DESCRIPTION

Title of Invention: PIPERAZINE DERIVATIVE

Technical Field

[0001]

The present invention relates to a piperazine derivative or a salt thereof, which has a melanocortin 4 receptor (hereinafter referred to as an MC_4 receptor) agonistic action, and can be used an active ingredient of a pharmaceutical composition, in particular, a pharmaceutical composition for preventing or treating bladder and/or urinary tract diseases.

Background Art

[0002]

Important roles of the lower urinary tract are urine storage and voiding, which are regulated by a coordinated action of the bladder and the urethra. That is, during urine storage, the bladder smooth muscle is relaxed and the urethral smooth muscle and the urethral sphincter are contracted, whereby a state of high urethral resistance is maintained and urinary continence is thus maintained. On the other hand, during voiding, while the bladder smooth muscle is contracted, the urethral smooth muscle is relaxed, and contraction of the external urethral sphincter is also suppressed. Examples of dysfunctions in the lower urinary tract include urine storage dysfunctions such as overactive bladder in which urine cannot be retained during urine storage, and voiding dysfunctions in which urine cannot be drained sufficiently during voiding due to increase in the urethral resistance or decrease in the bladder contractile force. These two dysfunctions may develop simultaneously in some cases.

[0003]

Voiding dysfunctions are caused by an increase in urethral resistance or a decrease in the bladder contractile force during voiding, and lead to voiding difficulty, straining during voiding, attenuation of the urinary stream, extension of voiding time, an increase in residual urine, a decrease in voiding efficiency, or the like. As a cause of an increase in urethral resistance, a voiding dysfunction associated with benign prostatic hyperplasia is well-known, which is characterized by partial obstruction of the urethra due to nodular hypertrophy of the prostate tissues. Adrenergic α_1 receptor antagonists have now been used as therapeutic agents for the voiding dysfunction associated with benign prostatic hyperplasia (Pharmacology, 65, 119-128 (2002)). An increase in the urethral resistance is also caused by functional obstruction in detrusor-external urethral sphincter dyssynergia due to neurological diseases or neurological disorders, or the like. With patients with

these diseases, the effectiveness of adrenergic α_1 receptor antagonists is unclear (Journal of Pharmacological Sciences, 112, 121-127 (2010)).

[0004]

On the other hand, as a factor for decreasing the bladder contractile force during voiding, increasing age, diabetes, benign prostatic hyperplasia, neurological diseases such as Parkinson's disease and multiple sclerosis, spinal cord injury, nerve damage caused by pelvic surgery, and the like are known (Reviews in Urology, 15, 11-22 (2013)). As a therapeutic drug for a decrease in the bladder contractile force during voiding, bethanechol chloride which is a non-selective muscarinic receptor agonist, distigmine bromide which is a choline esterase inhibitor, and the like are known. However, it is known that these drugs have cholinergic side effects, such as diarrhea, abdominal pain, sweating, and the like. In addition, cholinergic crisis is sometimes expressed as a serious side effect, and caution is therefore required for the use (UBRETID (registered trademark) tablet 5 mg package insert, Torii Pharmaceutical Co., Ltd., Besacolin (registered trademark) powder 5% package insert, Eisai Co., Ltd.).

[0005]

In voiding dysfunctions caused by an increase in the urethral resistance or a decrease in the bladder contractile force as described above, residual urine after voiding may be observed in some cases. Increased residual urine may cause a decrease in effective bladder capacity, and thus cause overactive bladder symptoms such as urinary frequency, or severe symptoms such as hydronephrosis in some cases. Therefore, there is a demand for a therapeutic agent which is more effective on bladder and/or urinary tract diseases or symptoms thereof caused by an increase in the urethral resistance during voiding or a decrease in the bladder contractile force (Reviews in Urology, 15, 11-22 (2013)).

[0006]

Melanocortins are peptides that are generated by the processing from proopiomelanocortin, and examples thereof include an adrenocorticotropic hormone, and α-, β-, and γ- melanocyte stimulating hormones (α-, β-, and γ-MSH). Five subtypes (MC_1 to MC_5) have hitherto been reported as a melanocortin receptor. Any of the subtypes belong to a G protein-conjugated receptor of a class A, and activates an adenylate cyclase via the Gs protein to increase the amount of cAMPs. The MC_4 receptors are widely distributed in the central nervous system, and are known to play an important role in feeding behavior, energy metabolism regulation, sexual function, and the like (Journal of Pharmacological Sciences, 128, 53-55 (2006)).

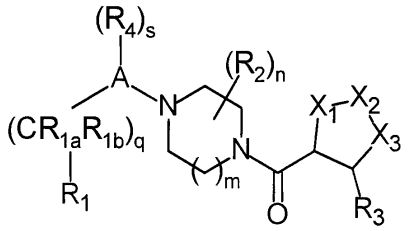
[0007]

As a representative MC_4 receptor agonist, the following ones have been reported.

[0008]

In Patent Document 1, it is disclosed that an MC receptor ligand represented by the following general formula is useful for eating disorder, sexual dysfunction, skin disorder, chronic pain, anxiety, depression, obesity, and the like.

[Chem. 1]

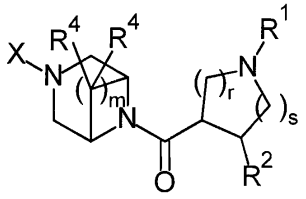


(In the formula, A represents C_{5-7} cycloalkyl, aryl, or heteroaryl. For the other symbols, refer to Patent Document 1.)

[0009]

In Patent Document 2, it is disclosed that an MC_4 receptor agonist represented by the following general formula is useful for obesity, diabetes, female sexual dysfunction, erectile dysfunction, and the like.

[Chem. 2]

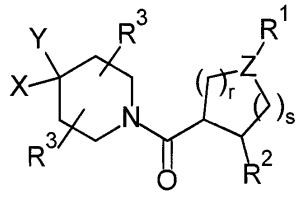


(In the formula, R_1 represents a C_{1-6} alkyl group, X represents $-(CH_2)_n$-phenyl or $-(CH_2)_nC(R^5)(R^6)(R^7)$, in which (CH_2) may have a substituent such as C_{1-4} alkyl, R^5 represents $-(CH_2)_n$-phenyl or the like, R^6 represents H, R^7 represents $-(CH_2)_nN(R^8)_2$, and m represents 0. For the other symbols, refer to Patent Document 2.)

[0010]

In Patent Document 3, it is disclosed that an MC_4 receptor modulator represented by the following general formula is useful for obesity, diabetes, male erectile dysfunction, or the like.

[Chem. 3]

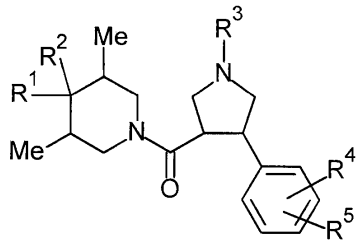


(For the symbols in the formula, refer to Patent Document 3.)

[0011]

In Patent Document 4, it is disclosed that an MC_4 receptor agonist represented by the following general formula is useful for obesity, diabetes, female sexual dysfunction, erectile dysfunction, or the like.

[Chem. 4]

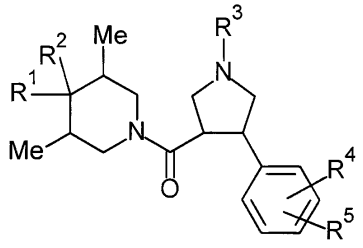


(For the symbols in the formula, refer to Patent Document 4.)

[0012]

In Patent Document 5, it is disclosed that the MC_4 receptor agonist is useful for lower urinary tract disorder, particularly urinary incontinence, and an MC_4 receptor agonist represented by the following general formula is disclosed.

[Chem. 5]



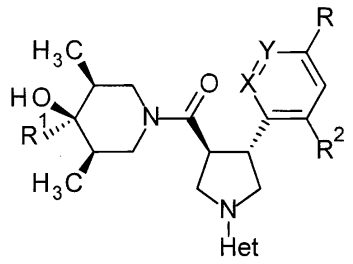
(For the symbols in the formula, refer to Patent Document 5.)

In Patent Document 5, it is described that the compound of Example 8 has an action of increasing the urethral pressure in the pharmacological data.

[0013]

In Patent Document 6, it is disclosed that an MC_4 receptor agonist represented by the following general formula is useful for sexual dysfunction, obesity, diabetes, lower urinary tract disorder, or the like.

[Chem. 6]

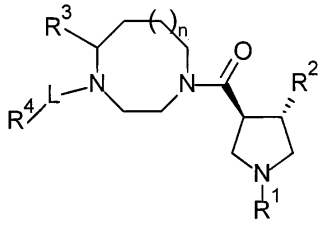


(For the other symbols, refer to Patent Document 6.)

[0014]

In Patent Document 7, it is disclosed that an MC_4 receptor agonist represented by the following general formula is useful for sexual dysfunction, obesity, diabetes, lower urinary tract disorder, or the like.

[Chem. 7]



(In the formula, R^3 represents phenyl or pyridyl, and n represents 0 or 1. For the other symbols, refer to Patent Document 7.)

Related Art

Patent Document

[0015]

[Patent Document 1] WO 2005/040109

[Patent Document 2] WO 2004/078716

[Patent Document 3] WO 2008/039418

[Patent Document 4] WO 2005/077935

[Patent Document 5] WO 2007/015157

[Patent Document 6] WO 2007/096763

[Patent Document 7] WO 2010/015972

Disclosure of Invention

Problems to Be Solved by the Invention

[0016]

The present invention has an object to provide a piperazine derivative which has an MC_4 receptor agonistic action and can be used as an active ingredient of a pharmaceutical composition for preventing or treating bladder and/or urinary tract diseases.

Means for Solving the Problems

[0017]

The present inventors have made extensive studies for the creation of a novel therapeutic agent for bladder and/or urinary tract diseases, and as a result, they have found that an MC_4 receptor agonist relaxes the urethra to decrease the urethral pressure. Further, the present inventors have found that in model rats with drug-induced voiding dysfunctions, there is an action of inhibiting a decrease in voiding efficiency and an action of inhibiting an increase in the amount of the residual urine.

On the other hand, known MC_4 receptor agonists all have an action against central nervous system diseases such as eating disorders, obesity, sexual disorder, and the like In the case where they are used for preventing or treating bladder and/or urinary tract diseases, it is not preferable that the MC_4 receptor agonists express an action on central nervous system diseases (including, for example, an erection-inducing action) when administered at an effective amount. From this viewpoint, the present inventors have considered it preferable to separate an action on bladder and/or urinary tract diseases from an action on central nervous system diseases. Therefore, the present inventors have conducted further extensive studies for the purpose of creating a compound having a potent action on bladder and/or urinary tract diseases.

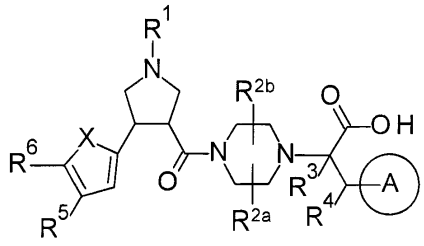
[0018]

As a result, the present inventors have found that the piperazine derivative of the formula (I) has an excellent MC_4 receptor agonistic activity, and have also discovered that the piperazine derivative is useful as a drug for preventing or treating bladder and/or urinary tract diseases, thereby completing the present invention.

[0019]

That is, the present invention relates to a compound of the formula (I) or a salt thereof, as well as a pharmaceutical composition comprising a compound of the formula (I) or a salt thereof and a pharmaceutically acceptable excipient.

[Chem. 8]



(I)

(In the formula,

R^1 is H, C_{1-6} alkyl which may be substituted with OH, C_{3-8} cycloalkyl which may be substituted with R^{00}, heterocycloalkyl which may be substituted with R^{00}, phenyl which may be substituted with R^{00}, heteroaryl which may be substituted with R^{00}, -CO-C_{1-6} alkyl, or -CO-C_{3-8} cycloalkyl, in which R^{00} represents substituents selected from the group consisting of C_{1-6} alkyl, halogeno-C_{1-6} alkyl, and halogen,

R^{2a} is C_{1-6} alkyl which may be substituted with R^{01}, in which R^{01} represents substituents selected from the group consisting of C_{3-8} cycloalkyl, -O-(C_{1-6} alkyl), -N(C_{1-6} alkyl)$_2$,

-NH(C_{1-6} alkyl), and -NH_2,

R^{2b} is H or C_{1-6} alkyl,

R^{2a} and R^{2b} may be combined with the same carbon atom in the piperazine ring to form C_{3-8} cycloalkyl,

R^3 is H or C_{1-6} alkyl,

R^4 is H or C_{1-6} alkyl,

X is *-CR^7=CR^8-, *-CR^7=N-, *-N=CR^8-, or S, in which * represents a bond with a carbon atom substituted with R^6,

R^5, R^6, and R^7 are the same as or different from each other, and are H, C_{1-6} alkyl, -O-(C_{1-6} alkyl), halogen, or CN,

R^5 and R^6 may be combined with each other to form C_{5-7} cycloalkenyl,

R^8 is H or F, and

the ring A is aryl which may be substituted with R^{02}, C_{5-7} cycloalkenyl-fused phenyl which may be substituted with R^{02}, heteroaryl which may be substituted with R^{02}, or C_{6-8} cycloalkyl which may be substituted with R^{02}, in which R^{02} represents substituents selected from the group consisting of C_{1-6} alkyl, halogeno-C_{1-6} alkyl, C_{3-8} cycloalkyl, -O-(C_{1-6} alkyl), -O-(halogeno-C_{1-6} alkyl), halogen, and -CN.)

[0020]

In addition, unless otherwise specified, when symbols in a certain chemical formula in the present specification are also used in another chemical formula, the same symbol represents the same meaning.

[0021]

The present invention relates to a pharmaceutical composition, in particular, a pharmaceutical composition for preventing or treating bladder and/or urinary tract diseases, comprising the compound of the formula (I) or a salt thereof. Further, the pharmaceutical composition in the present invention includes a pharmaceutical composition, in particular, a pharmaceutical composition for preventing or treating bladder and/or urinary tract diseases, comprising the compound of the formula (I) or a salt thereof and a pharmaceutically acceptable excipient, and an agent for preventing or treating bladder and/or urinary tract diseases, comprising the compound of the formula (I) or a salt thereof and a pharmaceutically acceptable excipient.

The present invention relates to use of the compound of the formula (I) or a salt thereof for the manufacture of a pharmaceutical composition for preventing or treating bladder and/or urinary tract diseases; use of the compound of the formula (I) or a salt thereof for preventing or treating bladder and/or urinary tract diseases; the compound of the formula (I) or a salt thereof for preventing or treating bladder and/or urinary tract diseases; and a method for preventing or treating bladder and/or urinary tract diseases, including administering an effective amount of the compound of the formula (I) or a salt thereof to a subject. In addition, the "subject" is a human or another animal in need of such prevention or treatment, and in a certain aspect, a human in need of such prevention or treatment.

In addition, the present invention further includes a pharmaceutical composition for preventing or treating bladder and/or urinary tract diseases, comprising an MC_4 receptor agonist as an active ingredient.

Effects of the Invention

[0022]

The compound of the formula (I) or a salt thereof is a compound having an MC_4 receptor agonistic activity, and can be used as an active ingredient of a pharmaceutical composition for preventing or treating bladder and/or urinary tract diseases.

Embodiments for Carrying Out the Invention

[0023]

Hereinafter, the present invention will be described in detail.

In the present specification, the "bladder and/or urinary tract diseases" particularly refers to voiding dysfunctions in the bladder and/or urinary tract diseases, and they are, for example, voiding dysfunctions in underactive bladder, hypotonic bladder, acontractile bladder, detrusor underactivity, neurogenic bladder, urethral relaxation failure, detrusor-external urethral sphincter dyssynergia, overactive bladder, urinary frequency, nocturia, urinary incontinence, benign prostatic hyperplasia, interstitial cystitis, chronic prostatitis,

and urethral calculus, or the like, and preferably voiding dysfunctions in underactive bladder, hypotonic bladder, acontractile bladder, detrusor underactivity, neurogenic bladder, urethral relaxation failure, detrusor-external urethral sphincter dyssynergia, and benign prostatic hyperplasia.

[0024]

The "C_{1-6} alkyl" refers to linear or branched alkyl having 1 to 6 carbon atoms (hereinafter abbreviated C_{1-6}). Examples thereof include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl, and the like. In a certain aspect, the C_{1-6} alkyl is C_{1-4} alkyl; in a certain aspect, methyl, ethyl, n-propyl, or tert-butyl; in a certain aspect, methyl or tert-butyl; in a certain aspect, methyl; and in a certain aspect, tert-butyl.

[0025]

The "halogeno-C_{1-6} alkyl" refers to C_{1-6} alkyl substituted with one or more halogen atoms. In a certain aspect, the halogeno-C_{1-6} alkyl is C_{1-6} alkyl substituted with 1 to 5 halogen atoms; in a certain aspect, difluoromethyl or trifluoromethyl; and in a certain aspect, trifluoromethyl.

[0026]

The "C_{3-8} cycloalkyl" refers to a C_{3-8} saturated hydrocarbon ring group, which may have a bridge and may form a spiro ring. Examples thereof include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2,2,1]heptyl, bicyclo[3,1,0]hexyl, bicyclo[3,1,1]heptyl, spiro[2,5]octyl, and the like. In a certain aspect, the C_{3-8} cycloalkyl is C_{3-5} cycloalkyl; and in a certain aspect, C_{6-8} cycloalkyl. In a certain aspect, the C_{3-5} cycloalkyl is cyclopropyl. In a certain aspect, the C_{6-8} cycloalkyl is cyclohexyl or cycloheptyl; in a certain aspect, cyclohexyl; and in a certain aspect, cycloheptyl. Further, the "C_{6-8} cycloalkyl" refers to a C_{6-8} saturated hydrocarbon ring group included in the "C_{3-8} cycloalkyl".

[0027]

The "C_{5-7} cycloalkenyl" refers to a C_{5-7} hydrocarbon ring group having one or more unsaturated bonds, which may have a bridge and form a spiro ring. Examples thereof include cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexadienyl, and the like. Further, the "C_{5-7} cycloalkenyl-fused phenyl" refers to phenyl fused at the site of an unsaturated bond of C_{5-7} cycloalkenyl, and examples thereof include 1-tetrahydronaphthyl, 2-tetrahydronaphthyl, dihydroinden-4-yl, 2,3-dihydro-1H-inden-5-yl, 1-indenyl, 2-indenyl, and the like. In a certain aspect, the C_{5-7} cycloalkenyl-fused phenyl is 2-tetrahydronaphthyl; and in a certain aspect, 2,3-dihydro-1H-inden-5-yl.

[0028]

The "aryl" is a monocyclic to tricyclic aromatic hydrocarbon ring group having 6 to 14 carbon atoms, and examples thereof include phenyl, naphthyl, anthracenyl, and the like. In a certain aspect, the aryl is phenyl; and in a certain aspect, naphthyl.

[0029]

The "heteroaryl" refers to a 5- or 6-membered monocyclic heteroaryl including one or more hetero atoms selected from O, N, and S as a ring-constituting atom, or a bicyclic heteroaryl in which the monocyclic heteroaryl is fused with a benzene ring. Further, some of the bonds may be unsaturated. Incidentally, the carbon atom which is a ring-constituting atom may be substituted with oxo. Examples of the 5-membered heteroaryl include imidazolyl, triazolyl, tetrazolyl, thiazolyl, pyrazolyl, isothiazolyl, oxazolyl, isoxazolyl, thiadiazolyl, oxadiazolyl, thienyl, furyl, pyrrolyl and the like; examples of the 6-membered heteroaryl include pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1,6-dihydro-6-oxopyridazinyl, and the like; and examples of the bicyclic heteroaryl in which the monocyclic heteroaryl is fused with a benzene ring include indolyl, isoindolyl, benzofuryl, benzothienyl, indazolyl, benzoimidazolyl, benzoxazolyl, benzothiazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, and the like. In a certain aspect, the heteroaryl is thiazolyl, thienyl, pyridyl, pyridazinyl, 1,6-dihydro-6-oxopyridazinyl, or indolyl; in a certain aspect, pyridyl; in a certain aspect, pyridazinyl; and in a certain aspect, 1,6-dihydro-6-oxopyridazinyl.

[0030]

The "heterocycloalkyl" refers to a 3- to 7-membered monocyclic heterocycloalkyl including one or more hetero atoms selected from O, N, and S as a ring-constituting atom. Examples thereof include aziridinyl, azetidinyl, oxetanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, tetrahydrofuranyl, oxazolidinyl, piperidyl, piperazinyl, 4-tetrahydropyranyl, morpholinyl, thiomorpholinyl, thiazolidinyl, isothiazolidinyl, oxazolidinyl, azepanyl, diazepanyl, and the like. In a certain aspect, the heterocycloalkyl is tetrahydrofuranyl or 4-tetrahydropyranyl; and in a certain aspect, 4-tetrahydropyranyl.

[0031]

In the present specification, the expression "which may be substituted" means "which is not substituted" or "which is substituted with 1 to 5 substituent(s)". Further, if it has a plurality of substituents, the substituents may be the same as or different from each other.

[0032]

R^{00} represents substituents selected from the group consisting of $C_{1\text{-}6}$ alkyl, halogeno-$C_{1\text{-}6}$ alkyl, and halogen. Examples thereof include, in a certain aspect, substituents selected from the group consisting of methyl, difluoromethyl, trifluoromethyl, and -F; and in a certain aspect, substituents selected from the group consisting of methyl and difluoromethyl.

[0033]

R^{01} represents substituents selected from the group consisting of C_{3-8} cycloalkyl, -O-(C_{1-6} alkyl), -N(C_{1-6} alkyl)$_2$, -NH(C_{1-6} alkyl), and -NH_2 ; and examples thereof include, in a certain aspect, substituents selected from the group consisting of R^{03}.

[0034]

R^{02} represents substituents selected from the group consisting of C_{1-6} alkyl, halogeno-C_{1-6} alkyl, C_{3-8} cycloalkyl, -O-(C_{1-6} alkyl), -O-(halogeno-C_{1-6} alkyl), halogen, and -CN. Examples thereof include, in a certain aspect, substituents selected from the group consisting of methyl, tert-butyl, trifluoromethyl, cyclopropyl, methoxy, difluoromethoxy, trifluoromethoxy, halogen, and -CN; in a certain aspect, substituents selected from the group consisting of methyl, tert-butyl, cyclopropyl, and halogen; and in a certain aspect, substituents selected from the group consisting of methyl and halogen.

[0035]

R^{03} represents substituents selected from the group consisting of C_{3-5} cycloalkyl, -O-(C_{1-6} alkyl), and -N(C_{1-6} alkyl)$_2$; and examples thereof include, in a certain aspect, substituents selected from the group consisting of cyclopropyl, methoxy, and -N-dimethyl.

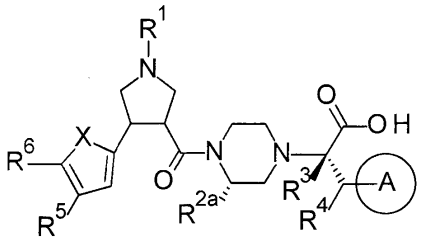
[0036]

The "halogen" refers to F, Cl, Br, or I; and in a certain aspect, F or Cl.

[0037]

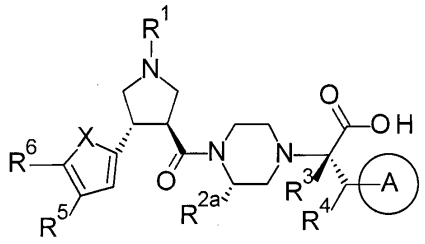
In a certain aspect of the formula (I), the compound is a compound defined by the following formula (Ia) or a salt thereof.

[Chem. 9]



In a certain aspect of the formulae (I) and (Ia), the compound is a compound defined by the following formula (Ib) or a salt thereof.

[Chem. 10]



(Ib)

[0038]

Some aspects of the compounds of the formulae (I), (Ia), and (Ib) of the present invention are shown below.

(1-1) The compound or a salt thereof, in which

R^1 is

i. tert-butyl which may be substituted with OH,

ii. C_{3-5} cycloalkyl which may be substituted with C_{1-6} alkyl,

iii. 4-tetrahydropyranyl which may be substituted with C_{1-6} alkyl,

iv. phenyl which may be substituted with halogen,

v. heteroaryl which may be substituted with substituents selected from the group consisting of C_{1-6} alkyl and halogeno-C_{1-6} alkyl,

vi. -CO-C_{1-6} alkyl, or

vii. -CO-C_{3-5} cycloalkyl.

(1-2) The compound or a salt thereof, in which

R^1 is

i. tert-butyl,

ii. 4-tetrahydropyranyl,

iii. pyridyl which may be substituted with halogeno-C_{1-6} alkyl, or

iv. 1,6-dihydro-6-oxopyridazinyl which may be substituted with C_{1-6} alkyl.

(1-3) The compound or a salt thereof, in which

R^1 is

i. tert-butyl,

ii. 4-tetrahydropyranyl,

iii. pyridyl which may be substituted with difluoromethyl, or

iv. 1,6-dihydro-6-oxopyridazinyl which may be substituted with methyl.

(1-4) The compound or a salt thereof, in which

R^1 is

i. tert-butyl or

ii. 4-tetrahydropyranyl.

[0039]

(2-1) The compound or a salt thereof, in which

R^{2a} is C_{1-6} alkyl which may be substituted with R^{03}, and

R^{03} represents substituents selected from the group consisting of C_{3-5} cycloalkyl, -O-(C_{1-6} alkyl), and -N(C_{1-6} alkyl)$_2$.

(2-2) The compound or a salt thereof, in which R^{2a} is C_{1-6} alkyl.

(2-3) The compound or a salt thereof, in which R^{2a} is methyl, ethyl, or n-propyl.

(2-4) The compound or a salt thereof, in which R^{2a} is methyl.

[0040]

(3-1) The compound or a salt thereof, in which R^{2b} is H or C_{1-6} alkyl.

(3-2) The compound or a salt thereof, in which R^{2b} is H.

[0041]

(4-1) The compound or a salt thereof, in which R^3 is H or C_{1-6} alkyl.

(4-2) The compound or a salt thereof, in which R^3 is H or methyl.

(4-3) The compound or a salt thereof, in which R^3 is H.

[0042]

(5-1) The compound or a salt thereof, in which R^4 is H or C_{1-6} alkyl.

(5-2) The compound or a salt thereof, in which R^4 is H or methyl.

(5-3) The compound or a salt thereof, in which R^4 is H.

[0043]

(6-1) The compound or a salt thereof, in which

X is *-CR^7=CR^8-, *-CR^7=N-, *-N=CR^8-, or S, and

* represents a bond with a carbon atom substituted with R^6.

(6-2) The compound or a salt thereof, in which

X is *-CR^7=CR^8- or *-N=CR^8-, and

* represents a bond with a carbon atom substituted with R^6.

(6-3) The compound or a salt thereof, in which

X is *-CR^7=CR^8-, and

* represents a bond with a carbon atom substituted with R^6.

[0044]

(7-1) The compound or a salt thereof, in which R^5, R^6, and R^7 are the same as or different from each other and represent H, C_{1-6} alkyl, or halogen.

[0045]

(8-1) The compound or a salt thereof, in which R^5 is H or halogen.

(8-2) The compound or a salt thereof, in which R^5 is H.

[0046]

(9-1) The compound or a salt thereof, in which R^6 is halogen.

(9-2) The compound or a salt thereof, in which R^6 is F or Cl.

(9-3) The compound or a salt thereof, in which R^6 is F.

(9-4) The compound or a salt thereof, in which R^6 is Cl.

