IR (KBr) 2951, 1645, 1593 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 2.29 (s, 3H), 2.31 (m, 2H), 2.40 (m, 1H), 3.57 (dd, J=13.6,31.9Hz, 1H), 3.84 (m, 2H), 3.89 (s, 3H), 4.06-4.25 (series of m, total 1H), 4.48 (m, 1H), 5.49 (series of d, J=52.7Hz, total 1H), 6.49 (series of d, J=2.4Hz, total 1H), 6.79 (series of d, J=2.4Hz, total 1H), 7.01 (m, 1H), 7.04 (d, J=8.8Hz, 2H), 7.22 (d, J=7.6Hz, 2H), 7.82 (d, J=8.8Hz, 1H), 7.87 (d, J=8.8Hz, 2H), 9.41 (br, 1H).

MS (ESI) m/z 550 $(M+H)^+$;

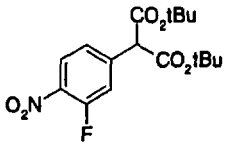
Anal. Calced for $C_{29}H_{28}FN_3O_7 \cdot 2H_2O$: C, 59.48; H, 5.51; N, 7.18.

Found: C, 59.61; H, 5.13; N, 6.89.

Example 17

4-(1-(2-(2-Methylphenylamino)-6-benzothiazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid Isomer A and Isomer B:

(Step 1) Synthesis of di-tert-butyl (3-fluoro-4-nitrophenyl)malonate

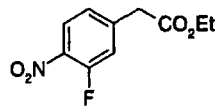


In THF (400 ml) were dissolved 2,4-difluoronitrobenzene (17.4 g, 109 mmol) and di-tert-butyl malonate (27.0 ml, 120 mmol). Under stirring at 0°C, sodium hydride (60% in oil, 4.82 g, 120 mmol) was added in portions. The reaction mixture was then stirred overnight at room temperature. The reaction mixture was poured in 1.0N-HCl (300 ml), followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (20:1 to 10:1) eluate fractions, di-tert-butyl (3-fluoro-4-nitrophenyl)malonate (5.17 g, 13%) was obtained as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.49 (s, 18H), 4.51 (s, 1H), 7.32 (d, J=8.4Hz, 2H), 7.42 (dd, J=11.6,2.0Hz, 1H), 8.05 (t,

J=8.4Hz, 1H).

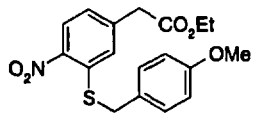
(Step 2) Synthesis of ethyl 3-fluoro-4-nitrophenylacetate



Trifluoroacetic acid (25 ml) was added to a solution of di-tert-butyl (3-fluoro-4-nitrophenyl)malonate (5.11 g, 14.4 mmol) in methylene chloride (50 ml). The resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure to yield a colorless solid substance. To the solid substance were added concentrated sulfuric acid (1 ml) and ethanol (50 ml) and the mixture was heated and refluxed for 2 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. Ice water (100 ml) was poured in the residue, followed by extraction with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent, whereby ethyl 3-fluoro-4-nitrophenylacetate (3.15 g, 96%) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.27 (t, J=7.2Hz, 3H), 3.69 (s, 2H), 4.18 (q, J=14.4,7.2Hz, 2H), 7.21 (d, J=8.8Hz, 1H), 7.25 (d, J=10.0Hz, 2H), 8.03 (t, J=8.0Hz, 1H).

(Step 3) Synthesis of ethyl 3-(4-methoxybenzylthio)-4-nitrophenylacetate

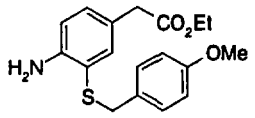


Sodium hydride (60% in oil, 440 mg, 11.0 mmol) was added in portions to a solution of ethyl 3-fluoro-4-nitrophenylacetate (2.09 g, 9.20 mmol) and 4-methoxyphenylbenzylthiol (3.85 ml, 27.6 mmol) in N-methylpyrrolidone (30 ml) under stirring at 0°C. After completion of the addition, the reaction mixture was stirred at room temperature for 5 hours. The reaction mixture was poured in 1.0N-HCl (30 ml), followed by extraction with ether. The extract was washed with water (twice), dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (3:1) eluate fractions, ethyl 3-(4-methoxybenzylthio)-4-nitrophenylacetate (3.37 g, quant.) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.27 (t, J=6.8Hz, 3H), 3.65 (s, 2H), 3.80 (s, 3H), 4.16 (s, 2H), 4.17 (q, J=14.4,7.2Hz, 2H), 6.87 (d, J=8.4Hz, 2H), 7.15 (dd, J=8.4,1.6Hz, 1H), 7.33 (d, J=8.4Hz, 2H), 8.17 (d, J=8.8Hz, 1H).

(Step 4) Synthesis of ethyl 3-(4-methoxybenzylthio)-4-

aminophenylacetate



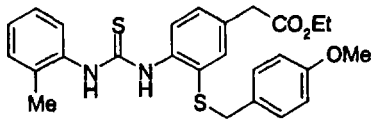
Under stirring, a solution of ethyl 3-(4-methoxybenzylthio)-4-nitrophenylacetate (3.33 g, 9.92 mmol), ammonium chloride (542 mg, 10.1 mmol) and reduced iron powder (2.57 g, 46.1 mmol) in ethanol/THF/water (2:2:1, 75 ml) was heated and refluxed for 1.5 hours. After the reaction mixture was cooled, the insoluble matter was filtered off. The filtrate was distilled under reduced pressure to remove the solvent. The residue was neutralized by pouring therein a saturated aqueous solution of sodium bicarbonate, followed by extraction with a chloroform-methanol mixture. The extract was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-ethyl acetate (20:1) eluate fractions, ethyl 3-(4-methoxybenzylthio)-4-aminophenylacetate (2.64 g, 86%) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.27 (t, J=6.8Hz, 3H), 3.45 (s, 2H), 3.81 (s, 3H), 3.90 (s, 2H), 4.16 (q, J=14.0,7.2Hz, 2H), 4.24 (brs, 2H), 6.69 (d, J=8.0Hz, 1H), 6.80 (d, J=8.4Hz, 2H), 7.06 (dd, J=8.4,2.0Hz, 1H), 7.17 (s, 1H), 7.18 (s, 1H),

7.29 (s, 1H).

MS (ESI) m/z, 332 (M^++H).

(Step 5) Synthesis of ethyl 4-(N'-(2-methylphenyl)thioureido)-3-(4-methoxybenzylthio)phenylacetate

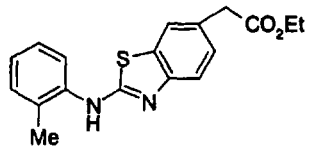


A solution of ethyl 3-(4-methoxybenzylthio)-4-aminophenylacetate (2.55 g, 7.69 mmol) and o-tolyl isocyanate (1.74 ml, 8.46 mmol) in acetonitrile (20 ml) was stirred overnight at 60°C. After the reaction mixture was cooled, the solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (3:1) eluate fractions, ethyl 4-(N'-(2-methylphenyl)thioureido)-3-(4-methoxybenzylthio)phenylacetate (1.66 g, 45%) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.24 (t, J=7.2Hz, 3H), 3.51 (s, 2H), 3.73 (s, 2H), 3.77 (s, 3H), 4.13 (q, J=14.4,7.2Hz, 2H), 6.69 (d, J=8.8Hz, 1H), 6.84 (d, J=8.8Hz, 2H), 7.21-7.34 (series of m, 6H), 7.60 (brs, 1H), 8.10 (brs, 1H), 8.32 (d, J=8.0Hz, 2H).

MS (ESI) m/z, 481 (M^++H).

(Step 6) Synthesis of ethyl 2-(2-methylphenylamino)-6-benzothiazolylacetate

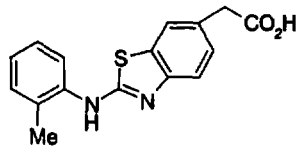


In ethanol (50 ml), ethyl 4-(N'-(2-methylphenyl)thioureido)-3-(4-methoxybenzylthio)phenylacetate (1.63 g, 3.40 mmol) and mercuric oxide (yellow) (1.10 g, 16.4 mmol) were stirred for one hour at 70°C. Water (50 ml) was added and the mixture was extracted with ethyl acetate. The extract was washed with water and a saturated aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (3:1) eluate fractions, ethyl 2-(2-methylphenylamino)-6-benzothiazolylacetate (922 mg, 83%) was obtained as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.25 (t, J=7.2Hz, 3H), 2.78 (s, 3H), 3.64 (s, 2H), 4.14 (q, J=14.4,7.6Hz, 2H), 7.17-7.22 (m, 2H), 7.29 (t, J=7.2Hz, 2H), 7.43 (d, J=8.0Hz, 1H), 7.51 (brs, 1H), 7.65 (d, J=8.0Hz, 1H), 8.00 (brs, 1H).

MS (ESI) m/z, 327 (M^++H).

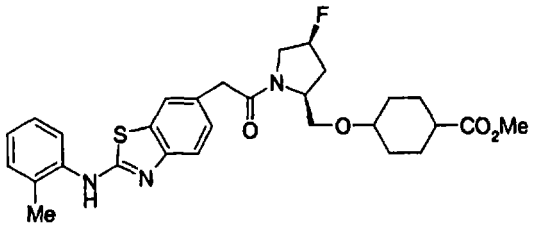
(Step 7) Synthesis of 2-(2-methylphenylamino)-6-benzothiazolylacetic acid



In THF-methanol (1:1, 20 ml) was dissolved ethyl 2-(2-methylphenylamino)-6-benzothiazolylacetate (907 mg, 2.78 mmol). To the resulting solution was added 1.0M-NaOH (8.34 ml, 8.34 mmol), followed by stirring overnight at room temperature. The reaction mixture was concentrated under reduced pressure. The residue was acidified with 1.0N HCl. The crystals thus obtained were collected by filtration under reduced pressure, washed with water and dried at 60°C under reduced pressure, whereby 2-(2-methylphenylamino)-6-benzothiazolylacetic acid (675 mg, 81%) was obtained as a white crystalline powder.

^{1}H-NMR (DMSO-d_6) δ: 2.59 (s, 3H), 3.88 (s, 2H), 7.37 (t, J=7.2Hz, 1H), 7.44-7.46 (m, 1H), 7.52 (t, J=7.6Hz, 2H), 7.69 (d, J=8.0Hz, 1H), 7.90 (s, 1H), 8.13 (d, J=8.0Hz, 1H). MS (ESI) m/z, 299 (M^++H).

(Step 8) Synthesis of methyl 4-(1-(2-(2-methylphenylamino)-6-benzothiazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



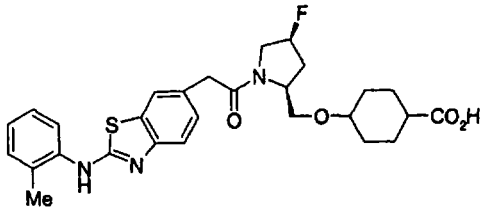
HOBt (14.0 mg, 0.10 mmol) was added to a solution of methyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (259 mg, 1.00 mmol), 2-(2-methylphenylamino)-6-benzothiazolylacetic acid (328 mg, 1.10 mmol) and EDC·HCl (288 mg, 1.50 mmol) in DMF (10 ml). The resulting mixture was stirred overnight at room temperature. The reaction mixture was poured in water (30 ml) and the mixture was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (1:4) eluate fractions, methyl 4-(1-(2-(2-methylphenylamino)-6-benzothiazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (409 mg, 76%), which was a mixture of two diastereomers, was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$), mixture of rotamars, δ: 1.20-1.30 (m, 1H), 1.39-1.55 (m, 2H), 1.56-1.72 (m, 2H), 1.77-1.92 (m, 3H), 1.99-2.15 (m, 3H), 2.20-2.55 (m, 2H), 2.34 (s, 3H), 3.20-3.40 (series of m, 6H), 3,66, 3.70 and 3.72 (s, total 3H),

5.15-5.30 (m, 1H), 7.16-7.20 (m, 2H), 7.26-7.28 (m, 3H), 7.45 (dd, J=8.4,3.6Hz, 1H), 7.50-7.53 (m, 1H), 7.64-7.67 (m, 1H).

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

(Step 9) Synthesis of 4-(1-(2-(2-methylphenylamino)-6-benzothiazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid, Isomer A and Isomer B



To a solution of methyl 4-(1-(2-(2-methylphenylamino)-6-benzothiazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (397 mg, 0.74 mmol), which was a mixture of two diastereomers, in methanol-THF (1:1, 10 ml) was added 0.25M-NaOH (8.83 ml, 2.21 mmol). The resulting mixture was stirred overnight at room temperature. The reaction mixture was poured in 1N-HCl (20 ml) and the mixture was extracted with a chloroform-methanol mixture. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent, whereby 4-(1-(2-(2-methylphenylamino)-6-benzothiazolylacetyl)-(4S)-fluoro-(2S)-

pyrrolidinylmethoxy)cyclohexanecarboxylic acid (468 mg, 89%), a mixture of two diastereomers, was obtained as a colorless amorphous substance. The mixture of these two diasteromers was separable by HPLC (Shimpack PRC-ODS/30 mm × 250 mm, acetonitrile: 0.02N sodium acetate buffer = 1:1, 20 ml/min) so that Isomer A and Isomer B were obtained each in the form of a colorless amorphous substance.

Isomer A;

^{1}H-NMR ($CDCl_3$), mixture of rotamars, δ: 1.18-1.31 (m, 2H), 1.43-1.55 (m, 2H), 2.05-2.15 (m, 6H), 2.21-2.48 (m, 3H), 2.41 (s, 3H), 3.23-4.24 (series of m, 6H), 5.16-5.30 (m, 1H), 7.17-7.29 (m, 4H), 7.44-7.52 (m, 3H), 7.58 (s, 1H).

MS (ESI) m/z, 526 (M^++H).

Isomer B;

^{1}H-NMR ($CDCl_3$), mixture of rotamars, δ: 1.22-1.30 (m, 2H), 1.43-1.52 (m, 2H), 1.68-2.02 (m, 6H), 2.10-2.18 (m, 1H), 2.30 (s, 3H), 2.22-2.50 (m, 2H), 3.33-4.48 (series of m, 6H), 5.14-5.29 (m, 1H), 7.17-7.27 (m, 5H), 7.43-7.50 (m, 3H);

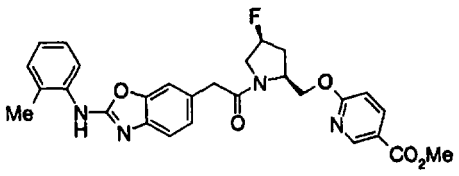
MS (ESI) m/z, 526 (M^++H).

Example 18

6-((4S)-Fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)nicotinic acid:

(Step 1) Synthesis of methyl 6-((4S)-fluoro-1-(2-(2-

methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)nicotinate

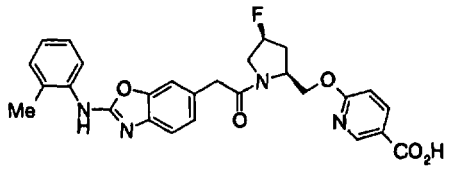


Methyl 6-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)nicotinate (202.0 mg, 0.794 mmol), 2-(2-methylphenylamino)-6-benzoxazolylacetic acid (224.2 mg, 0.794 mmol) and HOBt (21.5 mg, 0.159 mmol) were dissolved in DMF (8.5 ml). Under stirring at room temperature, EDC·HCl (228.4 mg, 1.192 mmol) was added to the resulting solution. The reaction mixture was further stirred overnight at room temperature. Water (30 ml) was added and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-ethyl acetate (5:1, v/v) eluate fractions, the title compound (370.1 mg, 90%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 2.02-2.30 (1H, m, CH_2), 2.34, 2.35 (total 3H, s, ArMe), 2.38-2.53 (1H, m, CH_2), 3.65-4.83 (total 10H, series of m, including 3H, s at (3.88, 3.90), 5.28 (1H, br

d, J=53.9), 6.71-8.88 (total 11H, series of m, ArH, NH).

(Step 2) Synthesis of 6-((4S)-fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)nicotinic acid



Methyl 6-((4S)-fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)nicotinate (370.1 mg, 0.714 mmol) was dissolved in THF (7.5 ml). At room temperature, 0.25N NaOH (7.5 ml) was added at room temperature. The reaction mixture was stirred overnight at 50°C. The reaction mixture was concentrated under reduced pressure. The concentrate was acidified with 1N HCl. The crystals thus obtained were collected by filtration under reduced pressure, washed with water and dried at 50°C under reduced pressure, whereby the title compound (214.8 mg, 60%) was obtained as a pale brown amorphous substance.

IR (KBr) 1683, 1637, 1600, 1573, 1244 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 2.13-2.41 (5H, m, including 3H, s at (2.31), 3.30-4.72 (total 7H, series of m), 5.43 (1H, br d, J=52.8Hz), 6.86-7.42 (total 9H, series of m), 7.79 (1H, m), 8.10-8.22 (1H, m), 8.71 (1H, m).

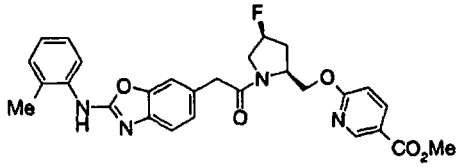
MS (ESI) m/z 505 (M^++1);

Anal. Calcd for $C_{27}H_{25}FN_4O_5 \cdot 0.25H_2O$: C, 59.01; H, 5.50; N, 10.19; F, 3.46.

Found: C, 59.38; H, 5.31; N, 9.73; F, 3.30.

Example 19

Methyl 6-((4S)-fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)nicotinate



In methanol/benzene (1/1, v/v) (1.5 ml) was dissolved 6-((4S)-fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)nicotinic acid (51.6 mg, 0.1023 mmol). Trimethylsilyldiazomethane (2.0M hexane solution, 0.08 ml, 0.1534 mmol) was added dropwise to the resulting solution under stirring at 0°C. After completion of the dropwise addition, the reaction mixture was stirred at room temperature for 3 hours. The solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (10:1, v/v) eluate fractions, the title compound (44.4 mg, 84%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 2.02-2.30 (1H, m), 2.34, 2.35 (total 3H,

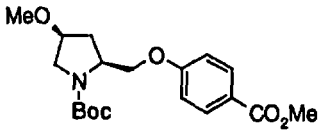
s), 2.38-2.53 (1H, m), 3.65-4.83 (total 10H, series of m, including total 3H, s at δ3.88, 3.90), 5.28 (1H, br d, J=53.9), 6.71-8.88 (total 11H, series of m).

MS (ESI) m/z 519 (M^++1).

Example 20

4-((4S)-Methoxy-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid, Isomer A and Isomer B:

(Step 1) Synthesis of methyl 4-(1-(tert-butoxycarbonyl)-(4S)-methoxy-(2S)-pyrrolidinylmethoxy)benzoate

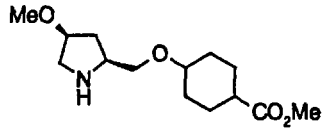


Methyl 4-(1-(tert-butoxycarbonyl)-(4S)-hydroxy-(2S)-pyrrolidinylmethoxy)benzoate (1.03 g, 2.92 mmol) and methyl iodide (300 µl, 5.91 mmol) were dissolved in DMF (20 ml). Under stirring at 0°C, sodium hydride (60% in oil, 145 g, 3.62 mmol) was added in portions. After the whole amount of sodium hydride was added, the reaction mixture was further stirred overnight at room temperature. The reaction mixture was then poured in water and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the

solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (4:1, v/v) eluate fractions, methyl 4-(1-(tert-butoxycarbonyl)-(4S)-methoxy-(2S)-pyrrolidinylmethoxy)benzoate (943 mg, 88%) was obtained as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.46 (s, 9H), 2.03 (br, 1H), 2.27 (dd, J=1.6,14.0Hz, 1H), 3.27 (s, 3H), 3.50 (m, 2H), 3.86 (s, 3H), 3.91-4.00 (br. m, 2H), 4.12-4.36 (br. m, 2H), 6.94 (br, 2H), 7.95 (d, J=8.8Hz, 2H).

(Step 2) Synthesis of methyl 4-((4S)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate

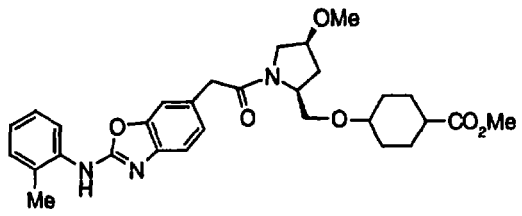


Methyl 4-(1-(tert-butoxycarbonyl)-(4S)-methoxy-(2S)-pyrrolidinylmethoxy)benzoate (943 mg, 2.56 mmol) was dissolved in ethanol (10 ml) and acetic acid (1 ml). To the resulting solution was added rhodium-alumina (500 mg) and the mixture was subjected to catalytic hydrogenation overnight at room temperature under 5 atm. The catalyst was filtered off and the filtrate was distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (3:1, v/v) eluate fractions, methyl 4-(1-(tert-butoxycarbonyl)-(4S)-methoxy-(2S)-

pyrrolidinylmethoxy)cyclohexanecarboxylate (819 mg, 86%) was obtained as a pale yellow oil. The resulting methyl 4-(1-(tert-butoxycarbonyl)-(4S)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (819 mg, 2.20 mmol) was then dissolved in methylene chloride (9 ml). After addition of trifluoroacetic acid (4 ml) at 0°C, the mixture was stirred at room temperature for 1.5 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue was basified by the treatment with 1N NaOH, followed by extraction with chloroform. The extract was washed saturated with brine, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent, whereby methyl 4-((4S)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (2.53 g, 81%) was obtained as a pale yellow oil (a mixture of two diasteromers).

^{1}H-NMR ($CDCl_3$) δ: 1.47 (m, 3H), 1.61 (m, 2H), 1.81 (m, 4H), 2.03 (m, 2H), 2.32 (m, 1H), 2.84 (dd, J=5.1,11.5Hz, 1H), 3.60 (d, J=11.5Hz, 1H), 3.21 (br, 1H), 3.24 (s, 3H), 3.35-3.44 (m, 3H), 3.63 (s, 3H), 3.68 (br, 1H).

(Step 3) Synthesis of methyl 4-((4S)-methoxy-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



In DMF (7 ml) were dissolved 2-(2-methylphenylamino)-6-benzoxazolylacetic acid (218 mg, 0.77 mmol) and methyl 4-((4S)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (210 mg, 0.77 mmol). EDC·HCl (235 mg, 1.22 mmol), HOBt (5.0 mg, 0.04 mmol) and DMAP (5.0 mg, 0.04 mmol) were added to the resulting solution, followed by stirring overnight at room temperature. The reaction mixture was diluted with ethyl acetate. The diluted mixture was then washed with saturated brine, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (10:1, v/v) eluate fractions, methyl 4-((4S)-methoxy-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (385 mg, 93%) was obtained as a pale brown oil (a mixture of two diastereomers).

IR (KBr) 2937, 1732, 1641, 1574 cm^{-1};

^{1}H-NMR ($CDCl_3$) δ: 1.47 (m, 2H), 1.62 (m, 2H), 1.76-1.88 (m, 4H), 1.91-2.05 (m, 2H), 2.23 (m, 1H), 2.33 (d, 3H), 2.35

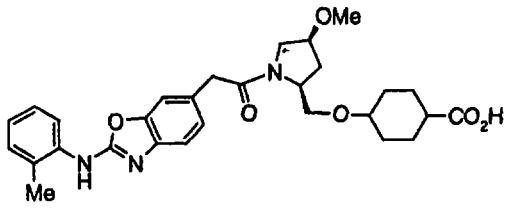
(m, 1H), 3.27 (d, 3H), 3.40-3.54 (m, 3H), 3.65 (d, 3H), 3.67 (m, 2H), 3.78-4.02 (series of m, total 2H), 4.12-4.26 (series of m, total 1H), 6.86 (br, 1H), 7.05 (q, J=7.6Hz, 2H), 7.15 (d, J=7.6Hz, 1H), 7.28 (m, 2H), 7.37 (dd, J=2.6,8.0Hz, 1H), 8.07 (d, J=8.0Hz, 1H).

MS (ESI) m/z 536 $(M+H)^+$;

Anal. Calced for $C_{30}H_{37}N_3O_6 \cdot 0.5H_2O$: C, 66.16; H, 7.03; N, 7.72.

Found: C, 66.06; H, 6.96; N, 7.57.

(Step 4) Synthesis of 4-((4S)-methoxy-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid, Isomer A and Isomer B



Methyl 4-((4S)-methoxy-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (940 mg, 1.79 mmol) was dissolved in THF (15 ml) and methanol (1 ml). To the resulting solution was added 0.25N NaOH (2 eq), followed by stirring overnight at room temperature. The reaction mixture was diluted with chloroform-methanol (5:1, v/v). The diluted mixture was washed with 1N HCl, dried

over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (20:1, v/v) eluate fractions, 4-((4S)-methoxy-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid (568 mg, 64%) was obtained as a mixture of two diastereomers. The mixture of two diastereomers was separable by HPLC (Shimpack PRC-ODS-30 mm × 250 mm, acetonitrile : 0.02N sodium acetate buffer = 1:1, 20 ml/min). Isomer A (39 mg, 11%) and Isomer B (246 mg, 67%) were obtained, each as a pale yellow crystalline powder.

Isomer A;

IR (KBr) 2933, 1697, 1641, 1574 cm^{-1};

^1H-NMR ($CDCl_3$) δ: 1.18 (m, 4H), 1.40 (m, 2H), 1.96 (m, 4H), 2.19 (m, 2H), 2.28 (s, 3H), 3.15 (m, 1H), 3.21 (d, J=4.4Hz, 3H), 3.40 (m, 2H), 3.60 (m, 3H), 3.64-3.90 (series of m, total 3H), 4.04-4.19 (m, 1H), 5.17 (br, 1H), 7.02 (t, J=7.4Hz, 2H), 7.16 (m, 1H), 7.23 (m, 2H), 7.66 (d, J=8.0Hz, 1H).

MS (ESI) m/z 522 $(M+H)^+$;

Anal. Calcd for $C_{29}H_{35}N_3O_6 \cdot 1.75H_2O$: C, 62.97; H, 7.02; N, 7.60.

Found: C, 63.39; H, 7.04; N, 6.90.

Isomer B;

IR (KBr) 2931, 1697, 1641, 1574 cm^{-1};

^{1}H-NMR ($CDCl_3$) δ: 1.48 (m, 2H), 1.64-1.98 (series of m, total 8H), 2.23 (m, 1H), 2.27 (s, 3H), 2.38 (m, 1H), 3.27 (d, J=6.8Hz, 1H), 3.39-3.47 (m, 3H), 3.54 (q, J=8.8Hz, 1H), 3.66 (m, 2H), 3.88 (m, 2H), 4.20 (m, 1H), 7.05 (t, J=7.0Hz, 2H), 7.19 (m, 1H), 7.30 (m, 2H), 7.81 (dd, J=8.0,44.4Hz, 1H).

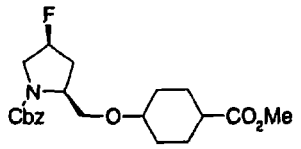
MS (ESI) m/z 522 $(M+H)^+$;

Anal. Calcd for $C_{29}H_{35}N_3O_6 \cdot H_2O$: C, 64.55; H, 6.91; N, 7.79. Found: C, 64.81; H, 7.17; N, 7.00.

Example 21

4-(1-(2-(2-Methylphenylamino)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid, Isomer G and Isomer H:

(Step 1) Synthesis methyl 4-(N-carbobenzoxy-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate, Isomer A and Isomer B



Methyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cycloehexanecarboxylate (529 mg, 2.04 mmol) and carbobenzoxy chloride (30 to 35% in toluene, 1.21 ml, 2.04 mmol) were dissolved in methylene chloride (20

ml). Under stirring, a saturated aqueous solution of sodium bicarbonate (5 ml) was added at room temperature. The reaction mixture was further stirred for 5.5 hours at room temperature. The reaction mixture was poured in water (20 ml) and the mixture was extracted with ethyl acetate. The extract was then dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (2:1) eluate fractions, methyl 4-(N-carbobenzoxy-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (648 mg, 85%), that is, a mixture of two diastereomers was obtained as a colorless oil. Since the mixture was separable into two diasteromers by medium-pressure chromatography on a silica gel column, from hexane-ethyl acetate (3:1) eluate fractions, two isomers were separated.

Isomer A:

^{1}H-NMR ($CDCl_3$) δ: 1.48 (brs, 2H), 1.64 (brs, 2H), 1.84 (brs, 4H), 2.01-2.18 (m, 1H), 2.41-2.51 (m, 1H), 3.33-3.51 (m, 2H), 4.60-3.75 (m, 3H), 3.67 (s, 3H), 4.11-4.15 (m, 1H), 5.10-5.29 (series of m, 3H), 7.30-7.37 (m, 5H).

MS (ESI) m/z, 394 (M^++H).;

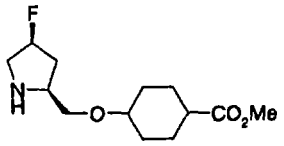
Isomer B:

^{1}H-NMR ($CDCl_3$) δ: 1.26 (brs, 2H), 1.44 (brs, 2H), 1.99-2.13 (m, 5H), 2.39 (brs, 1H), 2.39-2.48 (m, 1H), 3.18-3.36 (m,

2H), 3.61-3.86 (m, 3H), 3.67 (s, 3H), 4.14 (brs, 1H), 5.10-5.29 (series of m, 3H), 7.31-7.37 (m, 5H).

MS (ESI) m/z, 394 (M^++H).

(Step 2) Synthesis of methyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (Isomer C)



In methanol (10 ml), methyl 4-(N-carbobenzoxy-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the above-described Isomer A, 451 mg, 1.15 mmol) and 20% palladium hydroxide/carbon (42 mg) were subjected to catalytic hydrogenation overnight at room temperature and 1 atm. The catalyst was filtered off from the reaction mixture and the filtrate was distilled under reduced pressure to remove the solvent, whereby methyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (311 mg, 100%) was obtained as a colorless solid (Isomer C).

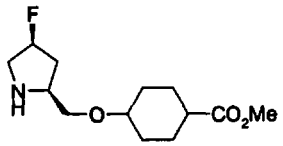
As a result of X-ray structural analysis, the derivative of this compound was confirmed to be methyl cis-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate whose substituents at the 1- and 4-positions on the cyclohexane ring had a cis relative configuration.

^{1}H-NMR ($CDCl_3$), mixture of rotamars, δ: 1.50 (brt,

J=14.0Hz, 2H), 1.61-1.66 (m, 2H), 1.80-2.01 (series of m, 5H), 2.17-2.37 (m, 2H), 3.05-3.18 (m, 1H), 3.40-3.61 (series of m, 5H), 3.64 (s, 3H), 5.01 (brs, 1H), 5.14-5.30 (m, 1H).

MS (ESI) m/z, 360 (M^++H).

(Step 3) Synthesis methyl of 4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (Isomer D)



In methanol (5 ml), methyl 4-(N-carbobenzoxy-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (Isomer B, 121 mg, 0.31 mmol) and 20% palladium hydroxide/carbon (19 mg) were subjected to catalytic hydrogenation overnight at room temperature and 1 atm. The catalyst was filtered off from the reaction mixture and the filtrate was distilled under reduced pressure to remove the solvent, whereby methyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (311 mg, quant.) was obtained as a colorless solid (Isomer D).

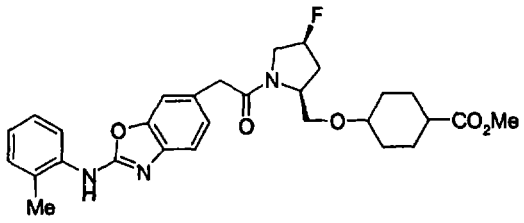
As a result of X-ray structural analysis, the derivative of this compound was confirmed to be methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate whose substituents at the 1- and 4-positions on the cyclohexane

ring had a trans relative configuration.

^{1}H-NMR ($CDCl_3$), mixture of rotamars, δ: 1.21-1.31 (m, 2H), 1.41-1.51 (m, 2H), 1.74-1.87 (m, 1H), 1.98-2.09 (m, 5H), 2.11-2.30 (m, 2H), 2.48 (brs, 1H), 2.85-2.98 (m, 1H), 3.22-3.59 (series of m, 5H), 5.12-5.26 (m, 1H).

MS (ESI) m/z, 360 (M^++H).

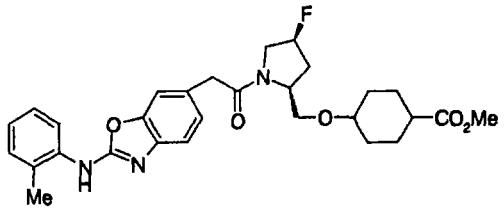
(Step 4) Synthesis of methyl 4-(1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (Isomer E)



In DMF (10 ml), HOBT (5.2 mg, 0.04 mmol) was added to methyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (Isomer C, 50 mg, 0.19 mmol), 2-(2-methylphenylamino)-6-benzoxazolylacetic acid (59.9 g, 0.21 mmol) and EDC·HCl (55.5 mg, 0.29 mmol) under stirring at room temperature. After stirring overnight at room temperature, the reaction mixture was poured in water (10 ml) and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel

column, whereby from hexane-ethyl acetate (1:5) eluate fractions, methyl 4-(1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (92.0 mg, 91%) was obtained as a colorless amorphous substance (Isomer E). ^{1}H-NMR ($CDCl_3$), mixture of rotamars, δ: 1.46-2.48 (series of m, 11H), 2.35 (s, 3H), 3.38-4.41 (series of m, 8H), 3.64-3.68 (m, 3H), 5.15-5.30 (m, 1H), 7.07 (dd, J=16.0,7.6Hz, 2H), 7.21 (d, J=8.0Hz, 1H), 7.30 (t, J=6.4Hz, 2H), 7.32-7.40 (m, 1H), 8.07 (d, J=8.4Hz, 1H).

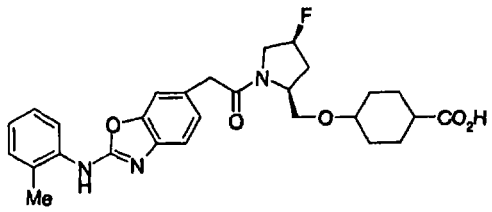
(Step 5) Synthesis of methyl 4-(1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (Isomer F)



In DMF (10 ml), HOBT (8.0 mg, 0.04 mmol) was added to methyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (Isomer D, 77 mg, 0.30 mmol), 2-(2-methylphenylamino)-6-benzoxazolylacetic acid (92.2 mg, 0.33 mmol) and EDC·HCl (85.4 mg, 0.45 mmol) under stirring at room temperature. After further stirring overnight at room temperature, the reaction mixture was poured in water (10 ml) and the

mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (1:5) eluate fractions, methyl 4-(1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (142 mg, 91%) was obtained as a colorless amorphous substance (Isomer F). ^{1}H-NMR ($CDCl_3$), mixture of rotamars, δ: 1.16-1.32 (m, 2H), 1.40-1.54 (m, 2H), 196-2.50 (series of m, 7H), 2.36 (s, 3H), 3.21-3.29 (m, 1H), 3.32-3.52 (m, 1H), 3.50-4.39 (series of m, 6H), 3.62-3.69 (m, 3H), 5.15-5.31 (m, 1H), 7.05-7.10 (m, 2H), 7.22 (d, J=7.2Hz, 1H), 7.29-7.31 (m, 3H), 7.39-7.43 (m, 1H), 8.06 (d, J=8.0Hz, 1H).

(Step 6) Synthesis of 4-(1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid (Isomer G)



Methyl 4-(1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (Isomer E, 92.0

mg, 0.18 mmol) was dissolved in methanol-THF (1:1, 10 ml). After addition of 0.25M-NaOH (0.53 ml, 2.11 mmol) under stirring at room temperature, the reaction mixture was stirred at room temperature for 15 hours. To the reaction mixture was further added 1.0M-NaOH (0.35 ml, 0.35 mmol), followed by stirring at 50°C for 2.5 hours. The reaction mixture was poured in 1N-HCl (20 ml) and the mixture was extracted with a chloroform-methanol mixture. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (10:1) eluate fractions, 4-(1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid (78.0 mg, 87%) was obtained as a colorless amorphous substance (Isomer G).

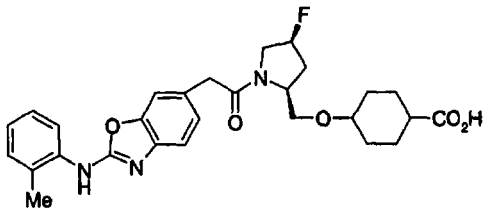
IR (KBr) 2933, 1693, 1641, 1575 cm^{-1};

^{1}H-NMR ($CDCl_3$) δ: 1.45-1.58 (m, 2H), 1.63-2.01 (series of m, total 6H), 2.10-2.25 (m, 1H), 2.40-2.62 (m, 1H), 2.34 and 2.35 (s, total 3H), 3.30-4.48 (series of m, 9H), 5.14-5.29 (m, 1H), 7.05-7.12 (series of m, 2H), 7.20-7.33 (series of m, 5H), 7.70 and 7.75 (d, J=8.0Hz, total 1H).

MS (FAB) m/z 510 (M^++H)

(Step 7) Synthesis of 4-(1-(2-(2-methylphenylamino)-6-

benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid (Isomer H)



Methyl 4-(1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (Isomer F, 130 mg, 0.25 mmol) was dissolved in methanol-THF (1:1, 10 ml). After addition of 0.25M-NaOH (1.99 ml, 0.50 mmol) at room temperature, the reaction mixture was stirred at room temperature for 1 hour. To the reaction mixture was added 1.0M-NaOH (0.74 ml, 0.74 mmol) and the mixture was stirred at 50°C for 3 hours. The reaction mixture was poured in 1N-HCl (20 ml) and the mixture was extracted with a chloroform-methanol mixture. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (10:1) eluate fractions, 4-(1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid (120 mg, 95%) was obtained as a colorless amorphous substance

(Isomer H).

IR (KBr) 2937, 1699, 1641, 1574 cm^{-1};

^{1}H-NMR ($CDCl_3$) δ: 1.20-1.31 (m, 2H), 1.43-1.56 (m, 2H), 2.10 (brs, 5H), 2.21-2.50 (m, 1H), 2.34 (s, 3H), 3.24-4.48 (series of m, 9H), 7.01 (brs, 1H), 7.11 (brs, 1H), 7.22-7.36 (series of m, 5H), 7.81 (brd, J=5.6Hz, 1H).

MS (FAB) m/z 510 (M^++H);

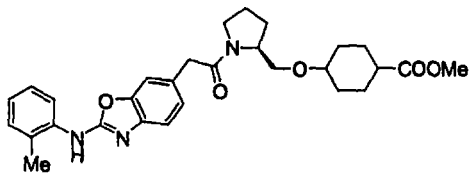
Anal. Calced for $C_{28}H_{32}FN_3O_5$: C, 66.00; H, 6.33; N, 8.25.

Found: C, 65.71; H, 6.42; N, 8.08.

Example 22

4-(1-(2-(2-Methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid, Isomer A and Isomer B:

(Step 1) Synthesis of methyl 4-(1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (cis and trans forms)

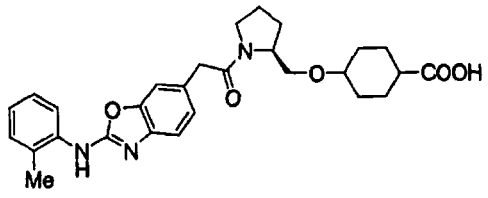


In methylene chloride (20 ml), EDC(HCl (691 mg, 3.6 mmol) was added at 0°C to methyl 4-(1-(tert-butoxycarbonyl)-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (580 mg, 2.4

mmol), 2-(2-methylphenylamino)-6-benzoxazolylacetic acid (678 mg, 2.4 mmol), HOBt (324 mg, 2.4 mmol) and triethylamine (1.0 ml, 7.2 mmol). The reaction mixture was stirred at room temperature for 16 hours. Ice water (10 ml) was added and the mixture was extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium bicarbonate, a 2M aqueous citric acid solution and a saturated aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (1:2, v/v) eluate fractions, the title compound (500 mg, 48%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.30-2.10 (m, 12H), 2.36 (s, 3H), 3.30-3.90 (m, 7H), 4.10-4.25 (m, 2H), 7.00-7.40 (m, 7H), 8.04-8.06 (m, 1H).

(Step 2) Synthesis of 4-(1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid, Isomer A and Isomer B



In THF (10 ml) and methanol (5 ml) was dissolved methyl 4-(1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (580 mg, 1.1 mmol), that is, a mixture of two diastereomers (cis and trans forms). After addition of 1N NaOH (1.5 ml, 1.5 mmol), the mixture was stirred at 70°C for 24 hours. The residue obtained by distilling off the solvent under reduced pressure, was acidified weakly with 1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure. The resulting crystals were washed with water and dried under reduced pressure, whereby 4-(1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid was obtained as a mixture of two diasteromers. The mixture was separated by HPLC (C18 column, eluting with 0.02N acetate buffer-acetonitrile (1:1, v/v)), whereby Isomer A (150 mg, 27%) was obtained as a white crystalline solid.

IR (KBr) 2937, 2867, 1641, 1573, 1440, 1243 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.39-1.85 (m, 10H), 2.23-2.28 (m, 2H), 2.29 (s, 3H), 3.41-4.03 (m, 9H), 7.01-7.08 (m, 2H), 7.21-7.28 (m, 4H), 7.80-7.82 (m, 1H).

MS (FAB) m/z 492 $(M+H)^+$;

Anal. calcd for $C_{28}H_{33}N_3O_5 \cdot 0.2H_2O$: C, 67.91; H, 6.80; N, 8.49.

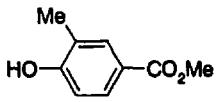
Found: C, 67.79; H, 6.77; N, 8.25.

From HPLC (C18 column, eluting with 0.02N acetate buffer-acetonitrile (1:1, v/v)) eluate fractions, Isomer B (10 mg, 1.7%) was obtained as a white crystalline solid. ^{1}H-NMR (DMSO-d_6) δ: 1.11-1.30 (m, 5H), 1.80-2.11 (m, 7H), 2.29 (s, 3H), 3.44-4.00 (m, 9H), 7.02-7.08 (m, 2H), 7.21-7.29 (m, 4H), 7.79-7.81 (m, 1H).

Example 23

4-(1-(2-(2-Methylphenylamino)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)-3-methylcyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl 4-hydroxy-3-methylbenzoate

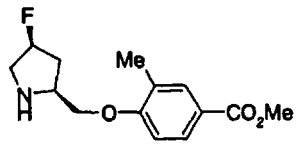


In DMSO (10 ml) and methanol (5 ml) were dissolved 4-hydroxy-3-methyliodobenzene (3.13 g, 13.4 mmol), triethylamine (4.11 ml, 29.5 mmol), palladium acetate (150 mg, 0.67 mmol) and 1,3-bis(diphenylphosphino)propane (276 mg, 0.67 mmol). Under stirring at room temperature, a carbon monoxide gas was introduced for 10 minutes. The reaction mixture was further stirred at 70°C for 2 days under a carbon monoxide gas stream. After cooling to room temperature, the reaction mixture was concentrated. The concentrate was poured in water (20 ml), followed by extraction with ethyl acetate. The extract was washed

successively with water (× 2) and saturated brine (× 2), dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (5:1) eluate fractions, methyl 4-hydroxy-3-methylbenzoate (2.00 g, 90%) was obtained as a white crystalline solid.

^{1}H-NMR ($CDCl_3$) δ: 2.28 (s, 3H), 3.90 (s, 3H), 6.20 (brs, 1H), 6.83 (d, J=8.4Hz, 1H), 7.79 (d, J=8.4Hz, 1H), 7.85 (s, 1H).

(Step 2) Synthesis of methyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)-3-methylbenzoate



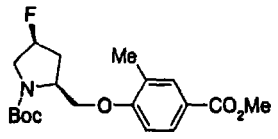
Methyl 4-hydroxy-3-methylbenzoate (1.98 g, 11.9 mmol), N-tert-butoxycarbonyl-(4S)-fluoro-(2S)-pyrrolidinylmethanol (2.87 g, 13.1 mmol) and triphenylphosphine (3.43 g, 13.1 mmol) were dissolved in THF (50 ml). Under stirring at room temperature, diisopropyl azodicarboxylate (2.57 ml, 13.1 mmol) was added and the reaction mixture was stirred overnight at 60°C. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (4:1) eluate

fractions, methyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)-3-methylbenzoate was obtained. This compound was not purified further. Methylene chloride (50 ml) and trifluoroacetic acid (25 ml) were added. The mixture was then stirred at room temperature for 20 minutes. To the residue obtained by distilling off the solvent under reduced pressure, a saturated aqueous saturated solution of sodium bicarbonate was added to make it alkaline, followed by extraction with chloroform. The extract was dried over anhydrous sodium sulfate and dried under reduced pressure to remove the solvent, whereby methyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)-3-methylbenzoate (551 mg, 17%) was obtained as a colorless solid (this compound was provided for the subsequent reaction without further purification).

^{1}H-NMR ($CDCl_3$) δ: 1.53 (brs, 1H), 1.63-1.76 (m, 1H), 1.86-2.01 (m, 1H), 1.92 (s, 3H), 2.58-2.71 (m, 1H), 3.01-3.10 (m, 1H), 3.26 (brs, 1H), 3.55 (s, 3H), 3.72-3.82 (m, 2H), 4.84-5.00 (m, 1H), 6.49 (d, J=8.4Hz, 1H), 7.51 (s, 1H), 7.53 (dd, J=8.8,2.8Hz, 1H).

MS (ESI) m/z, 309 (M^++CH_3CN).

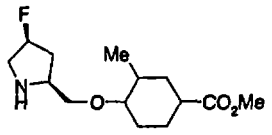
(Step 3) Methyl 4-(N-tert-butoxycarbonyl-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)-3-methylbenzoate



Methyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)-3-methylbenzoate (2.04 g, 7.63 mmol) and di-tert-butyl dicarbonate (2.00 g, 9.16 mmol) were dissolved in acetonitrile (50 ml). At room temperature, 1.0M-NaOH (9.16 ml, 9.16 ml) was added and the mixture was stirred for 30 minutes. The reaction mixture was poured in 1.0N-HCl (20 ml), followed by extraction with ethyl acetate. The extract was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The crude crystals thus obtained were recrystallized from ethyl acetate-hexane, whereby methyl 4-(N-tert-butoxycarbonyl-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)-3-methylbenzoate (2.43 g, 86%) was obtained as a colorless crystalline powder.

MS (ESI) m/z, 368 (M^++H).