[0047]

(10-1) The compound or a salt thereof, in which R^7 is H or halogen.

(10-2) The compound or a salt thereof, in which R^7 is H.

[0048]

(11-1) The compound or a salt thereof, in which R^8 is H or F.

(11-2) The compound or a salt thereof, in which R^8 is F.

[0049]

(12-1) The compound or a salt thereof, in which

the ring A is

i. aryl which may be substituted with substituents selected from the group consisting of C_{1-6} alkyl, halogeno-C_{1-6} alkyl, C_{3-5} cycloalkyl, -O-(C_{1-6} alkyl), -O-(halogeno-C_{1-6} alkyl), halogen, and -CN,

ii. C_{5-7} cycloalkenyl-fused phenyl which may be substituted with substituents selected from the group consisting of C_{1-6} alkyl and halogen,

iii. heteroaryl which may be substituted with halogen, or

iv. C_{6-8} cycloalkyl which may be substituted with C_{1-6} alkyl.

(12-2) The compound or a salt thereof, in which the ring A is

i. phenyl which may be substituted with substituents selected from the group consisting of C_{1-6} alkyl, C_{3-5} cycloalkyl, and halogen,

ii. naphthyl,

iii. 2,3-dihydro-1H-inden-5-yl which may be substituted with substituents selected from the group consisting of C_{1-6} alkyl and halogen,

iv. cyclohexyl which may be substituted with C_{1-6} alkyl, or

v. cycloheptyl which may be substituted with C_{1-6} alkyl.

(12-3) The compound or a salt thereof, in which

the ring A is

i. phenyl which may be substituted with substituents selected from the group consisting of C_{1-6} alkyl, C_{3-5} cycloalkyl, and halogen,

ii. naphthyl,

iii. 2,3-dihydro-1H-inden-5-yl which may be substituted with substituents selected from the group consisting of C_{1-6} alkyl and halogen, or

iv. cyclohexyl which may be substituted with C_{1-6} alkyl.

(12-4) The compound or a salt thereof, in which

the ring A is

i. phenyl which may be substituted with substituents selected from the group consisting of C_{1-6} alkyl and halogen,

ii. naphthyl, or

iii. 2,3-dihydro-1H-inden-5-yl.

(12-5) The compound or a salt thereof, in which

the ring A is

i. phenyl which may be substituted with substituents selected from the group consisting of methyl and F,

ii. naphthyl, or

iii. 2,3-dihydro-1H-inden-5-yl.

(12-6) The compound or a salt thereof, in which the ring A is phenyl which may be substituted with substituents selected from the group consisting of C_{1-6} alkyl and halogen.

[0050]

(13) The compound or a salt thereof, which is a combination of any two or more of the aspects described in (1-1) to (12-6) in the formulae (I), (Ia), and (Ib) in which the two or more of the aspects are not inconsistent to each other.

[0051]

Examples of the aspect (13) of the present invention include the compounds or a salt thereof shown below.

[0052]

(14-1)

The compound of the formula (I) or a salt thereof, in which

R^1 is

i. tert-butyl which may be substituted with OH,

ii. C_{3-5} cycloalkyl which may be substituted with C_{1-6} alkyl,

iii. 4-tetrahydropyranyl which may be substituted with C_{1-6} alkyl,

iv. phenyl which may be substituted with halogen,

v. heteroaryl which may be substituted with substituents selected from the group consisting of C_{1-6} alkyl and halogeno-C_{1-6} alkyl,

vi. -CO-C_{1-6} alkyl, or

vii. -CO-C_{3-5} cycloalkyl,

R^{2a} is C_{1-6} alkyl which may be substituted with R^{03},

in which R^{03} represents substituents selected from the group consisting of C_{3-5} cycloalkyl, -O-(C_{1-6} alkyl), and -N(C_{1-6} alkyl)$_2$,

R^{2b} is H or C_{1-6} alkyl,

R^3 is H or C_{1-6} alkyl,

R^4 is H or C_{1-6} alkyl,

X is *-CR^7=CR^8-, *-CR^7=N-, *-N=CR^8-, or S,

in which * represents a bond with a carbon atom substituted with R^6,

R^5, R^6, and R^7 are the same as or different from each other, and are H, C_{1-6} alkyl, or halogen,

R^8 is H or F, and

the ring A is

i. aryl which may be substituted with substituents selected from the group consisting of C_{1-6} alkyl, halogeno-C_{1-6} alkyl, C_{3-5} cycloalkyl, -O-(C_{1-6} alkyl), -O-(halogeno-C_{1-6} alkyl), halogen, and -CN,

ii. C_{5-7} cycloalkenyl-fused phenyl which may be substituted with substituents selected from the group consisting of C_{1-6} alkyl and halogen,

iii. heteroaryl which may be substituted with halogen, or

iv. C_{6-8} cycloalkyl which may be substituted with C_{1-6} alkyl.

[0053]

(14-2) The compound of the formula (I) or a salt thereof, in which

R^1 is

i. tert-butyl,

ii. 4-tetrahydropyranyl,

iii. pyridyl which may be substituted with halogeno-C_{1-6} alkyl, or

iv. 1,6-dihydro-6-oxopyridazinyl which may be substituted with C_{1-6} alkyl,

R^{2a} is C_{1-6} alkyl,

R^{2b} is H,

R^3 is H or methyl,

R^4 is H or methyl,

X is *-CR^7=CR^8- or *-N=CR^8-,

in which * represents a bond with a carbon atom substituted with R^6,

R^5 is H or halogen,

R^6 is halogen,

R^7 is H or halogen,

R^8 is F, and

the ring A is

i. phenyl which may be substituted with substituents selected from the group consisting of C_{1-6} alkyl, C_{3-5} cycloalkyl and halogen,

ii. naphthyl,

iii. 2,3-dihydro-1H-inden-5-yl which may be substituted with substituents selected from the group consisting of C_{1-6} alkyl and halogen,

iv. cyclohexyl which may be substituted with C_{1-6} alkyl, or

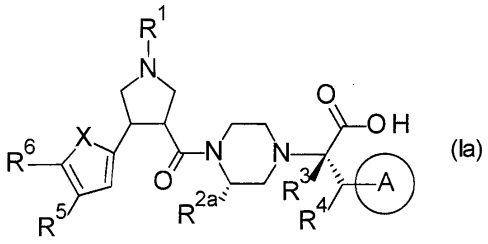
v. cycloheptyl which may be substituted with C_{1-6} alkyl.

[0054]

(14-3)

The compound of the formula (I) or a salt thereof as described in (14-2), in which the formula (I) is the following the formula (Ia):

[Chem. 11]



R^1 is

i. tert-butyl,

ii. 4-tetrahydropyranyl,

iii. pyridyl which may be substituted with difluoromethyl, or

iv. 1,6-dihydro-6-oxopyridazinyl which may be substituted with methyl,

R^{2a} is methyl, ethyl, or n-propyl,

R^3 is H or methyl,

R^4 is H or methyl,

X is *-CR^7=CR^8-,

in which * represents a bond with a carbon atom substituted with R^6,

R^5 is H,

R^6 is F or Cl,

R^7 is H,

R^8 is F, and

the ring A is

i. phenyl which may be substituted with substituents selected from the group consisting of C_{1-6} alkyl, C_{3-5} cycloalkyl and halogen,

ii. naphthyl,

iii. 2,3-dihydro-1H-inden-5-yl which may be substituted with substituents selected from the group consisting of C_{1-6} alkyl and halogen, or

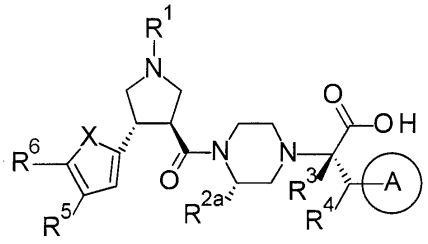
iv. cyclohexyl which may be substituted with C_{1-6} alkyl.

[0055]

(14-4)

The compound or a salt thereof as described in (14-3), in which the formula (Ia) is the following formula (Ib):

[Chem. 12]



(Ib)

R^1 is

i. tert-butyl, or

ii. 4-tetrahydropyranyl,

R^{2a} is methyl, ethyl, or n-propyl,

R^3 is H,

R^4 is H,

X is *-CR^7=CR^8-,

in which * represents a bond with a carbon atom substituted with R^6,

R^5 is H,

R^6 is F or Cl,

R^7 is H,

R^8 is F, and

the ring A is

i. phenyl which may be substituted with substituents selected from the group consisting of C_{1-6} alkyl and halogen,

ii. naphthyl, or

iii. 2,3-dihydro-1H-inden-5-yl.

[0056]

Examples of the specific compounds included in the present invention include the following compounds or salts thereof.

Compounds selected from the group consisting of the following compounds or salts thereof:

(2S)-2-[(3S)-4-{[(3S,4R)-4-(4-chloro-2-fluorophenyl)-1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-(2-fluoro-4-methylphenyl)propanoic acid,

(2S)-2-[(3S)-4-{[(3S,4R)-4-(4-chloro-2-fluorophenyl)-1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-(2-fluoro-4,6-dimethylphenyl)propanoic acid,

(2S)-2-[(3S)-4-{[(3S,4R)-1-tert-butyl-4-(4-chloro-2-fluorophenyl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-mesitylpropanoic acid,

(2S)-2-[(3S)-4-{[(3S,4R)-1-tert-butyl-4-(4-chloro-2-fluorophenyl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-(2-fluoro-4-methylphenyl)propanoic acid,

(2S)-2-[(3S)-4-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-(2,3-dihydro-1H-inden-5-yl)propanoic acid,

(2S)-2-[(3S)-4-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}-3-propylpiperazin-1-yl]-3-(2-naphthyl)propanoic acid, and

(2S)-2-[(3S)-4-{[(3S,4R)-1-tert-butyl-4-(4-chloro-2-fluorophenyl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-(4-methylphenyl)propanoic acid.

[0057]

The following descriptions about the compound of the formula (I) also apply to the compounds of the formula (Ia) and the formula (Ib) unless otherwise specified.

The compound of the formula (I) may exist in the form of tautomers or geometrical isomers depending on the kind of substituents. In the present specification, the compound of the formula (I) shall be described in only one isomer form, yet the present invention includes any other isomers, in their isolated form, or as mixtures thereof.

In addition, the compound of the formula (I) may have asymmetric carbon atoms or axis chirality with no indication of stereochemistry in some cases, and therefore, optical isomers may exist based thereon. The present invention includes isolated forms of optical isomers of the compound of the formula (I) or any mixture thereof.

[0058]

Moreover, the present invention also includes a pharmaceutically acceptable prodrug of the compound of the formula (I). The pharmaceutically acceptable prodrug is a compound having a group that can be converted into an amino group, a hydroxyl group, a carboxyl group, or the like through solvolysis or under physiological conditions. Examples of the group forming the prodrug include the groups described in Prog. Med., 5, 2157-2161 (1985) and "Pharmaceutical Research and Development" (Hirokawa Publishing Company, 1990), Vol. 7, Molecular Design, 163-198.

[0059]

Moreover, the salt of the compound of the formula (I) is a pharmaceutically acceptable salt of the compound of the formula (I) and may form an acid addition salt or a salt with a base depending on the kind of substituents. Specific examples thereof include acid addition salts with inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, and phosphoric acid, and with organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, mandelic acid, tartaric acid, dibenzoyltartaric acid, ditoluoyltartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, aspartic acid, and glutamic acid, and salts with inorganic bases such as sodium, potassium, magnesium, calcium, and aluminum, or organic bases such as methylamine, ethylamine, ethanolamine, lysine, and ornithine, salts

with various amino acids or amino acid derivatives such as acetylleucine, ammonium salts, and the like.

A salt of the compound of the formula (I) can also be prepared by an ordinary method.

[0060]

Isolation and purification are carried out by employing ordinary chemical operations such as extraction, fractional crystallization, and various types of fractional chromatography.

Various isomers can be prepared by selecting appropriate starting compounds or by separation using differences in physicochemical properties between the isomers. For example, optical isomers can be obtained by means of a general optical resolution method for racemic products (for example, fractional crystallization for inducing diastereomer salts with optically active bases or acids, and chromatography using a chiral column or the like), and further, the isomers can also be prepared from an appropriate optically active starting compound.

[0061]

Furthermore, the present invention also includes various hydrates or solvates, and polymorphic crystalline substances of the compound of the formula (I) or a salt thereof. In addition, the present invention also includes compounds labeled with various radioactive or non-radioactive isotopes.

[0062]

In the powder X-ray diffraction pattern described in the present specification, the numeral values obtained from various patterns have some errors caused by the direction of the crystal growth, the size of particles, measurement conditions, or the like in some cases. The error range of a diffraction angle (2θ (°)) in the powder X-ray diffraction is ±0.2° in a certain aspect. Further, for example, in the case of performing measurement in the state of a mixture with additives of a pharmaceutical product, a peak may be apparently shifted by approximately ±0.3° in a peak which exists in the vicinity of a peak derived from the additives of a pharmaceutical product and is on the slope of the peak derived from the additives of the pharmaceutical product in some cases. In addition, in the powder X-ray diffraction pattern, crystal lattice intervals or overall patterns are important for identification of crystals in terms of the properties of the data, and since the diffraction angle and the diffraction intensity may vary slightly depending on the direction of crystal growth, the particle size, and the measurement conditions, they should not be strictly construed.

[0063]

(Preparation Methods)

The compound of the formula (I) or a salt thereof can be prepared using the characteristics based on the basic structure or the type of substituents thereof and by applying various known synthesis methods. During the preparation, replacing the relevant functional group with a suitable protective group (a group that can be easily converted into the relevant functional group) at the stage from starting material to an intermediate may be effective depending on the type of the functional group in the production technology in some cases. The protective group for such a functional group may include, for example, the protective groups described in "Greene's Protective Groups in Organic Synthesis (4th edition, 2006)", P. G. M. Wuts and T. W. Greene, and one of these may be selected and used as necessary depending on the reaction conditions. In this kind of method, a desired compound can be obtained by introducing the protective group, by carrying out the reaction and by eliminating the protective group as necessary.

In addition, prodrugs of the compound of the formula (I) can be prepared by introducing a specific group or by carrying out the reaction using the obtained compound of the formula (I) at the stage from a starting material to an intermediate, just as in the case of the above-mentioned protective group. The reaction can be carried out using methods known to a person skilled in the art, such as ordinary esterification, amidation, dehydration, and the like.

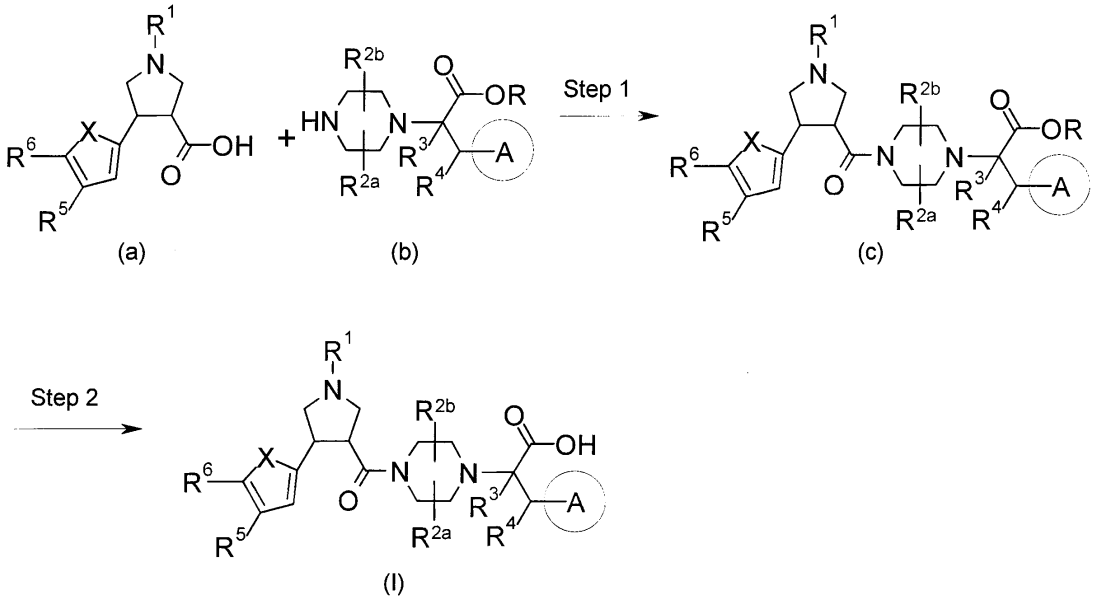
[0064]

Hereinbelow, representative preparation methods for the compound of the formula (I) will be described. Each production process may also be carried out with reference to the References appended in the present description. Further, the preparation methods of the present invention are not limited to the examples shown below.

[0065]

(Production Process 1)

[Chem. 13]



(In the formulae, R represents a protective group. The same shall apply hereinafter.)

The present production process is a method for preparing the compound of the formula (I) which is the compound of the present invention.

Here, examples of the protective group R include a methyl group, an ethyl group, a tert-butyl group, and the like.

[0066]

(Step 1)

The present step is a step of obtaining a compound of the formula (c) by subjecting a compound of the formula (a) and a compound of the formula (b) to an amidation reaction.

In this reaction, the compound of the formula (a) and the compound of the formula (b) are used in equivalent amounts, or either thereof in an excess amount, and their mixture is stirred in a range from cooling to heating, preferably at -20°C to 60°C, usually for 0.1 hours to 5 days, in a solvent which is inert to the reaction, in the presence of a condensing agent. Examples of the solvent used herein are not particularly limited, but include aromatic hydrocarbons such as benzene, toluene, xylene, and the like, halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, chloroform, and the like, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, and the like, N,N-dimethylformamide, dimethylsulfoxide, ethyl acetate, acetonitrile, or water, and any mixture thereof. Examples of the condensing agent include, but are not limited to, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or a hydrochloride thereof, dicyclohexylcarbodiimide, 1,1'-carbonyldiimidazole, diphenylphosphoryl azide, phosphorous oxychloride, O-(7-aza-1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium

hexafluorophosphate (HATU), and the like. It may be preferable in some cases for the reaction to use an additive (for example, 1-hydroxybenzotriazole). It may be advantageous in some cases for smooth progress of the reaction to carry out the reaction in the presence of organic bases such as triethylamine, N,N-diisopropyl ethylamine, N-methylmorpholine, and the like, or inorganic bases such as potassium carbonate, sodium carbonate, potassium hydroxide, and the like.

Furthermore, it is also possible to use a method in which a carboxylic acid (a) is converted to a reactive derivative and afterward reacted with an amine (b). Examples of the reactive derivative of the carboxylic acid include acid halides that can be obtained by the reaction with a halogenating agent such as phosphorus oxychloride, thionyl chloride, and the like, mixed acid anhydrides obtained by the reaction with isobutyl chloroformate, or the like, and active esters obtained by condensation with 1-hydroxybenzotriazole or the like. The reaction of these reactive derivatives with the compound (b) can be carried out in a range from cooling to heating, and preferably from -20°C to 60°C, in a solvent which is inert to the reaction, such as halogenated hydrocarbons, aromatic hydrocarbons, ethers, and the like.

For a reference for the present reaction, reference can be made to, for example, the following one.

"Courses in Experimental Chemistry (5th edition)" edited by The Chemical Society of Japan, Vol. 16 (2005) (Maruzen)

[0067]

(Step 2)

The present step is a method for preparing the compound of the formula (I) which is the compound of the present invention by deprotecting the compound of the formula (c).

The present reaction is carried out by stirring in a range from cooling to heating and refluxing, usually for 0.1 hours to 5 days. Examples of the solvent used herein are not particularly limited, but include alcohols such as methanol, ethanol, and the like, aromatic hydrocarbons such as benzene, toluene, xylene, and the like, halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, chloroform, and the like, ethers such as diethyl ether, tetrahydrofuran, dioxane, dimethoxyethane, and the like, N,N-dimethylformamide, dimethylsulfoxide, ethyl acetate, acetonitrile, or water, and a mixture thereof. Examples of the deprotecting reagent are not particularly limited, but include bases such as an aqueous sodium hydroxide solution, an aqueous potassium hydroxide solution, an aqueous lithium hydroxide solution, and the like, and acids such as hydrochloric acid, trifluoroacetic acid, and the like.

For a reference for the present reaction, reference can be made to, for example, the following one.

"Courses in Experimental Chemistry (5th edition)" edited by The Chemical Society of Japan, Vol. 16 (2005) (Maruzen)

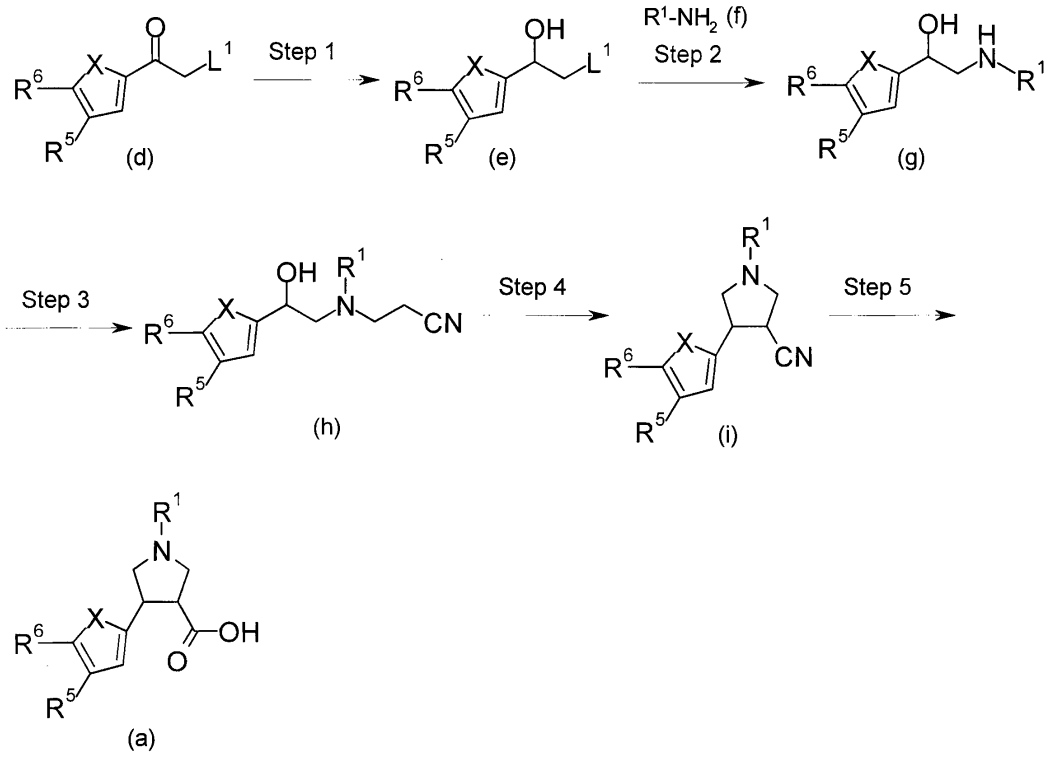
(Preparation of Starting Compounds)

The starting compounds in the preparation methods above can be prepared by, for example, the following method, the methods described in Preparation Examples which will be described later, well-known methods, or modified methods thereof.

[0068]

(Starting Material Synthesis 1)

[Chem. 14]



(In the formulae, L^1 represents a leaving group. This shall apply hereinafter.)

The present production process is a method for preparing the compound of the formula (a) which is a starting material for the compound of the formula (c).

Here, examples of the leaving group L^1 include a chloro group and the like.

[0069]

(Step 1)

The present step is a method for preparing a compound of the formula (e) by subjecting the compound of the formula (d) to a reduction reaction.

The present reaction is carried out by reacting the compound of the formula (d) and a reducing agent in equivalent amounts, or either thereof in an excess amount in a range from cooling to heating and refluxing, preferably at -20°C to 40°C, usually for 0.1

hours to 5 days, in a solvent which is inert to the reaction. Examples of the solvent used herein are not particularly limited, but include aromatic hydrocarbons such as benzene, toluene, xylene, and the like, ethers such as diethyl ether, methyl tert-butyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, and the like, alcohols such as methanol, ethanol, and the like, or water, and a mixture thereof. Examples of the reducing agent include, but at not limited to, sodium borohydride, a borane-N,N-diethylaniline complex, and the like. Further, it may be advantageous in some cases for smooth progress of the reaction to use various additives. In addition, it may be preferable for obtaining the compound of the formula (e) in an optically active form in some cases to use an asymmetric agent catalyst together with the reducing agent (for example, a borane-N,N-diethylaniline complex and (S)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine ((S)-MeCBS)).

For a reference for the present reaction, reference can be made to, for example, the following ones.

"Courses in Experimental Chemistry (5th edition)" edited by The Chemical Society of Japan, Vol. 14 (2005) (Maruzen)

"Courses in Experimental Chemistry (5th edition)" edited by The Chemical Society of Japan, Vol. 19 (2005) (Maruzen)

J. Org. Chem. 70, 3592-3601 (2005)

[0070]

(Step 2)

The present step is a step of preparing the compound of the formula (g) by reacting the compound of the formula (e) with a compound of the formula (f).

The present reaction is carried out by using the compound of the formula (e) and the compound of the formula (f) in equivalent amounts, or the compound of the formula (f) in an excess amount, and reacting the mixture in a range from cooling to heating and refluxing, preferably at 0°C to 80°C, usually for 0.1 hours to 5 days, in a solvent which is inert to the reaction, in the presence of a base. Examples of the solvent used herein are not particularly limited, but include aromatic hydrocarbons such as benzene, toluene, xylene, and the like, alcohols such as methanol, ethanol, and the like, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, and the like, halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, chloroform, and the like, N,N-dimethylformamide, dimethylsulfoxide, ethyl acetate, acetonitrile, and a mixture thereof. Examples of the base are not particularly limited, but include organic bases such as triethylamine, N,N-diisopropylethylamine, 1,8-diazabicyclo[5.4.0]-7-undecene, n-butyllithium, and the like, and inorganic bases such as sodium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, potassium tert-butoxide, and the like. It may be advantageous in some cases to carry out the reaction in

the presence of a phase transfer catalyst such as tetra-n-butylammonium chloride and the like.

For a reference for the present reaction, reference can be made to, for example, the following one.

"Courses in Experimental Chemistry (5th edition)" edited by The Chemical Society of Japan, Vol. 14 (2005) (Maruzen)

[0071]

(Step 3)

The present step is a step of preparing a compound of the formula (h) by subjecting the compound of the formula (g) and acrylonitrile to a conjugate addition reaction.

The present reaction is carried out by reacting the compound of the formula (g) and acrylonitrile in an excess amount in a range from cooling to heating, preferably at 40°C to 80°C, usually for 12 hours to 5 days, in a solvent which is inert to the reaction. Further, it may be preferable in some cases to carry out the reaction in the absence of a solvent. In addition, it may be advantageous in some cases for smooth progress of the reaction to carry out the reaction to use ethanol, formamide, or the like as the additive.

For a reference for the present reaction, reference can be made to J. Org. Chem. 70, 3592-3601 (2005) as mentioned above.

[0072]

(Step 4)

The present step is a step of preparing a compound of the formula (i) by subjecting the compound of the formula (h) to a cyclization reaction.

The present reaction is carried out by reacting the compound of the formula (h) with p-toluenesulfonic anhydride, methanesulfonic anhydride, diethyl chlorophosphate, or the like under cooling, preferably in a range from -78°C to under ice-cooling, usually for 0.1 hours to 5 days, in a solvent which is inert to the reaction, in the presence of a base. Examples of the base are not particularly limited, but include lithium bis(trimethylsilyl)amide, sodium bis(trimethylsilylamide), potassium bis(trimethylsilyl)amide, and the like.