(Step 4) Methyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)-3-methylcyclohexanecarboxylate



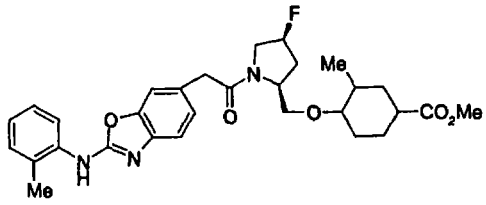
In ethanol-acetic acid (10:1, 16.5 ml), methyl 4-(N-tert-butoxycarbonyl-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)-3-methylbenzoate (2.26 g, 6.17 mmol) and 5%-rhodium-alumina were subjected to catalytic hydrogenation at room temperature under stirring in a hydrogen gas stream of 5

atm. The catalyst was filtered off and from the filtrate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (4:1) eluate fractions, methyl 4-(N-tert-butoxycarbonyl-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)-3-methylcyclohexanecarboxylate (2.22 g, 96%) was obtained as a colorless oil. The resulting methyl 4-(N-tert-butoxycarbonyl-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)-3-methylcyclohexanecarboxylate (2.22 g, 5.94 mmol) was dissolved in methylene chloride (30 ml). Trifluoroacetic acid (10 ml) was added and the mixture was stirred at room temperature for 30 minutes. A saturated aqueous solution of sodium bicarbonate was added to the residue, which had been obtained by distilling off the solvent under reduced pressure, to neutralize it, followed by extraction with a chloroform-methanol (about 10:1). The extract was then dried over anhydrous sodium sulfate and the solvent was distilled off under reduced pressure, whereby methyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)-3-methylcyclohexanecarboxylate (1.58 g, 98%), a mixture of diasteromers, was obtained as a colorless oil (this compound was provided for the subsequent reaction without further purification).

^{1}H-NMR ($CDCl_3$), mixture of diastereomers, δ: 0.97-1.00 (m,

3H), 1.23-1.33 (m, 1H), 1.54-1.69 (m, 5H), 1.80-1.94 (m, 1H), 2.05-2.22 (m, 3H), 2.28-2.35 (m, 1H), 2.78-2.91 (m, 1H), 3.24-3.37 (m, 4H), 3.59-3.69 (m, 1H), 3.65 and 3.66 (s, total 3H), 5.10-5.26 (m, 1H).

(Step 5) Synthesis of methyl 4-(1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)-3-methylcyclohexanecarboxylate



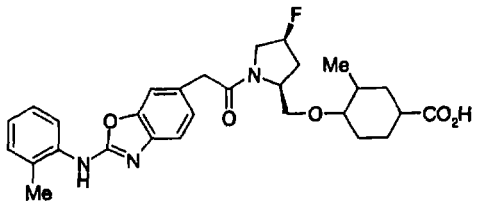
At room temperature, DMF (10 ml) and EDC·HCl (169 mg, 0.88 mmol) were added to methyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)-3-methylcyclohexanecarboxylate (219 mg, 0.59 mmo), 2-(2-methylphenylamino)-6-benzoxazolylacetic acid (182 mg, 0.65 mmol), HOBt (8.0 mg, 0.06 mmol) and DMAP (7.2 mg, 0.06 mmol). The mixture was stirred overnight at room temperature. The reaction mixture was poured in water (30 ml), followed by extraction with ethyl acetate. The extract was washed with saturated brine (three times), dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue thus obtained was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (1:5) eluate fractions, methyl 4-(1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)-

3-methylcyclohexanecarboxylate (344 mg, quant.), a mixture of two diastereomers, was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$), mixture of diastereomers and rotamers, δ: 0.94-1.03 (m, 3H), 1.18-2.55 (series of m, 12H), 2.36 (s, 3H), 3.18-4.52 (series of m, 7H), 3.54-3.68 (m, 3H), 5.15-5.31 (m, 1H), 7.05-7.40 (series of m, 7H), 8.05 (d, J=8.4Hz, 1H).

MS (ESI) m/z, 538 (M^++H).

(Step 6) Synthesis of 4-(1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)-3-methylcyclohexanecarboxylic acid



Methyl 4-(1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)-3-methylcyclohexanecarboxylate (329 mg, 0.61 mmol) was dissolved in methanol-THF (15:2, 17 ml). To the resulting solution was added 0.25M-NaOH (4.90 ml, 1.22 mmol) and the mixture was stirred overnight at room temperature. The reaction mixture was poured in 1N-HCl (10 ml), followed by extraction with a chloroform-methanol (10:1, v/v) mixture. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced

pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (1:4) eluate fractions, 4-(1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)-3-methylcyclohexanecarboxylic acid (259 mg, 81%), a mixture of diasteromers, was obtained as a colorless oil.

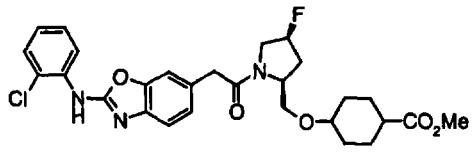
^{1}H-NMR ($CDCl_3$), mixture of diastereomers and rotamers, δ: 0.95-1.03 (m, 3H), 1.24-2.55 (series of m, 12H), 2.34, 2.35 and 2.36 (s, total 3H), 3.16-4.40 (series of m, 7H), 5.10-5.30 (m, 1H), 7.06-7.85 (series of m, 8H).

MS (ESI) m/z, 524 (M^++H).

Example 24

4-(1-(2-(2-Chlorophenylamino)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid, Isomer A and Isomer B

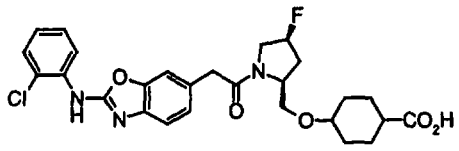
(Step 1) Synthesis of methyl 4-(1-(2-(2-chlorophenylamino)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



In DMF (10 ml), a mixture of 2-(2-chlorophenylamino)-6-benzoxazolylacetic acid (605 mg, 2.0 mmol), methyl 4-

((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (519 mg, 2.0 mmol, a mixture of cis and trans forms), EDC·HCl (575 mg, 3.0 mmol), HOBt (405 mg, 3.0 mmol) and triethylamine (1.39 ml, 10.0 mmol) was stirred at room temperature for 16 hours. The reaction mixture was poured in ice water (30 ml), followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica gel: 50 g), whereby from chloroform/acetone (10/1) eluate fractions, the title compound (770 mg, 71%), a mixture of diasteromers, was obtained as a brown oil (this compound was provided for the subsequent reaction without further purification).

(Step 2) Synthesis of 4-(1-(2-(2-chlorophenylamino)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid, Isomer A and Isomer B



Methyl 4-(1-(2-(2-chlorophenylamino)-6-

benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (770 mg, 1.42 mmol), a mixture of diasteromers, was dissolved in THF (20 ml). After addition of 0.25N NaOH (20 ml), the resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was then concentrated under reduced pressure. The concentrate was acidified with 1N HCl, followed by extraction with a chloroform/methanol (10/1) mixture. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. From the residue, two diasteromers were separated and purified by HPLC (C_{18}, 30 × 300 mm, 0.02M sodium acetate buffer/acetonitrile (1/1), 20 ml/min). Their fractions were distilled under reduced pressure to remove the solvent. After the residue was acidified with 1N HCl, extraction was performed with a chloroform/methanol (10/1) mixture. The extracts were washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent, whereby Isomer A (161 mg, 21%) was obtained as a pale brown amorphous substance, while Isomer B (631 mg, 71%) was obtained as a pale brown amorphous substance.

Isomer A:

IR (KBr) 3406, 2937, 2862, 1724, 1703, 1637, 1587, 1572, 1533 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 0.82-1.41 (m, 4H), 1.83-2.20 (m, 6H), 3.16-4.32 (m, 9H), 5.22-5.43 (m, 1H), 706 (t, J=9.3Hz, 1H), 7.18 (t, J=7.0Hz, 1H), 7.32 (m, 2H), 7.41 (t, J=8.0Hz, 1H), 8.67 (m, 1H).

MS (ESI) m/z, 530 (M^++1), 532 (M^++3).

Isomer B:

IR (KBr) 3404, 2939, 1868, 1720, 1701, 1637, 1597 cm^{-1};

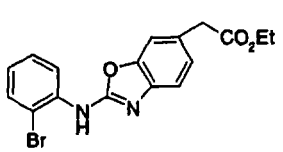
^{1}H-NMR (DMSO-d_6) δ: 1.44-1.72 (m, 7H), 2.12-2.36 (m, 3H), 3.14 (t, J=9.3Hz, 1H), 3.37-4.42 (m, 8H), 5.24-5.44 (m, 1H), 7.06 (t, J=9.3Hz, 1H), 7.18 (t, J=7.3Hz, 1H), 7.29 and 7.31 (each s, total 1H, amide isomers), 7.32 and 7.33 (each s, total 1H, amide isomers), 7.41 (t, J=7.6Hz, 1H), 7.52 (d, J=8.3Hz, 1H), 8.08 (d, J=8.0Hz, 1H).

MS (ESI), m/z 530 (M^++1), 532 (M^++3).

Example 25

4-(1-(2-(2-Bromophenylamino)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid, Isomer A and Isomer B:

(Step 1) Synthesis of ethyl 2-(2-bromophenylamino)-6-benzoxazolylacetate



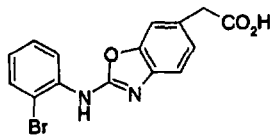
Methyl 3-hydroxy-4-aminophenylacetate (2.97 g, 16.4

mmol) was dissolved in methanol (30 ml). Under stirring at room temperature, 2-bromophenyl isothiocyanate (2.65 ml, 19.7 mmol) was added to the resulting solution. The reaction mixture was then stirred at room temperature for 1.5 hours. Mercuric oxide (yellow) (3.55 g, 16.4 mmol) was added to the reaction mixture, followed by heating and refluxing for 50 minutes. After cooling the reaction mixture to room temperature, the insoluble matter was filtered off through Celite under reduced pressure. The filtrate was distilled under reduced pressure to remove the solvent. The residue was then purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (4:1) eluate fractions, ethyl 2-(2-bromophenylamino)-6-benzoxazolylacetate (3.87 g, 66%) was obtained as a colorless solid.

^{1}H-NMR ($CDCl_3$) δ: 3.71 (s, 3H), 3.73 (d, J=16.8Hz, 2H), 6.94-6.98 (m, 1H), 7.15 (d, J=8.0Hz, 1H), 7.32 (s, 1H), 7.38-7.43 (m, 1H), 7.46 (d, J=8.4Hz, 1H), 7.53 (brs, 1H), 7.55-7.58 (m, 1H), 8.52 (dd, J=8.4,1.2Hz, 1H).

MS (ESI) m/z 361 (M^+), 363 (M^++2).

(Step 2) Synthesis of 2-(2-bromophenylamino)-6-benzoxazolylacetic acid

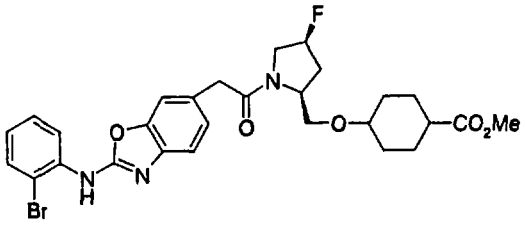


Ethyl 2-(2-bromophenylamino)-6-benzoxazolylacetate (3.82 g, 10.6 mmol) was dissolved in THF-methanol (1:1, 40 ml). To the resulting solution, 1.0M-NaOH (52.0 ml, 52.0 mmol) was added, followed by stirring at room temperature for 1.5 hours. To the residue, which had been obtained by distilling off the solvent under reduced pressure, was acidified with 1.0N-HCl. The crystals thus obtained were collected by filtration under reduced pressure, washed with water and dried overnight under reduced pressure at 60°C, whereby 2-(2-bromophenylamino)-6-benzoxazolylacetic acid (3.40 g, 93%) was obtained as a white crystalline powder.

^{1}H-NMR (DMSO-d_6) δ: 3.71 (s, 2H), 7.16 (d, J=8.0Hz, 2H), 7.21 (t, J=8.0Hz, 1H), 7.36 (d, J=8.0Hz, 1H), 7.50 (s, 1H), 7.52 (t, J=7.6Hz, 1H), 7.77 (d, J=8.0Hz, 1H), 8.01 (d, J=7.6Hz, 1H).

MS (ESI) m/z, 347 (M^+), 349 (M^++2).

(Step 3) Synthesis of methyl 4-(1-(2-(2-bromophenylamino)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



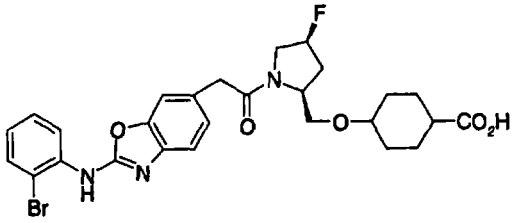
Methyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (267 mg, 1.03 mmol), 2-(2-bromophenylamino)-6-benzoxazolylacetic acid (357 mg, 1.03 mmol) and HOBt (14.0 mg, 0.10 mmol) were dissolved in DMF (10 ml). EDC·HCl (217 mg, 1.13 mmol) was added to the resulting solution and the mixture was stirred overnight at room temperature. The reaction mixture was poured in water (20 ml), followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (1:5) eluate fractions, methyl 4-(1-(2-(2-bromophenylamino)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (580 mg, 96%), a mixture of two diasteromers, was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$), mixture of diasteromers and rotamars, δ: 1.24-2.54 (series of m, 11H), 3.20-4.42 (series of m, 8H), 3.64-3.69 (m, 3H), 5.15-5.35 (m, 1H), 6.95 (t, J=7.8Hz, 1H), 7.12 (t, J=8.1Hz, 1H), 7.31-7.57 (m, 3H), 7.95 (d,

J=9.0Hz, 1H), 8.52 (d, J=8.3Hz, 2H).

MS (ESI) m/z, 588 (M^+), 590 (M^++2).

(Step 4) Synthesis of 4-(1-(2-(2-bromophenylamino)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid, Isomer A and Isomer B



Methyl 4-(1-(2-(2-bromophenylamino)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (562 mg, 0.96 mmol), a mixture of two diasteromers, was dissolved in methanol-THF (15:2, 17 ml). To the resulting solution was added 0.25M-NaOH (7.64 ml, 1.191 mmol) and the mixture was stirred overnight at room temperature. The reaction mixture was poured in 1N-HCl (10 ml), followed by extraction with a chloroform-methanol mixture. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from ethyl acetate eluate fractions, 4-(1-(2-(2-bromophenylamino)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-

pyrrolidinylmethoxy)cyclohexanecarboxylic acid (345 mg, 63%), a mixture of two diasteromers, was obtained as a colorless amorphous substance. The mixture of two diastereomers was separable by HPLC (Shimpack PRC-ODS-30 mm × 250 mm, acetonitrile : 0.02N-sodium acetate buffer = 1:1, 20 ml/min) so that Isomer A (polar fraction) and Isomer B (less polar fraction) were obtained, each as a colorless amorphous substance.

Isomer A;

^{1}H-NMR ($CDCl_3$), mixture of rotamars, δ: 1.23-1.35 (m, 2H), 1.43-1.53 (m, 2H), 2.01-2.48 (series of m, 6H), 3.28-3.53 (series of m, 2H), 3.63-3.92 (series of m, 6H), 4.01 (d, J=15.2Hz, 1H), 4.22-4.42 (m, 1H), 5.17-5.33 (m, 1H), 6.98 (t, J=7.6Hz, 1H), 7.12-7.14 (m, 1H), 7.27 (s, 1H), 7.34 (d, J=6.8Hz, 1H), 7.40-7.47 (m, 2H), 7.58 (d, J=8.0Hz, 1H), 8.47 (d, J=8.4Hz, 1H).

MS (ESI) m/z 574 (M^+), 576 (M^++2).

Isomer B;

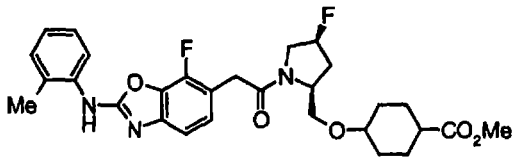
^{1}H-NMR ($CDCl_3$), mixture of rotamars, δ: 1.26-1.55 (m, 2H), 1.67-1.75 (m, 2H), 1.81-1.93 (m, 4H), 2.00-2.53 (series of m, 3H), 3.34-4.09 (series of m, 7H), 4.22-4.43 (series of m, 1H), 5.17-5.32 (m, 1H), 6.95-6.99 (m, 1H), 7.13 (t, J=8.0Hz, 1H), 7.26 (s, 1H), 7.34 (d, J=11.6Hz, 1H), 7.39-7.46 (m, 2H), 7.58 (d, J=8.0Hz, 1H), 8.47 (t, J=6.8Hz, 1H).

MS (ESI) m/z, 574 (M^+), 576 (M^++2).

Example 26

4-(1-(7-Fluoro-2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid, Isomer A and Isomer B:

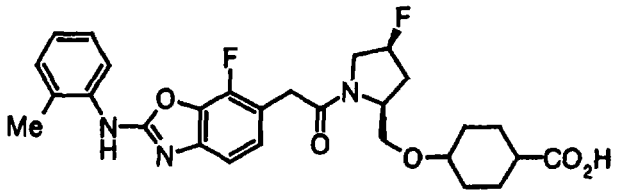
(Step 1) Synthesis of methyl 4-(1-(7-fluoro-2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



In DMF (5 ml), a mixture of 7-fluoro-2-(2-methylphenylamino)-6-benzoxazolylacetic acid (240 mg, 0.8 mmol), methyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (207 mg, 0.8 mmol, a mixture of cis and trans forms), EDC·HCl (230 mg, 1.2 mmol), HOBt (162 mg, 1.2 mmol) and triethylamine (0.56 ml, 4.0 mmol) was stirred at room temperature for 22 hours. The reaction mixture was poured in ice water (30 ml) and the mixture was extracted with ethyl acetate. The extract was washed with ice water and saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica gel: 40

g), whereby from chloroform/acetone (10/1) eluate fractions, the title compound (710 mg, 100%), a mixture of two diastereomers, was obtained as a colorless amorphous substance (this compound was provided for the subsequent reaction without further purification).

(Step 2) Synthesis of 4-(1-(7-fluoro-2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid, Isomer A and Isomer B



To a solution of methyl 4-(1-(7-fluoro-2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (710 mg, 0.80 mmol) in THF (40 ml) was added 0.25N NaOH (40 ml). The resulting mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated under reduced pressure. The residue was acidified with 1N HCl, followed by extraction with a chloroform/methanol (10/1) mixture. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. From the residue, two diasteromers were separated and purified by HPLC (C_{18}, 30 ×

300 mm, 0.02 M sodium acetate buffer/acetonitrile (1/1), 20 ml/min). Their fractions were distilled under reduced pressure to remove the solvent. The residue was acidified with 1N HCl, followed by extraction with a chloroform/methanol (10/1) mixture. The extracts were washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent, whereby the title compound (Isomer A) (68 mg, 16% (2 steps)) was obtained as a colorless solid, while the title compound (Isomer B) (206 mg, 49% (2 steps), including 5% of Isomer A) was obtained as a colorless solid.

Isomer A:

IR (ATR) 2937, 2864, 2330, 1637, 1579 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 0.86 (t, J=5.4Hz, 1H), 1.17-1.40 (m, 5H), 1.85-2.22 (m, 6H), 2.30 (s, 3H), 3.19 (t, J=8.3Hz, 1H), 3.38-4.37 (m, 6H), 5.25-5.47 (m, 1H), 6.99-7.13 (m, 3H), 7.25 (d, J=6.8Hz, 2H), 7.80 (d, J=8.6Hz, 1H), 9.87 (br, 1H), 12.05 (br, 1H).

MS (ESI), m/z 528 (M^++1).

Isomer B:

IR (ATR) 2939, 2870, 1722, 1699, 1639, 1579, 1454 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 0.86 (s, 1H), 1.18 (s, 1H), 1.24 (s, 1H), 1.40-1.82 (m, 6H), 1.91 and 1.99 (each s, total 1H, amide isomers), 2.10-2.29 (m, 2H), 2.37 (s, 3H), 3.17 (t, J=7.6Hz, 1H), 3.44-4.50 (m, 6H), 5.33 and 5.41 (each d,

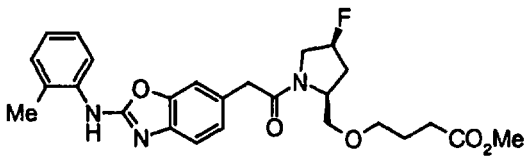
J=54.8 and 53.6Hz respectively, total 1H, amide isomers), 7.04 (m, 1H), 7.11 (s, 2H), 7.25 (s, 3H), 7.80 (d, J=7.3Hz, 1H), 9.88 (br, 1H), 12.01 (br, 1H).

MS (ESI), m/z 528 (M^++1).

Example 27

4-((2S,4S)-4-Fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-2-pyrrolidinylmethoxy)-n-butyric acid:

(Step 1) Synthesis of methyl 4-((2S,4S)-4-fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-2-pyrrolidinylmethoxy)-n-butyrate



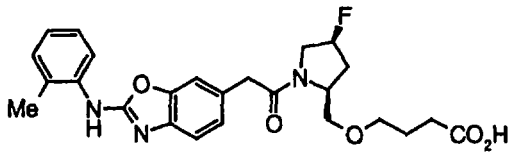
In DMF (4 ml), 2-(2-methylphenylamino)-6-benzoxazolyl-n-acetic acid (282 mg, 1.0 mmol), methyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)-n-butyrate (219 mg, 1.0 mmol), EDC·HCl (288 mg, 1.5 mmol), HOBT (203 mg, 1.5 mmol) and triethylamine (5.0 ml, 0.70 mmol) were stirred at room temperature for 23 hours. The reaction mixture was poured in ice water, followed by extraction with ethyl acetate. The extract was washed with ice water and saturated brine. The organic layer was dried over anhydrous sodium sulfate and then, distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a

silica gel column (silica gel: 50g, chloroform/acetone (10/1)), followed by further separation and purification by thin-layer silica gel column chromatography (TLC) (chloroform/acetone (10/1)), whereby the title compound (378 mg, 78%) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.22 (t, J=6.9Hz, 2H), 1.88-2.30 (m, 3H), 2.35 (s, 3H), 2.37-2.45 (m, 3H), 3.28-4.00 (m, 9H), 4.12-4.48 (m, 1H), 7.07 (m, 2H), 7.22 (d, J=7.3Hz, 1H), 7.29-7.32 (m, 3H), 7.38 (dd, J=8.1,4.9Hz, 1H), 8.05 (d, J=8.1Hz, 1H).

MS (ESI) m/z 484 (M^++1).

(Step 2) Synthesis of 4-((2S,4S)-4-fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-2-pyrrolidinylmethoxy)-n-butyric acid



Methyl 4-((2S,4S)-4-fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-2-pyrrolidinylmethoxy)-n-butyrate (378 mg, 0.782 mmol) was dissolved in THF (20 ml). To the resulting solution was added 0.25N NaOH (20 ml) and the mixture was stirred at 50°C for 18 hours. The reaction mixture was concentrated under reduced pressure. The residue was acidified with 1N HCl, followed by extraction

with a chloroform/methanol (10/1) mixture. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was then purified by thin-layer silica gel column chromatography (TLC), whereby from chloroform/methanol (10/1) eluate fractions, 4-((2S,4S)-4-fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-2-pyrrolidinylmethoxy)-n-butyric acid (99 mg, 27%) was obtained as a yellow oil. Ethanol (3 ml) and 1N NaOH (211 µl, 0.211 mmol) were added to the resulting 4-((2S,4S)-4-fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-2-pyrrolidinylmethoxy)-n-butyric acid (99 mg, 0.211 mmol) under stirring to dissolve the latter in the former. The resulting solution was concentrated to dryness. Ether was added to crystallize the residue, whereby sodium 4-((2S,4S)-4-fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-2-pyrrolidinylmethoxy)-n-butyrate (81 mg) was obtained as a solid.

Sodium salt IR (KBr) 3410, 3251, 2964, 2870, 1641, 1574, 1439 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.68-2.30 (m, 5H), 2.24 (s, 3H), 2.42 (m, 2H), 3.30-4.00 (m, 7H), 4.26 and 4.40 (q and m, J=6.8Hz respectively, total 1H, amide isomers), 5.21 (dd, J=53.6,3.9Hz, 1H), 7.07 (d, J=6.6Hz, 2H), 7.14-7.26 (m, 4H), 7.30 (d, J=7.6Hz, 1H), 7.72 (m, 1H).

MS (ESI) m/z 470 (M^++1);

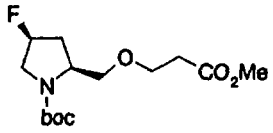
Anal. Calcd for $C_{25}H_{27}FN_3O_5 \cdot Na \cdot 3H_2O$: C, 55.04; H, 6.10; N, 7.70.

Found: C, 55.26; H, 5.95; N, 7.38.

Example 28

5-((2S,4S)-4-Fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-2-pyrrolidinyl)methoxypentanoic acid:

(Step 1) Synthesis of methyl 3-(1-tert-butoxycarbonyl-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)propionate



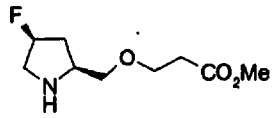
Sodium hydride (60% in oil, 365 mg, 9.12 mmol) was suspended in THF (20 ml). Under stirring at -50°C, a solution of (2S,4S)-1-(tert-butoxycarbonyl)-4-fluoro-2-prolinol (1.00 g, 4.56 mmol) in THF (15 ml) was added to the resulting suspension and the mixture was stirred at the same temperature for 5 minutes. To the reaction mixture was added methyl acrylate (0.95 ml, 10.5 mmol) at the same temperature. The reaction mixture was stirred for 15 minutes at the same temperature, followed by stirring for further 14 hours at -40°C. The reaction mixture was acidified with acetic acid (1 ml). After addition of water (20 ml), the mixture was extracted with ethyl acetate. The

extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica gel: 50 g), whereby from hexane/ethyl acetate (2/1) eluate fractions, the title compound (670 mg, 48%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.47 (s, 9H), 1.98-2.15 (m, 1H), 2.36 (dd, J=20.5,5.6Hz, 1H), 2.58 (t, J=6.6Hz, 1H), 3.35 (t, J=9.0Hz, 1H), 3.48-3.80 (m, 7H), 3.94-4.17 (m, 1H), 5.19 (d, J=53.1Hz, 1H).

MS (ESI) m/z 306 (M^++1).

(Step 2) Synthesis of methyl 3-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)propionate

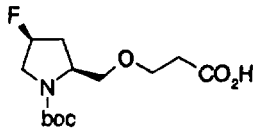


In methylene chloride (20 ml), trifluoroacetic acid (10 ml) was added to methyl 3-(1-tert-butoxycarbonyl-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)propionate (670 mg, 2.19 mmol) and the mixture was stirred at room temperature for 7 hours. The reaction mixture was concentrated under reduced pressure. Under ice cooling, the residue was basified with 1N NaOH, followed by extraction with methylene chloride. The extract was washed with saturated

brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent, whereby the title compound (480 mg, 100%) was obtained as a yellow oil (this compound was provided for the subsequent reaction without further purification).

^{1}H-NMR ($CDCl_3$) δ: 1.79 (m, 1H), 2.02 (br, 1H), 2.04-2.21 (m, 1H), 2.60 (t, J=6.3Hz, 2H), 2.90 (m, 1H), 3.31 (m, 1H), 3.49 (dd, J=9.5,6.6Hz, 1H), 3.56 (dd, J=9.5,4.6Hz, 1H), 3.69 (s, 3H), 3.75 (dt, J=6.6,2.2Hz, 2H), 5.18 (dt, J=54.8,3.7Hz, 1H).

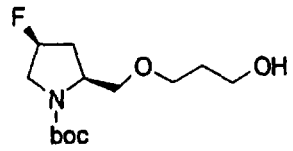
(Step 3) Synthesis of 3-((2S,4S)-1-(tert-butoxycarbonyl)-4-fluoro-2-pyrrolidinylmethoxy)propionic acid



Methyl 3-((2S,4S)-1-(tert-butoxycarbonyl)-4-fluoro-2-pyrrolidinylmethoxy)propionate (2.84 g, 9.30 mmol) was dissolved in THF (40 ml). To the resulting solution was added 0.25N NaOH (40 ml) and the mixture was stirred at room temperature for 19 hours. The solvent was distilled off under reduced pressure. After the residue was acidified with 1N HCl, extraction was conducted with ethyl acetate. The extract was washed with ice water and brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent, whereby the title

compound (2.48 g, 92%) was obtained as a colorless oil (this compound was provided for the subsequent reaction without further purification).

(Step 4) Synthesis of 3-((2S,4S)-1-(tert-butoxycarbonyl)-4-fluoro-2-pyrrolidinylmethoxy)propanol



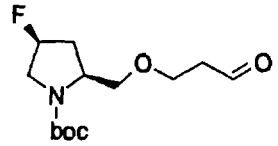
In THF (100 ml) was dissolved 3-((2S,4S)-1-(tert-butoxycarbonyl)-4-fluoro-2-pyrrolidinylmethoxy)propionic acid (2.48 g, 8.51 mmol). At room temperature, a 10.0M borane-dimethyl sulfide solution (2.79 ml, 27.9 mmol) was added and the mixture was stirred at room temperature for 3.5 hours and then, at 60°C for 30 minutes. After cooling to room temperature, the reaction mixture was poured in ice water (100 ml), followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica gel: 50 g), whereby from chloroform/methanol (20/1) eluate fractions, the title compound (2.84 g, 100%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.47 (s, 9H), 1.64-1.73 (m, 1H), 1.83 (br, 2H), 2.00-2.41 (m, 2H), 3.37 (t, J=9.1Hz, 1H), 3.50-

4.23 (m, 7H), 5.11 (d, J=53.1Hz, 1H).

MS (ESI), m/z 278 (M^++1).

(Step 5) Synthesis of 3-((2S,4S)-1-(tert-butoxycarbonyl)-4-fluoro-2-pyrrolidinylmethoxy)propionaldehyde

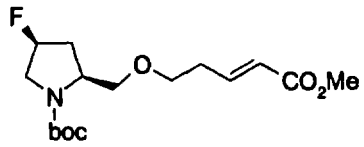


In methylene chloride (43 ml) were dissolved 3-((2S,4S)-1-(tert-butoxycarbonyl)-4-fluoro-2-pyrrolidinylmethoxy)propanol (2.84 g, 9.30 mmol), triethylamine (7.78 ml, 55.8 mmol) and DMSO (6.61 ml, 93.7 mmol). Under stirring at 0°C, a pyridine - sulfur trioxide complex (4.44 g, 27.9 mmol) was added dropwise to the resulting solution. After completion of the dropwise addition, the reaction mixture was stirred at room temperature for 2 hours. Water (50 ml) was added to the residue obtained by distilling off the solvent under reduced pressure, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica gel: 50 g), whereby hexane/ethyl acetate (4/1) eluate fractions, the title compound (1.35 g, 53%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.47 (s, 9H), 1.95-2.16 (m, 1H), 2.34 (t, J=17.1Hz, 1H), 2.65 (br, 2H), 3.36 (t, J=9.8Hz, 1H), 3.46-4.19 (m, 6H), 5.20 (d, J=53.7Hz, 1H), 9.79 (s, 1H).

MS (ESI), m/z 278 (M^++1).

(Step 6) Synthesis of methyl (E)-5-((2S,4S)-1-(tert-butoxycarbonyl)-4-fluoro-2-pyrrolidinylmethoxy)-2-pentenoate

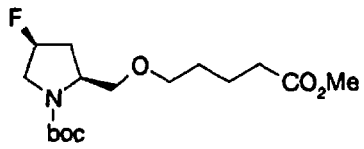


Trimethyl phosphonoacetate (0.95 ml, 5.88 mmol) was dissolved in THF (40 ml). Under a nitrogen gas stream, sodium hydride (60% in oil, 235 mg, 5.88 mmol) was added in portions to the resulting solution, while stirring at 0°C. After stirring the reaction mixture at the same temperature for 10 minutes, a solution of 3-((2S,4S)-1-(tert-butoxycarbonyl)-4-fluoro-2-pyrrolidinylmethoxy)propionaldehyde (1.35 g, 4.90 mmol) in THF (40 ml) was added dropwise at 0°C. The reaction mixture was further stirred for 2 hours at 0°C and poured in ice water (50 ml), followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica

gel: 50 g), whereby from chloroform/acetone (10/1) eluate fractions, the title compound (1.40 g, 86%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.47 (s, 9H), 2.02-2.221 (m, 1H), 2.30-2.58 (m, 3H), 3.34 (t, J=10.0Hz, 1H), 3.45-3.71 (m, 7H), 3.73 (s, 3H), 5.21 (d, J=55.3Hz, 1H), 5.89 (d, J=15.9Hz, 1H), 6.95 (dt, J=15.9,7.1Hz, 1H).

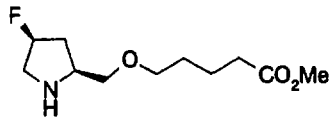
(Step 7) Synthesis methyl 5-((2S,4S)-1-(tert-butoxycarbonyl)-4-fluoro-2-pyrrolidinylmethoxy)pentanoate



Methyl 5-((2S,4S)-1-(tert-butoxycarbonyl)-4-fluoro-2-pyrrolidinylmethoxy)-2-pentenoate (1.40 g, 4.22 mmol) and 5% palladium/carbon (wet.) (700 mg) were suspended in methanol (50 ml). Under stirring at room temperature, the resulting suspension was subjected to catalytic hydrogenation at normal pressure for 20 hours. The catalyst was filtered off and the filtrate was distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica gel: 20 g), whereby from hexane/ethyl acetate (4/1) eluate fractions, the title compound (1.09 g, 78%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.47 (s, 9H), 1.61-1.74 (m, 3H), 1.98-2.18 (m, 2H), 2.31-2.42 (m, 3H), 3.31 (dt, J=7.9,1.5Hz, 1H), 3.40-3.66 (m, 4H), 3.67 (s, 3H), 3.73 (m, 1H), 4.09 (br, 1H), 5.20 (d, J=52.7Hz, 1H).

(Step 8) Synthesis of methyl 5-((2S,4S)-4-fluoro-2-pyrrolidinylmethoxy)pentanoate

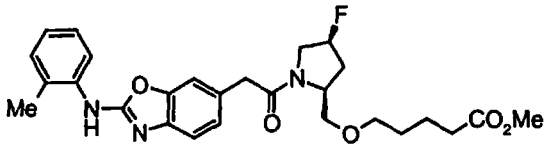


Methyl 5-((2S,4S)-1-(tert-butoxycarbonyl)-4-fluoro-2-pyrrolidinylmethoxy)pentanoate (1.09 g, 3.27 mmol) was dissolved in methylene chloride (50 ml). At room temperature, trifluoroacetic acid (10 ml) was added to the resulting solution. The mixture was stirred at the same temperature for 3.5 hours. The residue obtained by distilling off the solvent under reduced pressure was diluted with methylene chloride (50 ml). The solution was basified with 1N NaOH, followed by extraction with methylene chloride. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent, whereby the title compound (590 mg, 77%) was obtained as a yellow oil (this compound was provided for the subsequent reaction without further purification).

^{1}H-NMR ($CDCl_3$) δ: 1.59-1.96 (m, 5H), 2.15 (m, 1H), 2.34 (t,

J=7.1Hz, 2H), 2.86 (ddd, J=35.7,13.2,3.9Hz, 1H), 3.27-3.35 (m, 2H), 3.42-3.53 (m, 4H), 3.67 (s, 3H), 5.18 (m, 1H). MS (ESI), m/z 234 (M^++1).

(Step 9) Synthesis of methyl 5-((2S,4S)-4-fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-2-pyrrolidinylmethoxy)pentanoate



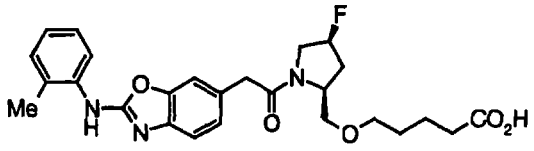
In DMF (5 ml), a mixture of 2-(2-methylphenylamino)-6-benzoxazolylacetic acid (357 mg, 1.26 mmol), methyl 5-((2S,4S)-4-fluoro-2-pyrrolidinylmethoxy)pentanoate (295 mg, 1.26 mmol), EDC·HCl (362 mg, 1.89 mmol), HOBt (255 mg, 1.89 mmol) and triethylamine (0.88 ml, 6.30 mmol) was stirred at room temperature for 1 hour. The reaction mixture was poured in ice water (50 ml), followed by extraction with ethyl acetate. The extract was washed with ice water and saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica gel: 70 g), whereby from chloroform/acetone (10/1) eluate fractions, the title compound (1.05 g, 100%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.55-1.72 (m, 4H), 1.98-2.34 (m, 2H), 2.36 (s, 3H), 2.37-2.51 (m, 1H), 3.29-3.59 (m, 3H), 3.65

(s, 3H), 3.66-4.01 (m, 6H), 4.23-4.46 (m, 1H), 5.13-5.33 (m, 1H), 7.06 (t, J=7.1Hz, 2H), 7.21 (d, J=7.3Hz, 1H), 7.24-7.35 (m, 4H), 7.96 (m, 3H).

MS (ESI), m/z 497 (M^++1).

(Step 10) Synthesis of 5-((2S,4S)-4-fluoro-1-((2-(2-methylphenylamino)-6-benzoxazolylacetyl)-2-pyrrolidinylmethoxy)pentanoic acid



Methyl 5-((2S,4S)-4-fluoro-1-((2-(2-methylphenylamino)-6-benzoxazolylacetyl)-2-pyrrolidinylmethoxy)pentanoate (1.26 mmol) was dissolved in THF (40 ml). After addition of 0.25N NaOH (40 ml), the mixture was stirred at room temperature for 14 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue was acidified with 1N HCl, followed by extraction with a chloroform/methanol (10/1) mixture. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent, whereby 5-((2S,4S)-4-fluoro-1-((2-(2-methylphenylamino)-6-benzoxazolylacetyl)-2-pyrrolidinylmethoxy)pentanoic acid (390 mg, 60%) was obtained as a brown oil. Ethanol (10 ml) and 1N NaOH (0.750 ml, 0.750 mmol) were added to 5-((2S,4S)-4-fluoro-1-

((2-(2-methylphenylamino)-6-benzoxazolylacetyl)-2-pyrrolidinylmethoxy)pentanoic acid (390 mg, 0.750 mmol). After stirring for 15 minutes, ether was added to the residue, which had been obtained by distilling off the solvent under reduced pressure, to solidify the same, whereby sodium 5-((2S,4S)-4-fluoro-1-((2-(2-methylphenylamino)-6-benzoxazolylacetyl)-2-pyrrolidinylmethoxy)pentanoate (283 mg) was obtained.

IR (KBr) 3425, 3251, 2939, 2868, 1643, 1574, 1439 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.01-1.30 (m, 3H), 1.45 (m, 4H), 1.86 (m, 2H), 2.03-2.23 (m, 2H), 2.28 (s, 3H), 3.15-4.43 (m, 6H), 5.23-5.41 (m, 1H), 6.99 (m, 2H), 7.19 (m, 5H), 7.85 (m, 1H).

MS (ESI), m/z 484 (M^++1).

Example 29

Sodium 6-((2S,4S)-4-fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-2-pyrrolidinylmethoxy)hexanoate:

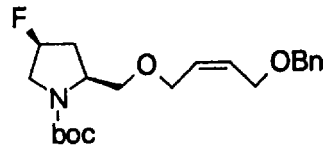
(Step 1) Synthesis of (Z)-4-benzyloxy-1-bromo-2-butene



To a solution of (Z)-4-benzyloxy-2-buten-1-ol (2.0 g, 11.2 mmol) in methylene chloride (40 ml) were added carbon tetrabromide (4.46 g, 13.4 mmol) and triphenylphosphine (3.51 g, 13.4 mmol) at 0°C under stirring in a nitrogen gas stream. After stirring at room temperature for 1.5 hours,

the reaction mixture was concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (silica gel: 50 g), whereby from hexane/ethyl acetate (4/1) eluate fractions, the title compound (2.76 g, 100%) was obtained as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 3.98 (d, J=8.3Hz, 2H), 4.15 (d, J=6.1Hz, 2H), 4.53 (s, 2H), 5.77 (m, 1H), 5.90 (m, 1H), 7.28-7.36 (m, 5H).

(Step 2) Synthesis of (Z)-(2S,4S)-2-(4-benzyloxy-2-butenyloxymethyl)-1-(tert-butoxycarbonyl)-4-fluoropyrrolidine



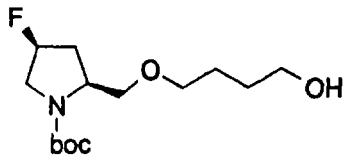
To a solution of (2S,4S)-1-(tert-butoxycarbonyl)-4-fluoro-2-pyrrolidinylmethanol (2.46 g, 11.2 mmol) in THF (100 ml), sodium hydride (60% in oil; 896 mg, 22.4 mmol) was added in portions under stirring at 0°C in a nitrogen gas stream. After stirring at the same temperature for 20 minutes, a solution of (Z)-4-benzyloxy-1-bromo-2-butene (2.76 g, 11.2 mmol) in THF (100 ml) was added. The reaction mixture was stirred for 5 minutes. To the reaction mixture was added tetra-n-butyl ammonium iodide (100 mg, 0.27 mmol) at 0°C and the mixture was stirred for 15 minutes. The reaction mixture was stirred further at

room temperature for 19 hours. Water (50 ml) was added while stirring the reaction mixture under ice cooling, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica gel: 120 g), whereby from hexane/ethyl acetate (4/1) eluate fractions, the title compound (3.30 g, 78%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.47 (s, 9H), 1.98-2.25 (m, 1H), 2.39 (dd, J=20.6,14.9Hz, 1H), 3.31 (t, J=9.3Hz, 1H), 3.48-3.81 (m, 3H), 3.95-4.18 (m, 5H), 4.51 (s, 2H), 5.20 (m, 1H), 5.70-5.84 (m, 2H), 7.27-7.53 (m, 5H).

MS (ESI) m/z 380 (M^++1).

(Step 3) Synthesis of 4-((2S,4S)-1-(tert-butoxycarbonyl)-4-fluoro-2-pyrrolidinylmethoxy)-1-butanol

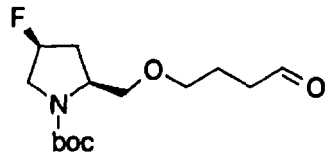


In ethanol (200 ml) were suspended (Z)-(2S,4S)-2-(4-benzyloxy-2-butenyloxymethyl)-1-(tert-butoxycarbonyl)-4-fluoropyrrolidine (4.58 g, 12.1 mmol) and 20% palladium hydroxide (4.0 g). The resulting suspension was subjected to catalytic hydrogenation at room temperature under normal

pressure for 14 hours. The catalyst was then filtered off and the filtrate was distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica gel: 100 g), whereby from chloroform/acetone (10/1) eluate fractions, the title compound (2.42 g, 67%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.47 (s, 9H), 1.6 (s, 2H), 1.98-2.23 (m, 2H), 2.38 (m, 1H), 3.36 (dt, J=10.5,1.7Hz, 1H), 3.52-3.82 (m, 8H), 4.01 and 4.13 (each br, total 1H, amide isomers), 5.21 (d, J=53.3Hz, 1H).

(Step 4) Synthesis of 4-((2S,4S)-1-(tert-butoxycarbonyl)-4-fluoro-2-pyrrolidinylmethoxy)butylaldehyde

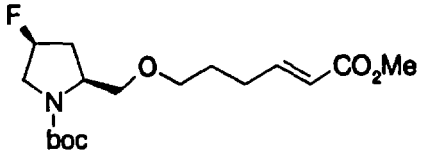


In methylene chloride (40 ml) were dissolved 4-((2S,4S)-1-(tert-butoxycarbonyl)-4-fluoro-2-pyrrolidinylmethoxy)-1-butanol (2.42 g, 8.31 mmol), triethylamine (6.95 ml, 49.9 mmol) and DMSO (5.90 ml, 83.1 mmol). Under stirring at 0°C, a pyridine - sulfur trioxide complex (3.97 g, 24.9 mmol) was added. The resulting mixture was stirred for 4 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. To

the residue was added water (50 ml), followed by extraction with ethyl acetate. The extract was washed with 1N HCl and saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica gel: 30 g), whereby from hexane/ethyl acetate (2/1) eluate fractions, the title compound (1.72 g, 72%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.47 (s, 9H), 1.91 (t, J=6.6Hz, 2H), 1.96-2.17 (m, 1H), 2.36 (t, J=15.4Hz, 1H), 2.52 (t, J=7.1Hz, 2H), 3.32 (t, J=9.8Hz, 1H), 3.49-4.14 (m, 5H), 5.20 (d, J=53.5Hz, 1H), 9.77 (s, 1H).

(Step 5) Synthesis of methyl (E)-6-((2S,4S)-1-(tert-butoxycarbonyl)-4-fluoro-2-pyrrolidinylmethoxy)-2-hexenoate

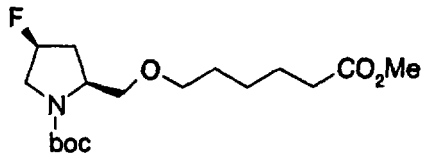


Trimethyl phosphonoacetate (1.15 ml, 7.13 mmol) was dissolved in THF (50 ml). Under a nitrogen gas stream, sodium hydride (60% in oil, 285 mg, 7.13 mmol) was added to the resulting solution in portions under stirring at 0°C. After stirring at the same temperature for 20 minutes, a solution of 4-((2S,4S)-1-(tert-butoxycarbonyl)-4-fluoro-2-pyrrolidinylmethoxy)butylaldehyde (1.72 g, 5.94 mmol) in

THF (20 ml) was added dropwise. After completion of the dropwise addition, the reaction mixture was further stirred at the same temperature for 2.5 hours. The reaction mixture was poured in ice water (50 ml), followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica gel: 100 g), whereby from hexane/ethyl acetate (4/1) eluate fractions, the title compound (1.90 g, 93%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.47 (s, 9H), 1.73 (br, 1H), 1.99-2.51 (m, 4H), 3.32 (dt, J=10.0,1.7Hz, 1H), 3.41-3.71 (m, 6H), 3.73 (s, 3H), 3.97-4.20 (m, 1H), 5.21 (d, J=53.1Hz, 1H), 5.83 (d, J=15.4Hz, 1H), 6.97 (dt, J=15.4,6.8Hz, 1H).

(Step 6) Methyl 6-((2S,4S)-1-(tert-butoxycarbonyl)-4-fluoro-2-pyrrolidinylmethoxy)hexenoate

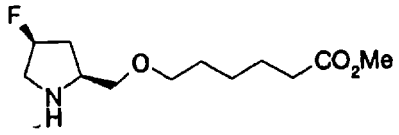


Methyl (E)-6-((2S,4S)-1-(tert-butoxycarbonyl)-4-fluoro-2-pyrrolidinylmethoxy)-2-hexenoate (1.90 g, 5.50 mmol) and 5% palladium/carbon (1.0 g) were suspended in methanol (80 ml). The resulting suspension was subjected

to catalytic hydrogenation under normal pressure for 19 hours under stirring at room temperature. The catalyst was filtered off and the filtrate was distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica gel: 3 g), whereby from ethyl acetate eluate fractions, the title compound (1.92 g, 100%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.38 (q, J=6.6Hz, 2H), 1.48 (s, 9H), 1.57-1.70 (m, 4H), 1.98-2.18 (m, 1H), 2.31 (t, J=7.3Hz, 3H), 2.39 (dd, J=20.7,15.1Hz, 1H), 3.31 (t, J=8.8Hz, 1H), 3.41-3.60 (m, 3H), 3.67 (s, 3H), 3.68-4.18 (m, 2H), 5.20 (d, J=53.0Hz, 1H).