For a reference for the present reaction, reference can be made to, for example, J. Org. Chem. 70, 3592-3601 (2005) as described above.

[0073]

(Step 5)

The present step is a step of preparing the compound of the formula (a) by subjecting the compound of the formula (i) to alkali hydrolysis.

The present reaction is carried out by stirring in a range of cooling to heating and refluxing, usually 0.1 hours to 5 days. Examples of the solvent used herein are not

particularly limited, but include alcohols, acetone, N,N-dimethylformamide, tetrahydrofuran, and the like. Further, it may be suitable for the reaction in some cases to use a mixed solvent of the above solvent with water. Examples of the hydrolysis reagent are not particularly limited, but include bases such as an aqueous sodium hydroxide solution, an aqueous potassium hydroxide solution, and the like.

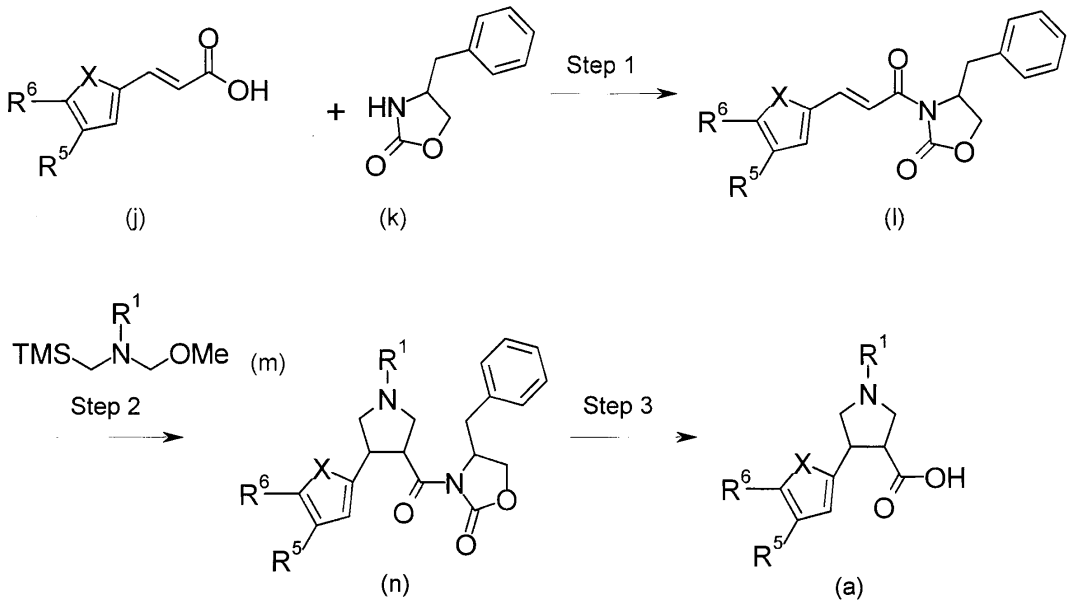
For a reference for the present reaction, reference can be made to, for example, the following one.

"Courses in Experimental Chemistry (5th edition)" edited by The Chemical Society of Japan, Vol. 16 (2005) (Maruzen)

[0074]

(Starting Material Synthesis 2)

[Chem. 15]



The present production process is a method for preparing the compound of the formula (a) which is a starting material for the compound of the formula (c).

[0075]

(Step 1)

The present step is a step of preparing a compound of the formula (l) by subjecting the compound of the formula (j) and the compound of the formula (k) to an amidation reaction.

The present reaction can be carried out by the same method as Step 1 of Production Process 1 as described above. In addition, the reaction products after the next step can be obtained as an optically active form such as the compound of the formula (Ib) by using an optically active form as the compound of the formula (k) in some cases.

[0076]

(Step 2)

The present step is a step of obtaining a compound of the formula (n) by subjecting the compound of the formula (l) and the compound of the formula (m) to a 1,3-dipolar cycloaddition reaction.

In the present reaction, the compound of the formula (l) and the compound of the formula (m) in equivalent amounts, or either thereof in an excess amount are used, and a mixture thereof is stirred in a range from cooling to heating, preferably at -20°C to 60°C, usually for 0.1 hours to 5 days, in a solvent which is inert to the reaction, in the presence of an acid. Examples of the solvent used herein are not particularly limited, but include aromatic hydrocarbons such as benzene, toluene, xylene, and the like, and halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, chloroform, and the like. Examples of the acid include trifluoroacetic acid and the like.

For a reference for the present reaction, reference can be made to, for example, the following one.

Tetrahedron: Asymmetry, 8, 883-887 (1997)

[0077]

(Step 3)

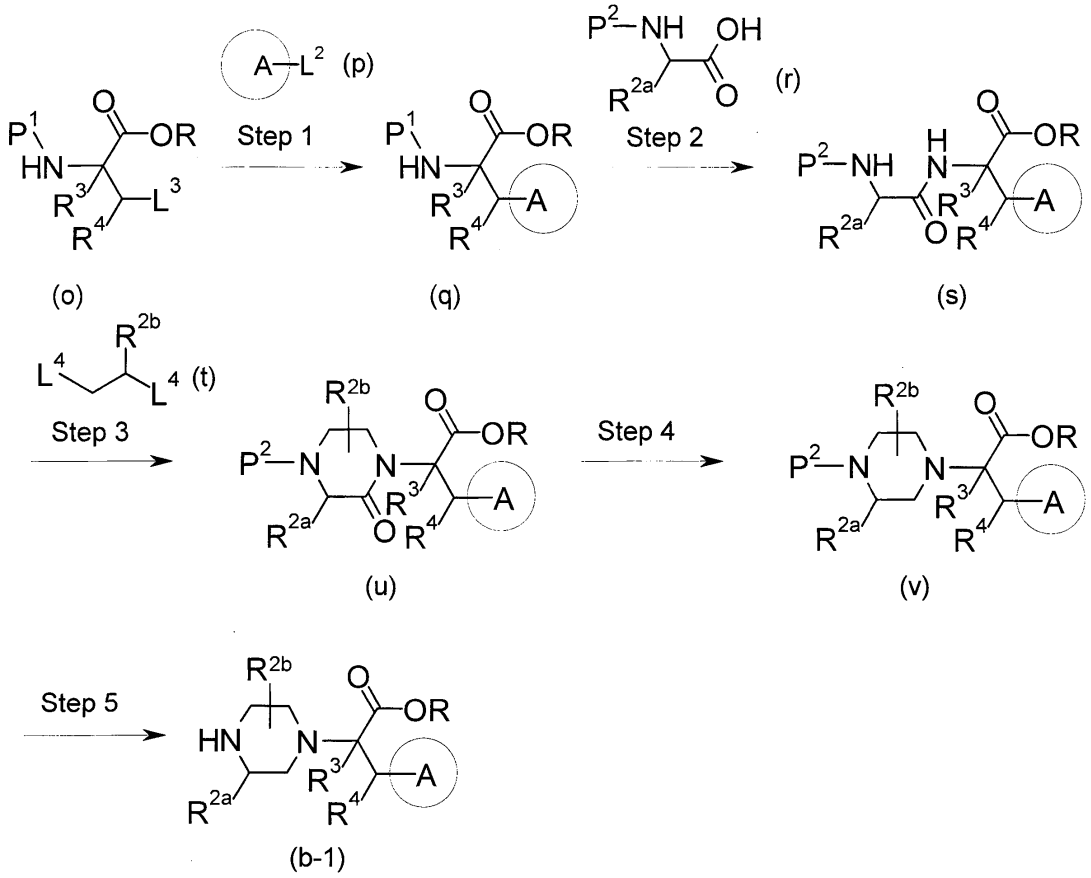
The present step is a step of preparing the compound of the formula (a) by subjecting the compound of the formula (n) to alkali hydrolysis.

The present reaction can be carried out by the same method as for Step 5 of Starting Material Synthesis 1 as described above.

[0078]

(Starting Material Synthesis 3)

[Chem. 16]



(In the formula, L^2 and L^3 represent halogen, P^1 or P^2 represents a protective group, and L^4 represents a leaving group. This shall apply hereinafter.)

The present production process is a method for preparing the compound of the formula (b-1) which is a starting material for the compound of the formula (c).

Here, examples of halogen, L^2 or L^3, include a bromo group and an iodine group. Examples of the protective group P^1 include a tert-butoxycarbonyl group and the like. Examples of the protective group P^2 include a 2-nitrobenzenesulfonyl group and the like. Examples of the leaving group L^4 include a bromo group and the like.

[0079]

(Step 1)

The present step is a step of preparing the compound of the formula (q) from the compound of the formula (o) and the compound of the formula (p).

In the present reaction, zinc powder or the like is used as a metal reagent, and a so-called Negishi reaction of cross-coupling of an organic zinc compound and an organic halogen compound, can be used, which is a well-known reaction to a person skilled in the art.

The present reaction is carried out by performing a reaction in a range of cooling to heating and refluxing, preferably at -20°C to 80°C, usually for 0.1 hours to 5 days, in a

solvent which is inert to the reaction. Examples of the solvent used herein include tetrahydrofuran, N,N-dimethylformamide, and the like. Further, examples of the catalyst used include a nickel catalyst and a palladium catalyst. In addition, it may be advantageous to carry out the reaction in the presence of a phosphine ligand or the like in some cases.

For a reference for the present reaction, reference can be made to, for example, the following ones.

"Courses in Experimental Chemistry (5th edition)" edited by The Chemical Society of Japan, Vol. 13 (2005) (Maruzen)

J. Org. Chem. 75, 245-248 (2010)

[0080]

(Step 2)

The present step is a step of preparing the compound of the formula (s) by deprotecting the protective group P^1 of the compound of the formula (q), and then subjecting it to an amidation reaction with the compound of the formula (r).

The present reaction can be carried out by deprotecting the protective group P^1 with reference to "Protective Groups in Organic Synthesis", Greene and Wuts, 4th edition, John Wiley & Sons Inc, 2006, and then performing the same method as Step 1 of Production Process 1 as described above.

[0081]

(Step 3)

The present step is a step of preparing the compound of the formula (u) from the compound of the formula (s) and the compound of the formula (t).

The present reaction is carried out by performing a reaction in a range of cooling to heating and refluxing, preferably at 0°C to 80°C, usually for 0.1 hours to 5 days, in a solvent which is inert to the reaction. Examples of the solvent used herein include acetonitrile, N,N-dimethylformamide, and the like. Examples of the base include, but are not limited to, inorganic bases such as potassium carbonate and the like.

[0082]

(Step 4)

The present step is a step of preparing a compound of the formula (v) by subjecting the compound of the formula (u) to a reduction reaction.

The present reaction is carried out by reacting the compound of the formula (u) and a reducing agent in equivalent amounts or in an excess amount in a range from cooling to heating and refluxing, preferably at -20°C to 40°C, usually for 0.1 hours to 5 days, in a solvent which is inert to the reaction. Examples of the solvent used herein are not particularly limited, but include aromatic hydrocarbons such as benzene, toluene, xylene, and the like, and ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-

dimethoxyethane, and the like. Examples of the reducing agent include, but at not limited to, lithium aluminum hydride, a borane-tetrahydrofuran complex, diborane, and the like.

For a reference for the present reaction, reference can be made to, for example, the following one.

"Courses in Experimental Chemistry" (5th edition) edited by The Chemical Society of Japan, Vol. 14 (2005) (Maruzen)

[0083]

(Step 5)

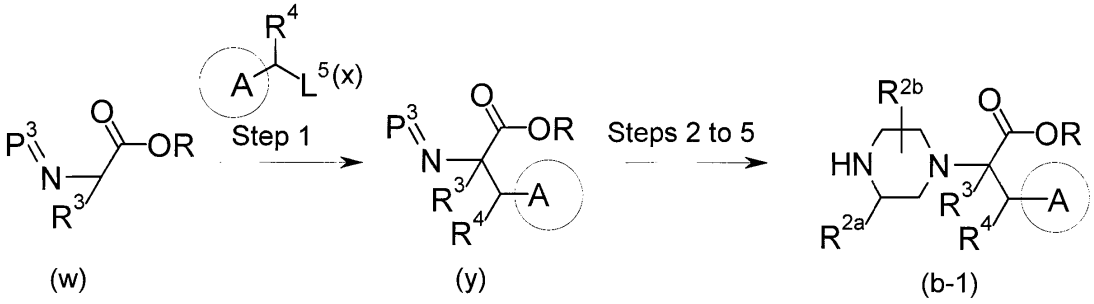
The present step is a step of preparing the compound of the formula (b-1) by deprotecting the protective group P^2 of the compound of the formula (v).

The present reaction can be carried out with reference to "Protective Groups in Organic Synthesis", Greene and Wuts, 4th edition, John Wiley & Sons Inc, 2006 as described above.

[0084]

(Starting Material Synthesis 4)

[Chem. 17]



(w) (y) (b-1)

(In the formula, L^5 represents halogen and P^3 represents a protective group. This shall apply hereinafter.)

The present production process is a method for preparing the compound of the formula (b-1) which is a starting material for the compound of the formula (c).

Here, examples of the protective group P^3 include diphenylmethylidene group.

[0085]

(Step 1)

The present step is a step of preparing a compound of the formula (y) from the compound of the formula (w) and the compound of the formula (x).

In the present reaction, the compound of the formula (w) and the compound of the formula (x) in equivalent amounts, or either thereof in an excess amount are used, and the mixture is stirred in a range from cooling to heating, and preferably under cooling, usually for 1 day to 10 days, in a solvent which is inert to the reaction, in the presence of a base. Examples of the solvent used herein are not particularly limited, but include aromatic

hydrocarbons such as benzene, toluene, xylene, and the like, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, and the like, or water, and a mixture thereof. Examples of the base include organic bases such as lithium diisopropylamide, triethylamine, N,N-diisopropyl ethylamine, potassium hexamethylenedisilazide, 1,8-diazabicyclo[5.4.0]-7-undecene, n-butyllithium, and the like, and inorganic bases such as sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, potassium hydroxide, potassium tert-butoxide, and the like.

In addition, the compound of the formula (y) can be obtained in the form of an optically active form by using a phase transfer catalyst that is optically active in some cases.

For a reference for the present reaction, reference can be made to, for example, the following ones.

"Courses in Experimental Chemistry (5^{th} edition)" edited by The Chemical Society of Japan, Vol. 14 (2005) (Maruzen)

Angew. Chem. Int. Ed. 44, 1549-1551 (2005)

[0086]

(Steps 2 to 5)

The present reaction can be carried out by deprotecting the protective group P^3 of the compound of the formula (y), and then performing the same methods as Steps 2 to 5 of Starting Material Synthesis 3 as described above.

[0087]

(Test Examples)

The pharmacological activities of the compound of the formula (I) were confirmed in the following tests. Further, in the present specification, the doses of the test compounds are expressed in conversion to the weight of free forms.

Unless otherwise specified, the present Test Examples can be accomplished according to known methods, and in the case of using commercially available reagents, kits, or the like, can be accomplished according to the instructions attached to the commercially available products.

[0088]

Test Example 1: Test for Evaluating Human MC Receptor Activation, Using Cells Expressing Human MC_4, MC_1, or MC_3 Receptor

Experiment Method

(1) Construction of Human MC Receptor-Expressing Vector

A human MC_4 receptor gene (GenBank Accession No.: NM_005912.2), a human MC_1 receptor gene (GenBank Accession No.: NM_002386.3), or a human MC_3 receptor gene (GenBank Accession No.: NM_019888.3) was introduced into an expression vector pcDNA™ 3.1/V5-His TOPO (registered trademark) (Thermo Fisher Scientific Inc.).

(2) Construction of Cells Transiently Expressing Human MC Receptor

An expression vector for a human MC_4, MC_1, or MC_3 receptor was introduced into FreeStyle™ 293-F cell (Thermo Fisher Scientific Inc., product number: R790-07). For the introduction, electroporation was employed. That is, 1×10^7 FreeStyle™ 293-F cell were suspended in 80 μL of an electroporation buffer (Thermo Fisher Scientific Inc., product number: B201-100), and 20 μg of the expression vector was added thereto. The resultant was put into a cuvette (OC-100 Processing Assembly, MaxCyte, Inc.) and electroporated with MaxCyte STX (registered trademark) (MaxCyte, Inc.). The cells were cultured over one day, suspended in a Cell Banker (registered trademark) 1 (JUJI FIELD Inc.), product number: BLC-1), and stored frozen until their use.

(3) Measurement of Amount of cAMP Produced

Measurement was carried out by using a LANCE (registered trademark) Ultra cAMP Kit (PerkinElmer, Inc.) in accordance with the attached instructions. That is, after dissolution in DMSO, the test compound (a final concentration of 1 pM to 30 μM) diluted with an assay buffer (Hank's balanced salt solution, 5 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES), 0.5 mM 3-isobutyl-1-methylxanthine (IBMX), 0.1% bovine serum albumin, pH 7.4), or α-MSH (Bachem Inc., a final concentration of 1 pM to 30 μM) was added to OptiPlate-384 (PerkinElmer, Inc.). Furthermore, a suspension of cells transiently expressing the human MC_4, MC_1, or MC_3 receptor prepared by using the assay buffer was added thereto at 1,000 cells/well, followed by being left to stand at room temperature for about 1 hour. Thereafter, an Eu-cAMP tracer solution and an ULight™-anti-cAMP solution were added thereto, followed by being left to stand at room temperature for about 1 hour. The amount of cAMP was calculated using EnVision (registered trademark) (PerkinElmer Inc.).

For the agonistic activity, an efficacy (EC_{50} (μM)) was calculated by a non-linear regression method with a Sigmoid-Emax model, by defining the maximum reaction with α-MSH as 100% and the reaction with the vehicle alone as 0%, respectively.

[0089]

The EC_{50} values of some Example compounds of the present invention are shown in Tables 1 and 2. Ex represents the Example No. of the test compound. In addition, NA represents Not Applicable and NT represents Not Tested.

[0090]

[Table 1]

Ex	EC_{50} (μM)		
	Human MC_4	Human MC_1	Human MC_3
4	0.0015	0.070	0.18
5	0.025	1.3	4.2
9	0.0032	0.39	0.91
11	0.017	0.86	3.7
76	0.00096	0.10	0.33
87	0.011	1.1	0.92
88	0.012	2.7	0.88
89	0.0030	1.3	0.78

[0091]

[Table 2]

Ex	EC_{50} (μM)		
	Human MC_4	Human MC_1	Human MC_3
6	0.48	6.4	> 30
13	0.048	NA	5.0
15	0.49	NT	NT
16	4.9	NT	NT
17	2.4	NT	NT
21	1.7	NT	NT
24	0.0032	15	0.58
27	1.0	NT	NT
28	0.15	3.9	10
33	0.61	NT	NT
35	0.14	NT	NT
36	0.0019	NT	NT
45	1.1	NT	NT
47	0.062	> 30	11
50	0.064	NT	NT
53	0.19	NT	NT
55	0.27	NT	NT
57	0.12	1.9	2.4
68	0.53	NT	NT
69	0.0051	0.72	2.9
72	0.040	2.1	5.3
74	0.030	1.4	1.0
78	0.016	1.0	0.68
83	0.19	NT	NT
84	0.018	NT	NT
92	0.012	1.7	1.8

From the above results, it was confirmed that the Example compounds of the present invention described above have an agonistic activity for the human MC_4 receptor. It was also confirmed that in the Example compounds which had been evaluated on the human MC_1 and MC_3 receptors among the Example compounds of the present invention described above, the EC_{50} values for the human MC_1 and MC_3 receptors were at higher concentrations than those for the human MC_4 receptor, and the compounds act selectively on the MC_4 receptor.

[0092]

Test Example 2: Test for Evaluating Rat MC_4 Receptor Activation, Using Cells Expressing Rat MC_4 Receptor

Experiment Method

(1) Construction of Rat MC_4 Receptor-Expressing Vector

A rat MC_4 receptor gene (GenBank Accession No.: NM_013099.2) was introduced into an expression vector pcDNA™ 3.1/V5-His TOPO (registered trademark) (Thermo Fisher Scientific Inc.).

(2) Construction of Cells Transiently Expressing Rat MC_4 Receptor

An expression vector for a rat MC_4 receptor was introduced into FreeStyle™ 293-F cell (Thermo Fisher Scientific Inc.). For the introduction, electroporation was employed. That is, 1×10^7 FreeStyle™ 293-F cell were suspended in 80 μL of an electroporation buffer (Thermo Fisher Scientific Inc.), and 20 μg of the expression vector was added thereto. The resultant was put into a cuvette (OC-100 Processing Assembly, MaxCyte, Inc.) and electroporated with MaxCyte STX (registered trademark) (MaxCyte, Inc.). The cells were cultured over one day, suspended in a Cell Banker (registered trademark) 1 (JUJI FIELD Inc.), and stored frozen until use.

(3) Measurement of Amount of cAMP Produced

Measurement was carried out in accordance with the attached instructions, using a LANCE (registered trademark) Ultra cAMP Kit (PerkinElmer, Inc.). That is, after dissolution in DMSO, the test compound (a final concentration of 1 pM to 30 μM) diluted with an assay buffer (Hank's balanced salt solution, 5 mM HEPES, 0.5 mM IBMX, 0.1% bovine serum albumin, pH 7.4), or α-MSH (Bachem Inc., a final concentration of 1 pM to 30 μM) was added to OptiPlate-384 (PerkinElmer, Inc.). Furthermore, a suspension of cells transiently expressing the rat MC_4 receptor, that had been prepared using the assay buffer, was added thereto at 1,000 cells/well, followed by being left to stand at room temperature for about 1 hour. Thereafter, an Eu-cAMP tracer solution and an ULight™-anti-cAMP solution were added thereto, followed by being left to stand at room temperature for about 1 hour. The amount of cAMP was calculated using EnVision (registered trademark) (PerkinElmer Inc.).

For the agonistic activity, an efficacy (EC_{50} (μM)) was calculated by a non-linear regression method with a Sigmoid-Emax model, by defining the maximum reaction with α-MSH as 100% and the reaction with the vehicle alone as 0%, respectively.

[0093]

The EC_{50} values of some Example compounds of the present invention are shown in Table 3. Ex represents the Example No. of the test compound.

[0094]

[Table 3]

Ex	EC_{50} (μM)
	Rat MC_4
4	0.0013
5	0.026
9	0.0026
11	0.021
76	0.0017
87	0.021
88	0.011
89	0.0031

From the above results, it was confirmed that the Example compounds of the present invention described above have an agonistic activity for the rat MC_4 receptor.

[0095]

Test Example 3: Action on Rat Urethral Pressure

Experiment Method

The present Test Example was carried out by partially modifying the technique reported as a testing system for evaluating an urethral resistance-reducing action (European Journal of Pharmacology, 679, 127-131 (2012)). Male Wistar rats (Charles River Laboratories Japan, Inc.) were anesthetized with urethane (1.2 g/kg ip), and placed in a supine position. The lower abdominal portion was midline-incised, and thus, the bladder was exposed. The bladder apex was incised, a microchip pressure transducer catheter (3.5 Fr, Millar) was inserted into the inside of the urethra, and then placed therein. In addition, a cannula for administration of a drug was placed into the femoral vein. After stabilization of the urethral pressure, phenylephrine hydrochloride (Sigma-Aldrich, 30 μg/kg) was administered intravenously to induce an increase in the urethral pressure. At an interval of about 30 minutes, this operation was repeated twice or more to confirm the stability of the reaction of a phenylephrine hydrochloride-induced increase in the urethral pressure. Thereafter, a test compound (dissolved in 20% dimethyl acetamide, 10% Cremophor (registered trademark) and 70% physiological saline) was intravenously

administered, and then 5 minutes later, phenylephrine hydrochloride was administered. The procedure of administration of the test compound and administration of phenylephrine hydrochloride was repeated at an interval of about 30 minutes, and 3 to 5 doses of the test compound was evaluated (the test compound was administered at increasing doses). The data of reaction was introduced into a personal computer through PowerLab (registered trademark) (ADInstruments, Inc.), and analyzed with LabChart (registered trademark) (ADInstruments, Inc.). For the evaluation, the value of the area under the urethral pressure (mmHg·s) for one minute before and after administration of phenylephrine hydrochloride was determined to calculate the difference between before and after administration of phenylephrine hydrochloride (ΔAUC value). By taking the ΔAUC value obtained before administering the test compound as 100%, the ratio (reaction rate) of the ΔAUC value of the test compound at each dose was calculated. The rate at which the obtained reaction rate becomes 60% (40% as an inhibition rate) was defined as ID_{40}, and the ID_{40} values of the test compounds were calculated by non-linear regression.

[0096]

The ID_{40} values of some Example compounds of the present invention are shown in Table 4. Ex represents the Example No. of the test compound.

[0097]

[Table 4]

Ex	ID_{40} (mg/kg)
4	0.0094
5	0.13
9	0.047
11	0.088
76	0.0047
87	0.040
88	0.040
89	0.024

From the above results, it was found that the Example compounds of the present invention described above have inhibitory effect on phenylephrine-induced increase in urethral pressure.

[0098]

Test Example 4: Action on Drug-Induced Voiding Dysfunction Model Rat

Experiment Method

Male Sprague Dawley (SD) rats (Japan SLC, Inc.) were anesthetized with isoflurane and a cannula was placed in bladder, the stomach, and the jugular vein. Then, the rats were awakened in a Ballman cage (Natsume Seisakusho Co., Ltd.). After a post-

operative stabilization period, physiological saline was continuously infused into the bladder by an infusion pump (Terumo Corporation, product number: TE-331S) to induce voiding. Infusion of the physiological saline was stopped at the time of voiding, and the amount of the voided urine was measured using an electronic top-loading balance placed under the Ballman cage. After completion of voiding, the residual urine was collected by gravity through the cannula placed in the bladder, and weighed, and the weight was defined as the amount of the residual urine. Further, the intravesical pressure was measured by a pressure transducer (Nihon Kohden Corporation, product numbers: TP-400, TDX-100) through the bladder cannula. The test compound or the vehicle was administered into the stomach, and atropine sulfate (Sigma-Aldrich, Inc., 0.01 mg/kg), which is an anticholinergic drug, and midodrine hydrochloride (Sigma-Aldrich, Inc., 0.3 mg/kg), which is an α_1 adrenergic receptor stimulant, were administered intravenously to induce voiding dysfunctions. The voiding efficiency (= [voided amount/(voided amount + amount of residual urine)] × 100) and the amount of the residual urine before and after administration of the test compound or the vehicle were measured, and the amount changed was evaluated. The value with vehicle administration and the value with the test compound administration were compared in a Dunnett's multiple comparison test with a statistically significant difference ($P < 0.05$), and the minimum dose at which the inhibitory effect on a decrease in voiding efficiency or an increase of the amount of residual urine had been observed was defined as a minimal effective dose (3 to 12 animals per group).

[0099]

The minimum effective doses of some Example compounds of the present invention are shown in Table 5. Ex represents the Example No. of the test compound.

[0100]

[Table 5]

Ex	Minimum effective dose (mg/kg)
4	0.03
5	0.3
9	3
11	0.3
76	0.03
87	0.1
88	0.1
89	0.1

From the above results, it was confirmed that the Example compounds of the present invention described above have inhibitory effect on a decrease in voiding efficiency or an increase of the amount of residual urine.