(Step 7) Synthesis of methyl 6-((2S,4S)-4-fluoro-2-pyrrolidinylmethoxy)-2-hexanoate



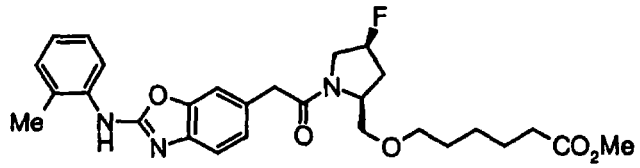
Methyl 6-((2S,4S)-1-(tert-butoxycarbonyl)-4-fluoro-2-pyrrolidinylmethoxy)hexanoate (1.92 g, 5.50 mmol) was dissolved in methylene chloride (100 ml). At room temperature, trifluoroacetic acid (10 ml) was added and the mixture was stirred for 1 hour. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue was basified with 1N NaOH, followed by

extraction with methylene chloride. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent, whereby the title compound (1.15 mg, 85%) was obtained as a pale yellow oil (this compound was provided for the subsequent reaction without further purification).

^{1}H-NMR ($CDCl_3$) δ: 1.38-1.70 (m, 6H), 2.21-2.30 (m, 1H), 2.34 (t, J=6.8Hz, 2H), 2.46-2.61 (m, 1H), 3.50-3.74 (m, 9H), 4.15 (m, 1H), 5.30-5.45 (m, 1H).

MS (ESI), m/z 248 (M^++1).

(Step 8) Synthesis of methyl 6-((2S,4S)-4-fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-2-pyrrolidinylmethoxy)hexanoate



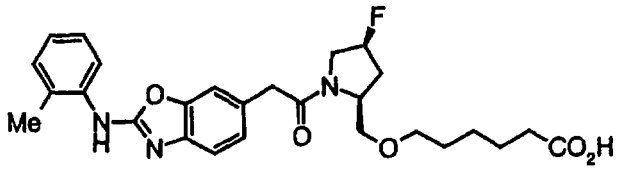
In DMF (10 ml), 2-(2-methylphenylamino)-6-benzoxazolylacetic acid (282 mg, 1.00 mmol), 6-((2S,4S)-4-fluoro-2-pyrrolidinylmethoxy)hexanoate (247 mg, 1.00 mmol), EDC·HCl (288 mg, 1.50 mmol), HOBT (203 mg, 1.50 mmol) and triethylamine (0.70 ml, 5.00 mmol) were stirred at room temperature for 22 hours. The reaction mixture was poured in ice water (50 ml), followed by extraction with ethyl acetate. The extract was washed with ice water and

saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue thus obtained was purified by thin-layer silica gel chromatography, followed by separation by using chloroform/acetone (10/1), whereby the title compound (330 mg, 65%) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.35-1.47 (m, 2H), 1.53-1.74 (m, 4H), 1.90-2.32 (m, 4H), 2.35 (s, 3H), 3.29-3.50 (m, 3H), 3.57-4.48 (m, 9H), 5.12-5.29 (m, 1H), 7.07 (dt, J=8.3,1.2Hz, 2H), 7.21 (d, J=7.3Hz, 1H), 7.29 (d, J=8.3Hz, 2H), 7.36 (dd, J=7.8,3.4Hz, 2H), 8.01 (t, J=7.1Hz, 1H).

MS (ESI), m/z 512 (M^++1).

(Step 9) Synthesis of sodium 6-((2S,4S)-4-fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-2-pyrrolidinylmethoxy)hexanoate



Methyl 6-((2S,4S)-4-fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-2-pyrrolidinylmethoxy)hexanoate (330 mg, 0.645 mmol) was dissolved in THF (30 ml). At room temperature, 0.25N NaOH (30 ml) was added and the mixture was stirred for 24 hours. The reaction mixture was distilled under reduced pressure to remove the solvent.

The residue was acidified with 1N HCl, followed by extraction with a chloroform/methanol (10/1) mixture. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by thin-layer silica gel chromatography, followed by separation by using chloroform/methanol (20/1), whereby the title compound (238 mg, 74%) was obtained as a yellow oil. Ethanol (10 ml) and 1N NaOH (0.478 ml, 0.478 mmol) were added to the resulting carboxylic acid derivative (238 mg, 0.478 mmol). After stirring for 10 minutes, ether was added to crystallize the residue, which had been obtained by distilling off the solvent under reduced pressure, whereby sodium 6-((2S,4S)-4-fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-2-pyrrolidinylmethoxy)hexanoate (199 mg) was obtained.

IR (KBr) 3423, 3211, 2937, 2864, 1643, 1574, 1485, 1574 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.36-1.72 (m, 6H), 1.92-2.28 (m, 4H), 2.34 (s, 3H), 3.26-4.00 (m, 8H), 4.20-4.43 (m, 1H), 5.21 (dt, J=54.0,4.6Hz, 1H), 7.04-7.11 (m, 2H), 7.21-7.34 (m, 5H), 7.76 (t, J=7.3Hz, 1H).

MS (ESI), m/z 498 (M^++1);

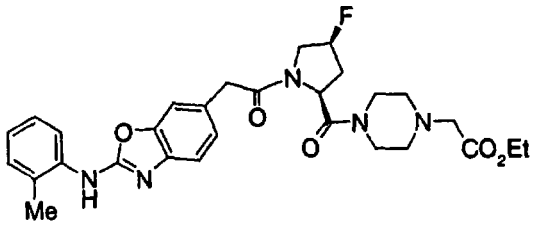
Anal. Calcd for $C_{27}H_{32}FN_3O_5 \cdot Na \cdot 1.0H_2O$: C, 60.21; H, 6.36; F, 3.53; N, 7.80.

Found: C, 60.11; H, 6.19; F, 3.28; N, 7.41.

Example 30

4-((4S)-Fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylcarbonyl)-1-piperazinylacetic acid:

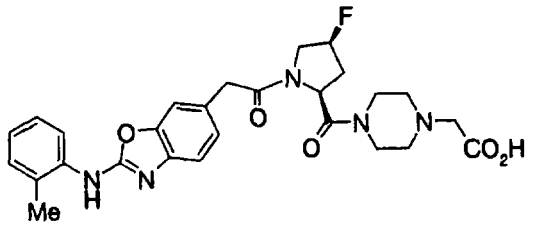
(Step 1) Synthesis of ethyl 4-((4S)-fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylcarbonyl)-1-piperazinylacetate



Ethyl 4-((4S)-fluoro-(2S)-pyrrolidinylcarbonyl)-1-pyrazinylacetate (300 mg, 1.04 mmol) was dissolved in DMF (10 ml). At room temperature, 2-(2-methylphenylamino)-6-benzoxazolylacetic acid (294 mg, 1.04 mmol), EDC·HCl (299 mg, 1.56 mmol), DMAP (cat.) and HOBt (cat.) were added successively to the resulting solution. The mixture was stirred for 15 hours. Saturated brine (100 ml) was added to the reaction mixture, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue thus obtained was purified by chromatography on a silica gel column, whereby from chloroform-methanol (20:1) eluate

fractions, the title compound (107 mg, 19%) was obtained as a yellow oil.

(Step 2) Synthesis of 4-((4S)-fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylcarbonyl)-1-piperazinylacetic acid.



Ethyl 4-((4S)-fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylcarbonyl)-1-piperazinylacetate (107 mg, 0.194 mmol) was dissolved in THF (4 ml). After addition of 0.25N NaOH (1.6 ml, 0.388 mmol), the mixture was stirred at room temperature for 15 hours. The reaction mixture was neutralized with 1N HCl and then concentrated under reduced pressure. The residue was purified using an ion exchange resin (HP20) and eluted with water and methanol, whereby the title compound (61 mg, 60%) was obtained as a yellow amorphous substance.

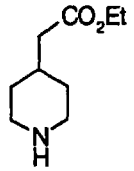
^{1}H-NMR (DMSO-d_6) δ: 1.75-2.61 (series of m, 9H, s, including 3H at δ 2.30), 2.80-4.00 (series of m, 10H), 4.82-6.02 (series of m, 2H), 6.98-7.46 (series of m, 6H), 7.82-7.94 (m, 1H).

MS (FAB) m/z, 524 (M^++1).

Example 31

1-((4S)-Fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylcarbonyl)-4-piperidinylacetic acid:

(Step 1) Synthesis of ethyl 4-piperidinylacetate

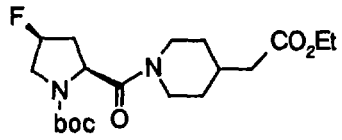


Ethyl 4-(1-(tert-butoxycarbonyl))piperidinylacetate (2.93 g, 10.8 mmol) was dissolved in methylene chloride (20 ml). After addition of trifluoroacetic acid (8 ml) at 0°C, the mixture was stirred at room temperature for 3 hours. The residue, which had been obtained by distilling the reaction mixture under reduced pressure to remove the solvent, was neutralized with a saturated aqueous solution of sodium bicarbonate, followed by extraction with a chloroform-methanol (5:1, v/v) mixture. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent, whereby ethyl 4-piperidnylacetate (1.48 g, 80%) was obtained as a yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 1.25 (t, J=7.2Hz, 3H), 1.30 (m, 2H), 1.76 (d, J=13.2Hz, 2H), 1.90 (m, 1H), 2.24 (d, J=7.2Hz, 2H), 2.63 (dt, J=1.6,13.1Hz, 1H), 2.85 (br, 1H), 3.16 (d,

J=12.4Hz, 2H), 4.13 (q, J=7.5Hz, 2H).

(Step 2) Synthesis of ethyl 1-(1-(tert-butoxycarbonyl)-(4S)-fluoro-(2S)-pyrrolidinylcarbonyl)-4-piperidinylacetate

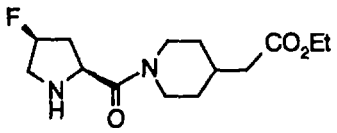


Ethyl 4-piperidinylacetate (1.48 g, 8.64 mmol) and 1-(tert-butoxycarbonyl)-(4S)-fluoro-(2S)-pyrrolidinecarboxylic acid (2.02 mg, 8.66 mmol) were dissolved in DMF (30 ml). EDC·HCl (2.49 g, 2.61 mmol), HOBt and DMAP were added to the resulting solution and the mixture was stirred overnight at room temperature. Water (50 ml) was added to the reaction mixture, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (15:1, v/v) eluate fractions, ethyl 1-(1-(tert-butoxycarbonyl)-(4S)-fluoro-(2S)-pyrrolidinylcarbonyl)-4-piperidinylacetate (1.05 g, 32%) was obtained as a brown oil.

^{1}H-NMR ($CDCl_3$) δ: 1.17 (dt, J=4.0,12.0Hz, 1H), 1.26 (t, J=7.2Hz, 3H), 1.47 (s, 9H), 1.70 (s, 2H), 1.75 (m, 2H), 2.03 (m, 1H), 2.20 (br, 1H), 2.24 (dd, J=4.4,7.2Hz, 2H),

2.43 (m, 1H), 2.57 (m, 1H), 3.02 (m, 1H), 3.77 (m, 2H), 4.14 (q, J=7.2Hz, 2H), 4.60 (d, J=9.6Hz, 1H), 5.20 (d, J=53.9Hz, 1H).

(Step 3) Synthesis of ethyl 1-((4S)-fluoro-(2S)-pyrrolidinylcarbonyl)-4-piperidinylacetate

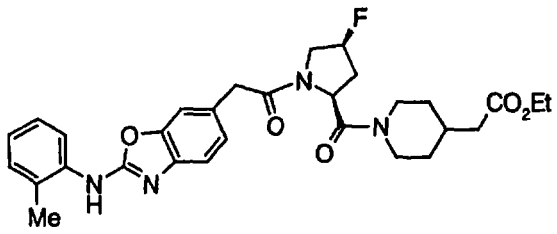


Ethyl 1-(1-(tert-butoxycarbonyl)-(4S)-fluoro-(2S)-pyrrolidinylcarbonyl)-4-piperidinylacetate (1.05 g, 2.74 mmol) was dissolved in methylene chloride (10 ml). After addition of trifluoroacetic acid (4 ml) to the resulting solution at 0°C, the reaction mixture was stirred at 50°C for 3 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue was neutralized with a saturated aqueous solution of sodium bicarbonate, followed by extraction with a chloroform-methanol (5:1, v/v) mixture. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent, whereby ethyl 1-((4S)-fluoro-(2S)-pyrrolidinylcarbonyl)-4-piperidinylacetate (768 mg, 100%) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.17 (dt, J=4.0,12.0Hz, 1H), 1.26 (t,

J=7.2Hz, 3H), 1.79 (m, 2H), 2.02 (m, 3H), 2.24 (m, 2H), 2.38 (m, 1H), 2.66 (series of m, total 1H), 2.78 (ddd, J=2.8,13.6,37.5Hz, 1H), 3.03 (ddd, J=2.4,13.6,18.8Hz, 1H), 3.77 (m, 1H), 3.90 (m, 1H), 4.14 (q, J=7.2Hz, 2H), 4.61 (br, 1H), 5.17 (d, J=53.9Hz, 1H).

(Step 4) Synthesis of ethyl 1-((4S)-fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylcarbonyl)-4-piperidinylacetate



In DMF (9 ml) were dissolved 2-(2-methylphenylamino)-6-benzoxazolylacetic acid (350 mg, 1.24 mmol) and ethyl 1-((4S)-fluoro-(2S)-pyrrolidinylcarbonyl)-4-piperidinylacetate (357 mg, 1.24 mmol). EDC·HCl (356 mg, 1.86 mmol), HOBt and DMAP were added to the resulting solution. The mixture was stirred overnight at room temperature. Water (30 ml) was added to the reaction mixture, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform/methanol (10:1, v/v) eluate fractions, ethyl 1-

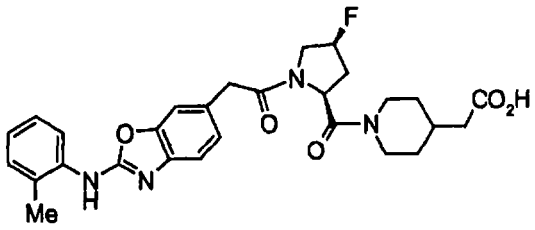
((4S)-fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylcarbonyl)-4-piperidinylacetate (525 mg, 77%) was obtained as a brown oil.

IR (ATR) 1726, 1637, 1573, 1440 cm^{-1};

^{1}H-NMR ($CDCl_3$) δ: 1.15 (dt, J=4.0,12.0Hz, 1H), 1.26 (m, 3H), 1.78 (m, 2H), 2.03 (m, 1H), 2.29 (m, 3H), 2.35 (s, 3H), 2.44 (br, 1H), 2.56 (m, 1H), 3.02 (m, 1H), 3.79 (series of m, total 3H), 3.95 (m, 1H), 4.14 (m, 2H), 4.60 (m, 1), 5.01 (m, 1H), 5.25 (series of d, J=53.5Hz, total 1H), 6.88 (br, 1H), 7.06 (d, J=8.0Hz, 1H), 7.11 (d, J=8.0Hz, 1H), 7.22 (d, J=8.0Hz, 1H), 7.30 (t, J=8.0Hz, 2H), 7.39 (m, 2H), 8.08 (d, J=8.0Hz, 1H).

MS (ESI) m/z 551 $(M+H)^+$.

(Step 5) Synthesis of 1-((4S)-fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylcarbonyl)-4-piperidinylacetic acid



Ethyl 1-((4S)-fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylcarbonyl)-4-piperidinylacetate (550 mg, 0.95 mmol) was dissolved in THF (6 ml). To the resulting solution was added 0.25N NaOH (2

eq) and the mixture was stirred overnight at room temperature. Water (30 ml) was added to the reaction mixture, followed by extraction with a chloroform-methanol (5:1, v/v) mixture. The extract was washed with 1N HCl, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (20:1, v/v) eluate fractions, 1-((4S)-fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylcarbonyl)-4-piperidinylacetic acid (258 mg, 52%) was obtained as a white crystalline powder.

IR (ATR) 1712, 1639, 1573 cm^{-1};

^{1}H-NMR ($CDCl_3$) δ: 1.26 (m, 2H), 1.80 (m, 2H), 2.04 (m, 1H), 2.29 (m, 3H), 2.35 (s, 3H), 2.44 (br, 1H), 2.61 (m, 1H), 3.06 (m, 1H), 3.77 (m, total 3H), 3.92 (m, 1H), 4.59 (br, 1H), 5.02 (t, J=8.0Hz, 1H), 5.24 (m, 1H), 7.10 (m, 2H), 7.22 (d, J=7.6Hz, 2H), 7.29 (m, 2H), 7.33 (m, 2H), 7.88 (d, J=8.8Hz, 1H).

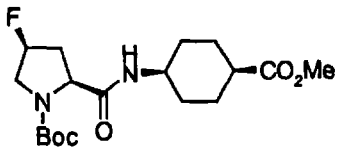
MS (ESI) m/z 523 $(M+H)^+$.

Example 32

cis-4-((4S)-Fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylcarbonylamino)cyclohexanecarboxylic acid

(Step 1) Synthesis of methyl cis-4-(1-(tert-

butoxycarbonyl)-(4S)-fluoro-(2S)-pyrrolidinylcarbonylamino)cyclohexanecarboxylate



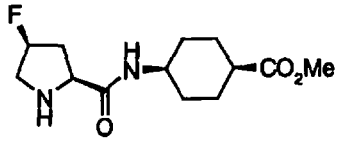
In acetonitrile-water (1:1, v/v, 60 ml) was dissolved cis-4-aminocyclohexanecarboxylic acid (1.32 g, 9.22 mmol). To the resulting solution were added di-tert-butyl dicarbonate (2.05 g, 9.39 mmol) and triethylamine (2.39 ml, 9.07 mmol) and the mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated under reduced pressure. The residue was acidified with 1N HCl, followed by extraction with a chloroform-methanol (5:1, v/v) mixture. The extract was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent, whereby cis-4-((tert-butoxycarbonyl)amino)cyclohexanecarboxylic acid (2.30 g, 97%) was obtained as a white crystalline powder. In methanol-benzene (5:1, v/v, 100 ml) was dissolved cis-4-((tert-butoxycarbonyl)amino)cyclohexanecarboxylic acid (2.30 g, 8.94 mmol). Trimethylsilyldiazomethane (a 2M hexane solution, 9 ml) was added dropwise to the resulting solution under stirring at room temperature. After completion of the dropwise addition, the reaction mixture

was stirred at room temperature for 1 hour. The residue, which had been obtained by distilling the reaction mixture under reduced pressure to remove the solvent, was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (3:1, v/v) eluate fractions, methyl cis-4-((tert-butoxycarbonyl)amino)cyclohexanecarboxylate (2.30 g, 100%) was obtained as a colorless oil. The resulting methyl cis-4-((tert-butoxycarbonyl)amino)cyclohexanecarboxylate (2.30 g, 8.93 mmol) was dissolved in methylene chloride (18 ml). After addition of trifluoroacetic acid (7 ml) to the resulting solution at 0°C, the reaction mixture was stirred at room temperature for 1.5 hours. The residue, which had been obtained by distilling the reaction mixture under reduced pressure to remove the solvent, was neutralized with a saturated aqueous solution of sodium bicarbonate, followed by extraction with a chloroform-methanol (5:1, v/v) mixture. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent, whereby methyl cis-4-aminocyclohexanecarboxylate (1.39 g, 99%) was obtained as a colorless oil. In DMF (40 ml) were dissolved the resulting methyl cis-4-aminocyclohexanecarboxylate (1.39 g, 8.87 mmol) and 1-(tert-butoxycarbonyl)-(4S)-fluoro-(2S)-pyrrolidinecarboxylic acid (2.07 g, 8.87 mmol). EDC·HCl (2.56 g, 13.3 mmol), HOBt (5.0 mg, 0.04 mmol) and DMAP (5.0

mg, 0.04 mmol) were added to the resulting solution and the mixture was stirred overnight at room temperature. Saturated brine was poured in the reaction mixture, followed by extraction with ethyl acetate. The extract was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (20:1, v/v) eluate fractions, methyl cis-4-(1-(tert-butoxycarbonyl)-(4S)-fluoro-(2S)-pyrrolidinylcarbonylamino)cyclohexanecarboxylate (2.96 g, 90%) was obtained as a pale yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 1.47 (s, 9H), 1.56 (br, 2H), 1.72 (br, 4H), 1.88 (br, 2H), 2.27 (br, 1H), 2.49 (br, 2H), 2.56 (m, 1H), 3.68 (s, 3H), 3.78 (br, 1H), 3.95 (br, 1H), 5.13 (d, J=51.6Hz, 1H), 7.72 (br, 1H).

(Step 2) Synthesis of methyl cis-4-((4S)-fluoro-(2S)-pyrrolidinylcarbonylamino)cyclohexanecarboxylate

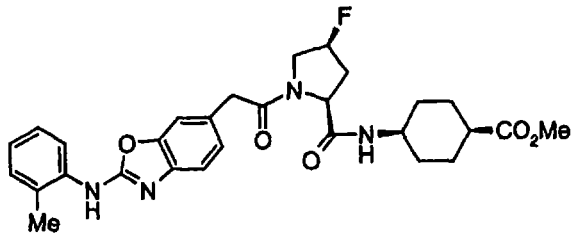


Methyl cis-4-(1-(tert-butoxycarbonyl)-(4S)-fluoro-(2S)-pyrrolidinylcarbonylamino)cyclohexanecarboxylate (440 mg, 1.18 mmol) was dissolved in methylene chloride (7 ml). Trifluoroacetic acid (3 ml) was added to the resulting

solution at 0°C. The reaction mixture was then stirred at room temperature for 2 hours. From the reaction mixture, the solvent was distilled off under reduced pressure. The residue was neutralized with a saturated aqueous solution of sodium bicarbonate, followed by extraction with a chloroform-methanol (5:1, v/v) mixture. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent, whereby methyl cis-4-((4S)-fluoro-(2S)-pyrrolidinylcarbonylamino)cyclohexanecarboxylate (270 mg, 84%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.58 (m, 2H), 1.71 (m, 4H), 1.86 (m, 2H), 2.28 (m, 2H), 2.47 (m, 2H), 2.63 (series of dd, J=3.6,35.5Hz, total 1H), 3.31 (series of d, J=35.5Hz, total 1H), 3.69 (s, 3H), 3.81 (dd, J=2.8,10.4Hz, 1H), 3.90 (br, 1H), 5.16 (d, J=53.1Hz, 1H), 7.72 (br, 1H).

(Step 3) Synthesis of methyl cis-4-((4S)-fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylcarbonylamino)cyclohexanecarboxylate



In DMF (5 ml) were dissolved 2-(2-methylphenylamino)-

6-benzoxazolylacetic acid (147 mg, 0.52 mmol) and methyl cis-4-((4S)-fluoro-(2S)-pyrrolidinylcarbonylamino)cyclohexanecarboxylate (142 mg, 0.52 mmol). EDC·HCl (151 mg, 0.78 mmol), HOBt (5.0 mg, 0.04 mmol) and DMAP (5.0 mg, 0.04 mmol) were added to the resulting solution. The mixture was stirred overnight at room temperature. After dilution with ethyl acetate (50 ml), the mixture was washed with saturated brine, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (10:1, v/v) eluate fractions, methyl cis-4-((4S)-fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylcarbonylamino)cyclohexanecarboxylate (299 mg, 100%) was obtained as a brown oil.

IR (ATR) 1726, 1637, 1531, 1437 cm^{-1};

^{1}H-NMR ($CDCl_3$) δ: 1.46 (m, 2H), 1.63 (m, 3H), 1.78 (m, 3H), 1.78 (m, 1H), 1.90 (m, 2H), 2.39 (s, 3H), 2.49 (m, 1H), 2.9 (series of m, total 2H), 3.70 (s, 3H), 3.76 (m, 1H), 3.82 (m, 1H), 5.21 (m, 1H), 7.08 (m, 2H), 7.22 (m, 1H), 7.28 (m, 1H), 7.44 (d, J=7.6Hz, 1H), 8.01 (s, 2H), 8.15 (d, J=7.6Hz, 1H).

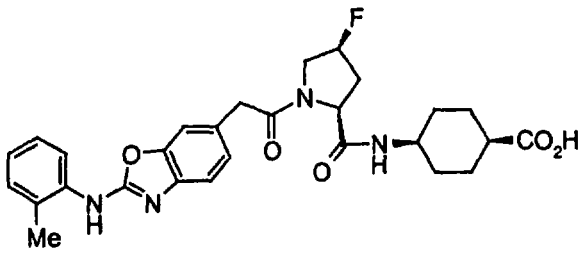
MS (ESI) m/z 537 $(M+H)^+$;

Anal. Calcd for $C_{29}H_{33}FN_4O_5 \cdot 1.5H_2O$: C, 61.80; H, 6.44; N,

9.94.

Found: C, 62.21; H, 6.30; N, 9.02.

(Step 4) Synthesis of cis-4-((4S)-fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylcarbonylamino)cyclohexanecarboxylic acid



Methyl cis-4-((4S)-fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylcarbonylamino)cyclohexanecarboxylate (299 mg, 0.55 mmol) was dissolved in THF (5 ml). To the resulting solution was added 0.25N NaOH (2 eq) and the mixture was stirred overnight at room temperature. After dilution with chloroform-methanol (5:1, v/v, 50 ml), the mixture was washed with 1N HCl, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby chloroform-methanol (10:1, v/v) eluate fractions, cis-4-((4S)-fluoro-1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylcarbonylamino)cyclohexanecarboxylic acid (248 mg, 86%) was obtained as a white crystalline solid.

IR (ATR) 1639, 1573, 1428 cm^{-1};

^{1}H-NMR ($CDCl_3$) δ: 1.24 (br, 2H), 1.54 (br, 1H), 1.66 (br, 4H), 1.76 (br, 2H), 1.99 (br, 1H), 2.17 (m, 1H), 2.31 (s, 3H), 2.44 (br, 1H), 2.83 (series of t, J=16.0Hz, total 1H), 3.61-3.82 (series of m, total 4H), 3.86 (br, 2H), 5.24 (d, J=52.4Hz, 1H), 7.10 (m, 2H), 7.20 (m, 1H), 7.25 (m, 2H), 7.32 (m, 2H), 7.80 (m, 1H).

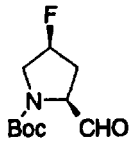
MS (ESI) m/z 523 $(M+H)^+$;

Anal. Calcd for $C_{28}H_{31}FN_4O_5 \cdot H_2O$: C, 62.21; H, 6.15; N, 10.36. Found: C, 63.06; H, 6.23; N, 9.07.

Example 33

4-(1-(2-(2-Methylphenylamino)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethylamino)benzoic acid:

(Step 1) Synthesis of N-tert-butoxycarbonyl-(4S)-fluoro-(2S)-prolinal



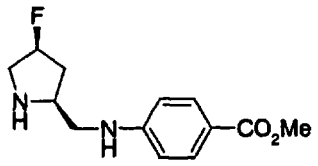
In methylene chloride (50 ml) was dissolved N-tert-butoxycarbonyl-(4S)-fluoro-(2S)-pyrrolidinylmethanol (1.22 g, 5.57 mmol). Under stirring at room temperature, 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (Dess-Martin Periodinate, 2.84 g, 6.69 mmol) was added to the resulting solution in portions. After completion of the

addition, the reaction mixture was stirred further for 2 hours at room temperature. The insoluble matter was filtered off under reduced pressure and then the filtrate was distilled under reduced pressure to remove the solvent. Ether was added to the residue. After filtering off the insoluble matter, the filtrate was distilled under reduced pressure. The above-described operation was repeated three times further to filter off the insoluble matter under reduced pressure, whereby N-tert-butoxycarbonyl-(4S)-fluoro-(2S)-prolinal (1.20 g, 99%) was obtained as a brown solid.

^{1}H-NMR ($CDCl_3$) δ: 1.63 and 1.68 (s, total 9H), 2.38-2.69 (m, 1H), 3.68-3.84 (m, 1H), 3.95-4.14 (m, 1H), 4.36-4.51 (m, 1H), 5.40 (brd, J=51.2Hz, 1H), 9.78 (d, J=18.4Hz, 1H).

MS (ESI) m/z, 218 (M^++H).

(Step 2) Synthesis of methyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethylamino)benzoate



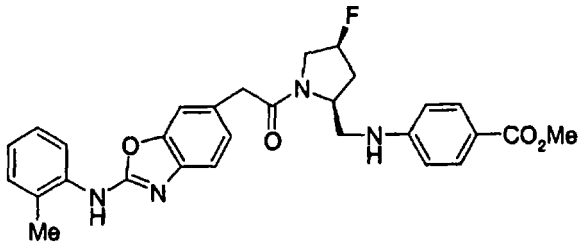
Methyl 4-aminobenzoate (728 mg, 4.82 mmol), acetic acid (290 ml, 4.82 mmol) and N-tert-butoxycarbonyl-(4S)-fluoro-(2S)-prolinal (6.97 mg, 3.21 mmol) were dissolved in methanol (15 ml). Under stirring at 0°C, sodium

cyanoborohydride (95%, 320 mg, 4.82 mmol) was added to the resulting solution. The mixture was stirred overnight at room temperature. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The extract was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue thus obtained was dissolved in methylene chloride (10 ml). Trifluoroacetic acid (7 ml) was added to the resulting solution and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was distilled under reduced pressure. After addition of a saturated aqueous solution of sodium bicarbonate to the residue, the resulting mixture was extracted with chloroform. The extract was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (10:1) eluate fractions, methyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethylamino)benzoate (458 mg, 57%) was obtained as a colorless solid.

^{1}H-NMR ($CDCl_3$) δ: 1.80-1.92 (m, 1H), 2.15-2.31 (m, 1H), 2.90-3.03 (m, 1H), 3.18-3.23 (m, 1H), 3.28-3.37 (m, 2H), 3.45-3.51 (m, 1H), 3.84 (s, 3H), 4.63 (br s, 1H), 5.14-5.30 (m, 1H), 6.57 (d, J=6.8Hz, 2H), 7.85 (d, J=7.2Hz, 2H).

(Step 3) Synthesis of methyl 4-(1-(2-(2-

methylphenylamino)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethylamino)benzoate

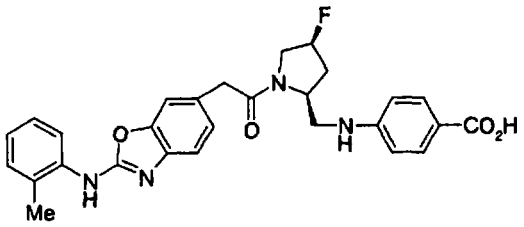


In DMF (10 ml), EDC·HCl (232 mg, 1.21 mmol) was added to methyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethylamino)benzoate (277 mg, 1.10 mmol), 2-(2-methylphenylamino)-6-benzoxazolylacetic acid (310 mg, 1.10 mmol) and DMAP (148 mg, 1.21 mmol) at room temperature. The mixture was stirred overnight at room temperature. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The extract was washed with saturated brine (three times), dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (1:4) eluate fractions, methyl 4-(1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethylamino)benzoate (580 mg, 100%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.70 (br s, 1H), 2.07-2.23 (m, 2H), 2.37 (s, 3H), 3.24-3.28 (m, 1H), 3.57-3.75 (m, 1H), 3.61-3.85 (m, 2H), 3.83 (s, 3H), 4.54 (br d, J=6.8Hz, 1H), 5.22-5.40

(m, 2H), 6.61 (d, J=8.8Hz, 2H), 7.03-7.09 (m, 2H), 7.14 (s, 1H), 7.22 (d, J=7.2Hz, 1H), 7.30 (t, J=8.0Hz, 1H), 7.38 (d, J=8.0Hz, 1H), 7.85 (d, J=8.8Hz, 2H), 8.05 (d, J=8.0Hz, 1H). MS (ESI) m/z, 517 (M^++H).

(Step 4) Synthesis of 4-(1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethylamino)benzoic acid



Methyl 4-(1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethylamino)benzoate (568 mg, 1.10 mmol) was dissolved in methanol-THF (1:1, 10 ml). After addition of 1.0M-NaOH (5.50 ml, 5.50 mmol) at room temperature, the resulting mixture was stirred at 60°C for 3 hours. The reaction mixture was poured in 1N-HCl (10 ml), followed by extraction with a chloroform-methanol mixture. The extract was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (10:1) eluate fractions, 4-(1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethylamino)benzoic acid (409 mg, 74%) was

obtained as a colorless amorphous substance.

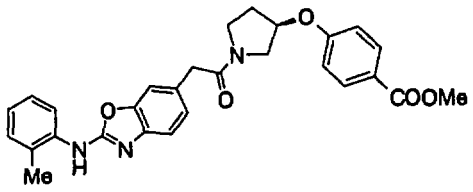
^{1}H-NMR (DMSO-d_6), mixture of rotamars, δ: 2.02-2.26 (m, 2H), 2.29 and 2.30 (s, total 3H), 2.93-2.99 (m, 1H), 3.58-4.33 (series of m, 6H), 5.38-5.47 (m, 1H), 6.64-7.83 (series of m, 12H).

MS (ESI) m/z, 503 (M^++H).

Example 34

4-(1-(2-(2-Methylphenylamino)-6-benzoxazolylacetyl)-(3R)-pyrrolidinyloxy)benzoic acid:

(Step 1) Synthesis of methyl 4-(1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(3R)-pyrrolidinyloxy)benzoate

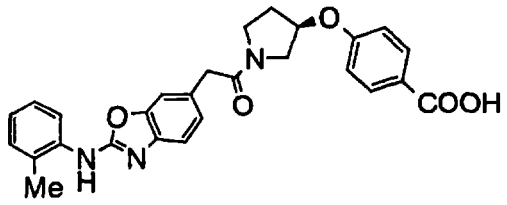


Methyl 4-(3R-pyrrolidinyl)oxybenzoate (221 mg, 1.0 mmol), 2-(2-methylphenylamino)-6-benzoxazolylacetic acid (282 mg, 1.0 mmol), HOBt (135 mg, 1.0 mmol) and triethylamine (417 μl, 3.0 mmol) were dissolved in methylene chloride (15 ml). At 0°C, EDC(HCl (288 mg, 1.5 mmol) was added and the mixture was stirred at room temperature for 16 hours. Ice water (20 ml) was added to the reaction mixture, followed by extraction with ethyl

acetate. The extract was washed successively with a saturated aqueous solution of sodium bicarbonate, a 2M aqueous solution of citric acid and a saturated aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (1:5, v/v) eluate fractions, the title compound (320 mg, 66%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 2.20-2.40 (m, 5H), 3.60-4.00 (m, 6H), 4.95-5.05 (m, 1H), 6.80-7.41 (m, 9H), 7.94-8.09 (m, 3H).

(Step 2) Synthesis of 4-(1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(3R)-pyrrolidinyl)benzoic acid



Methyl 4-(1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(3R)-pyrrolidinyloxy)benzoate (320 mg, 0.65 mmol) was dissolved in THF (5.0 ml) and methanol (3.0 ml). After addition of 1N NaOH (1.0 ml, 1.0 mmol) at room temperature, the reaction mixture was stirred for 18 hours at 70°C. From the reaction mixture, the solvent was distilled off under reduced pressure. The residue was acidified weakly with water (5 ml) and 1N HCl. The

resulting crystals were collected by filtration under reduced pressure, washed with water and then dried under reduced pressure, whereby the title compound (240 mg, 77%) was obtained as a white crystalline solid.

^{1}H-NMR (DMSO-d_6) δ: 2.01-2.20 (m, 2H), 2.30 (s, 3H), 3.55-3.90 (m, 6H), 5.11-5.20 (m, 1H), 7.01-7.09 (m, 4H), 7.23-7.32 (m, 4H), 7.81-7.89 (m, 3H).

MS (FAB) m/z 472 $(M+H)^+$;

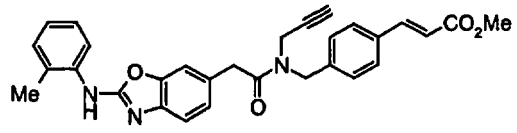
Anal. Calcd for $C_{27}H_{25}N_3O_5 \cdot 0.5H_2O$: C, 67.49; H, 5.45; N, 8.74.

Found: C, 67.33; H, 5.35; N, 8.57.

Example 35

4-(N-(3-Propinyl)-(2-(2-methylphenylamino)-6-benzoxazolylacetamido)methyl)cinnamic acid:

(Step 1) Synthesis of methyl 4-(N-(3-propinyl)-(2-(2-methylphenylamino)-6-benzoxazolylacetamido)methyl)cinnamate

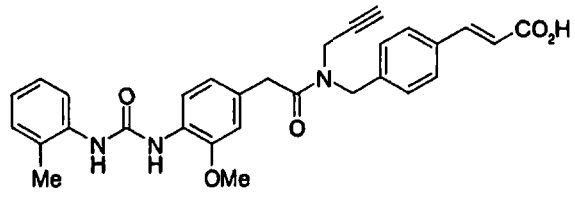


EDC·HCl (183 mg, 0.96 mmol) was added to a solution, in DMF (6 ml), of 2-(2-methylphenylamino)-6-benzoxazolylacetic acid (180 mg, 0.64 mmol), methyl 4-(N-(3-propinyl)aminomethyl)cinnamate (146 mg, 0.64 mmol), HOBt (17.0 mg, 0.13 mmol) and triethylamine (0.13 mL, 0.96

mmol). The resulting mixture was stirred overnight at room temperature. Water (20 ml) was added to the reaction mixture, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from ethyl acetate eluate fractions, the title compound (313 mg, 99%) was obtained as a red amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 2.23, 2.33 (each s, total 1H), 2.38 (s, 3H), 3.82 (s, 3H), 3.83, 3.96 (each s, total 2H), 4.27 (s, 2H), 4.72, 4.74 (each s, total 2H), 6.44 (m, 1H), 6.95-7.56 (m, 10H), 7.68 (m, 1H), 8.08 (m, 1H).

(Step 2) Synthesis of 4-(N-(3-Propinyl)-(2-(2-methylphenylamino)-6-benzoxazolylacetamido)methyl)cinnamic acid:



Under stirring at room temperature, 0.25N NaOH (4.70 mL, 1.17 mmol) was added to a solution of methyl 4-(N-(3-propionyl)-(2-(2-methylphenylamino)-6-benzoxazolylacetamido)methyl)cinnamate (313 mg, 0.63 mmol) in THF (8 mL). The reaction mixture was then stirred at

70°C for 2 hours. Under stirring at 0°C, the reaction mixture was poured in 1N HCl (5 ml). The crystals thus obtained were collected by filtration, washed with water and dried under reduced pressure, whereby the title compound (609 mg, 82%) was obtained as a pale yellow solid.

IR (KBr) 3353, 3288, 2960, 2127, 2119, 1687, 1629, 1600, 1533, 1454, 1417 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 2.17 (s, 1H), 2.30 (s, 3H), 3.80, 3.92 (each s, total 2H), 4.12, 4.23 (each s, total 2H), 4.61, 4.76 (each s, total 2H), 6.50 (m, 1H), 7.00 (d, J=8.1Hz, 1H), 7.08 (d, J=7.6Hz, 2H), 7.23-7.29 (m, 6H), 7.52-7.67 (m, 3H), 7.81 (m, 1H), 9.64 (broad s, 1H).

ESI-MS 512 (M^++1);

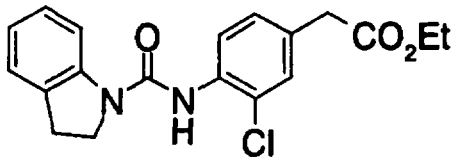
Anal. Calcd for $C_{30}H_{29}N_3O_5 \cdot 0.75H_2O$: C, 68.62; H, 5.85; N, 8.00.

Found: C, 68.76; H, 6.18; N, 7.16.

Example 36

4-(1-(3-Chloro-4-(1-indolinylcarbonylamino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of ethyl 3-chloro-4-(1-indolinylcarbonylamino)phenylacetate

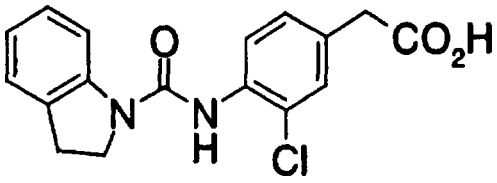


In methylene chloride (50 ml), triphosgene (926 mg, 3.12 mmol) and then pyridine (5 ml) were added to ethyl 4-amino-3-chlorophenylacetate (2.00 g, 9.36 mmol) under stirring at 0°C. After stirring at the same temperature for 15 minutes, indoline (1.05 ml, 9.36 mmol) was added. The reaction mixture was further stirred for 15 minutes at room temperature. Water (50 ml) was added to the reaction mixture, followed by extraction with ethyl acetate (300 ml). The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent, whereby ethyl 3-chloro-4-(1-indolinylcarbonylamino)phenylacetate (3.07 g, 91%) was obtained as a pale pink crystalline powder.

^{1}H-NMR ($CDCl_3$) δ: 1.25 (t, J=7.3Hz, 3H), 3.20-3.26 (m, 2H), 3.54 (d, J=2.7Hz, 2H), 4.08-4.18 (m, 4H), 6.93-6.98 (m, 1H), 7.09-7.31 (m, 5H), 7.94 (d, J=8.1Hz, 1H), 8.28 (d, J=8.1Hz, 1H);

MS (ESI) m/z 359 (M^++1).

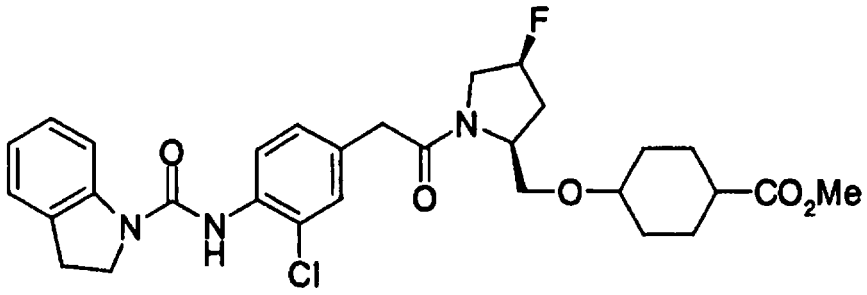
(Step 2) Synthesis of 3-chloro-4-(1-indolinylcarbonylamino)phenylacetic acid



To ethyl 3-chloro-4-(1-indolinylcarbonylamino)phenylacetate (3.07 g, 8.56 mmol) were added 0.25N NaOH (68.4 ml, 17.1 mmol) and THF (70 ml). The mixture was heated and refluxed for 4 hours. After cooling, the reaction mixture was poured in 1N hydrochloric acid (50 ml). The crystals thus precipitated were collected by filtration, and dried under reduced pressure for 12 hours, whereby 3-chloro-4-(1-indolinylcarbonylamino)phenylacetic acid (1.71 g, 60%) was obtained as a colorless crystalline powder.

^{1}H-NMR (DMSO-d_6) δ: 3.19 (t, J=8.8Hz, 2H), 3.61 (s, 2H), 4.13 (t, J=8.8Hz, 2H), 6.90 (t, J=7.3Hz, 1H), 7.11 (t, J=7.8Hz, 1H), 7.19-7.23 (m, 2H), 7.41 (d, J=2.0Hz, 1H), 7.54-7.58 (m, 1H), 7.82 (d, J=8.3Hz, 1H), 8.21 (s, 1H);
MS (ESI) m/z 331 (M^++1).

(Step 3) Synthesis of methyl 4-(1-(3-chloro-4-(1-indolinylcarbonylamino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



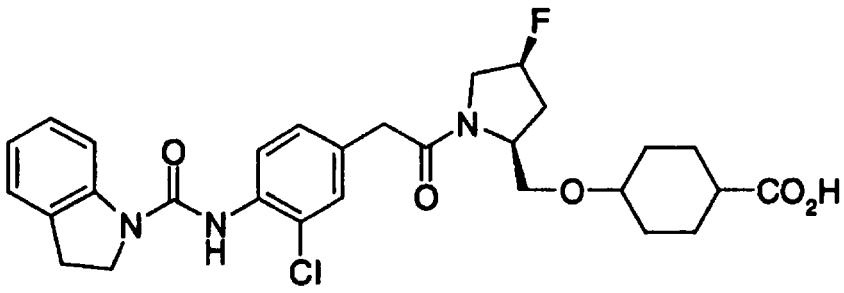
In DMF (10 ml), methyl ((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (143 mg, 0.55 mmol), 3-chloro-4-(1-indolinylcarbonylamino)phenylacetic acid (182 mg, 0.55 mmol), EDC·HCl (116 mg, 0.61 mmol) and HOBt (15 mg, 0.11 mmol) were stirred overnight at room temperature. Water (20 ml) was poured in the reaction mixture, followed by extraction with ethyl acetate. The extract was washed with saturated brine. The residue was purified by thin-layer column chromatography while using hexane/ethyl acetate (1/10) as a developing solvent, whereby methyl 4-(1-(3-chloro-4-(1-indolinylcarbonylamino))phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (259 mg, 82%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$), mixture of amide isomers, δ: 1.21-1.32 (m, 2H), 1.40-1.53 (m, 2H), 1.98-2.51 (series of m, 8H), 3.27 (t, J=8.4Hz, 2H), 3.22-3.34 (m, 2H), 3.50-4.01 (series of m, 4H), 3.66 and 3.67 (s, total 3H), 4.14 (t, J=8.8Hz, 2H), 4.10-4.38 (m, 1H), 5.16-5.33 (m, 1H), 6.98 (t, J=7.6Hz,

1H), 7.12-7.24 (series of m, 4H), 7.34 (br s, 1H), 7.95 (d, J=8.0Hz, 1H), 8.27 (t, J=8.4Hz, 1H);

MS (ESI) m/z 572 (M^++1).

(Step 4) Synthesis of 4-(1-(3-chloro-4-(1-indolinylcarbonylamino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



To methyl 4-(1-(3-chloro-4-(1-indolinylcarbonylamino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (224 mg, 0.39 mmol) were added 0.5N NaOH (4.7 ml), methanol (5 ml) and THF (5 ml). The mixture was stirred overnight at room temperature. The reaction mixture was poured in 1N hydrochloric acid (10 ml), followed by extraction with chloroform-methanol (10:1). The extract was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform/methanol (10/1) eluate fractions, the title compound (221 mg, 100%) was obtained as a colorless amorphous substance.

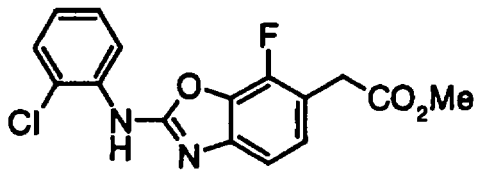
^{1}H-NMR ($CDCl_3$), mixture of amide isomers, δ: 1.21-1.33 (m, 2H), 1.42-1.54 (m, 2H), 2.00-2.50 (series of m, 8H), 3.26 (t, J=8.8Hz, 2H), 3.24-3.36 (m, 2H), 3.48-4.00 (series of m, 4H), 4.14 (t, J=8.8Hz, 2H), 4.16-4.37 (m, 1H), 5.17-5.32 (m, 1H), 6.97 (t, J=7.6Hz, 1H), 7.11-7.24 (series of m, 4H), 7.33 (s, 1H), 7.93 (d, J=8.0Hz, 1H), 8.25 (t, J=9.2Hz, 1H);

MS (ESI) m/z 558 (M^++1).