[0101]

Test Example 5: Rat Erection-Inducing Action

Experiment Method

Male SD rats (Charles River Laboratories Japan, Inc.) were used. A test compound (10 mg/kg) or the vehicle (20% dimethyl acetamide, 10% Cremophor (registered trademark), 70% physiological saline) was administered intravenously through the tail vein. After administration, the rats were transferred to transparent observation cages made of plastic to measure the erection times of up to one hour after administration. The measurements were carried out for five groups (3 to 7 animals per group): vehicle groups, Example compound groups (Ex 87, 88, and 89), and THIQ group, which had been known as an MC_4 receptor agonist (J. Med. Chem., 45, 4589-4593 (2002)), as a positive control. For a statistical significance test, Dunnett's multiple comparison test was used for the comparison with vehicle control group, and it was determined whether there was an erection-inducing effect with a statistically significant difference ($P < 0.05$). As a result, THIQ as the positive control exhibited a significant erection-inducing effect, whereas all of the Example compounds (Ex 87, 88, and 89) did not exhibit an erection-inducing effect.

[0102]

As seen from the results of each of the above tests, it was confirmed that the compound of the formula (I) has a human MC_4 receptor-selective agonistic activity, and it was also confirmed that the compound has inhibitory effect on phenylephrine-induced increase in urethral pressure in vivo. Further, it was confirmed that in a rat model with a voiding dysfunction, the compound has inhibitory effect on a decrease in voiding efficiency and an increase of the amount of residual urine. In addition, it was confirmed that some of the compounds of the formula (I) do not exhibit an erection-inducing effect which is an action on the central nervous system. Therefore, the compound of the formula (I) can be used for preventing or treating bladder and/or urinary tract diseases, in particular, voiding dysfunctions in bladder and/or urinary tract diseases. For example, the compound of the formula (I) can be used for preventing or treating voiding dysfunctions in underactive bladder, hypotonic bladder, acontractile bladder, detrusor underactivity, neurogenic bladder, urethral relaxation failure, detrusor-external urethral sphincter dyssynergia, overactive bladder, urinary frequency, nocturia, urinary incontinence, benign prostatic hyperplasia, interstitial cystitis, chronic prostatitis, urethral calculus, or the like. In particular, the compound of the formula (I) can be used for preventing or treating voiding dysfunctions in underactive bladder, hypotonic bladder, acontractile bladder,

detrusor underactivity, neurogenic bladder, urethral relaxation failure, detrusor-external urethral sphincter dyssynergia, and benign prostatic hyperplasia.

[0103]

A pharmaceutical composition containing one or more kinds of the compound of the formula (I) or a salt thereof as an active ingredient can be prepared using excipients that are usually used in the art, that is, excipients for pharmaceutical preparation, carriers for pharmaceutical preparation, and the like according to the methods usually used.

Administration can be accomplished either by oral administration via tablets, pills, capsules, granules, powders, solutions, and the like, or parenteral administration, such as injections such as intraarticular, intravenous, and intramuscular injections, suppositories, transdermal solutions, ointments, transdermal patches, transmucosal solutions, transmucosal patches, inhalers, and the like.

[0104]

Solid compositions for oral administration are used in the form of tablets, powders, granules, or the like. In such solid compositions, one or more active ingredient(s) are mixed with at least one inactive excipient. In a conventional method, the composition may contain inactive additives, such as lubricants, disintegrating agents, stabilizers, or solubilization assisting agents. If necessary, tablets or pills may be coated with sugar or s gastric- or enteric-soluble substance films.

Liquid compositions for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, elixirs, or the like, and also include generally used inert diluents, for example, purified water or ethanol. In addition to the inert diluent, liquid compositions may also contain auxiliary agents, such as solubilization assisting agents, moistening agents, and suspending agents, sweeteners, flavors, aromatics, or antiseptics.

[0105]

Injections for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Aqueous solvents include, for example, distilled water for injection or physiological saline. Examples of non-aqueous solvents include alcohols such as ethanol. Such compositions may further contain tonicity agents, antiseptics, moistening agents, emulsifying agents, dispersing agents, stabilizers, or solubilization assisting agents. These are sterilized, for example, by filtration through bacteria retaining filter, blendings of bactericide, or irradiation. In addition, these can also be used by preparing sterile solid compositions, and dissolving or suspending in sterile water or sterile solvents for injection prior to use.

[0106]

Agents for external use includes ointments, plasters, creams, jellies, poultices, sprays, lotions, and the like. The agents contain generally used ointment bases, lotion bases, aqueous or non-aqueous solutions, suspensions, emulsions, and the like.

[0107]

As transmucosal agents such as inhalers, transnasal agents, and the like, those in the form of a solid, liquid, or semi-solid state are used, and can be prepared in accordance with conventionally known methods. For example, known excipients, and furthermore pH adjusting agents, antiseptics, surfactants, lubricants, stabilizers, thickening agents, or the like may be appropriately added thereto. For their administration, appropriate devices for inhalation or blowing can be used. For example, a compound may be administered alone or as a powder of formulated mixture, or as a solution or suspension in combination with pharmaceutically acceptable carriers, using a known device or sprayer, such as a measured administration inhalation device, and the like. Dry powder inhalers or the like may be for single or multiple administration use, and dry powder or powder-containing capsules may be used. Alternatively, these may be a pressurized aerosol spray which uses appropriate ejection agents, for example, a suitable gas such as chlorofluoroalkane, carbon dioxide, and the like.

[0108]

For oral administration, a daily dose is generally about 0.001 mg/kg to 100 mg/kg, preferably 0.1 mg/kg to 30 mg/kg, and more preferably 0.1 mg/kg to 10 mg/kg, per body weight, administered in one portion or in 2 to 4 separate portions. In the case of intravenous administration, a daily dose to be administered is suitably about 0.0001 mg/kg to 10 mg/kg per body weight, once a day or two or more times a day. In addition, a transmucosal agent is administered at a dose from about 0.001 mg/kg to 100 mg/kg per body weight, once a day or two or more times a day. Doses are appropriately determined according to the individual according to the symptoms, age, gender, and the like.

[0109]

Although varying depending on administration routes, formulations, administration sites, or the types of excipients or additives, the pharmaceutical composition of the present invention contains 0.01% by weight to 100% by weight, and in a certain embodiment, 0.01% by weight to 50% by weight of one or more kinds of the compound of the formula (I) or a salt thereof, which is an active ingredient.

[0110]

The compound of the formula (I) can be used in combination with various agents for treating or preventing the diseases for which the compound of the formula (I) is considered to be effective, as described above. The combined preparation may be administered simultaneously, or separately and continuously, or at a desired time interval.

The preparations to be administered simultaneously may be a mixture, or may be prepared individually.

[Examples]

[0111]

Hereinbelow, the preparation methods for the compound of the formula (I) will be described in more detail with reference to Examples. Further, the present invention is not limited to the compounds described in Examples below. Incidentally, the production processes for the starting compounds will be described in Preparation Examples. Further, the preparation methods for the compound of the formula (I) are not limited to the preparation methods in specific Examples shown below, and the compound of the formula (I) can be prepared according to a combination of these preparation methods or methods apparent to those skilled in the art.

[0112]

Moreover, the following abbreviations are used in tables below in some cases.

PEx: Preparation Example No., Ex: Example No., PSyn: Preparation method for Preparation Example compound (The number in the PSyn section indicates that the compound is prepared using the corresponding starting material by the same method as that for the compound with the number as the Preparation Example compound No. For example, a compound with 3 in the PSyn section means that the compound is prepared by the same method as that for the compound of Preparation Example 3), Syn: Preparation method for Example compound (The number in the Syn section indicates that the compound is prepared using the corresponding starting material by the same method as that for the compound with the number as the Example compound No. For example, a compound with 1 in the Syn section means that the compound is prepared by the same method as that for the compound of Example 1), Str: Chemical structural formula, DAT: Physicochemical data.

ESI+: m/z values in mass spectroscopy (Ionization ESI, representing $[M+H]^+$ unless specified), ESI-: m/z values in mass spectroscopy (Ionization ESI, representing $[M-H]^-$ unless specified), APCI/ESI+: APCI/ESI-MS (Atmospheric pressure chemical ionization APCI, APCI/ESI represents simultaneous measurement of APCI and ESI, representing $[M+H]^+$ unless specified), APCI/ESI-: APCI/ESI-MS (Atmospheric pressure chemical ionization APCI, APCI/ESI represents simultaneous measurement of APCI and ESI, representing $[M-H]^-$ unless specified), EI: m/z values in mass spectroscopy (Ionization EI, representing $[M]^+$ unless specified), CI: m/z values in mass spectroscopy (Ionization CI, representing $[M+H]^+$ unless specified).

^{1}H-NMR (400 MHz, DMSO-d6): δ (ppm) of signals in ^{1}H-NMR in DMSO-d_6, ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) of signals in ^{1}H-NMR in $CDCl_3$, ^{1}H-NMR (500 MHz,

pyridine-d5, 90°C): δ (ppm) of signals in ^{1}H-NMR at a measurement temperature of 90°C in pyridine-d5, s: singlet, d: doublet, t: triplet, q: quartet, br: broad line, m: multiplet.

[0113]

Unless otherwise specified, the compound represents an optical isomer having the absolute steric configuration described in the chemical structural formula. The compound attached with "**" represents an optical isomer having the absolute steric configuration described in the chemical formula, in which the steric configuration in the asymmetric carbon moiety with no description of the steric configuration is single but undetermined. The compound attached with "$" has the denoted steric configuration, in which the steric form in the asymmetric carbon moiety with no description of the steric configuration is single but undetermined, and the steric configurations in the asymmetric carbon moiety between one compound and another compound described the same structural formula are in inverse relationship. The compound attached with "#" has the denoted steric configuration, in which the steric form in the asymmetric carbon moiety with no description of the steric configuration is a mixture of R and S forms. In the structural formula, HCl indicates that the compound is monohydrochloride, 2HCl indicates that the compound is dihydrochloride, and 3HCl indicates that the compound is trihydrochloride. In addition, the compound indicated by both HCl and HBr represents monohydrobromide-monohydrochloride.

[0114]

Incidentally, in the present specification, nomenclature software such as ACD/Name (registered trademark, Advanced Chemistry Development, Inc.) may be used in some cases for the nomenclature of the compounds.

[0115]

The powder X-ray diffraction was measured using RINT-TTRII under the conditions of a tube of Cu, a tube current of 300 mA, a tube voltage of 50 kV, a sampling width of 0.020°, a scanning speed of 4°/min, a wavelength of 1.54056 angstroms, and a range of diffraction angles to be measured (2θ) of 2.5° to 40°. Further, devices including data processing was handled according to the methods and procedures, respectively instructed in each of the devices.

[0116]

Furthermore, for convenience, the concentration mol/L is represented by M. For example, a 1 M aqueous sodium hydroxide solution means a 1 mol/L aqueous sodium hydroxide solution.

[0117]

Preparation Example 1

Under a nitrogen atmosphere, a mixture of borane-N,N-diethylaniline complex (46.2 g), (S)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxaoxazaborolidine (1 M toluene

solution, 5 mL), and tert-butylmethyl ether (250 mL) was heated at 35°C. Then, a solution of 2-chloro-1-(4-chloro-2-fluorophenyl)ethanone (51 g) in tert-butylmethyl ether (300 mL) was added dropwise thereto at 40°C for 2 hours. After completion of dropwise addition, the mixture was stirred overnight while being left to be cooled to room temperature. The reaction mixture was ice-cooled and methanol (150 mL) was added dropwise thereto. Thereafter, a mixture of concentrated hydrochloric acid (80 mL) and water (220 mL) was added dropwise thereto, followed by stirring for 1 hour still under ice-cooling. The aqueous layer and the organic layer were separated, and then the aqueous layer was extracted with tert-butylmethyl ether. The organic layer was combined, washed with brine, and dried over anhydrous magnesium sulfate. The insoluble materials were separated by filtration and the filtrate was concentrated under reduced pressure. To the obtained residue was added hexane (100 mL), followed by stirring at room temperature for 1 hour and then stirring for 1 hour under ice-cooling. The resulting solid was collected by filtration and washed with ice-cooled hexane. The obtained solid was dried under reduced pressure at room temperature to obtain (1S)-2-chloro-1-(4-chloro-2-fluorophenyl)ethanol (42.4 g) as a solid.

[0118]

Preparation Example 2

A mixture of (1S)-2-chloro-1-(4-chloro-2-fluorophenyl)ethanol (8 g) and methanol (4 mL) was ice-cooled, and tetrahydro-2H-pyran-4-amine (20 mL) and sodium hydroxide (1.7 g) were added thereto. The reaction mixture was stirred at 60°C overnight.

The reaction mixture was cooled to room temperature and then poured into water (320 mL), followed by stirring at room temperature for 1 hour. The resulting solid was collected by filtration, and the obtained solid was dried at 50°C under reduced pressure. The obtained solid was added to a mixed solution of hexane (160 mL) and diisopropyl ether (16 mL), followed by stirring at 70°C for 4 hours, then ice-cooling to room temperature, and stirring overnight. The solid was collected by filtration and dried at 50°C under reduced pressure to obtain (1S)-1-(4-chloro-2-fluorophenyl)-2-(tetrahydro-2H-pyran-4-ylamino)ethanol (7.90 g) as a solid.

[0119]

Preparation Example 3

Under a nitrogen atmosphere, a mixture of (1S)-1-(4-chloro-2-fluorophenyl)-2-(tetrahydro-2H-pyran-4-ylamino)ethanol (7.9 g) and acrylonitrile (34 mL) was stirred at 70°C for 47 hours. The reaction mixture was cooled to room temperature and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate = 6:4 to 0:10) to obtain 3-{[(2S)-2-(4-chloro-2-fluorophenyl)-2-hydroxyethyl](tetrahydro-2H-pyran-4-yl)amino}propanenitrile (9.38 g) as an oil.

[0120]

Preparation Example 4

Under an argon atmosphere, to a mixture of 3-{[(2S)-2-(4-chloro-2-fluorophenyl)-2-hydroxyethyl](tetrahydro-2H-pyran-4-yl)amino}propanenitrile (9.38 g) and tetrahydrofuran (47 mL) was added diethyl chlorophosphate (4.33 mL) at -15°C. Then, to the reaction mixture was added dropwise lithium bis(trimethylsilyl)amide (1.1 M tetrahydrofuran solution, 60 mL) while keeping the temperature at -5°C or lower. The reaction mixture was stirred at a temperature in the range from -7°C to -15°C for 1.5 hours, and then water (110 mL) was added thereto, followed by extracting with diisopropyl ether. The organic layer was washed with brine, then ice-cooled, and extracted with 3 M hydrochloric acid. The obtained aqueous layer was basified by the addition of a 50% aqueous sodium hydroxide solution, and extracted with diisopropyl ether. The organic layer was washed with brine, and then dried over anhydrous sodium sulfate. The insoluble materials were separated by filtration and the filtrate was concentrated under reduced pressure, 3-ambo-(3R, 4R)-4-(4-chloro-2-fluorophenyl)-1-(tetrahydro-2H-pyran-4-yl)pyrrolidine-3-carbonitrile (8.96 g) as an oil.

[0121]

Preparation Example 5

Under a nitrogen atmosphere, to a solution of 3-ambo-(3R,4R)-4-(4-chloro-2-fluorophenyl)-1-(tetrahydro-2H-pyran-4-yl)pyrrolidine-3-carbonitrile (8.96 g) in ethanol (40 mL) was added a 50% aqueous sodium hydroxide solution (4.30 mL), followed by stirring at 100°C for 5 hours. The reaction mixture was cooled to room temperature, and then ethanol (45 mL) and methanol (80 mL) were added thereto. The mixture was ice-cooled and concentrated sulfuric acid (2.20 mL) was added thereto. To the mixture were added anhydrous sodium sulfate and Celite, and then the insoluble materials were removed by filtration through Celite. The solid was washed with a mixed solution of ethanol:methanol (1:1) and the obtained filtrate was concentrated under reduced pressure. To the obtained residue was added 2-propanol (25 mL), followed by stirring at room temperature for 10 minutes, and tert-butylmethyl ether (80 mL) was added thereto. The mixture was stirred at 70°C for 4 hours and then stirred at room temperature overnight. The resulting solid was collected by filtration, washed with a mixed solution of 2-propanol:tert-butylmethyl ether (1:3), and then dried at 50°C under reduced pressure to obtain (3S,4R)-4-(4-chloro-2-fluorophenyl)-1-(tetrahydro-2H-pyran-4-yl)pyrrolidine-3-carboxylic acid (5.55 g) as a solid.

[0122]

Preparation Example 6

Zinc powder (9 g) was dried with a heating gun for 15 minutes under reduced pressure and left to be cooled to room temperature. Then, N,N-dimethylformamide (50

mL) was added thereto under an argon atmosphere. Iodine (250 mg) was added thereto at room temperature, followed by stirring, and then to the reaction mixture were added iodine (250 mg) and methyl N-(tert-butoxycarbonyl)-3-iodo-L-alaninate (15.5 g) at room temperature, followed by stirring for 35 minutes. To the reaction mixture were added tris(dibenzylideneacetone)dipalladium (0) (2.2 g), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (2.0 g), and 1-bromo-2-fluoro-4-methylbenzene (9 mL) at room temperature, followed by stirring at 60°C for 18 hours. To the reaction mixture was added a saturated aqueous ammonium chloride solution, followed by filtering through Celite. The filtrate was extracted with ethyl acetate and the organic layer was washed with brine. The organic layer was dried over anhydrous magnesium sulfate, the insoluble materials were then separated by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate = 97:3 to 83:17), and then purified by basic silica gel column chromatography (hexane:ethyl acetate = 97:3 to 83:17) to obtain methyl N-(tert-butoxycarbonyl)-2-fluoro-4-methyl-L-phenylalaninate (10 g) as a solid.

[0123]

Preparation Example 7

To a solution of methyl N-(tert-butoxycarbonyl)-2-fluoro-4-methyl-L-phenylalaninate (10 g) in dioxane (10 mL) was added hydrogen chloride (4 M solution in dioxane, 100 mL) at room temperature, followed by stirring for 1.5 hours. The solvent was evaporated under reduced pressure and the resulting solid was suspended in N,N-dimethylformamide (100 mL). To the suspension were added N-[(2-nitrophenyl)sulfonyl]-L-alanine (9.69 g) and O-(7-aza-1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (13.4 g) at room temperature, and then N,N-diisopropyl ethylamine (18 mL) was added thereto at room temperature, followed by stirring for 3 hours. To the reaction mixture was added a saturated aqueous sodium hydrogen carbonate solution, followed by extracting with ethyl acetate. The organic layer was washed with brine. The organic layer was dried over anhydrous magnesium sulfate, the insoluble materials were then separated by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform:methanol = 100:0 to 95:5) to obtain methyl N-[(2-nitrophenyl)sulfonyl]-L-alanyl-2-fluoro-4-methyl-L-phenylalaninate (13.6 g) as a solid.

[0124]

Preparation Example 8

To a solution of methyl N-[(2-nitrophenyl)sulfonyl]-L-alanyl-2-fluoro-4-methyl-L-phenylalaninate (13.6 g) in N,N-dimethylformamide (100 mL) were added 1,2-dibromoethane (20 mL) and potassium carbonate (32.1 g) at room temperature, followed by stirring at 60°C overnight. The reaction mixture was filtered and the filtrate was

concentrated under reduced pressure. To the residue were added ethyl acetate and water, and the organic layer was washed with brine. The organic layer was dried over anhydrous magnesium sulfate, the insoluble materials were then separated by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform:methanol = 100:0 to 95:5) to obtain a solid. The obtained solid was triturated with toluene to obtain methyl (2S)-3-(2-fluoro-4-methylphenyl)-2-{(3S)-3-methyl-4-[(2-nitrophenyl)sulfonyl]-2-oxopiperazin-1-yl}propanoate (13.6 g) as a solid.

[0125]

Preparation Example 9

To a solution of methyl (2S)-3-(2-fluoro-4-methylphenyl)-2-{(3S)-3-methyl-4-[(2-nitrophenyl)sulfonyl]-2-oxopiperazin-1-yl}propanoate (13.6 g) in tetrahydrofuran (200 mL) was added a borane-tetrahydrofuran complex (0.85 M tetrahydrofuran solution, 26 mL) at -14°C or lower for 20 minutes under a nitrogen atmosphere, followed by stirring 0°C for 1 hour. The reaction mixture was warmed to room temperature and stirred at room temperature overnight. The reaction mixture was poured into a saturated aqueous sodium hydrogen carbonate solution, followed by extracting with ethyl acetate. The organic layer was washed with brine. The organic layer was dried over anhydrous magnesium sulfate, the insoluble materials were then separated by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate = 90:10 to 50:50) to obtain methyl (2S)-3-(2-fluoro-4-methylphenyl)-2-{(3S)-3-methyl-4-[(2-nitrophenyl)sulfonyl]piperazin-1-yl}propanoate (8.45 g) as a solid.

[0126]

Preparation Example 10

To a solution of methyl (2S)-3-(2-fluoro-4-methylphenyl)-2-{(3S)-3-methyl-4-[(2-nitrophenyl)sulfonyl]piperazin-1-yl}propanoate (8.45 g) in N,N-dimethylformamide (100 mL) were added potassium carbonate (4.87 g) and 4-tert-butylbenzenethiol (4.74 mL), followed by stirring overnight. The reaction mixture was concentrated under reduced pressure, and to the obtained residue were added ethyl acetate and 1 M hydrochloric acid, followed by stirring. The aqueous layer was washed with ethyl acetate and adjusted to pH = 8 by the addition of sodium hydroxide. The mixture was extracted with chloroform, the organic layer was then dried over anhydrous sodium sulfate, the insoluble materials were then separated by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was diluted with ethyl acetate, and hydrogen chloride (4 M solution in ethyl acetate, 9.25 mL) was added thereto, followed by stirring. The precipitated solid was filtered to obtain methyl (2S)-3-(2-fluoro-4-methylphenyl)-2-[(3S)-3-methylpiperazin-1-yl]propanoate dihydrochloride (6.02 g) as a solid.

[0127]

Preparation Example 11

To a solution of (3S,4R)-4-(4-chloro-2-fluorophenyl)-1-(tetrahydro-2H-pyran-4-yl)pyrrolidine-3-carboxylic acid (1.35 g) in N,N-dimethylformamide (20 mL) were added methyl (2S)-3-(2-fluoro-4-methylphenyl)-2-[(3S)-3-methylpiperazin-1-yl]propanoate dihydrochloride (1.47 g) and O-(7-aza-1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (1.72 g) under ice-cooling, followed by stirring, and then N,N-diisopropyl ethylamine (3.0 mL) was added thereto, followed by stirring for 1.5 hours under ice-cooling. The reaction mixture was poured into a saturated aqueous sodium hydrogen carbonate solution, followed by extracting with ethyl acetate. The organic layer was washed with brine. The organic layer was dried over anhydrous magnesium sulfate, the insoluble materials were then separated by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform:methanol = 100:0 to 95:5) to obtain methyl (2S)-2-[(3S)-4-{[(3S,4R)-4-(4-chloro-2-fluorophenyl)-1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-(2-fluoro-4-methylphenyl)propanoate (2.28 g) as a solid.

[0128]

Preparation Example 12

To a solution of (2-fluoro-4,6-dimethylphenyl) methanol (2 g) in dichloromethane (20 mL) was added phosphorus tribromide (1.28 mL) under ice-cooling. The reaction mixture was stirred at room temperature for 1 hour. To the reaction mixture were added a saturated aqueous sodium hydrogen carbonate solution. The mixture was extracted with dichloromethane and the organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The insoluble materials were separated by filtration and the filtrate was concentrated under reduced pressure to obtain 2-(bromomethyl)-1-fluoro-3,5-dimethylbenzene (2.52 g) as an oil.

[0129]

Preparation Example 13

To a suspension of tert-butyl N-(diphenylmethylidene) glycinate (3.43 g) in toluene (25 mL) was added a solution of 2-(bromomethyl)-1-fluoro-3,5-dimethylbenzene (2.52 g), (R)-4,4-dibutyl-2,6-bis(3,4,5-trifluorophenyl)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepinium bromide (44 mg), and potassium hydroxide (12.5 g) in water (25 mL) under ice-cooling. The reaction mixture was stirred at 0°C for 4 days. To the reaction mixture was added water. The mixture was extracted with diethyl ether and the organic layer was washed with brine. The organic layer was dried over anhydrous magnesium sulfate. The insoluble materials were separated by filtration and the filtrate was

concentrated under reduced pressure to obtain tert-butyl N-(diphenylmethylidene)-2-fluoro-4,6-dimethyl-L-phenylalaninate (5.91 g) as an oil.

[0130]

Preparation Example 14

To a mixture of tert-butyl N-(diphenylmethylidene)-2-fluoro-4,6-dimethyl-L-phenylalaninate (5.91 g), tetrahydrofuran (60 mL), and water (30 mL) was added citric acid (10.9 g) at room temperature. The reaction mixture was stirred at room temperature for 1 hour. To the reaction mixture was added diisopropyl ether, water was added thereto, and the aqueous layer was separated. The aqueous layer was washed with diisopropyl ether, and potassium carbonate was added thereto. The aqueous layer was extracted with ethyl acetate and the organic layer was washed with brine. The organic layer was dried over anhydrous magnesium sulfate. The insoluble materials were separated by filtration and the filtrate was concentrated under reduced pressure to obtain tert-butyl 2-fluoro-4,6-dimethyl-L-phenylalaninate (3.1 g) as an oil.

[0131]

Preparation Example 15

To a solution of tert-butyl 2-fluoro-4,6-dimethyl-L-phenylalaninate (3.1 g) in N,N-dimethylformamide (47 mL) were added for N-[(2-nitrophenyl)sulfonyl]-L-alanine (3.3 g), O-(7-aza-1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (5.7 g), and N,N-diisopropyl ethylamine (6 mL) at room temperature. The reaction mixture was stirred at room temperature for 1 day. To the reaction mixture was added water. The aqueous layer was extracted with ethyl acetate and the organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The insoluble materials were separated by filtration and the filtrate was concentrated under reduced pressure to obtain tert-butyl N-[(2-nitrophenyl)sulfonyl]-L-alanyl-2-fluoro-4,6-dimethyl-L-phenylalaninate (7.78 g) as an oil.

[0132]

Preparation Example 16

To a solution of methyl (2S)-3-mesityl-2-{(3S)-3-methyl-4-[(2-nitrophenyl)sulfonyl]piperazin-1-yl}propanoate (28.9 g) in N,N-dimethylformamide (185 mL) were added potassium carbonate (16.3 g) and 4-tert-butylbenzenethiol (16 mL) under ice-cooling. The reaction mixture was stirred at room temperature for 1 day. To the reaction mixture was added water, ethyl acetate was added thereto, and the organic layer was separated. The organic layer was extracted with 1 M hydrochloric acid, and to the aqueous layer was added potassium carbonate. The aqueous layer was extracted with ethyl acetate. The organic layer was sequentially washed with water and brine, and then dried over anhydrous magnesium sulfate. The insoluble materials were separated by

filtration and the filtrate was concentrated under reduced pressure to obtain methyl (2S)-3-mesityl-2-[(3S)-3-methylpiperazin-1-yl]propanoate (16.9 g) as an oil.

[0133]

Preparation Example 17

To a solution of methyl 2,4,6-trimethyl-L-phenylalaninate hydrochloride (47.8 g) in N,N-dimethylformamide (717 mL) were added for N-[(2-nitrophenyl)sulfonyl]-L-alanine (51.4 g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (42.7 g), 1-hydroxybenzotriazole (30.1 g), and triethylamine (77.5 mL) at 10°C. The reaction mixture was stirred at room temperature for 2 hours. To the reaction mixture was added water. The aqueous layer was extracted with ethyl acetate and the organic layer was washed with water. The organic layer was washed with brine and the organic layer was dried over anhydrous magnesium sulfate. The insoluble materials were separated by filtration and the filtrate was concentrated under reduced pressure to obtain methyl N-[(2-nitrophenyl)sulfonyl]-L-alanyl-2,4,6-trimethyl-L-phenylalaninate (74.8 g) as an oil.

[0134]

Preparation Example 18

To a solution of tert-butyl (2S)-3-(2,3-dihydro-1H-inden-5-yl)-2-[(diphenylmethylidene)amino]propanoate (971 mg) in tetrahydrofuran (11.7 mL) was added a solution of citric acid (2.19 g) in water (5.8 mL) at room temperature. The reaction mixture was stirred at room temperature for 6 hours. To the reaction mixture was added diethyl ether, and the aqueous layer was separated. To the aqueous layer was added potassium carbonate under ice-cooling and the aqueous layer was extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate. The insoluble materials were separated by filtration and the filtrate was concentrated under reduced pressure. To the obtained residue were added dioxane (10 mL) and hydrogen chloride (4 M solution in dioxane, 0.7 mL), followed by stirring at room temperature. The precipitated solid was collected by filtration, then washed with dioxane, and dried under reduced pressure. The solid was washed with acetonitrile and dried under reduced pressure to obtain tert-butyl (2S)-2-amino-3-(2,3-dihydro-1H-inden-5-yl)propanoate monohydrochloride (251 mg) as a solid.

[0135]

Preparation Example 19

To a mixture of methyl (2S)-3-(4-bromophenyl)-2-{(3S)-3-methyl-4-[(2-nitrophenyl)sulfonyl]-2-oxopiperazin-1-yl}propanoate (500 mg), toluene (10 mL), and water (0.25 mL) were added cyclopropylboronic acid (397 mg), tripotassium phosphate (982 mg), palladium (II) acetate (41.5 mg), and 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (152 mg) at room temperature. The reaction mixture was warmed to 90°C under an argon atmosphere and stirred for 15 hours. The reaction mixture was

filtered through Celite and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate = 5:1 to 3:2) to obtain methyl (2S)-3-(4-cyclopropylphenyl)-2-{(3S)-3-methyl-4-[(2-nitrophenyl)sulfonyl]-2-oxopiperazin-1-yl}propanoate (196 mg) as an oil.

[0136]

Preparation Example 20

A mixture of methyl (2R)-2-bromo-3-(2-naphthyl)propanoate (500 mg), cis-2,6-dimethylpiperazine (1.90 g), and N,N-dimethylformamide (10 mL) was stirred at room temperature overnight. To the reaction mixture was added water, followed by extracting with ethyl acetate. The organic layer was washed with brine and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform:methanol = 98:2 to 90:10) to obtain methyl (2S)-2-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-3-(2-naphthyl)propanoate (107 mg) as an oil.

[0137]

Preparation Example 21

A mixture of tert-butyl (3R)-4-(2-methoxy-2-oxoethyl)-3-methylpiperazine-1-carboxylate (818 mg) and tetrahydrofuran (8.00 mL) was cooled to -78°C. To the reaction mixture was added potassium bis(trimethylsilyl)amide (1 M tetrahydrofuran solution, 6.00 mL) at -78°C, followed by stirring at the same temperature for 40 minutes. To the reaction mixture was added 4-(bromomethyl)-1,2-dichlorobenzene (2.15 g) at -78°C, followed by stirring at the same temperature for 30 minutes. Thereafter, the mixture was warmed to room temperature for 30 minutes, and subsequently stirred at room temperature for 2 hours. To the reaction mixture was added an aqueous ammonium chloride solution, followed by extracting with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, the insoluble materials were then separated by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate = 85:15) to obtain tert-butyl (3R)-4-[3-(3,4-dichlorophenyl)-1-methoxy-1-oxopropan-2-yl]-3-methylpiperazine-1-carboxylate (267 mg, Preparation Example 21, the earlier eluted fraction) as an oil. Further, a single isomer having a different steric configuration at the α-position of the ester group (70.0 mg, Preparation Example 335, the later eluted fraction) was obtained as an oil.

[0138]

Preparation Example 22

To a solution of tert-butyl (3R)-4-[3-(3,4-dichlorophenyl)-1-methoxy-1-oxopropan-2-yl]-3-methylpiperazine-1-carboxylate (246 mg, Preparation Example 21, the earlier eluted fraction) in dioxane (984 μL) was added hydrogen chloride (4 M solution in dioxane, 712 μL) under ice-cooling, followed by stirring at room temperature overnight.

To the reaction mixture was added a saturated aqueous sodium hydrogen carbonate solution, followed by extracting with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, the insoluble materials were then separated by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform:methanol = 95:5) to obtain methyl 3-(3,4-dichlorophenyl)-2-[(2R)-2-methylpiperazin-1-yl]propanoate (153 mg) as a solid.

[0139]

Preparation Example 23

A mixture of methyl (2S)-3-(4-bromophenyl)-2-{(3S)-3-methyl-4-[(2-nitrophenyl)sulfonyl]piperazin-1-yl}propanoate (484 mg), zinc cyanide (550 mg), bis(tri-tert-butylphosphine)palladium (0) (180 mg), zinc powder (15 mg), and N,N-dimethylacetamide (10 mL) was stirred at 90°C for 2 hours under an argon atmosphere. The reaction mixture was warmed to 130°C, and heated and stirred for 5.5 hours. The reaction mixture was left to be cooled to room temperature and then water was added thereto, followed by extracting with ethyl acetate. The organic layer was washed with brine and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate = 80:20 to 40:60) to obtain methyl (2S)-3-(4-cyanophenyl)-2-{(3S)-3-methyl-4-[(2-nitrophenyl)sulfonyl]piperazin-1-yl}propanoate (88 mg) as an oil.

[0140]

Preparation Example 24

To a mixture of methyl (2S)-2-[(3S)-3-(2-aminoethyl)-4-{[(3S,4R)-4-(2,4-difluorophenyl)-1-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)pyrrolidin-3-yl]carbonyl}piperazin-1-yl]-3-(2-naphthyl)propanoate dihydrochloride (210 mg), formaldehyde (a 37% aqueous solution, 140 mg), and dichloromethane (6.00 mL) was added sodium triacetoxyborohydride (184 mg) at room temperature, followed by stirring at room temperature for 12 hours. To the reaction mixture was added a saturated aqueous sodium hydrogen carbonate solution, followed by extracting with chloroform. The organic layer was washed with brine and dried over anhydrous magnesium sulfate, the insoluble materials were then separated by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform:methanol = 99:1) to obtain methyl (2S)-2-{(3S)-4-{[(3S,4R)-4-(2,4-difluorophenyl)-1-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)pyrrolidin-3-yl]carbonyl}-3-[2-(dimethylamino)ethyl]piperazin-1-yl}-3-(2-naphthyl)propanoate (82.0 mg) as an oil.

[0141]

Preparation Example 25

To a solution of methyl (3S,4R)-4-(2,4-difluorophenyl)pyrrolidine-3-carboxylic acid (275 mg) in dioxane (3.0 mL) were added 2-chloro-5-(difluoromethyl)pyridine (225 mg), tris(dibenzylideneacetone)dipalladium (0) (21 mg), 2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl (22 mg), and sodium tert-butoxide (275 mg) under an argon atmosphere. The reaction mixture was stirred at 100°C overnight and left to be cooled to room temperature, and then water was added thereto, followed by extracting with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate, the insoluble materials were then separated by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform:methanol = 10:0 to 9:1) to obtain (3S,4R)-1-[5-(difluoromethyl)pyridin-2-yl]-4-(2,4-difluorophenyl)pyrrolidine-3-carboxylic acid (118 mg) as a solid.

[0142]

Preparation Example 26

To a solution of methyl (3S,4R)-4-(2,4-difluorophenyl)-1-[(2-nitrophenyl)sulfonyl]pyrrolidine-3-carboxylate (2.80 g) in tetrahydrofuran (25 mL) - water (6 mL) was added lithium hydroxide monohydrate (554 mg), followed by stirring at room temperature overnight. To the reaction mixture was added 1 M hydrochloric acid (14.0 mL) under ice-cooling, followed by extracting with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The insoluble materials were separated by filtration and the filtrate was concentrated under reduced pressure to obtain (3S,4R)-4-(2,4-difluorophenyl)-1-[(2-nitrophenyl)sulfonyl]pyrrolidine-3-carboxylic acid (2.69 g) as a solid.

[0143]

Preparation Example 27

A mixture of tert-butyl (2S)-2-[(3R)-4-{[(3S,4R)-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}-3-(methoxymethyl)piperazin-1-yl]-3-(2,3-dihydro-1H-inden-5-yl)propanoate (90 mg), 1-bromo-4-fluorobenzene (33 μL), tris(dibenzylideneacetone)dipalladium (0) (5 mg), 2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl (5 mg), sodium tert-butoxide (37 mg), and dioxane (2 mL) was stirred at 100°C overnight under an argon atmosphere. The reaction mixture was left to be cooled to room temperature, and then water was added thereto, followed by extracting with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate, the insoluble materials were then separated by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate = 9:1 to 1:1) to obtain tert-butyl (2S)-2-[(3R)-4-{[(3S,4R)-4-(2,4-difluorophenyl)-1-(4-fluorophenyl)pyrrolidin-3-yl]carbonyl}-3-

(methoxymethyl)piperazin-1-yl]-3-(2,3-dihydro-1H-inden-5-yl)propanoate (68 mg) as a solid.

[0144]

Preparation Example 28

A mixture of methyl 2-bromo-1,3-thiazole (555 mg), (3S,4R)-4-(2,4-difluorophenyl)pyrrolidine-3-carboxylate (400 mg), potassium carbonate (459 mg), and N,N-dimethylformamide (5 mL) was stirred at 100°C for 2 days. To the reaction mixture was added water at room temperature, followed by extracting with ethyl acetate. The organic layer was washed with brine and then dried over anhydrous magnesium sulfate, the insoluble materials were then separated by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate = 90:10 to 50:50) to obtain methyl (3S,4R)-4-(2,4-difluorophenyl)-1-(1,3-thiazol-2-yl)pyrrolidine-3-carboxylate (171 mg) as an oil.

[0145]

Preparation Example 29

To a solution of tert-butyl 3-(4,4-dimethylcyclohex-1-en-1-yl)-L-alaninate (2.68 g) in ethanol (53.0 mL) was added 10% palladium hydroxide on carbon (540 mg) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 5 hours under a hydrogen atmosphere, and to the reaction mixture was added Celite, followed by stirring at room temperature for 15 minutes. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. To the residue were added ethanol (53.0 mL) and 10% palladium hydroxide on carbon (540 mg) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 15 hours under a hydrogen atmosphere of 3 atm. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to obtain tert-butyl 3-(4,4-dimethylcyclohexyl)-L-alaninate monohydrochloride (2.67 g) as a solid.

[0146]

Preparation Example 30

To a solution of tert-butyl (2S)-2-[(3S)-4-{[(3S,4R)-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-(2,3-dihydro-1H-inden-5-yl)propanoate (70.0 mg) in tetrahydrofuran (1.40 mL) were added triethylamine (53 μL) and cyclopropanecarbonyl chloride (18 μL) under ice-cooling. The reaction mixture was warmed to room temperature and stirred for 1 hour. To the reaction mixture was added a saturated aqueous sodium hydrogen carbonate solution under ice-cooling, followed by extracting with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate, the insoluble materials were then separated by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue

was purified by silica gel column chromatography (chloroform:methanol = 10:0 to 9:1) to obtain tert-butyl (2S)-2-[(3S)-4-{[(3S,4R)-1-(cyclopropylcarbonyl)-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-(2,3-dihydro-1H-inden-5-yl)propanoate (70.0 mg) as an oil.

[0147]

Preparation Example 31

To a suspension of 3-cyclopropyl-L-alanine (2 g) in tetrahydrofuran (5 mL) - water (17 mL) were added triethylamine (7 mL) and 2-nitrobenzenesulfonyl chloride (4.4 g) under ice-cooling. The reaction mixture was warmed to room temperature and stirred for 22.5 hours. The reaction mixture was ice-cooled and adjusted to approximately pH 1 by the addition of concentrated hydrochloric acid, and then water was added thereto, followed by extracting with ethyl acetate. The organic layer was then dried over anhydrous sodium sulfate, the insoluble materials were then separated by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform:methanol = 10:0 to 9:1) to obtain 3-cyclopropyl-N-[(2-nitrophenyl)sulfonyl]-L-alanine (4.75 g) as a solid.

[0148]

Preparation Example 32

To a suspension of 4-tert-butyl-L-phenylalanine (1.00 g) in tert-butyl acetate (13 mL) was added hydrochloric acid (0.62 mL) under ice-cooling. The reaction mixture was stirred at room temperature for 15 hours. To the reaction mixture was added a 1 M aqueous sodium hydroxide solution (6.00 mL) under ice-cooling, and a saturated aqueous sodium hydrogen carbonate solution was added thereto. The mixture was extracted with ethyl acetate and the organic layer was washed with brine. The organic layer was dried over anhydrous magnesium sulfate. The insoluble materials were separated by filtration and the filtrate was concentrated under reduced pressure to obtain tert-butyl 4-tert-butyl-L-phenylalaninate (1.17 g) as an oil.

[0149]

Preparation Example 33

To a mixed solution of tetrahydrofuran (1.70 mL) - water (550 μL) were added methyl 1-tert-butyl-4-(2-fluoro-4-methylphenyl)pyrrolidine-3-carboxylate (138 mg, Preparation Example 350) and lithium hydroxide monohydrate (43 mg) at room temperature, followed by stirring at room temperature overnight. To the reaction mixture was added 1 M hydrochloric acid (1.1 mL) at room temperature, and then the reaction mixture was concentrated under reduced pressure. A mixture of the obtained residue, N,N-dimethylformamide (2 mL), N,N-diisopropyl ethylamine (322 μL), tert-butyl (2S)-3-(2,3-dihydro-1H-inden-5-yl)-2-[(3S)-3-methylpiperazin-1-yl]propanoate dihydrochloride (216 mg), and O-(7-aza-1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium

hexafluorophosphate (233 mg) was stirred at room temperature overnight. To the reaction mixture were added O-(7-aza-1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (44 mg), tert-butyl (2S)-3-(2,3-dihydro-1H-inden-5-yl)-2-[(3S)-3-methylpiperazin-1-yl]propanoate dihydrochloride (50 mg), and N,N-diisopropyl ethylamine (161 μL), followed by stirring at room temperature for 1 hour. To the reaction mixture was added water, followed by extracting with ethyl acetate, and the organic layer was washed with brine. The organic layer was dried over anhydrous magnesium sulfate, the insoluble materials were then separated by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform:methanol = 10:0 to 9:1) to obtain tert-butyl (2S)-2-[(3S)-4-{[1-tert-butyl-4-(2-fluoro-4-methylphenyl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-(2,3-dihydro-1H-inden-5-yl)propanoate (102 mg) as a solid.

[0150]

Preparation Example 34

To an ice-cooled mixture of diethyl {2-[(4S)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]-2-oxoethyl}phosphonate (2.10 g), lithium chloride (315 mg), and acetonitrile (42.0 mL) was added N,N-diisopropyl ethylamine (1.20 mL), followed by stirring at the same temperature for 10 minutes. To the reaction mixture was added 5-chloro-2-pyridine carboxyaldehyde (840 mg), followed by warming to room temperature and stirring overnight. The reaction mixture was poured into water, followed by stirring at room temperature for 1 hour. The resulting solid was collected by filtration and washed with water. The obtained solid was dried at 60°C under reduced pressure to obtain (4S)-4-benzyl-3-[(2E)-3-(5-chloropyridin-2-yl)prop-2-enoyl]-1,3-oxazolidin-2-one (1.65 g) as a solid.

[0151]

Preparation Example 35

To a solution of (4S)-4-benzyl-3-{[1-tert-butyl-4-(5-chloropyridin-2-yl)pyrrolidin-3-yl]carbonyl}-1,3-oxazolidin-2-one (925 mg, Preparation Example 356) in methanol (15.0 mL) was added samarium trifluoromethanesulfonate (III) (100 mg), followed by stirring at room temperature overnight. The reaction mixture was concentrated under reduced pressure. The obtained residue was purified by basic silica gel column chromatography (chloroform alone) to obtain methyl 1-tert-butyl-4-(5-chloropyridin-2-yl)pyrrolidine-3-carboxylate (504 mg) as an oil.

[0152]

Preparation Example 36

To a mixture of methyl 1-tert-butyl-4-(5-chloropyridin-2-yl)pyrrolidine-3-carboxylate (500 mg, Preparation Example 35) and dioxane (6.00 mL) was added concentrated hydrochloric acid (6.00 mL) at room temperature. The reaction mixture was

stirred at 60°C for 6 hours. The reaction mixture was left to be cooled to room temperature and then concentrated under reduced pressure. To the obtained residue was added toluene, followed by concentrating under reduced pressure. The obtained residue was dissolved in 2-propanol and diluted in diisopropyl ether. The mixture was stirred at room temperature for 1 hour and the resulting solid was collected by filtration. The obtained solid was dried at 50°C under reduced pressure to obtain 1-tert-butyl-4-(5-chloropyridin-2-yl)pyrrolidine-3-carboxylic acid monohydrochloride (493 mg) as a solid.

[0153]

Preparation Example 37

To a suspension of (2E)-3-(4-methoxyphenyl)acrylic acid (2.00 g) in dichloromethane (35 mL) was added N,N-dimethylformamide (40 μL) at room temperature. Under an argon atmosphere, to the ice-cooled reaction mixture was added dropwise a solution of oxalyl chloride (2 mL) in dichloromethane (10 mL) over approximately 10 minutes. The reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was concentrated under reduced pressure and the obtained residue was dissolved in dichloromethane (10 mL). This solution was added dropwise to an ice-cooled suspension of (4S)-4-benzyl-1,3-oxazolidin-2-one (2 g) and lithium chloride (2.4 g) in triethylamine (8 mL) and dichloromethane (35 mL) for 10 minutes under an argon atmosphere. The reaction mixture was warmed to room temperature and stirred overnight. To the reaction mixture was added a 5% aqueous citric acid solution, and the aqueous layer and the organic layer were separated. The aqueous layer was extracted with chloroform, and the combined organic layer was washed with brine and then dried over anhydrous sodium sulfate. The insoluble materials were then separated by filtration and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform:methanol = 100:0 to 95:5) to obtain (4S)-4-benzyl-3-[(2E)-3-(4-methoxyphenyl)prop-2-enoyl]-1,3-oxazolidin-2-one (2.93 g) as a solid.

[0154]

Preparation Example 38

To a solution of (4S)-4-benzyl-3-[(2E)-3-(4-methoxyphenyl)prop-2-enoyl]-1,3-oxazolidin-2-one (400 mg) in dichloromethane (4 mL) was added trifluoroacetate (100 μL) at room temperature, and then a solution of N-(methoxymethyl)-2-methyl-N-[(trimethylsilyl)methyl]propane-2-amine (500 mg) in dichloromethane (2 mL) was added thereto, followed by stirring for 3 days. To the reaction mixture was added a solution of N-(methoxymethyl)-2-methyl-N-[(trimethylsilyl)methyl]propane-2-amine (200 mg) in dichloromethane (2 mL), followed by stirring overnight. To the reaction mixture were added chloroform and a saturated aqueous sodium hydrogen carbonate solution, and the aqueous layer and the organic layer was separated. The aqueous layer was extracted with

chloroform, the combined organic layer was then dried over anhydrous sodium sulfate, the insoluble materials were then separated by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform:methanol = 10:0 to 9:1) to obtain (4S)-4-benzyl-3-{[1-tert-butyl-4-(4-methoxyphenyl)pyrrolidin-3-yl]carbonyl}-1,3-oxazolidin-2-one (225 mg, the earlier eluted fraction) as a solid. Further, a single isomer having a different steric configuration at the 3- and 4-positions of the pyrrolidine group (235 mg, Preparation Example 38, the later eluted fraction) was obtained as a solid.

[0155]

Preparation Example 39

To a solution of (4S)-4-benzyl-3-{[1-tert-butyl-4-(4-methoxyphenyl)pyrrolidin-3-yl]carbonyl}-1,3-oxazolidin-2-one (231 mg, Preparation Example 38, the later eluted fraction) in tetrahydrofuran (3 mL) - water (1 mL) was added lithium hydroxide monohydrate (46 mg) under ice-cooling. The reaction mixture was warmed to room temperature, followed by stirring for 2 days. The reaction mixture was diluted with water, ethyl acetate was added thereto, and the aqueous layer and the organic layer were separated. To the aqueous layer was added 1 M hydrochloric acid (1.1 mL), the aqueous layer was then concentrated under reduced pressure. To the residue was added ethanol, and the mixture was concentrated in vacuo to obtain 1-tert-butyl-4-(4-methoxyphenyl)pyrrolidine-3-carboxylic acid (252 mg) as a solid.

[0156]

Preparation Example 40

To a mixture of tert-butyl (2S)-3-(2,3-dihydro-1H-inden-5-yl)-2-[(3S)-3-methylpiperazin-1-yl]propanoate (30.9 g) and ethyl acetate (200 mL) was added hydrogen chloride (4 M solution in dioxane, 46.0 mL) under ice-cooling. The reaction mixture was warmed to room temperature and stirred for 2 hours. The resulting solid was filtered to obtain tert-butyl (2S)-3-(2,3-dihydro-1H-inden-5-yl)-2-[(3S)-3-methylpiperazin-1-yl]propanoate dihydrochloride (37.4 g) as a solid.

[0157]

Preparation Example 41

To a solution of diethyl {2-[(4S)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]-2-oxoethyl}phosphonate (548 mg) in tetrahydrofuran (10 mL) was added sodium hydride (55% oil dispersion, 69 mg) under ice-cooling, followed by stirring at the same temperature for 10 minutes. To the reaction mixture was added 3-fluoro-4-formyl benzonitrile (209 mg) at the same temperature, followed by warming to room temperature and stirring for 1 hour. To the reaction mixture were added ethyl acetate and water, and the organic layer was separated and washed with brine. The organic layer was dried over anhydrous magnesium sulfate, the insoluble materials were then separated by filtration,

and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform:methanol = 100:0 to 95:5) to obtain 4-{(1E)-3-[(4S)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]-3-oxoprop-1-en-1-yl}-3-fluorobenzonitrile (387 mg) as a solid.

[0158]

Preparation Example 42

To a solution of 4-chloro-2-methyl-L-phenylalanine (1.00 g) in methanol (10.0 mL) was added thionyl chloride (500 μL) under ice-cooling. The reaction mixture was stirred at 60°C for 4 hours. The reaction mixture was left to be cooled to room temperature and then concentrated under reduced pressure. To the obtained residue was added diethyl ether, and the solid was collected by filtration to obtain methyl 4-chloro-2-methyl-L-phenylalaninate monohydrochloride (1.05 g) as a solid.

[0159]

Preparation Example 43

To a solution of 1-(bromomethyl)-2,3-difluoro-4-methylbenzene (1 g) in toluene (10 mL) were added tert-butyl (E)-N-(4-chlorobenzylidene)-L-alaninate (1.2 g), (R)-4,4-dibutyl-2,6-bis(3,4,5-trifluorophenyl)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepinium bromide (34 mg), and cesium hydroxide monohydrate (3.8 g) at -50°C. The reaction mixture was stirred at -17°C for 20 hours. To the reaction suspension was added water. The aqueous layer was extracted with diethyl ether and the organic layer was washed with brine. The organic layer was dried over anhydrous magnesium sulfate. The insoluble materials were separated by filtration and the filtrate was concentrated under reduced pressure to obtain tert-butyl (E)-N-(4-chlorobenzylidene)-2,3-difluoro-α,4-dimethyl-L-phenylalaninate (1.90 g) as an oil.

[0160]

Preparation Example 44

To a solution of (1S)-2-chloro-1-(4-chloro-2-fluorophenyl)ethanol (514 mg) in tetrahydrofuran (5 mL) was added a 10% aqueous sodium hydroxide solution (5 mL) under ice-cooling, followed by warming to room temperature and stirring for 3 hours. Water was added thereto, followed by extracting with ethyl acetate. The organic layer was washed with brine. The organic layer was dried over anhydrous magnesium sulfate, the insoluble materials were then separated by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate = 10:1) to obtain (2S)-2-(4-chloro-2-fluorophenyl)oxirane (316 mg) as an oil.

[0161]

Preparation Example 45

To 2,2,2-trifluoroethanol (12 mL) was added sodium hydride (a 60% oil dispersion, 340 mg) under ice-cooling, followed by stirring for 20 minutes. To the reaction mixture was added 1-methylcyclopropaneamine monohydrochloride (1 g) at the same temperature, and a solution of (2S)-2-(4-chloro-2-fluorophenyl)oxirane (1.39 g) in 2,2,2-trifluoroethanol (5 mL) was added thereto. The reaction mixture was stirred for 7 days and then concentrated. To the obtained residue was added ethyl acetate, water was added thereto, followed by performing liquid separation, and the organic layer was washed with brine. The organic layer was then dried over anhydrous sodium sulfate, the insoluble materials were then separated by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 to 0:100) to obtain (1S)-1-(4-chloro-2-fluorophenyl)-2-[(1-methylcyclopropyl)amino]ethanol (473 mg) as a solid.

[0162]

Preparation Example 46

To a mixture of 6-bromo-5-fluoroindan-1-one (885 mg) and trifluoroacetic acid (10 mL) was added triethylsilane (1.8 mL) at room temperature, followed by heating and stirring at 80°C for 3.5 hours. To the reaction mixture was added triethylsilane (0.6 mL), followed by stirring at 80°C for additional 1 hour, and then stirring at room temperature for 3 days. To the reaction mixture was added water, followed by extracting with hexane. The organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over anhydrous magnesium sulfate, the insoluble materials were then separated by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0 to 90:10) to obtain 5-bromo-6-fluoroindane (902 mg) as an oil.

[0163]

Preparation Example 47

A mixture of methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-(6-fluoro-2,3-dihydro-1H-inden-5-yl)propanoate (873 mg) and hydrogen chloride (4 M solution in dioxane, 10 mL) was stirred at room temperature for 1 hour. The solvent was concentrated under reduced pressure to obtain methyl (2S)-2-amino-3-(6-fluoro-2,3-dihydro-1H-inden-5-yl)propanoate monohydrochloride (708 mg) as a solid.

[0164]

Preparation Example 48

To a mixture of tert-butyl (3R)-4-[3-(3,4-dichlorophenyl)-1-methoxy-1-oxopropan-2-yl]-3-methylpiperazine-1-carboxylate (266 mg, Preparation Example 21, the earlier eluted fraction) and ethanol (10 mL) was added 10% palladium on carbon (50% water content, 70 mg) under an argon atmosphere. The reaction mixture was stirred at room temperature for 40 hours under a 3-atm hydrogen atmosphere. The insoluble

materials were separated by filtration and the filtrate was concentrated under reduced pressure. To a mixture of the obtained residue and ethanol (10 mL) was added 5% rhodium on carbon (50% water content, 170 mg) under an argon atmosphere. The reaction mixture was stirred at room temperature for 15 hours under a 3-atm hydrogen atmosphere. The insoluble materials were separated by filtration and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate = 10:0 to 7:3) to obtain an oil. To a mixture of the obtained oil and dioxane (500 μL) was added hydrogen chloride (4 M solution in dioxane, 500 μL), followed by stirring at room temperature for 1 day. To the reaction mixture was added a saturated aqueous sodium hydrogen carbonate solution, followed by extracting with ethyl acetate. The organic layer was washed with brine and then dried over anhydrous magnesium sulfate. The insoluble materials were separated by filtration and the filtrate was concentrated under reduced pressure to obtain methyl 3-cyclohexyl-2-[(2R)-2-methylpiperazin-1-yl]propanoate (49 mg) as an oil.