Example 37

4-(1-(2-(2-Chlorophenyl)amino-7-fluoro-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl 2-(2-chlorophenyl)amino-7-fluoro-6-benzoxazolylacetate



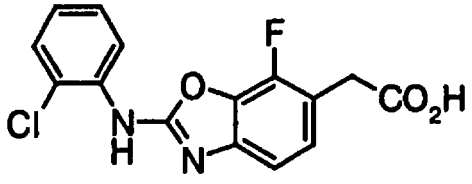
In methanol (50 ml) was dissolved 4-amino-2-fluoro-3-hydroxyphenylacetic acid (2.52 g, 12.7 mmol). At room temperature, 2-chlorophenyl isothiocyanate (1.99 ml, 12.7 mmol) was added to the resulting solution. After the resulting mixture was stirred at room temperature for 2.5 hours, mercuric oxide (yellow) (3.29 g, 15.2 mmol) was

added thereto. The mixture was stirred further for 14 hours at 70°C. The reaction mixture was allowed to cool down to room temperature. The insoluble matter was filtered off through Celite under reduced pressure, followed by washing with methanol. From the filtrate, the solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (silica gel: 100 g, chloroform/ethyl acetate (30/1)), whereby from eluate fractions, methyl 2-(2-chlorophenyl)amino-7-fluoro-6-benzoxazolylacetate (2.12 g, 50%) was obtained as a pale pink solid.

^{1}H-NMR ($CDCl_3$) δ: 3.73 (s, 3H), 3.77 (s, 2H), 7.05 (tt, J=7.3,1.0Hz, 1H), 7.12 (t, J=7.1Hz, 1H), 7.28 (s, 1H), 7.38 (dt, J=7.3,0.7Hz, 1H), 7.42 (d, J=8.0Hz, 1H), 7.60 (br, 1H), 8.53 (d, J=8.3Hz, 1H);

MS (ESI) m/z 335(M^++1), 337 (M^++3).

(Step 2) Synthesis of 2-(2-chlorophenyl)amino-7-fluoro-6-benzoxazolylacetic acid

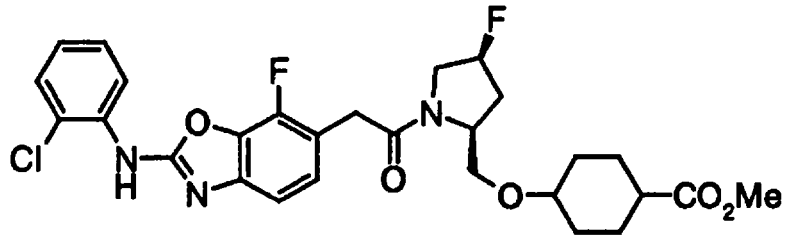


Methyl 2-(2-chlorophenyl)amino-7-fluoro-6-benzoxazolylacetate (2.12 g, 6.33 mmol) was dissolved in

THF/methanol (2:1, 90 ml). To the resulting solution was added 1N NaOH (30 ml) and the mixture was stirred at room temperature for 3.5 hours. The solvent was distilled off under reduced pressure. The residue was acidified with 1N hydrochloric acid. The crystals thus precipitated were collected by filtration, washed with water and dried under reduced pressure, whereby 2-(2-chlorophenyl)amino-7-fluoro-6-benzoxazolylacetic acid (1.83 g, 90%) was obtained as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 3.71 (s, 2H), 7.12-7.19 (m, 3H), 7.23 (dt, J=7.6,1.7Hz, 1H), 7.43 (dt, J=7.6,1.5Hz, 1H), 7.55 (dd, J=8.1,1.5Hz, 1H), 8.04 (d, J=8.3Hz, 1H), 12.27 (br, 1H).

(Step 3) Synthesis of methyl 4-(1-(2-(2-chlorophenyl)amino-7-fluoro-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate:



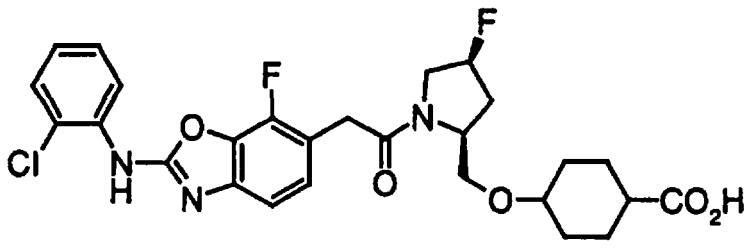
IN DMF (4 ml), methyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in Step 3 of Example 21) (210 mg, 0.81 mmol), 2-(2-chlorophenyl)amino-7-fluoro-6-benzoxazolylacetic acid

(260 mg, 0.81 mmol), EDC·HCl (233 mg, 1.22 mmol), HOBT (165 mg, 1.22 mmol) and triethylamine (0.56 ml, 4.05 mmol) were stirred at room temperature for 15 hours. The reaction mixture was poured in ice water (30 ml), followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica gel: 50 g, chloroform/acetone (20/1)), whereby from eluate fractions, methyl 4-(1-(2-(2-chlorophenyl)amino-7-fluoro-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (420 mg, 92%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.17-1.54 (m, 5H), 1.92-2.53 (m, 7H), 3.28 (m, 1H), 3.35 and 3.54 (each m, total 1H, amide isomers), 3.64 and 3.67 (each s, total 3H, amide isomers), 3.70 (s, 1H), 3.72-4.04 (m, 3H), 4.31 and 4.38 (each m, total 1H, amide isomers), 5.26 and 5.30 (each m, total 1H, amide isomers), 7.04 (t, J=7.8Hz, 1H), 7.13 (q, J=8.8Hz, 1H), 7.26 (t, J=7.3Hz, 1H), 7.37 (d, J=8.0Hz, 1H), 7.41 (d, J=7.8Hz, 1H), 7.62 (s, 1H), 8.52 (d, J=8.3Hz, 1H);

MS (ESI) m/z 562 (M^++1), 564 (M^++3).

(Step 4) Synthesis of 4-(1-(2-(2-chlorophenyl)amino-7-fluoro-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



In THF/methanol (2:1, 15 ml) and 1N NaOH (5ml), methyl 4-(1-(2-(2-chlorophenyl)amino-7-fluoro-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (420 mg, 0.747 mmol) was stirred at room temperature for 17 hours. The solvent was distilled off under reduced pressure. The residue was acidified with 1N hydrochloric acid. The crystals thus obtained were collected by filtration under reduced pressure, washed with water and dried under reduced pressure, whereby the title compound (336 mg, 82%) was obtained as a pale brown solid.

IR (ATR) 3199, 2935, 2863, 1703, 1636, 1593, 1574, 1448 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.13-1.43 (m, 5H), 1.76-2.24 (m, 7H), 3.20 (t, J=8.8Hz, 2H), 3.59-4.41 (m, 5H), 5.24-5.49 (m, 1H), 7.02-7.10 (m, 1H), 7.16 (d, J=8.1Hz, 1H), 7.22 (t, J=7.6Hz, 1H), 7.43 (t, J=7.6Hz, 1H), 7.54 (d, J=7.8Hz, 1H), 8.04 (d, J=8.1Hz, 1H);

MS (ESI) m/z 548 (M^++1), 550 (M^++3);

Anal. Calcd for $C_{27}H_{28}ClF_2N_3O_5 \cdot 0.5H_2O$: C, 58.22; H, 5.25; N,

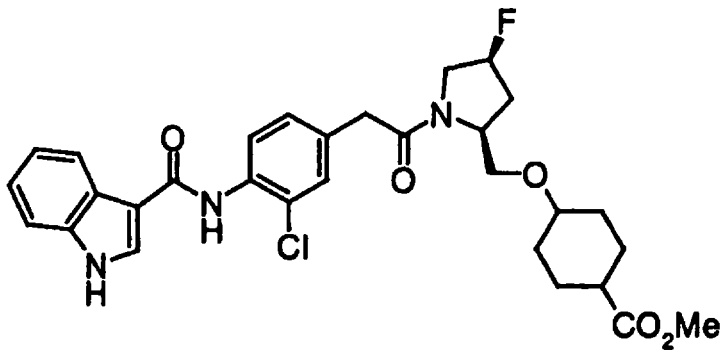
7.57; Cl, 6.37; F, 6.82.

Found: C, 58.44; H, 5.17; N, 7.45; Cl, 6.55; F, 6.64.

Example 38

4-(1-(3-Chloro-4-(3-indolylcarbonylamino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl 4-(1-(3-chloro-4-(3-indolylcarbonylamino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



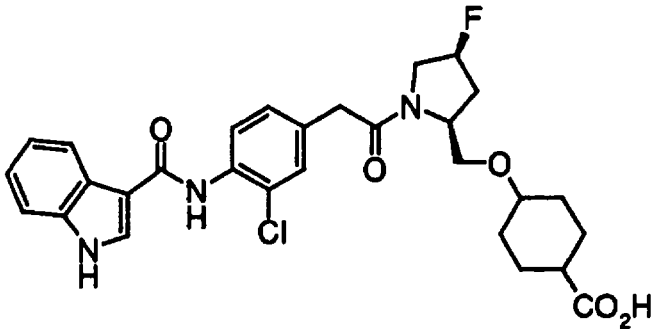
EDC·HCl (168 mg, 0.87 mmol) was added to a solution of 3-chloro-4-(3-indolylcarbonylamino)phenylacetic acid (240 mg, 0.67 mmol), methyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (174 mg, 0.67 mmol), HOBt (18.0 mg, 0.13 mmol) and DMAP (16.0 mg, 0.13 mmol) in DMF (5.0 mL), followed by stirring at room temperature for 4 hours. Water (10 mL) was added to the reaction mixture. The precipitate was collected by filtration, washed with Et 20 and dried under reduced pressure, whereby methyl 4-(1-

(3-chloro-4-(3-indolylcarbonylamino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (320 mg, 84%) was obtained as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 1.15-1.28 (m, 2H), 1.32-1.44 (m, 2H), 1.87-2.07 (m, 4H), 2.10-2.33 (m, 3H), 3.21 (m, 1H), 3.30 and 3.45 (each m, total 1H), 3.57 (s, 3H), 3.60-3.93 (m, 5H), 4.15 and 4.33 (each m, total 1H), 5.31 and 5.38 (each m, total 1H), 7.12-7.21 (m, 3H), 7.37 and 7.39 (each d, J=1.4Hz, total 1H), 7.46 (d, J=7.8Hz, 1H), 7.65 and 7.66 (each d, J=8.3Hz, total 1H), 8.13 (d, J=7.8Hz, 1H), 8.28 (s, 1H), 9.28 (s, 1H), 11.73 (broad s, 1H);

MS (ESI) m/z 570 (M^++1), 572 (M^++3).

(Step 2) Synthesis of 4-(1-(3-chloro-4-(3-indolylcarbonylamino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



To a suspension of methyl 4-(1-(3-chloro-4-(3-indolylcarbonylamino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (320 mg, 0.56

mmol) in THF (14 mL) was added 0.25N NaOH (8.20 mL, 2.05 mmol). The mixture was stirred at room temperature for 5 hours. The reaction mixture was poured in 1N HCl under ice cooling. The crystals thus precipitated were collected by filtration, washed with water and dried under reduced pressure, whereby the title compound (295 mg, 88%) was obtained as a colorless solid.

IR (ATR) ν 3423, 3210, 2940, 2863, 1697, 1627, 1513, 1432 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.15-1.28 (m, 2H), 1.32-1.44 (m, 2H), 1.87-2.07 (m, 4H), 2.10-2.33 (m, 3H), 3.21 (m, 1H), 3.30 and 3.45 (each m, total 1H), 3.57 (s, 3H), 3.60-3.93 (m, 5H), 4.15 and 4.33 (each m, total 1H), 5.31 and 5.38 (each m, total 1H), 7.12-7.21 (m, 3H), 7.37 and 7.39 (each d, J=1.4Hz, total 1H), 7.46 (d, J=7.8Hz, 1H), 7.65 and 7.66 (each d, J=8.3Hz, total 1H), 8.13 (d, J=7.8Hz, 1H), 8.28 (s, 1H), 9.28 (s, 1H), 11.73 (broad s, 1H);

MS (ESI) m/z 556 (M^++1), 558 (M^++3);

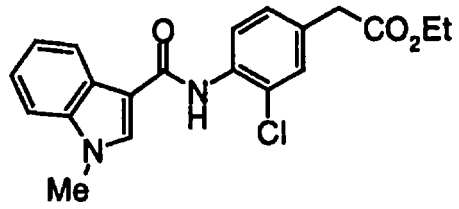
Anal. Calcd for $C_{29}H_{31}ClFN_3O_5 \cdot H_2O$: C, 60.68; H, 5.79; N, 7.32.

Found: C, 60.90; H, 5.29; N, 7.32.

Example 39

4-(1-(3-Chloro-4-(1-methyl-3-indolylcarbonylamino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of ethyl 3-chloro-4-(1-methyl-3-indolylcarbonylamino)phenylacetate

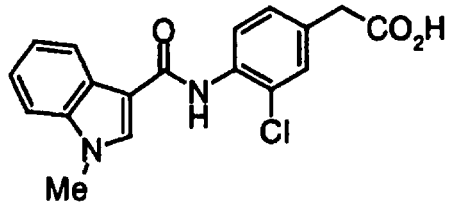


EDC·HCl (1.44 g, 7.49 mmol) was added to a solution of 1-methylindole-3-carboxylic acid (1.01 g, 5.71 mmol), ethyl 4-amino-3-chlorophenylacetate (1.22 g, 5.71 mmol), HOBt (0.86 g, 6.34 mmol) and DMAP (0.14 g, 1.15 mmol) in DMF (20 mL), followed by stirring at 70°C for 18 hours. After cooling to room temperature, water (30 mL) was added to the reaction mixture, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (1:1, v/v) eluate fractions, ethyl 3-chloro-4-(1-methyl-3-indolylcarbonylamino)phenyl acetate (639 mg, 30%) was obtained as a yellow solid. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (t, J=7.1Hz, 3H), 3.58 (s, 2H), 3.89 (s, 3H), 4.17 (q, J=7.1Hz, 2H), 7.24 (dd, J=8.3,2.0Hz, 1H), 7.32-7.43 (m, 4H), 7.81 (s, 1H), 8.16 (m, 1H), 8.28 (broad

s, 1H), 8.59 (d, J=8.3Hz, 1H);

MS (ESI) m/z 371 (M^++1), 373 (M^++3).

(Step 2) Synthesis of 3-chloro-4-(1-methyl-3-indolylcarbonylamino)phenylacetic acid

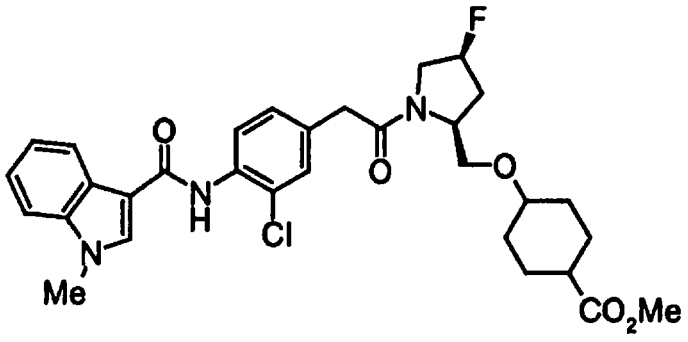


To a solution of ethyl 3-chloro-4-(1-methyl-3-indolylcarbonylamino)phenylacetate (639 mg, 1.72 mmol) in THF (17.5 mL) was added 0.25N NaOH (10.3 mL, 2.58 mmol). The resulting mixture was stirred at room temperature for 4 hours. Under ice cooling, the reaction mixture was poured in 1N HCl (15 ml). The crystals thus precipitated were collected by filtration, washed with water and dried under reduced pressure, whereby 3-chloro-4-(1-methyl-3-indolylcarbonylamino)phenylacetic acid (549 mg, 93%) was obtained as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 3.61 (s, 2H), 3.89 (s, 3H), 7.17-7.28 (m, 3H), 7.43 (d, J=1.7Hz, 1H), 7.53 (d, J=8.3Hz, 1H), 7.69 (d, J=8.3Hz, 1H), 8.14 (d, J=7.8Hz, 1H), 8.26 (s, 1H), 9.26 (s, 1H).

(Step 3) Synthesis of methyl 4-(1-(3-chloro-4-(1-methyl-3-

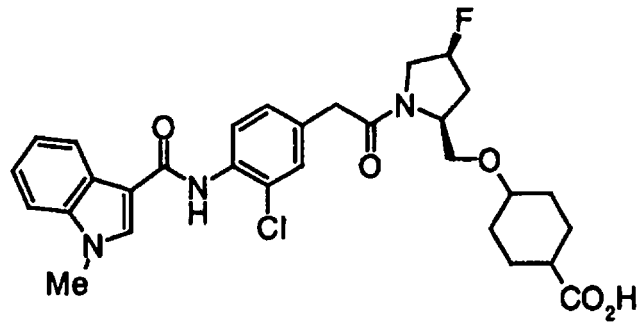
indolylcarbonylamino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



After addition of EDC·HCl (60.0 mg, 0.31 mmol) to a solution of 3-chloro-4-(1-methyl-3-indolylcarbonylamino)phenylacetic acid (82.0 mg, 0.24 mmol), methyl ((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (62.0 mg, 0.24 mmol), HOBt (6.0 mg, 0.05 mmol) and DMAP (6.0 mg, 0.05 mmol) in DMF (2.0 mL), the mixture was stirred at room temperature for 6 hours. The reaction mixture was poured in water (10 mL), followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from ethyl acetate eluate fractions, methyl 4-(1-(3-chloro-4-(1-methyl-3-indolylcarbonylamino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (115

mg, 82%) was obtained as a pale yellow amorphous substance. ^{1}H-NMR ($CDCl_3$) δ: 1.21-1.32 (m, 2H), 1.40-1.53 (m, 2H), 1.97-2.50 (m, 7H), 3.26 (m, 1H), 3.33 and 3.50 (each m, total 1H), 3.57-4.01 (m, 11H (3.64 and 3.66 (each s, total 3H), 3.88 (s, 3H)), 4.21 and 4.38 (each m, total 1H), 5.24 (m, 1H), 7.18 (m, 1H), 7.31-7.42 (m, 4H), 7.79 (s, 1H), 8.14 (m, 1H), 8.26 (broad s, 1H), 8.57 (d, J=8.3Hz, 1H); MS (ESI) m/z 584 (M^++1), 586 (M^++3).

(Step 4) Synthesis of 4-(1-(3-chloro-4-(1-methyl-3-indolylcarbonylamino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



After addition of 0.25N NaOH (1.50 mL, 0.38 mmol) to a solution of methyl 4-(1-(3-chloro-4-(1-methyl-3-indolylcarbonylamino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (115 mg, 0.20 mmol) in THF (2.5 mL), the mixture was stirred at room temperature for 5 hours. Under ice cooling, the reaction mixture was poured in 1N HCl (3.0 mL). The crystals thus precipitated were collected by filtration, washed with

water and dried under reduced pressure, whereby the title compound (94 mg, 88%) was obtained as a colorless solid.

IR (ATR) 2938, 2863, 1724, 1646, 1577, 1511, 1465 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.19-1.39 (m, 4H), 1.90-2.11 (m, 4H), 2.14-2.27 (m, 3H), 3.20 (m, 1H), 3.43-3.87 (m, 6H), 3.89 (s, 3H), 4.16 and 4.34 (each m, total 1H), 5.31 and 5.38 (each m, total 1H), 7.18-7.28 (m, 3H), 7.37 and 7.39 (each s, total 1H), 7.52 (d, J=8.1Hz, 1H), 7.70 and 7.71 (each d, J=8.1Hz, total 1H), 8.15 (d, J=7.8Hz, 1H), 8.27 (d, J=7.8Hz, 1H), 9.23 (s, 1H), 11.95 (broad s, 1H);

MS (ESI) m/z 570 (M^++1), 572 (M^++3);

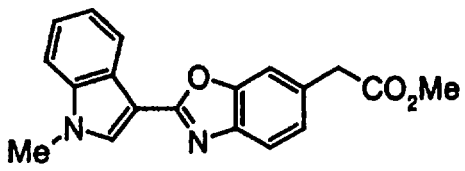
Anal. Calcd for $C_{30}H_{33}ClFN_3O_5 \cdot 0.75H_2O$: C, 61.75; H, 5.96; N, 7.20.

Found: C, 61.85; H, 5.92; N, 6.83.

Example 40

4-((4S)-Fluoro-1-(2-(1-methyl-3-indolyl)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl 2-(1-methyl-3-indolyl)-6-benzoxazolylacetate

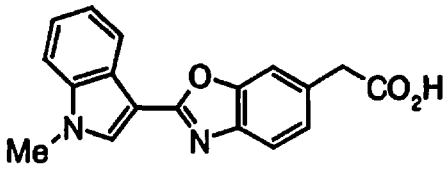


In xylene (20 mL), a mixture of 1-methyl-3-

indolecarboxylic acid (1.00 g, 5.71 mmol), methyl 4-amino-3-hydroxyphenylacetate (1.03 g, 5.71 mmol) and boric acid (1.05 g, 17.1 mmol) was heated and refluxed for 24 hours by using a Dean-Stark trap. After the reaction mixture was cooled down to room temperature, the solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column, whereby from chloroform-ethyl acetate (4:1, v/v) eluate fractions, methyl 2-(1-methyl-3-indolyl)-6-benzoxazolylacetate (0.20 g, 11%) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 3.72 (s, 3H), 3.76 (s, 2H), 3.88 (s, 3H), 7.21 (dd, J=8.1,1.5Hz, 1H), 7.32-7.40 (m, 3H), 7.49 (s, 1H), 7.65 (d, J=8.1Hz, 1H), 7.91 (s, 1H), 8.45 (m, 1H); MS (ESI) m/z 321 (M^++1).

(Step 2) Synthesis of 2-(1-methyl-3-indolyl)-6-benzoxazolylacetic acid



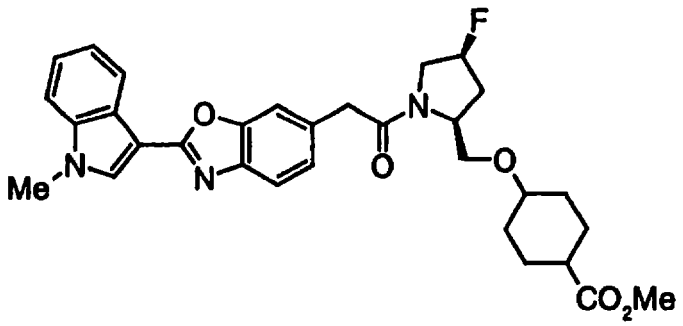
After addition of 0.25N NaOH (3.75 mL, 0.93 mmol) to a solution of methyl 2-(1-methyl-3-indolyl)-6-benzoxazolylacetate (200 mg, 0.62 mmol) in THF (6.5 mL), the mixture was stirred at room temperature for 2 hours. Under ice cooling, the reaction mixture was poured in 1N

HCl (10 mL). The crystals thus precipitated were collected by filtration, washed with water and dried under reduced pressure, whereby 2-(1-methyl-3-indolyl)-6-benzoxazolylacetic acid (189 mg, 99%) was obtained as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 3.73 (s, 2H), 3.94 (s, 3H), 7.24 (dd, J=7.8,1.5Hz, 1H), 7.31 (td, J=7.8,1.5Hz, 1H), 7.35 (td, J=7.8,1.5Hz, 1H), 7.60-7.64 (m, 3H), 8.32 (dd, J=8.1,1.5Hz, 1H), 8.34 (s, 1H), 12.37 (broad s, 1H);

MS (ESI) m/z 307 (M^++1).

(Step 3) Synthesis of methyl 4-((4S)-fluoro-1-(2-(1-methyl-3-indolyl)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



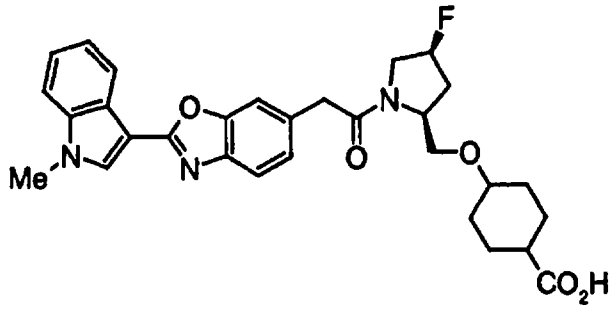
After addition of EDC·HCl (204 mg, 1.07 mmol) to a solution of 2-(1-methyl-3-indolyl)-6-benzoxazolylacetic acid (251 mg, 0.82 mmol), methyl ((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (212 mg, 0.82 mmol), HOBt (22.0 mg, 0.16 mmol) an DMAP (20.0 mg, 0.16 mmol) in

DMF (5.0 mL), the resulting mixture was stirred at room temperature for 4 hours. The reaction mixture was poured in water (10 mL), followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from ethyl acetate fractions, methyl 4-((4S)-fluoro-1-(2-(1-methyl-3-indolyl)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (431 mg, 96%) was obtained as a yellow amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.21-1.34 (m, 2H), 1.40-1.53 (m, 2H), 1.96-2.15 (m, 4H), 2.19-2.50 (m, 3H), 3.26 (m, 1H), 3.35 and 3.50 (each m, total 1H), 3.64 and 3.66 (each s, total 3H), 3.69-3.87 (m, 3H), 3.90 (s, 3H), 3.94-4.06 (m, 2H), 4.25 and 4.39 (each m, total 1H), 5.23 (m, 1H), 7.19 (m, 1H), 7.34-7.41 (m, 3H), 7.49 (m, 1H), 7.64 (m, 1H), 7.93 (s, 1H), 8.44 (m, 1H);

MS (ESI) m/z 548 (M^++1).

(Step 4) Synthesis of 4-((4S)-fluoro-1-(2-(1-methyl-3-indolyl)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



After addition of 0.25N NaOH (5.00 mL, 1.25 mmol) to a solution of methyl 4-((4S)-fluoro-1-(2-(1-methyl-3-indolyl)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (431 mg, 0.79 mmol) in THF (8.0 mL), the mixture was stirred at room temperature for 5 hours. Under ice cooling, the reaction mixture was poured in 1N HCl (10 mL). Crystals thus precipitated were collected by filtration, washed with water and dried under reduced pressure, whereby the title compound (396 mg, 94%) was obtained as a colorless solid.

IR (ATR) 2938, 2861, 1718, 1644, 1627, 1575, 1523, 1423 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.15-1.27 (m, 2H), 1.32-1.45 (m, 2H), 1.89-2.11 (m, 4H), 2.14-2.29 (m, 3H), 3.23 (m, 1H), 3.55 (m, 1H), 3.75-3.95 (m, 6H), 3.97 (s, 3H), 4.11 and 4.38 (each m, total 1H), 5.35 and 5.40 (each m, total 1H), 7.22 (m, 1H), 7.31-7.39 (m, 2H), 7.55-7.67 (m, 3H), 8.35 (s, 1H), 12.03 (broad s, 1H);

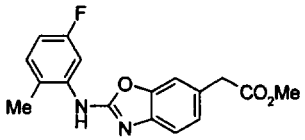
MS (ESI) m/z 534 (M^++1);

Anal. Calcd for $C_{30}H_{32}FN_3O_5$: C, 67.53; H, 6.04; N, 7.87. Found: C, 67.33; H, 6.06; N, 7.70.

Example 41

trans-4-(1-((2-(5-Fluoro-2-methylphenylamino)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl (2-(5-fluoro-2-methylphenylamino)-6-benzoxazolyl)acetate



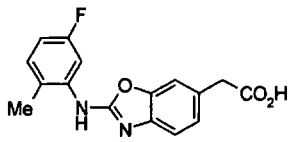
In methanol (50 ml), 5-fluoro-2-methylphenyl isothiocyanate (2.00 g, 12.0 mmol) was added to methyl 4-amino-3-hydroxyphenylacetate (2.17 g, 12.0 mmol) at room temperature. After stirring for 27 hours, mercuric oxide (yellow) (3.12 g, 14.4 mmol) was added to the reaction mixture and the resulting mixture was heated at 70°C for 4 hours. After cooling to room temperature, the reaction mixture was filtered through Celite. The filtrate was washed with methanol. The filtrate was distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform/ethyl acetate (10/1) eluate fractions, methyl (2-(5-fluoro-2-methylphenylamino)-6-benzoxazolyl)acetate (1.73 g, 46%) was obtained as a pale

brown oil.

^{1}H-NMR ($CDCl_3$) δ: 2.13 (s, 3H), 3.705 (s, 2H), 3.711 (s, 3H), 6.74 (dt, J=8.3,2.7Hz, 1H), 6.81 (br, 1H), 7.15 (dd, J=8.1,1.7Hz, 2H), 7.31 (d, J=1.2Hz, 1H), 7.44 (d, J=8.1Hz, 1H), 8.09 (dd, J=11.0,2.7Hz, 1H).

MS (ESI) m/z 315 (M^++1).

(Step 2) (2-(5-Fluoro-2-methylphenylamino)-6-benzoxazolyl)acetic acid



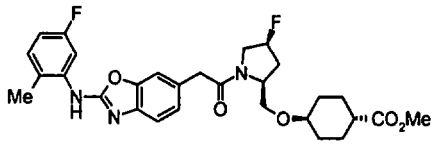
To a solution of methyl (2-(5-fluoro-2-methylphenylamino)-6-benzoxazolyl)acetate (1.73 g, 5.50 mmol) in THF/methanol (2:1, 30 ml) was added 1N NaOH (20 ml). After stirring at room temperature for 3.5 hours, the mixture was distilled under reduced pressure to remove the solvent. The residue was acidified with 1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give (2-(5-fluoro-2-methylphenylamino)-6-benzoxazolyl)acetic acid (1.60 g, 97%) as a colorless crystalline powder.

^{1}H-NMR (DMSO-d_6) δ: 2.49 (s, 3H), 3.64 (d, J=1.7Hz, 2H), 6.87 (dt, J=8.3,1.5Hz, 1H), 7.11 (d, J=8.1Hz, 1H), 7.25 (t, J=7.3Hz, 1H), 7.37 (d, J=8.1Hz, 1H), 7.41 (s, 1H), 7.95 and

7.98 (each s, total 1H, amide isomers), 9.80 (br, 1H).

MS (ESI) m/z 301 (M^++1).

(Step 3) Synthesis of methyl trans-4-(1-((2-(5-fluoro-2-methylphenylamino)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate

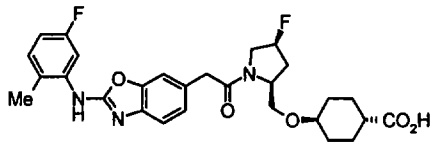


In DMF (5 ml), (2-(5-fluoro-2-methylphenyl)amino-6-benzoxazolyl)acetic acid, methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexancarboxylate (compound synthesized in (Step 3) of Example 21) (259 mg, 1.0 mmol), EDC HCl (288 mg, 1.5 mmol), HOBt (203 mg, 1.5 mmol) and triethylamine (0.70 ml, 5.0 mmol) were stirred at room temperature for 18 hours. The reaction mixture was poured in ice water, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane/ethyl acetate (1/4) eluate fractions, methyl trans-4-(1-((2-(5-fluoro-2-methylphenylamino)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (540 mg, 100%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.20-1.83 (m, 6H), 1.96-2.12 (m, 4H), 2.20-2.51 (m, 5H), 3.24 (m, 1H), 3.34 and 3.50 (t and dd, J=8.8 and 9.0,6.8Hz respectively, total 1H, amide isomers), 3.65 and 3.67 (each s, total 3H, amide isomers), 3.72-4.42 (m, 4H), 5.16-5.35 (m, 1H), 6.74 (t, J=7.8Hz, 1H), 6.97 (br, 1H), 7.06-7.17 (m, 2H), 7.32 (d, J=7.3Hz, 1H), 7.43 (t, J=6.8Hz, 1H), 8.07 and 8.09 (each s, total 1H, amide isomers).

MS (ESI) m/z 542 (M^++1).

(Step 4) Synthesis of trans-4-(1-((2-(5-fluoro-2-methylphenylamino)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid.



In THF/methanol (20/10 ml) was dissolved methyl trans-4-(1-((2-(5-fluoro-2-methylphenylamino)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (540 mg, 1.0 mmol), followed by the addition of 1N NaOH (20 ml). After stirring at room temperature for 14 hours, the mixture was distilled under reduced pressure to remove the solvent. The residue was acidified with 1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced

pressure to give the title compound (477 mg, 90%) as a colorless crystalline powder.

IR (ATR) ν 2939, 2864, 1701, 1639, 1610, 1576, 1437 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.10-1.41 (m, 4H), 1.82-2.01 (m, 4H), 2.10-2.21 (m, 3H), 2.29 (s, 3H), 3.14-3.57 (m, 3H), 3.62-3.95 (m, 4H), 4.14 and 4.32 (m and q, J=7.3Hz, total 1H, amide isomers), 5.31 and 5.37 (each d, J=53.4 and 53.4Hz respectively, total 1H, amide isomers), 6.87 (dt, J=8.4, 2.7Hz, 1H), 7.05 and 7.08 (each d, each J=8.3Hz, total 1H, amide isomers), 7.24 (t, J=6.8Hz, 1H), 7.35 (t, J=8.3Hz, 2H), 7.95 (d, J=11.5Hz, 1H), 9.77 (br, 1H), 12.03 (br, 1H).

MS (ESI) m/z 528 (M^++1);

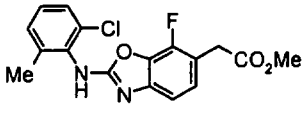
Anal. Calcd for $C_{28}H_{31}F_2N_3O_5$ 0.2H_2O: C, 63.31; H, 5.96; N, 7.91; F, 7.15.

Found: C, 63.13; H, 5.89; N, 7.71; F, 7.15.

Example 42

trans-4-(1-((2-(2-Chloro-6-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl (2-(2-chloro-6-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetate



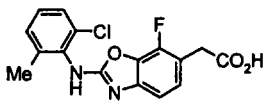
Methyl (4-amino-2-fluoro-3-hydroxyphenyl)acetate (1.0

g, 5.02 mmol) was dissolved in methanol (30 ml). To the resulting solution was added 2-chloro-6-methylphenyl isothiocyanate (841 mg, 4.58 mmol) at room temperature. After the resulting mixture was stirred for 5 days, mercuric oxide (yellow) (1.14 g, 4.36 mmol) was added thereto. The mixture was stirred at 70°C for 23 hours. After cooling, the reaction mixture was filtered through Celite and washed with methanol. The filtrate was distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform/ethyl acetate (30/1) eluate fractions, methyl (2-(2-chloro-6-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetate (1.45 g, 95%) was obtained as a red amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 2.38 (s, 3H), 3.71 (s, 2H), 3.74 (s, 3H), 7.05 (t, J=8.0Hz, 1H), 7.14 (d, J=8.3Hz, 1H), 7.20 (dd, J=7.6,2.2Hz, 1H), 7.23 (s, 1H), 7.34 (d, J=7.3Hz, 1H).

MS (ESI) m/z 349 (M^++1), 351 (M^++3).

(Step 2) Synthesis of (2-(2-chloro-6-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetic acid



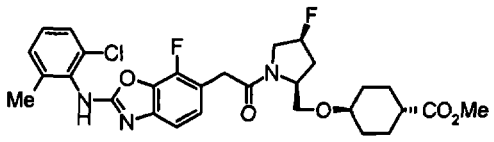
To a solution of methyl (2-(2-chloro-6-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetate (1.45 g,

4.16 mmol) in THF/methanol (4:1, v/v 100 ml) was added 1N NaOH (40 ml). After stirring at room temperature for 17 hours, the reaction mixture was distilled under reduced pressure to remove the solvent. The residue was acidified with 1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give (2-(2-chloro-6-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetic acid (1.30 g, 93%) as a colorless crystalline powder.

^{1}H-NMR (DMSO-d_6) δ: 2.28 (s, 3H), 3.36 (s, 2H), 7.01 and 7.03 (each s, total 1H, amide isomers), 7.07 (t, J=8.1Hz, 1H), 7.29 (d, J=7.6Hz, 1H), 7.32 (d, J=6.4Hz, 1H), 7.42 (d, J=7.6Hz, 1H).

MS (ESI) m/z 335 (M^++1), 337 (M^++3).

(Step 3) Synthesis of methyl trans-4-(1-((2-(2-chloro-6-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



In DMF (4 ml), (2-(2-chloro-6-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetic acid (167 mg, 0.50 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound

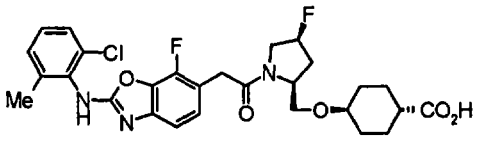
synthesized in (Step 3) of Example 21) (130 mg, 0.50 mmol), EDC HCl (144 mg, 0.75 mmol), HOBt (101 mg, 0.75 mmol) and triethylamine (0.35 ml, 2.50 mmol) were stirred at room temperature for 20 hours. The mixture was poured in ice water, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by thin-layer chromatography, whereby from chloroform/acetone (5/1) eluate fractions, methyl trans-4-(1-((2-(2-chloro-6-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (238 mg, 83%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.21-1.53 (m, 4H), 1.95-2.31 (m, 7H), 2.43 (s, 3H), 2.49 (m, 1H), 3.27 (m, 1H), 3.33 and 3.54 (t and dd, J=10.0 and 8.8, 6.4Hz respectively, total 1H, amide isomers), 3.65 (s, 1H), 3.67 (s, 3H), 3.68-4.04 (m, 3H), 4.30 and 4.36 (q and m, J=6.8Hz, total 1H, 5.25 and 5.30 (each dt, J=54.2, 3.8 and 53.2, 2.7Hz respectively, total 1H, amide isomers), 7.00-7.22 (m, 3H), 7.32 (d, J=7.3Hz, 1H).

MS (ESI) m/z 576 (M^++1), 578 (M^++3).

(Step 4) Synthesis of trans-4-(1-((2-(2-chloro-6-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-

fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



In THF/methanol (8/4, 12 ml) was dissolved methyl trans-4-(1-((2-(2-chloro-6-methylphenylamino)7-fluoro-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (238 mg, 0.413 mmol). To the resulting solution was added 1N NaOH (4 ml). After stirring at room temperature for 14 hours, the reaction mixture was distilled under reduced pressure to remove the solvent. The residue was acidified with 1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give the title compound (191 mg, 82%) as a colorless crystalline powder.

IR (ATR) ν 3743, 3674, 2939, 1704, 1635, 1583, 1504, 1452 cm^{-1};

^{1}H-NMR (DMSO) δ: 1.10-1.42 (m, 5H), 1.81-2.22 (m, 6H), 2.28 (s, 3H), 3.18 (t, J=9.5Hz, 1H), 3.42-4.02 (m, 6H), 4.11 and 4.35 (m and q, J=7.1Hz, total 1H, amide isomers), 5.31 and 5.39 (each d, J=55.2 and 54.7Hz respectively, total 1H, amide isomers), 6.96-7.03 (m, 2H), 7.28 (t, J=7.6Hz, 1H), 7.32 (d, J=7.3Hz, 1H), 7.42 (d, J=7.8Hz, 1H).

MS (ESI) m/z 562 (M^++1), 564 (M^++3);

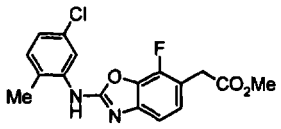
Anal. Calcd for $C_{28}H_{30}ClF_2N_3O_5$ $0.5H_2O$: C, 58.90; H, 5.47; N, 7.36; Cl, 6.21; F, 6.65.

Found: C, 58.85; H, 5.44; N, 7.19; Cl, 6.18; F, 6.47.

Example 43

trans-4-(1-((2-(5-Chloro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid :

(Step 1) Synthesis of methyl (2-(5-chloro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetate



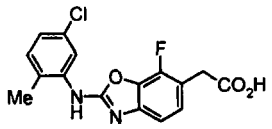
In methanol (30 ml) was dissolved methyl (4-amino-2-fluoro-3-hydroxyphenyl)acetate (1.0 g, 5.02 mmol). To the resulting solution was added 5-chloro-2-methylphenyl isothiocyanate (0.674 ml, 4.58 mmol). After the mixture was stirred at room temperature for 5 days, mercuric oxide (yellow) (1.14 g, 4.36 mmol) was added thereto. The resulting mixture was stirred at 70°C for 6 hours. After cooling to room temperature, the reaction mixture was filtered through Celite and washed with methanol. The filtrate was distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform/ethyl acetate (30/1, v/v) eluate fractions, methyl (2-(5-chloro-2-

methylphenylamino)-7-fluoro-6-benzoxazolyl)acetate (1.67 g, 100%) was obtained as a brown solid.

^{1}H-NMR ($CDCl_3$) δ: 2.32 (s, 3H), 3.73 (s, 3H), 3.76 (s, 2H), 7.04 (dd, J=8.1, 2.2Hz, 1H), 7.10 (dd, J=7.8, 2.2Hz, 1H), 7.13 (t, J=8.1Hz, 2H), 8.30 (d, J=2.2Hz, 1H).

MS (ESI) m/z 349 (M^++1), 351 (M^++3).

(Step 2) Synthesis of (2-(5-chloro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetic acid



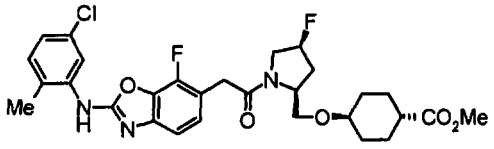
In THF/methanol (4:1, v/v, 100 ml) was dissolved methyl (2-(5-chloro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetate (1.67 g, 4.79 mmol). To the resulting solution was added 1N NaOH (40 ml). After stirring at room temperature for 12 hours, the reaction mixture was distilled under reduced pressure to remove the solvent. The residue was acidified with 1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give (2-(5-chloro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetic acid (1.39 g, 87%) as a colorless crystalline powder.

^{1}H-NMR (DMSO-d_6) δ: 2.30 (s, 3H), 3.71 (s, 2H), 7.12 (dd, J=8.1, 2.0Hz, 1H), 7.15 (d, J=7.3Hz, 1H), 7.23 (d, J=8.1Hz,

1H), 7.26 (d, J=8.1Hz, 1H), 8.09 (s, 1H), 10.06 (s, 1H), 12.46 (br, 1H).

MS (ESI) m/z 335 (M^++1), 337 (M^++3).

(Step 3) Synthesis of methyl trans-4-(1-((2-(5-chloro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



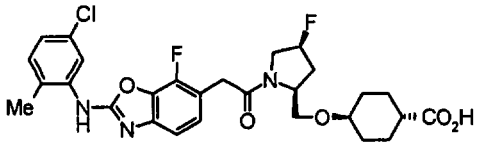
In DMF (4 ml), (2-(5-chloro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetic acid (167 mg, 0.50 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (130 mg, 0.50 mmol), EDC HCl (144 mg, 0.75 mmol), HOBt (101 mg, 0.75 mmol) and triethylamine (0.35 ml, 2.50 mmol) were stirred at room temperature for 19 hours. The mixture was poured in ice water, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography using a thin-layer plate, whereby from chloroform/acetone (5/1, v/v) eluate fractions, methyl trans-4-(1-((2-(5-chloro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-

pyrrolidinylmethoxy)cyclohexanecarboxylate (261 mg, 91%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.22-1.56 (m, 5H), 1.95-2.29 (m, 7H), 2.30 (s, 3H), 2.50 (m, 1H), 3.21-3.60 (m, 2H), 3.65 and 3.67 (each s, total 3H, amide isomers), 3.70 (s, 1H), 3.17-4.05 (m, 3H), 4.31-4.43 (m, 1H), 5.27 and 5.31(each dt, J=53.7, 4.4 and 52.7, 3.8Hz respectively, total 1H, amide isomers), 7.02-7.14 (m, 4H), 7.22 (d, J=8.8Hz, 1H), 8.26 (s, 1H).

MS (ESI) m/z 576 (M^++1), 578 (M^++3).

(Step 4) Synthesis of trans-4-(1-((2-(5-chloro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



In THF/methanol (4:1, v/v, 12 ml) was dissolved methyl trans-4-(1-((2-(5-chloro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (202 mg, 0.359 mmol). To the resulting solution was added 1N NaOH (4 ml). After stirring at room temperature for 14 hours, the reaction mixture was distilled under reduced pressure to remove the solvent. The residue was acidified with 1N HCl. The crystals thus precipitated were collected by filtration

under reduced pressure, washed with water and dried under reduced pressure to give the title compound (202 mg, 79%) as a colorless crystalline powder.

IR (ATR) ν 3168, 2937, 1702, 1639, 1577, 1450 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.09-1.41 (m, 5H), 1.83-2.22 (m, 6H), 2.30 (s, 3H), 3.19 (t, J=9.8Hz, 1H), 3.44-4.41 (m, 7H), 5.32 and 5.43 (each d, each J=54.4Hz, total 1H, amide isomers), 7.05-7.10 (m, 1H), 7.12 (d, J=8.1Hz, 1H), 7.22 (d, J=6.3Hz, 1H), 7.27 (d, J=8.1Hz, 1H), 8.10 (s, 1H), 10.04 (br, 1H).

MS (ESI) m/z 562 (M^++1), 564 (M^++3);

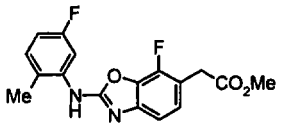
Anal. Calcd for $C_{28}H_{30}ClF_2N_3O_5$ $0.5H_2O$: C, 58.90; H, 5.47; N, 7.36; Cl, 6.21; F, 6.65.

Found: C, 59.13; H, 5.40; N, 7.15; Cl, 6.21; F, 6.48.

Example 44

trans-4-(1-((2-(5-Fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl (2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetate



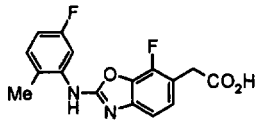
In methanol (30 ml) was dissolved methyl (4-amino-2-fluoro-3-hydroxyphenyl)acetate (1.0 g, 5.02 mmol). To the resulting solution was added 5-fluoro-2-methylphenyl isothiocyanate (1.0 g, 5.98 mmol). After the resulting mixture was stirred at room temperature for 5 days, mercuric oxide (yellow) (1.14 g, 4.36 mmol) was added thereto. The mixture was stirred at 70°C for 6 hours. After cooling to room temperature, the reaction mixture was filtered through Celite and washed with methanol. The filtrate was distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform/ethyl acetate (30/1, v/v) eluate fractions, methyl (2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetate (810 mg, 56%(2 steps)) was obtained as a pink solid.

^{1}H-NMR ($CDCl_3$) δ: 2.32 (s, 3H), 3.72 (s, 3H), 3.76 (s, 2H),

6.75 (dt, J=8.1, 2.7Hz, 1H), 6.87 (br, 1H), 7.11 (t, J=6.6Hz, 1H), 7.15 (t, J=6.9Hz, 1H), 8.11 (dd, J=11.0,6.7Hz, 1H).

MS (ESI) m/z 333 (M^++1).

(Step 2) Synthesis of (2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetic acid



In THF/methanol (2:1, v/v, 90 ml) was dissolved methyl (2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetate (810 mg, 2.44 mmol). To the resulting solution was added 1N NaOH (30 ml). After stirring at room temperature for 12 hours, the reaction mixture was distilled under reduced pressure to remove the solvent. The residue was acidified with 1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give (2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetic acid (700 mg, 90%) as a pale brown solid.

^{1}H-NMR (DMSO-d_6) δ: 2.29 (s, 3H), 3.68 (s, 2H), 6.89 (dt, J=7.0, 1.7Hz, 1H), 7.14 (t, J=6.4Hz, 1H), 7.20 and 7.22 (each s, total 1H, amide isomers), 7.25 (t, J=7.4Hz, 1H), 7.90 (d, J=11.3Hz, 1H), 10.06 (br, 1H).