[0165]

Preparation Example 49

To a mixture of 4-methyltetrahydro-2H-pyran-4-amine monohydrochloride (2.5 g) and acetonitrile (130 mL) were added (chloromethyl)trimethylsilane (8 mL), potassium carbonate (9.1 g), and potassium iodide (5.5 g), followed by stirring at 60°C for 2 days. The reaction mixture was cooled to room temperature, the solid was then separated by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform:methanol = 19:1 to 9:1) to obtain 4-methyl-N-[(trimethylsilyl)methyl]tetrahydro-2H-pyran-4-amine (1.74 g) as an oil.

To the ice-cooled 37% aqueous formaldehyde solution (1.4 mL) was added potassium carbonate (60 mg), and then methanol (700 μL) was added thereto. To the reaction mixture was added dropwise 4-methyl-N-[(trimethylsilyl)methyl]tetrahydro-2H-pyran-4-amine (1.74 g) for 10 minutes to 15 minutes. The reaction mixture was stirred for 1 hour under ice-cooling, and then stirred at 10°C to 15°C for 3 hours. The reaction mixture was again ice-cooled, and potassium carbonate (2.4 g) was added thereto, followed by stirring for 1 hour under ice-cooling and then stirring at room temperature overnight. To the reaction mixture was added diethyl ether, followed by washing with brine. The organic layer was then dried over anhydrous sodium sulfate and the insoluble materials were separated by filtration. The filtrate was concentrated under reduced pressure (water bath at 21°C, up to 100 mbar) to obtain an oil (1.48 g) including N-(methoxymethyl)-4-methyl-N-[(trimethylsilyl)methyl]tetrahydro-2H-pyran-4-amine.

To a mixture of the obtained oil (1.47 g), (4S)-4-benzyl-3-[(2E)-3-(2,4-difluorophenyl)prop-2-enoyl]-1,3-oxazolidin-2-one (1 g) and dichloromethane (10 mL) was added dropwise a solution of trifluoroacetic acid (350 μL) in dichloromethane (5 mL)

at room temperature under an argon atmosphere, followed by stirring at room temperature overnight. To the reaction mixture was added saturated aqueous sodium bicarbonate, followed by extracting with chloroform, and the organic layer was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform:methanol = 10:0 to 23:2) to obtain (4S)-4-benzyl-3-{[4-(2,4-difluorophenyl)-1-(4-methyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]carbonyl}-1,3-oxazolidin-2-one (542 mg, the earlier eluted fraction) as an oil. Further, a single isomer having a different steric configuration at the 3- and 4-positions of the pyrrolidine group (550 mg, Preparation Example 49, the later eluted fraction) was obtained as a solid. For the reaction for obtaining Preparation Example 372, Preparation Example 49 was used.

[0166]

Preparation Example 416

To a mixture of (4S)-4-benzyl-3-{[(3S,4R)-1-tert-butyl-4-(4-chloro-2-fluorophenyl)pyrrolidin-3-yl]carbonyl}-1,3-oxazolidin-2-one (135 mg), tetrahydrofuran (3 mL), and water (0.6 mL) was added lithium hydroxide monohydrate (25 mg) under ice-cooling. The mixture was warmed to room temperature and then stirred for 1 hour. To the reaction mixture was added 1 M hydrochloric acid (0.61 mL), followed by concentrating. Into another reaction flask were added (4S)-4-benzyl-3-{[(3S,4R)-1-tert-butyl-4-(4-chloro-2-fluorophenyl)pyrrolidin-3-yl]carbonyl}-1,3-oxazolidin-2-one (3.55 g), tetrahydrofuran (78 mL), and water (15 mL), and then lithium hydroxide monohydrate (660 mg) was added thereto under ice-cooling. The mixture was warmed to room temperature and then stirred for 1.5 hours. To the reaction mixture was added 1 M hydrochloric acid (16 mL), followed by concentrating. The residues obtained by the respective reactions were combined and purified by ODS silica gel column chromatography (water:acetonitrile = 9:1 to 0:10). To the obtained residue was added ethanol, followed by concentrating. To the obtained residue was added hydrogen chloride (4 M solution in dioxane, 5.8 mL), then diisopropyl ether was added thereto, and the precipitated solid was filtered. The obtained solid was dried at 40°C under reduced pressure to obtain (3S,4R)-1-tert-butyl-4-(4-chloro-2-fluorophenyl)pyrrolidine-3-carboxylic acid monohydrochloride (2.67 g) as a solid.

[0167]

Preparation Example 417

To a mixture of tert-butyl (2S)-3-(4-bromo-2-fluorophenyl)-2-{(3S)-3-methyl-4-[(2-nitrophenyl)sulfonyl]-2-oxopiperazin-1-yl}propanoate (2 g), dioxane (20 mL), and water (2.4 mL) were added methylboronic acid (206 mg), tripotassium phosphate (2.06 g), a [1,1'-bis(diphenylphosphino) ferrocene]palladium (II) dichloride dichloromethane adduct (280 mg), followed by irradiating with microwave under an argon atmosphere and stirring at 100°C for 1 hour. The reaction mixture was filtered through Celite and the filtrate was

concentrated. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate = 89:11 to 20:80). To the obtained oil were added ethyl acetate (1 mL) and hexane (2 mL), followed by stirring for 1 hour, and then hexane (5 mL) was added thereto. The solid was filtered and then dried under reduced pressure to obtain tert-butyl (2S)-3-(2-fluoro-4-methylphenyl)-2-{(3S)-3-methyl-4-[(2-nitrophenyl)sulfonyl]-2-oxopiperazin-1-yl}propanoate (1.41 g) as a solid.

[0168]

In the same manner as the methods described in above Preparation Examples, the compounds of Preparation Examples 50 to 415, 418 to 421 shown in the following tables were prepared.

The structures of the Preparation Example compounds are shown in Tables 6 to 48, and the physicochemical data and the preparation methods of Preparation Example compounds are shown in Tables 49 to 61.

[0169]

Example 1

To a solution of methyl (2S)-2-[(3S)-4-{[(3S,4R)-4-(4-chloro-2-fluorophenyl)-1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-(2-fluoro-4-methylphenyl)propanoate (2.28 g) in tetrahydrofuran (40 mL) was added a solution of lithium hydroxide monohydrate (396 mg) in water (10 mL) at room temperature, followed by stirring at room temperature overnight. To the reaction mixture was added 1 M hydrochloric acid (9.45 mL) at room temperature, followed by concentrating under reduced pressure. To the residue were added water (about 5 mL) and ethanol (about 5 mL), followed by stirring, and to the obtained suspension was added water (150 mL), followed by stirring at room temperature for 2 hours. The resulting solid was collected by filtration and then washed with water to obtain (2S)-2-[(3S)-4-{[(3S,4R)-4-(4-chloro-2-fluorophenyl)-1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-(2-fluoro-4-methylphenyl)propanoic acid (1.95 g) as a crystal.

[0170]

Example 2

To a solution of tert-butyl (2S)-2-[(3S)-4-{[(3S,4R)-4-(4-chloro-2-fluorophenyl)-1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-(2-fluoro-4,6-dimethylphenyl)propanoate (33.3 g) in dioxane (60 mL) was added concentrated hydrochloric acid (60 mL), followed by stirring at 50°C for 2 hours. The solvent was evaporated under reduced pressure and the residue was diluted with ethyl acetate and water. The mixture was adjusted to pH = 7.3 by the addition of a 5 M aqueous sodium hydroxide solution, and extracted with ethyl acetate. The organic layer was washed with brine which had been adjusted to pH = 7.3. The organic layer was then dried over anhydrous sodium sulfate, the insoluble materials were then separated by

filtration, and the filtrate was concentrated under reduced pressure. The obtained solid was suspended in a mixed solvent (185 mL) of ethanol:water (3:7) at 90°C, and then ethanol (33 mL) was added thereto to obtain a solution. The solution was left to be cooled to room temperature and the resulting solid was collected by filtration. The obtained solid was washed with a mixed solvent of ethanol:water (1:2) and then dried under reduced pressure to obtain (2S)-2-[(3S)-4-{[(3S,4R)-4-(4-chloro-2-fluorophenyl)-1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-(2-fluoro-4,6-dimethylphenyl)propanoic acid (27.5 g) as a crystal.

[0171]

Example 3

To a solution of methyl (2S)-2-[(3S)-4-{[(3S,4R)-1-tert-butyl-4-(4-chloro-2-fluorophenyl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-mesitylpropanoate (29.8 g) in tetrahydrofuran (595 mL) was added a solution of lithium hydroxide monohydrate (5.33 g) in water (149 mL) under ice-cooling. The reaction mixture was stirred at room temperature for 1 day. To the reaction mixture was added lithium hydroxide monohydrate (3.2 g). The reaction mixture was stirred at room temperature for 4 days. The reaction mixture was left to stand and the organic layer was separated. The organic layer was concentrated under reduced pressure, and the residue and the aqueous layer were combined. To the aqueous layer was added water (800 mL), followed by washing with diethyl ether (300 mL). The aqueous layer was adjusted to pH = 6 by the addition of 1 M hydrochloric acid (200 mL), and the reaction mixture was stirred at room temperature for 30 minutes. The insoluble materials were separated by filtration, and then to the filtrate were added ethanol (75 mL) and water (75 mL), followed by stirring at room temperature for 1 day. The precipitated solid was separated by filtration, washed with a mixed solvent of ethanol-water (1:1), and then dried under reduced pressure to obtain (2S)-2-[(3S)-4-{[(3S,4R)-1-tert-butyl-4-(4-chloro-2-fluorophenyl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-mesitylpropanoic acid (26 g) as a crystal.

[0172]

Example 4

To a mixed solution of methyl (2S)-2-[(3S)-4-{[(3S,4R)-1-tert-butyl-4-(4-chloro-2-fluorophenyl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-(2-fluoro-4-methylphenyl)propanoate (250 mg) in tetrahydrofuran (3 mL) - water (0.7 mL) was added lithium hydroxide monohydrate (45 mg), followed by stirring at room temperature overnight. To the reaction mixture was added 1 M hydrochloric acid (1.08 mL), and water was added thereto, followed by extracting with chloroform. The organic layer was dried over anhydrous magnesium sulfate, the insoluble materials were then separated by filtration, and the filtrate was concentrated under reduced pressure. The obtained residue was dissolved in ethyl acetate (5 mL), and hydrogen chloride (4 M solution in ethyl

acetate, 0.3 mL) was added thereto. To the reaction mixture was added hexane, followed by stirring. The precipitated solid was collected by filtration and then dried under reduced pressure to obtain (2S)-2-[(3S)-4-{[(3S,4R)-1-tert-butyl-4-(4-chloro-2-fluorophenyl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-(2-fluoro-4-methylphenyl)propanoic acid dihydrochloride (215 mg) as a solid.

[0173]

Example 5

To a solution of tert-butyl (2S)-2-[(3S)-4-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-(2,3-dihydro-1H-inden-5-yl)propanoate (0.84 g) in dioxane (7.4 mL) was added concentrated hydrochloric acid (7.4 mL), followed by stirring at room temperature for 6 hours. The reaction mixture was concentrated under reduced pressure, and the obtained residue was triturated using diisopropyl ether. The solid was filtered and then dried under reduced pressure to obtain (2S)-2-[(3S)-4-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-(2,3-dihydro-1H-inden-5-yl)propanoic acid dihydrochloride (0.77 g) as a solid.

[0174]

Example 6

A mixture of methyl (2S)-2-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-3-(2-naphthyl)propanoate (102 mg), (3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidine-3-carboxylic acid (89 mg), O-(7-aza-1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (160 mg), N,N-diisopropyl ethylamine (160 μL), and N,N-dimethylformamide (2 mL) was stirred at room temperature for 3 days. To the reaction mixture was added O-(7-aza-1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (80 mg), followed by stirring at room temperature for additional 4 days. To the reaction mixture was added water, followed by extracting with ethyl acetate. The organic layer was washed with brine and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform:methanol = 99:1 to 90:10). A mixture of the obtained oil (21 mg), tetrahydrofuran (2 mL), and water (400 μL) was ice-cooled, and then lithium hydroxide monohydrate (10 mg) was added thereto under stirring. The reaction mixture was stirred at room temperature overnight. To the reaction mixture was added lithium hydroxide monohydrate (10 mg), followed by further stirring at room temperature overnight. To the reaction mixture was added 1 M hydrochloric acid (0.5 mL), followed by extracting with ethyl acetate. The organic layer was washed with brine and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol = 94:6 to 80:20). To the obtained residue (13 mg) were added tetrahydrofuran and hydrogen chloride (4 M solution in dioxane, 100 μL), followed by

concentrating under reduced pressure. The residue was triturated by the addition of ethyl acetate and hexane, and the solid was collected by filtration and the dried at 40°C under reduced pressure to obtain (2S)-2-[(3R,5S)-4-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}-3,5-dimethylpiperazin-1-yl]-3-(2-naphthyl)propanoic acid dihydrochloride (7.2 mg) as a solid.

[0175]

Example 7

To a mixed solution of (2S)-2-[(3S)-4-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-(4-chloro-2-methylphenyl)propanoic acid dihydrochloride (100 mg) in ethanol (15 mL) was added 10% palladium on carbon (50% water content, 100 mg) under an argon atmosphere. The reaction mixture was stirred at room temperature for 24 hours under a 4-atm hydrogen atmosphere. After replacing to an argon atmosphere, the insoluble materials were separated by filtration, and the filtrate was concentrated under reduced pressure. To the obtained residue were added tetrahydrofuran (4 mL) and hydrogen chloride (4 M solution in dioxane, 0.5 mL). The solvent was concentrated under reduced pressure, the obtained residue was triturated by the addition of diethyl ether, and then the solid was collected by filtration to obtain (2S)-2-[(3S)-4-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-(2-methylphenyl)propanoic acid dihydrochloride (93 mg) as a solid.

[0176]

Example 8

To a solution of tert-butyl 3-ambo-(2S,3R)-2-[(3S)-4-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-(4-methylphenyl)butanoate (504 mg) in dioxane (4 mL) was added concentrated hydrochloric acid (4 mL), followed by stirring at 50°C for 1 hour. The reaction mixture was neutralized to pH = 7 with a 1 M aqueous sodium hydroxide solution and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The insoluble materials were separated by filtration and the filtrate was concentrated under reduced pressure. The obtained residue was purified by ODS silica gel column chromatography (water:methanol = 90:10 to 20:80). The earlier eluted fraction was concentrated, and dioxane (5 mL) and hydrogen chloride (4 M solution in dioxane, 633 μL) were added thereto, followed by concentrating under reduced pressure. To the obtained residue were added ethyl acetate and hexane, and the precipitated solid was collected by filtration and then dried under reduced pressure to obtain (2S,3S)-2-[(3S)-4-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-(4-methylphenyl)butanoate dihydrochloride (190 mg, Example 8) as a solid. The later eluted fraction was concentrated, and dioxane (5 mL) and hydrogen chloride (4 M

solution in dioxane, 633 μL) were added thereto, followed by concentrating under reduced pressure. To the obtained residue were added ethyl acetate and hexane, and the precipitated solid was collected by filtration and then dried under reduced pressure to obtain (2S,3R)-2-[(3S)-4-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-(4-methylphenyl)butanoate dihydrochloride (33 mg) as a solid.

[0177]

Example 87

To a solution of (2S)-2-[(3S)-4-{[(3S,4R)-4-(4-chloro-2-fluorophenyl)-1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-(2-fluoro-4-methylphenyl)propanoic acid (110 mg) in tetrahydrofuran (5 mL) was added hydrogen chloride (4 M solution in dioxane, 107 μL), followed by stirring at room temperature for 2 hours. The precipitated solid was collected by filtration, washed with ethyl acetate, and dried under reduced pressure to obtain (2S)-2-[(3S)-4-{[(3S,4R)-4-(4-chloro-2-fluorophenyl)-1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-(2-fluoro-4-methylphenyl)propanoic acid dihydrochloride (102 mg) as a solid.

[0178]

Example 101

A solution of methyl (2S)-3-(2-fluoro-4-methylphenyl)-2-{(3S)-3-methyl-4-[(2-nitrophenyl)sulfonyl]piperazin-1-yl}propanoate (23.47 g), cesium carbonate (47.8 g), and 1-dodecanethiol (35.2 mL) in acetonitrile (188 mL) was stirred at 60°C for 16 hours and 35 minutes. The insoluble materials were filtered and then washed with acetonitrile (281.6 mL). To the filtrate were added n-heptane (187.8 mL) and water (70.4 mL), followed by adjusting to pH 3.99 by the addition of 1 M hydrochloric acid. The aqueous layer was separated and washed four times with n-heptane (187.8 mL), and then isopropyl acetate (187.8 mL) and a 20% aqueous sodium chloride solution (140.8 mL) were added thereto, followed by adjusting to pH 9.03 by the addition of a 20% aqueous potassium carbonate solution. The organic layer was separated and washed with a 20% aqueous sodium chloride solution (140.8 mL) and then concentrated under reduced pressure. Acetonitrile (234.7 mL) was added thereto, followed by concentrating under reduced pressure, and acetonitrile (234.7 mL) was added thereto again, followed by concentrating under reduced pressure. Methyl (2S)-3-(2-fluoro-4-methylphenyl)-2-[(3S)-3-methylpiperazin-1-yl]propanoate was obtained as a concentrated solution in acetonitrile.

To the obtained concentrated solution of methyl (2S)-3-(2-fluoro-4-methylphenyl)-2-[(3S)-3-methylpiperazin-1-yl]propanoate in acetonitrile was added acetonitrile (211 mL), and (3S,4R)-4-(4-chloro-2-fluorophenyl)-1-(tetrahydro-2H-pyran-4-yl)pyrrolidine-3-carboxylic acid (17.65 g), N,N-diisopropyl ethylamine (20.1 mL), and O-(7-aza-1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (21.41 g) were

added thereto at 5°C, followed by stirring for 21 hours and 30 minutes. Toluene (234.7 mL) and water (234.7 mL) were added thereto, and then the organic layer was separated. The organic layer was washed twice with water (234.7 mL), twice with a 5% aqueous sodium hydrogen carbon solution (234.7 mL), twice with a 20% aqueous ammonium chloride solution (234.7 mL), and once with a 20% aqueous sodium chloride solution (234.7 mL), and then the organic layer was concentrated under reduced pressure. To the concentrated solution was added methanol (234.7 mL), followed by concentrating under reduced pressure, and then methanol (234.7 mL) was added thereto again, followed by concentrating under reduced pressure. Methyl (2S)-2-[(3S)-4-{[(3S,4R)-4-(4-chloro-2-fluorophenyl)-1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-(2-fluoro-4-methylphenyl)propanoate was obtained as a concentrated solution in methanol.

To the obtained concentrated solution of methyl (2S)-2-[(3S)-4-{[(3S,4R)-4-(4-chloro-2-fluorophenyl)-1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-(2-fluoro-4-methylphenyl)propanoate in methanol were added methanol (117 mL) and a solution of lithium hydroxide monohydrate (5.14 g) in water (47 mL), followed by stirring at 23.8°C to 24.3°C for 12 hours and 40 minutes. Toluene (187.8 mL) was added thereto, and then the aqueous layer was separated. The aqueous layer was washed 3 times with toluene (187.8 mL), and then isopropyl acetate (187.8 mL) was added thereto, followed by adjusting to pH 6.51 by the addition of 1 M hydrochloric acid. Then, a 20% aqueous sodium chloride solution (117.4 mL) was added thereto, and then the organic layer was separated. The aqueous layer was extracted twice with isopropyl acetate (187.8 mL), the obtained organic layer was combined with the previous organic layer and then concentrated under reduced pressure. To the concentrated solution was added ethanol (234.7 mL), followed by concentrating again under reduced pressure, and ethanol (234.7 mL) was added thereto again, followed by concentrating under reduced pressure. To the concentrated solution were added ethanol (117.4 mL) and water (46.9 mL), followed by dissolving and heating, and then water (93.9 mL) was added thereto, followed by stirring at 55°C for 2 hours and 30 minutes. Water (187.8 mL) was added thereto, followed by stirring at 50°C to 60°C for 1 hour, cooling to 25°C, and stirring for 18 hours and 55 minutes. Then, the mixture was adjusted to pH 6.48 by the addition of a 1 M aqueous sodium hydroxide solution. The mixture was cooled to 5°C and stirred for 3 hours and 15 minutes, and then the solid was collected by filtration, washed with a mixed solution of ethanol and water, and dried under reduced pressure to obtain (2S)-2-[(3S)-4-{[(3S,4R)-4-(4-chloro-2-fluorophenyl)-1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-(2-fluoro-4-methylphenyl)propanoic acid (24.68 g) as a solid.

To (2S)-2-[(3S)-4-{[(3S,4R)-4-(4-chloro-2-fluorophenyl)-1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-(2-fluoro-4-methylphenyl)propanoic acid (22.00 g) was added a mixed solution of 1-propanol (211.2 mL) and water (52.8 mL), followed by heating and dissolving. The insoluble materials were removed by filtration, followed by washing with a mixed solution of 1-propanol (8.8 mL) and water (35.2 mL). To the filtrate was added dropwise water (352 mL) at 62°C, and then seed crystals were added thereto, followed by stirring at 61.5°C to 61.9°C for 37 hours. The mixture was cooled and stirred at 20°C for 24 hours, and then water (220 mL) was added dropwise thereto, followed by stirring at 20°C for 68 hours and then stirring at 10°C for 26 hours. The solid was collected by filtration, washed with a mixed solution of 1-propanol (8.8mL) and water (35.2 mL), and dried under reduced pressure to obtain (2S)-2-[(3S)-4-{[(3S,4R)-4-(4-chloro-2-fluorophenyl)-1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-(2-fluoro-4-methylphenyl)propanoic acid (20.23 g) as a crystal.

2θ (°) = 13.7, 14.7, 16.0, 17.3, 18.4, 19.6, 20.4, 21.0, 21.6, 24.7, 26.1

Furthermore, the seed crystals used in Example 101 can be obtained by carrying out the same procedure without use of the seed crystals.

[0179]

In the same manner as the methods described in Examples, the compounds of Examples 9 to 86, 88 to 100 shown in the following tables were prepared.

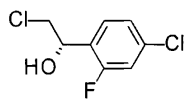
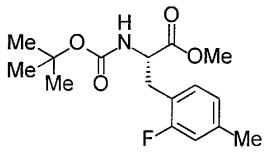
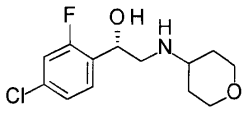
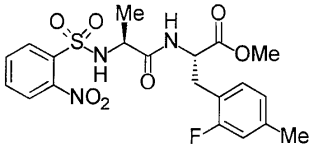
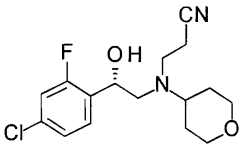
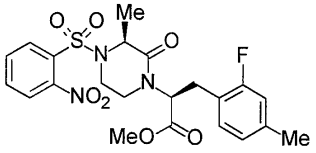
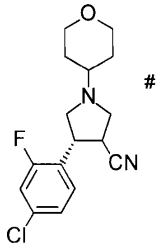
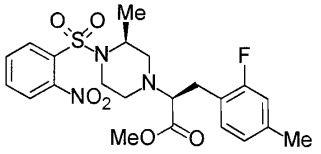
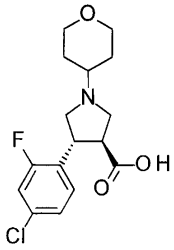
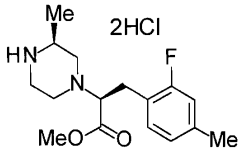
The structures of the Example compounds are shown in Tables 62 to 71, and the physicochemical data and the preparation methods of Example compounds are shown in Tables 72 to 76.

[0180]

These can be easily prepared by using the preparation methods as described above, or the method described in Examples, methods apparent to a person skilled in the art, or modified methods thereof.

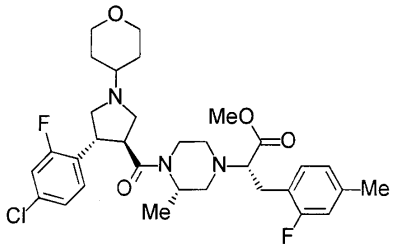
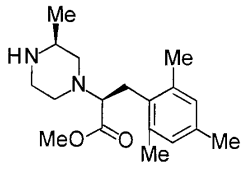
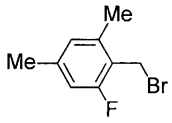
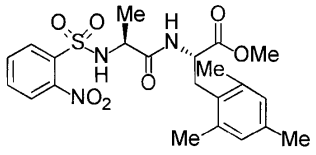
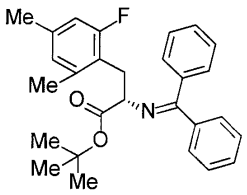
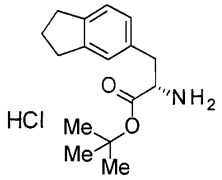
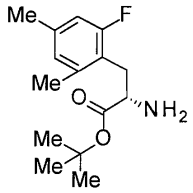
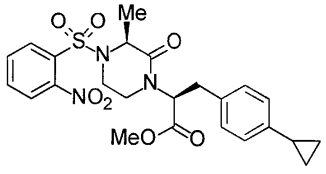
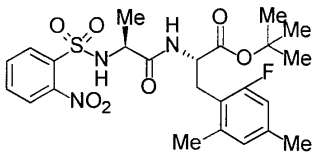
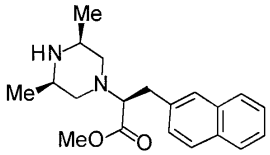
[0181]

[Table 6]

PEx	Str	PEx	Str
1		6	
2		7	
3		8	
4		9	
5		10	

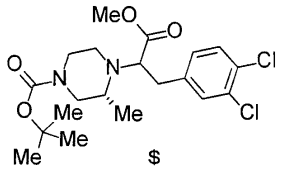
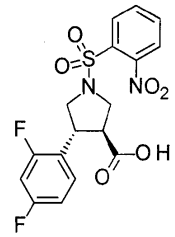
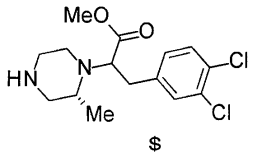
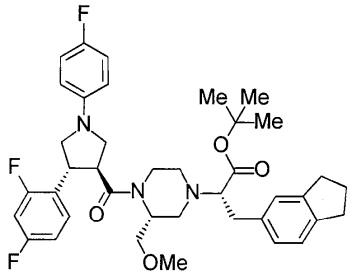
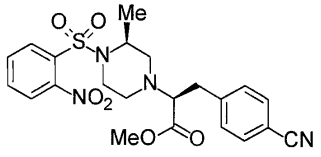
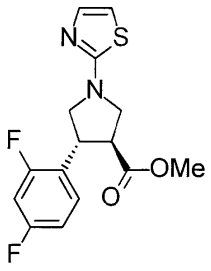
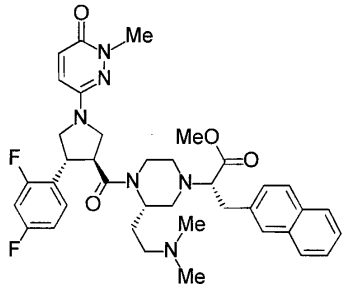
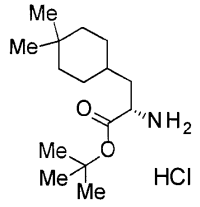
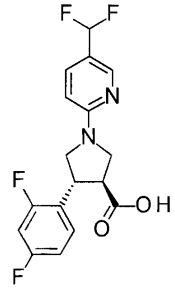
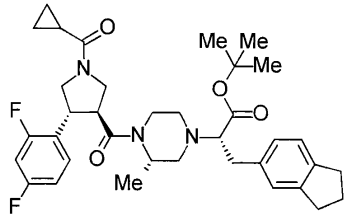
[0182]

[Table 7]

PEx	Str	PEx	Str
11		16	
12		17	
13		18	
14		19	
15		20	

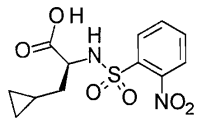
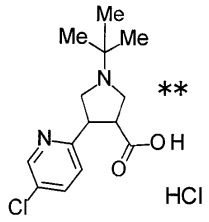
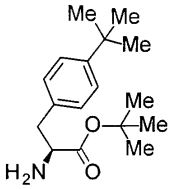
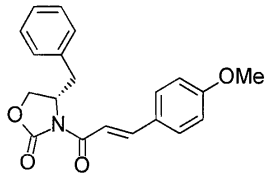
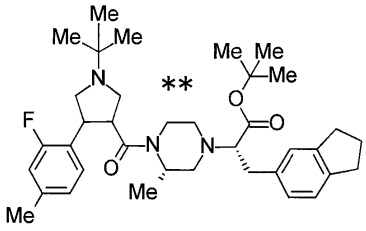
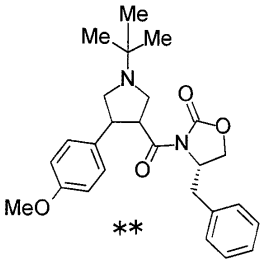
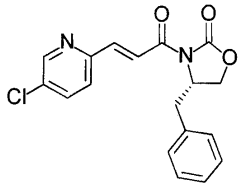
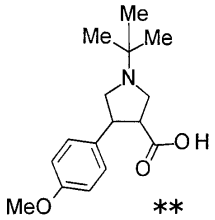
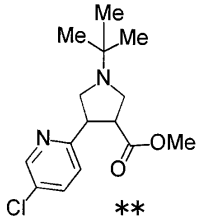
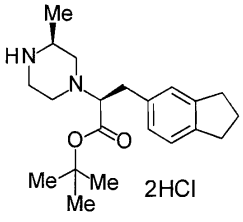
[0183]

[Table 8]

PEx	Str	PEx	Str
21		26	
22		27	
23		28	
24		29	
25		30	

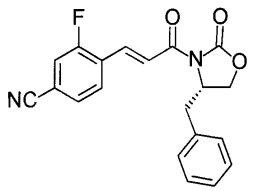
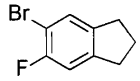
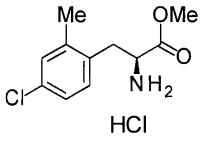
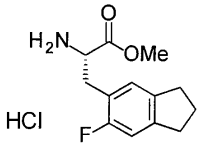
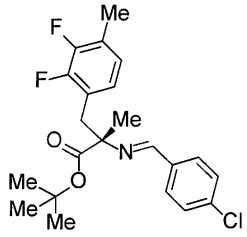
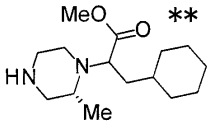
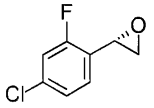
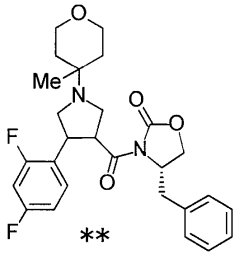
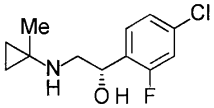
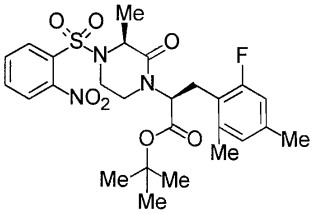
[0184]

[Table 9]

PEx	Str	PEx	Str
31		36	
32		37	
33		38	
34		39	
35		40	

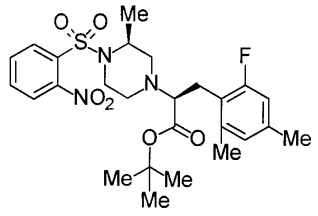
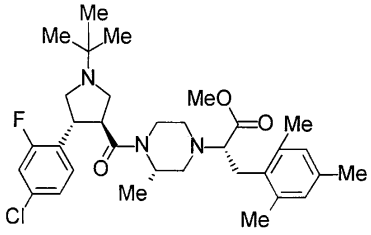
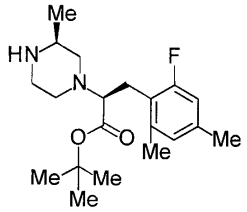
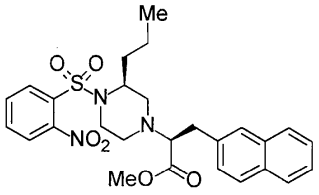
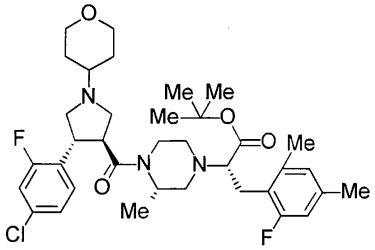
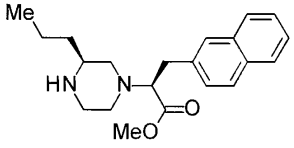
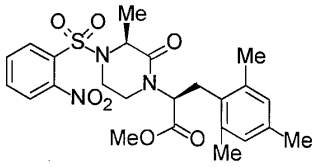
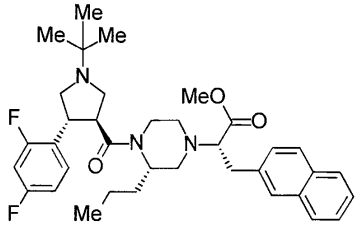
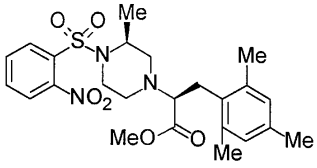
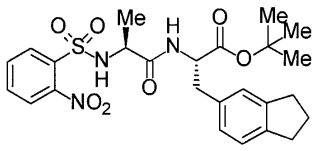
[0185]

[Table 10]

PEx	Str	PEx	Str
41		46	
42		47	
43		48	
44		49	
45		50	

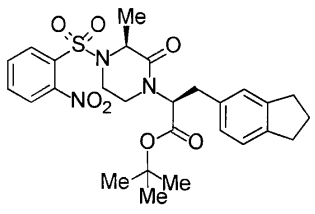
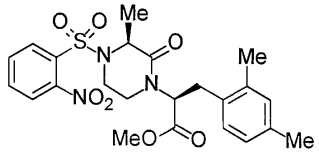
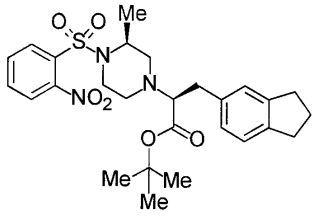
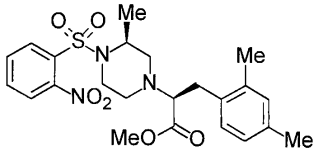
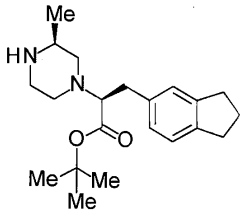
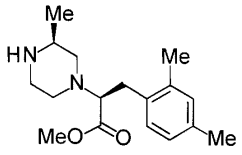
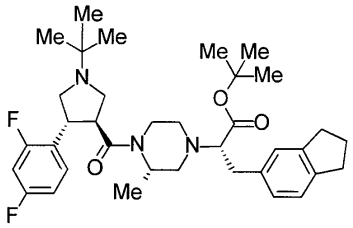
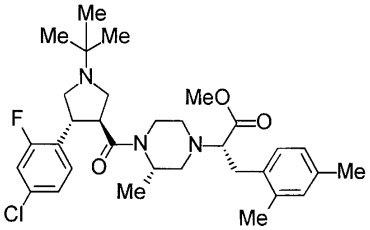
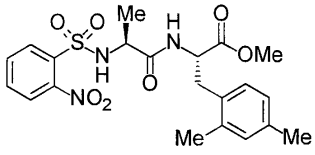
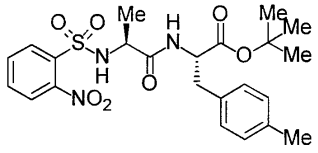
[0186]

[Table 11]

PEx	Str	PEx	Str
51		56	
52		57	
53		58	
54		59	
55		60	

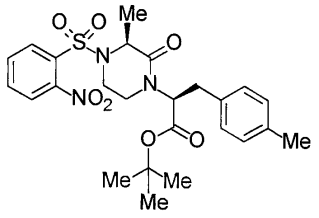
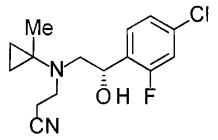
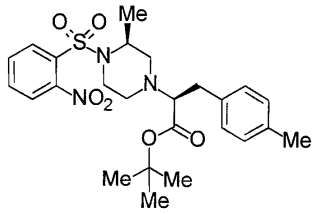
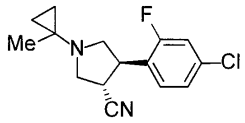
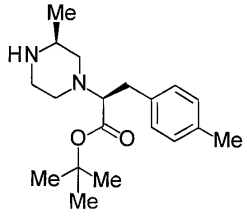
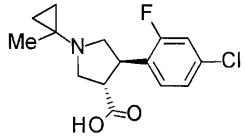
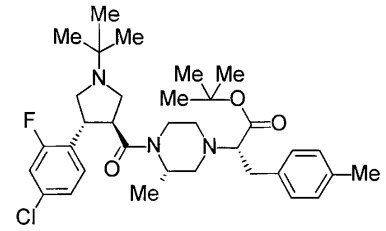
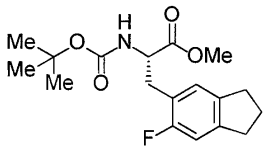
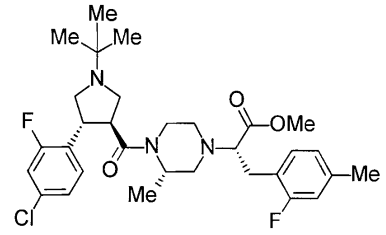
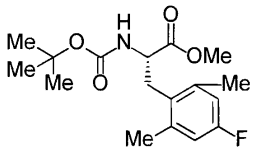
[0187]

[Table 12]

PEx	Str	PEx	Str
61		66	
62		67	
63		68	
64		69	
65		70	

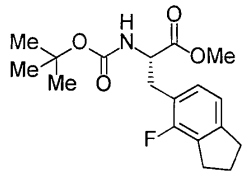
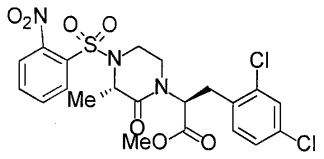
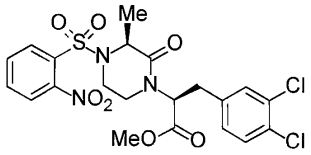
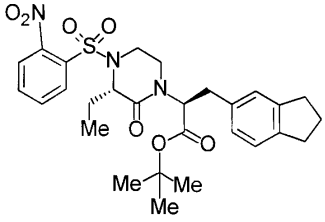
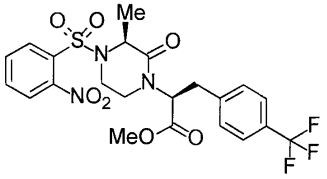
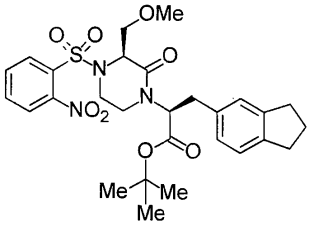
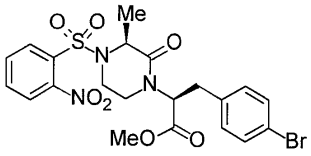
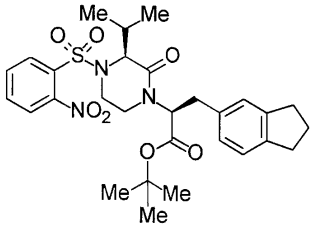
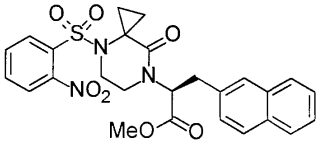
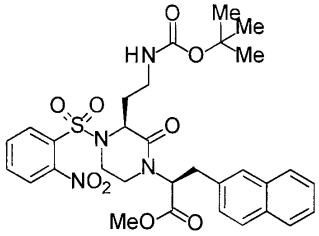
[0188]

[Table 13]

PEx	Str	PEx	Str
71		76	
72		77	
73		78	
74		79	
75		80	

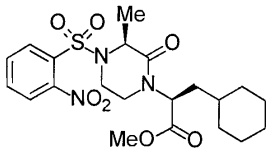
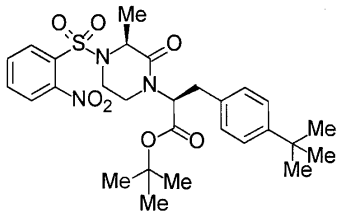
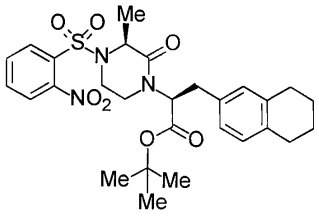
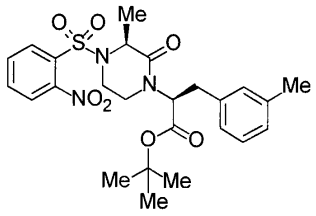
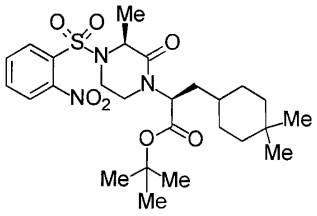
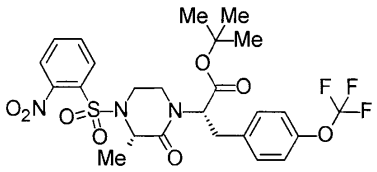
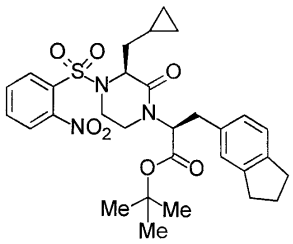
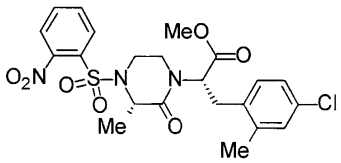
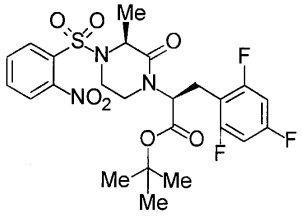
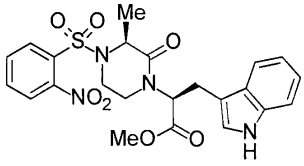
[0189]

[Table 14]

PEx	Str	PEx	Str
81		86	
82		87	
83		88	
84		89	
85		90	

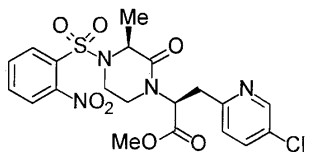
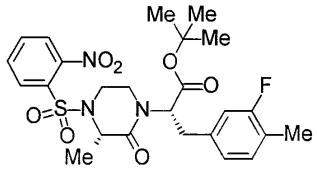
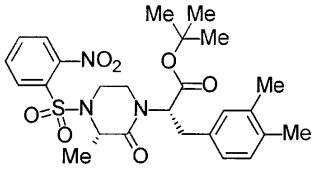
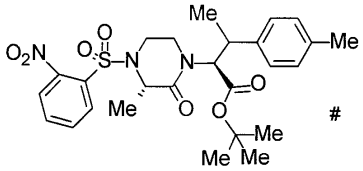
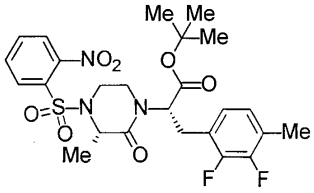
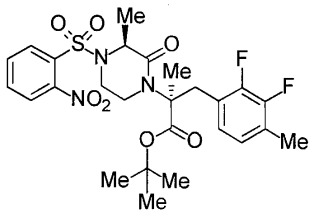
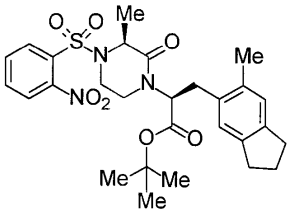
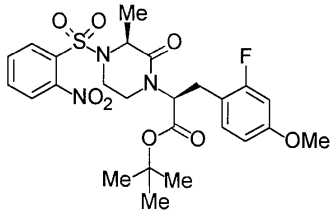
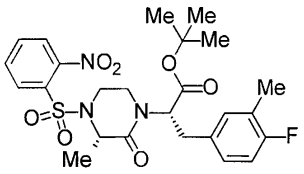
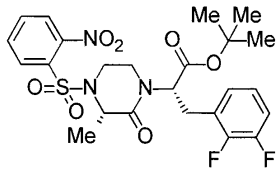
[0190]

[Table 15]

PEx	Str	PEx	Str
91		96	
92		97	
93		98	
94		99	
95		100	

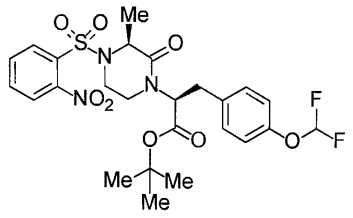
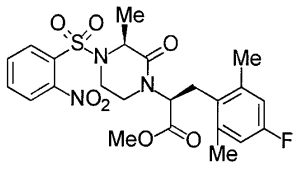
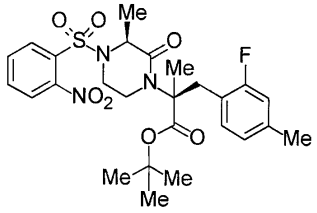
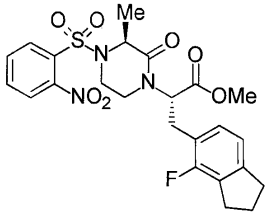
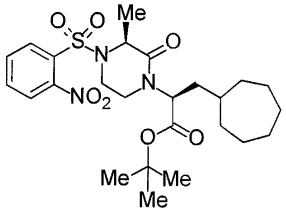
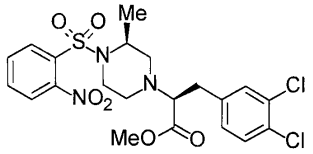
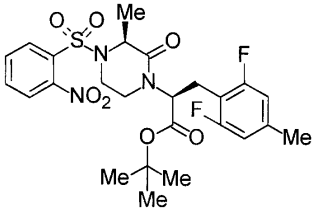
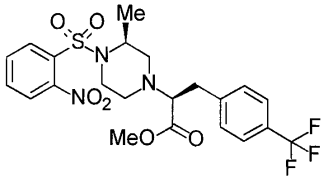
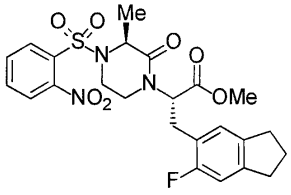
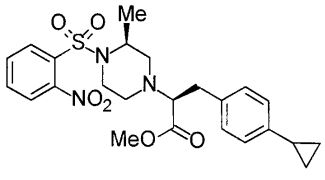
[0191]

[Table 16]

PEx	Str	PEx	Str
101		106	
102		107	
103		108	
104		109	
105		110	

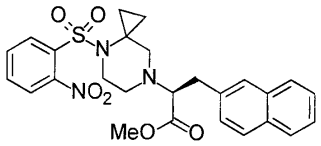
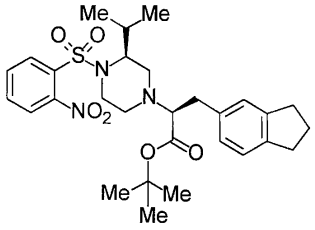
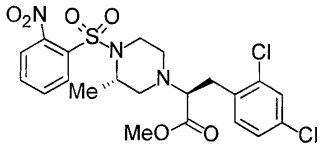
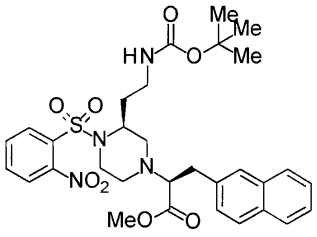
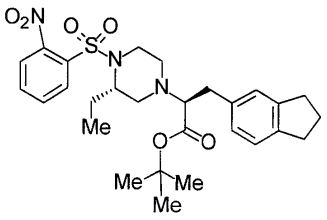
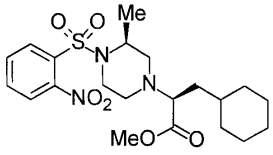
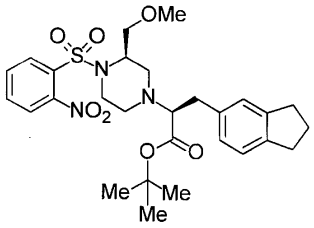
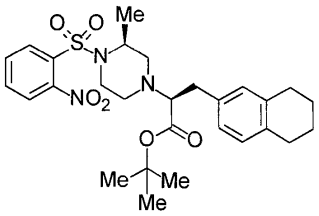
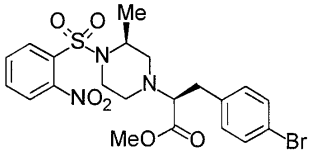
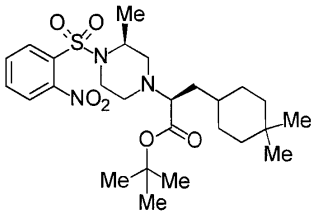
[0192]

[Table 17]

PEx	Str	PEx	Str
111		116	
112		117	
113		118	
114		119	
115		120	

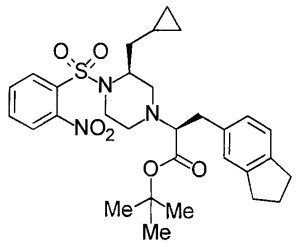
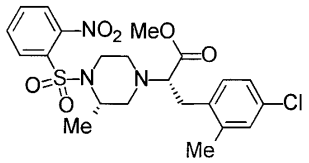
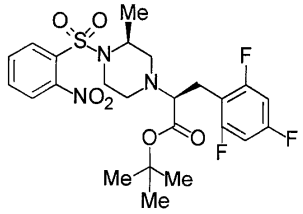
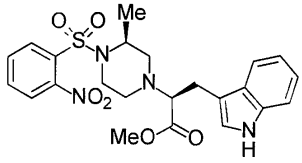
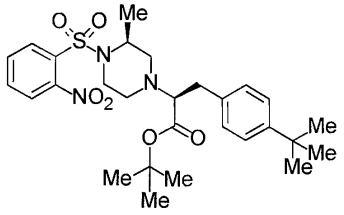
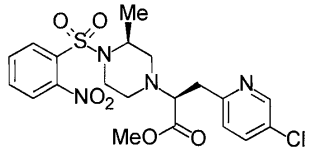
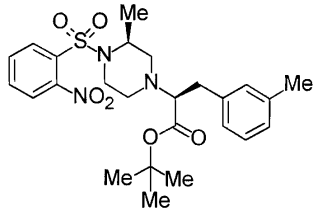
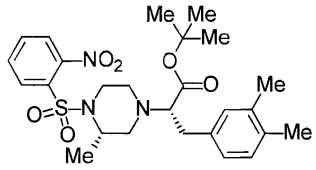
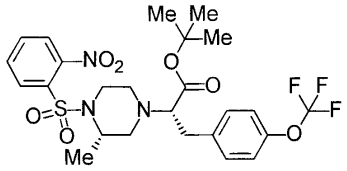
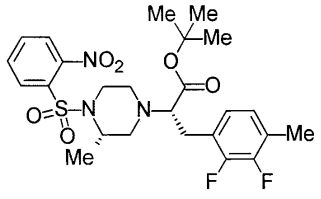
[0193]

[Table 18]

PEx	Str	PEx	Str
121		126	
122		127	
123		128	
124		129	
125		130	

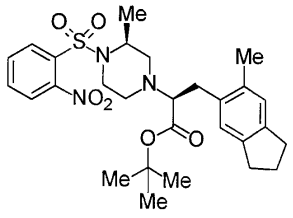
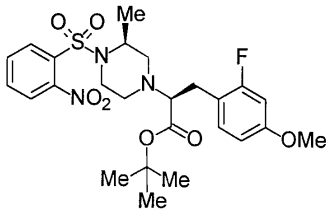
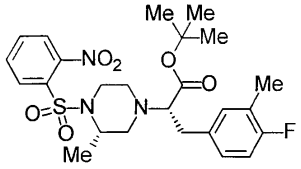
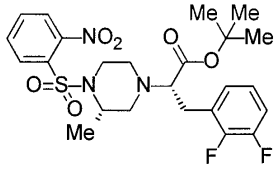
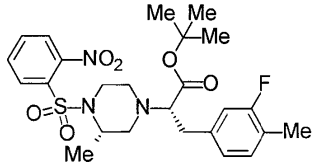
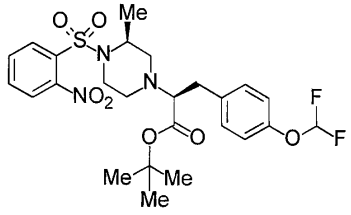
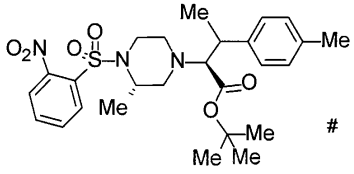
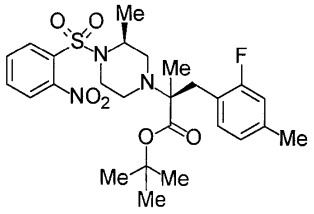
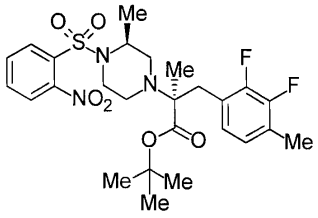
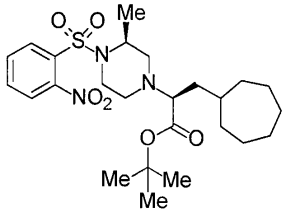
[0194]

[Table 19]

PEx	Str	PEx	Str
131		136	
132		137	
133		138	
134		139	
135		140	

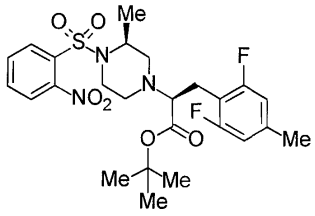
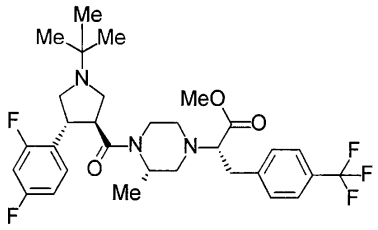
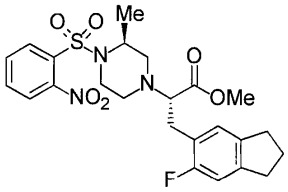
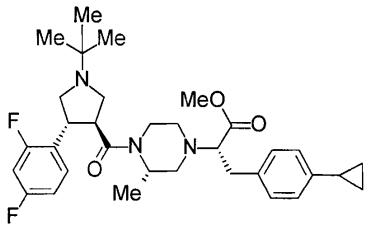
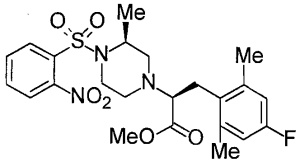
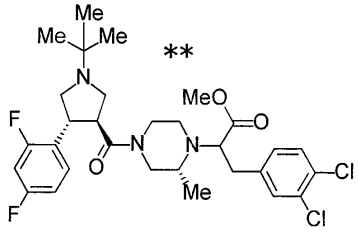
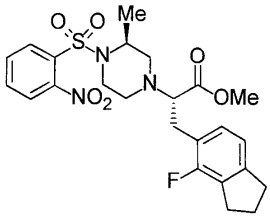
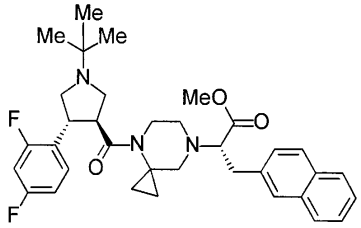
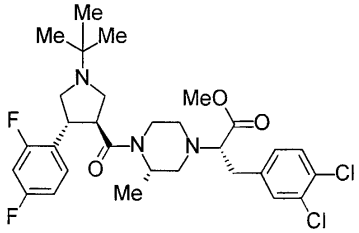
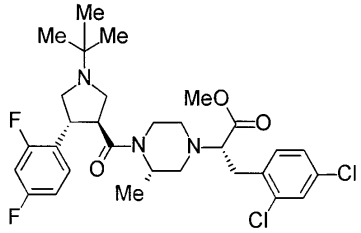
[0195]

[Table 20]

PEx	Str	PEx	Str
141		146	
142		147	
143		148	
144		149	
145		150	

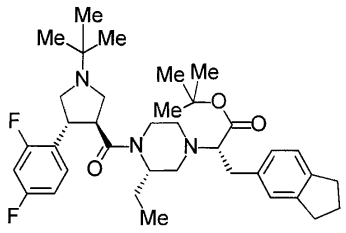
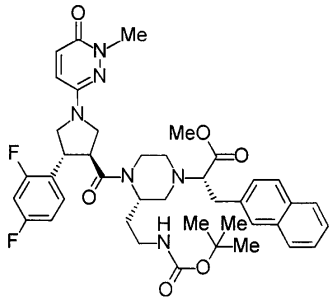
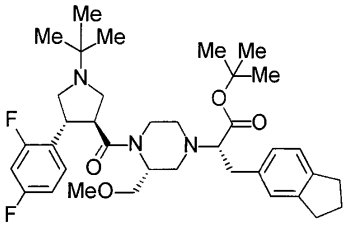
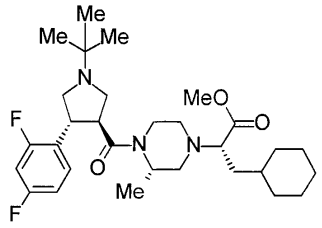
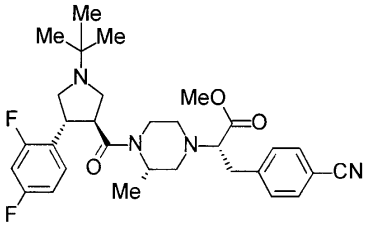
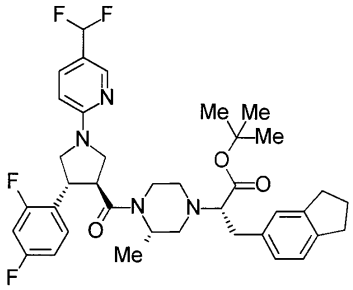
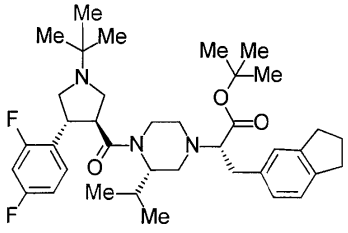
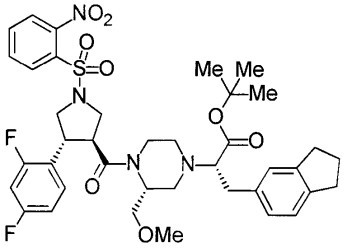
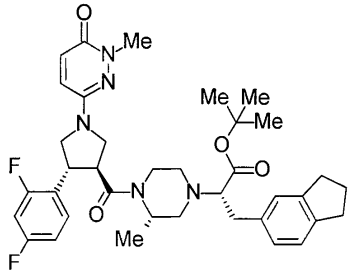
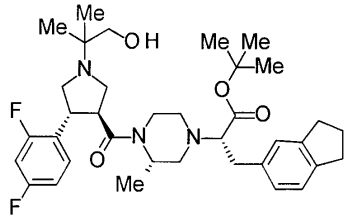
[0196]

[Table 21]

PEx	Str	PEx	Str
151		156	
152		157	
153		158	
154		159	
155		160	

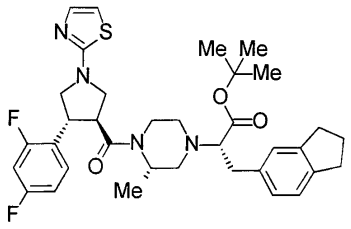
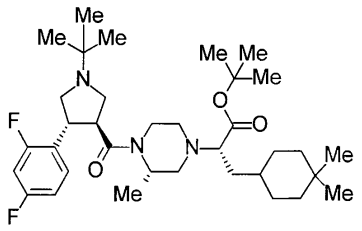
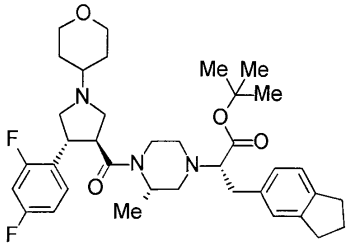
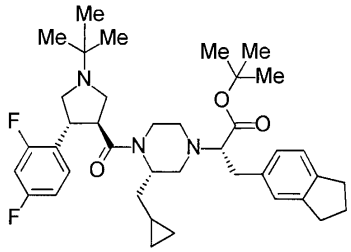
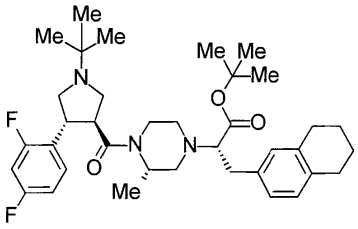
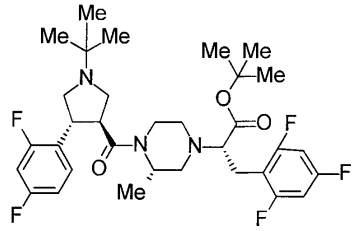
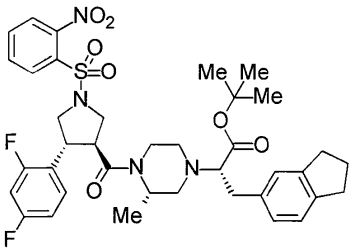
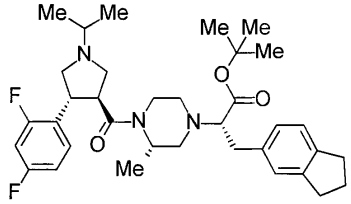
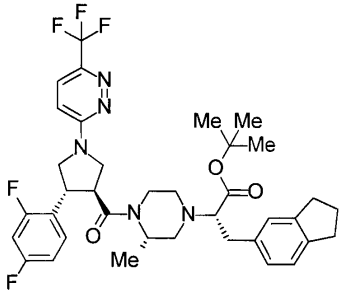
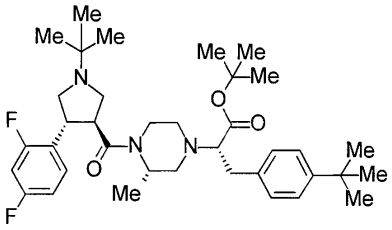
[0197]

[Table 22]

PEx	Str	PEx	Str
161		166	
162		167	
163		168	
164		169	
165		170	

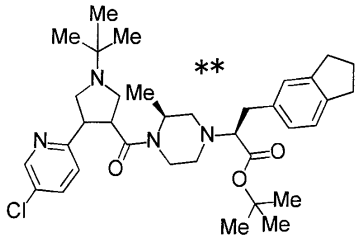
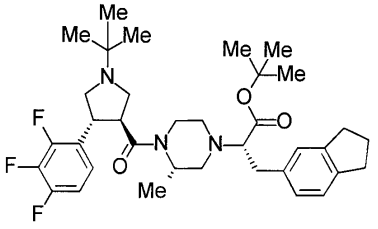
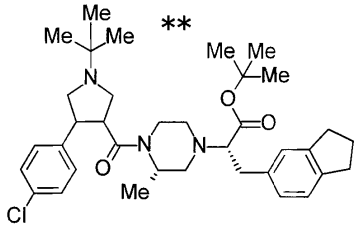
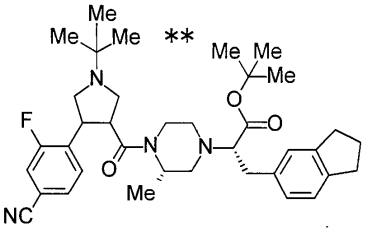
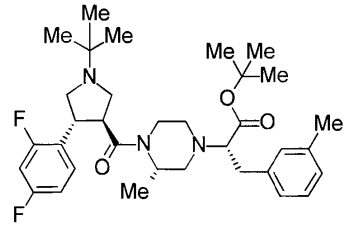
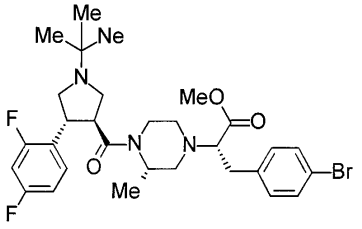
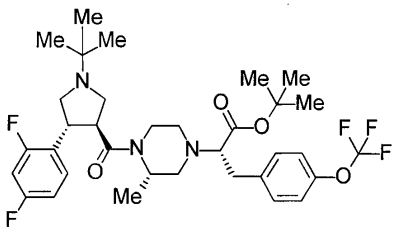
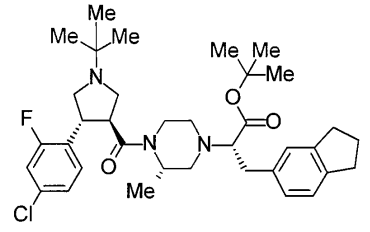
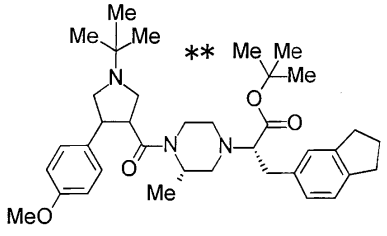
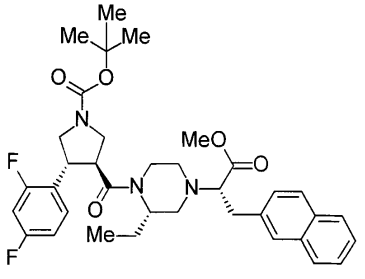
[0198]

[Table 23]

PEx	Str	PEx	Str
171		176	
172		177	
173		178	
174		179	
175		180	

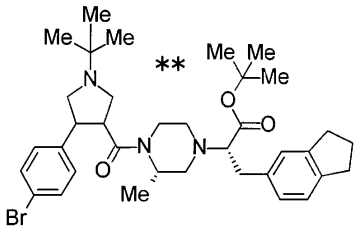
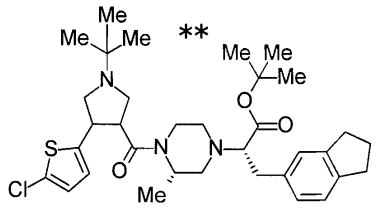
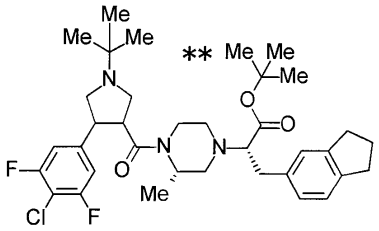
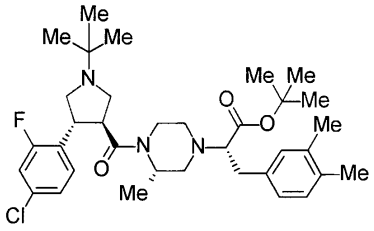
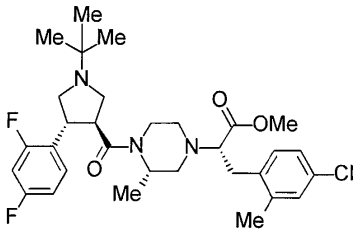
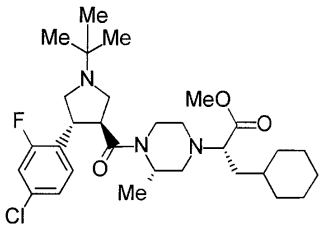
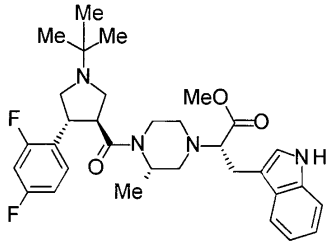
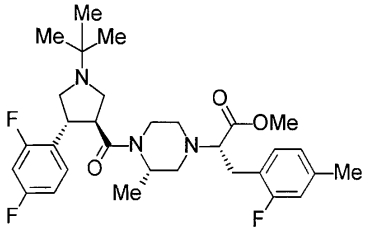
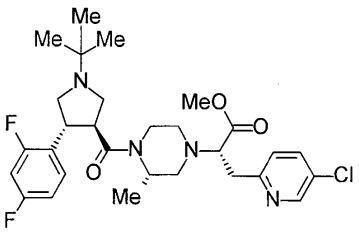
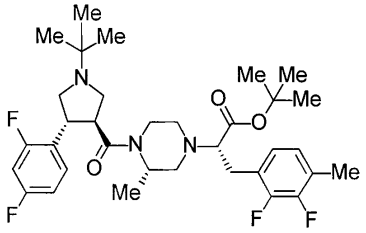
[0199]

[Table 24]

PEx	Str	PEx	Str
181		186	
182		187	
183		188	
184		189	
185		190	

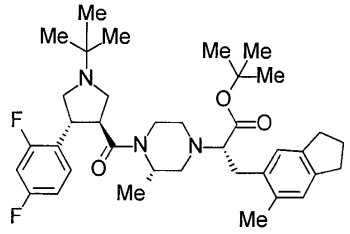
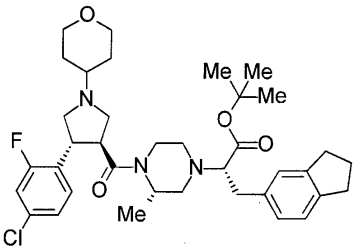
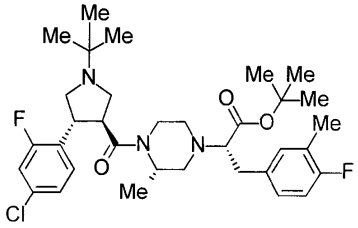
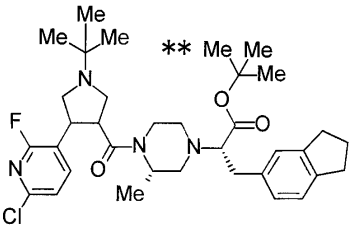
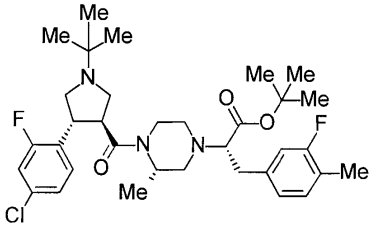
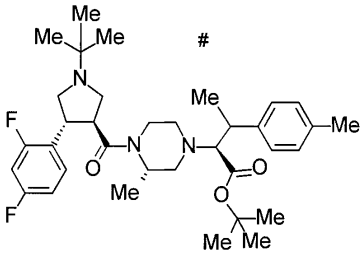
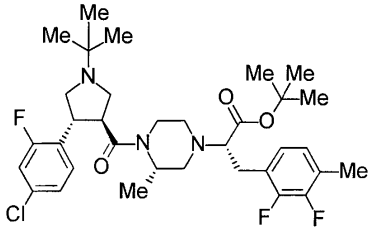
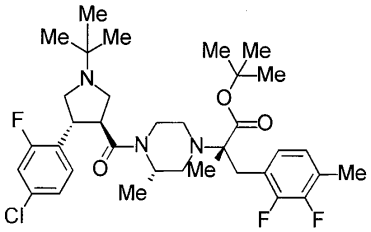
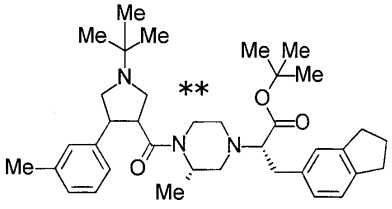
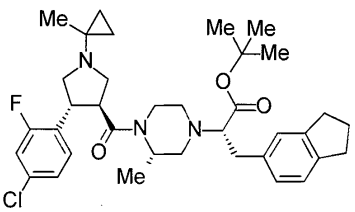
[0200]

[Table 25]

PEx	Str	PEx	Str
191		196	
192		197	
193		198	
194		199	
195		200	

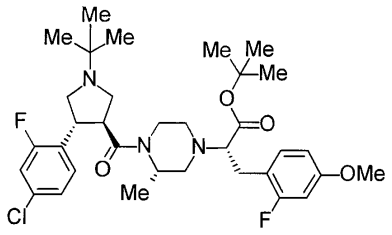
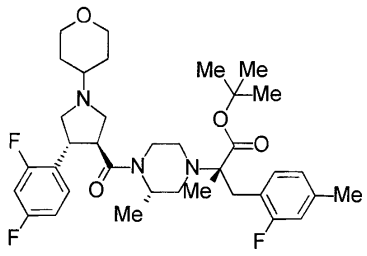
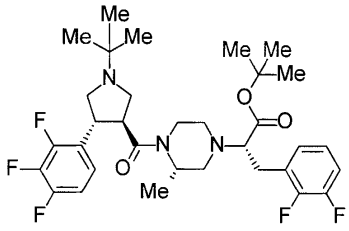
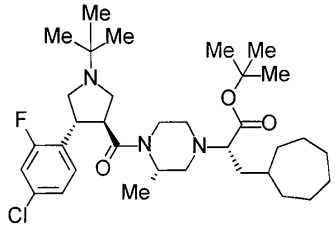
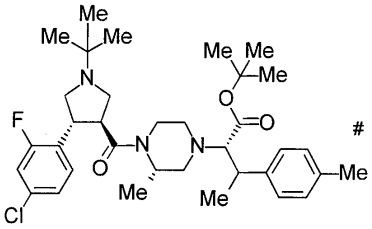
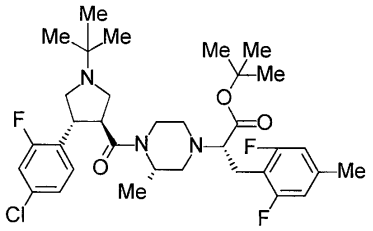
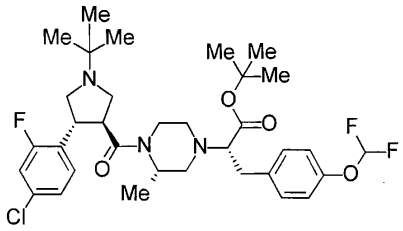
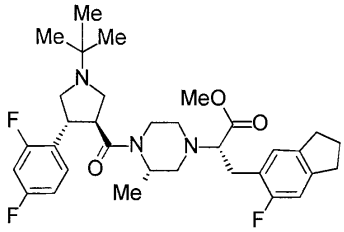
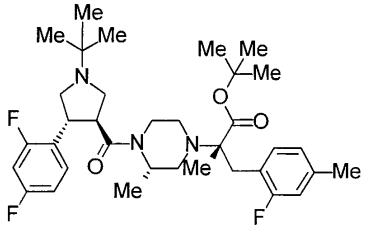
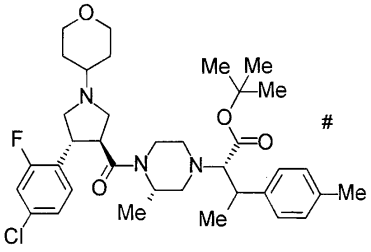
[0201]

[Table 26]

PEx	Str	PEx	Str
201		206	
202		207	
203		208	
204		209	
205		210	

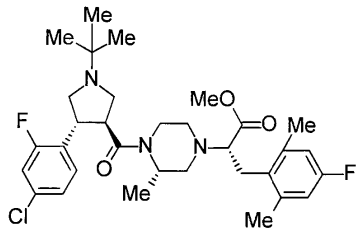
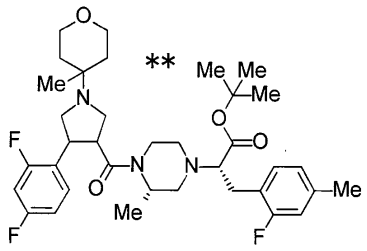
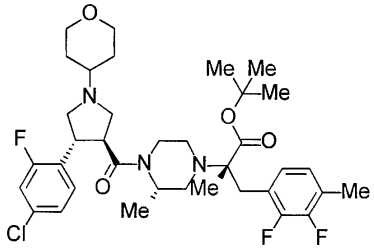
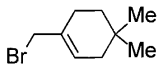
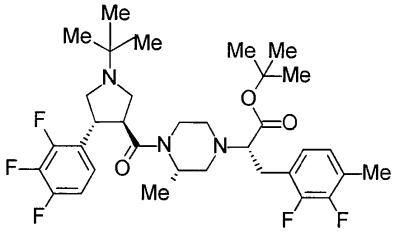
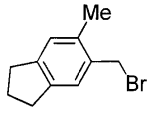
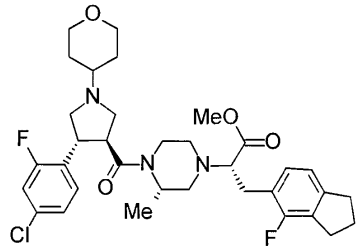
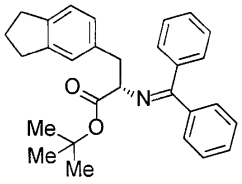
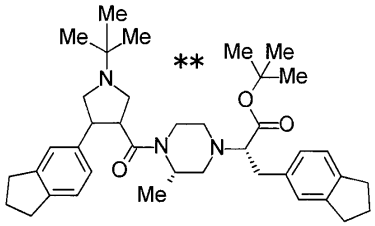
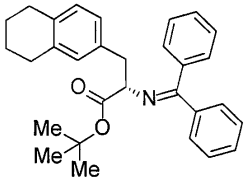
[0202]

[Table 27]

PEx	Str	PEx	Str
211		216	
212		217	
213		218	
214		219	
215		220	

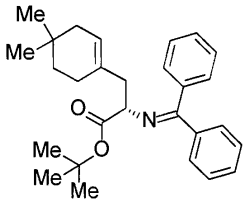
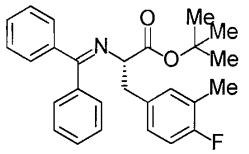
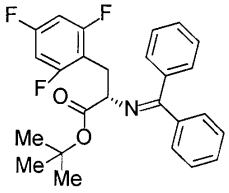
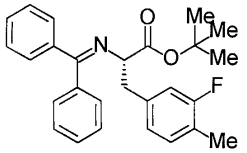
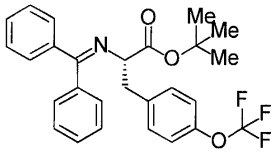
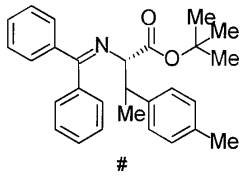
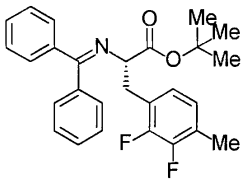
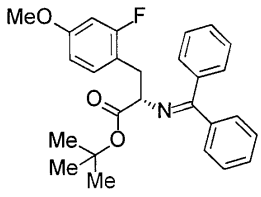
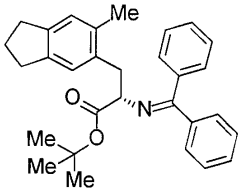
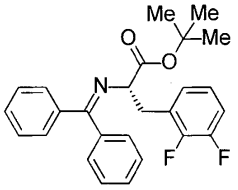
[0203]

[Table 28]

PEx	Str	PEx	Str
221		226	
222		227	
223		228	
224		229	
225		230	

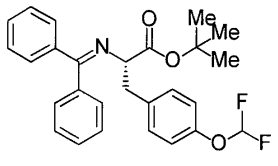
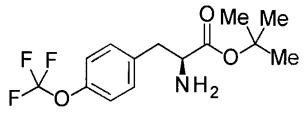
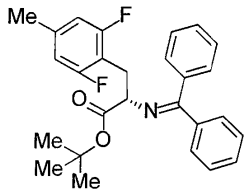
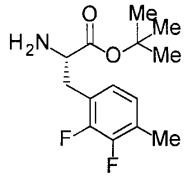
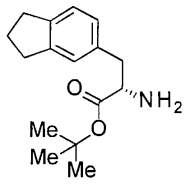
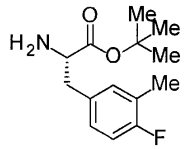
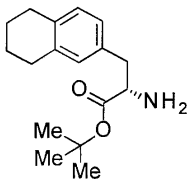
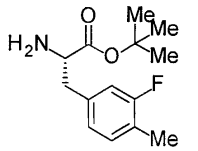
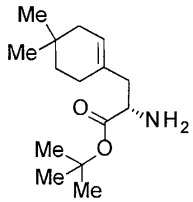
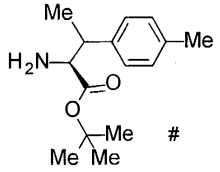
[0204]

[Table 29]

PEx	Str	PEx	Str
231		236	
232		237	
233		238	 #
234		239	
235		240	

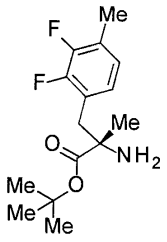
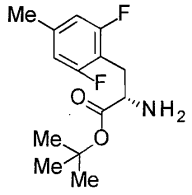
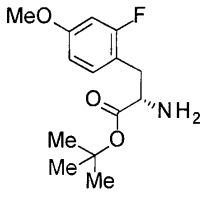
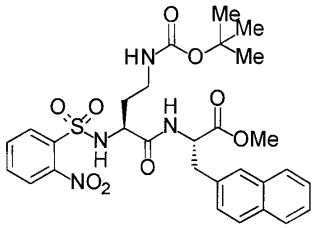
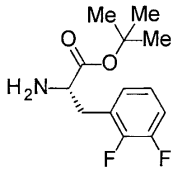
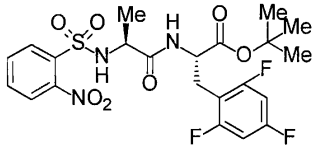
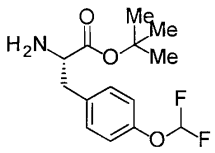
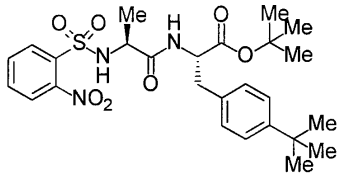
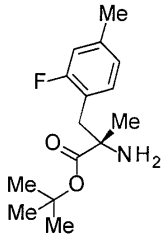
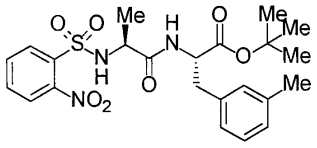
[0205]

[Table 30]

PEx	Str	PEx	Str
241		246	
242		247	
243		248	
244		249	
245		250	

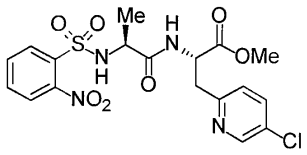
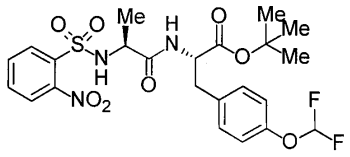
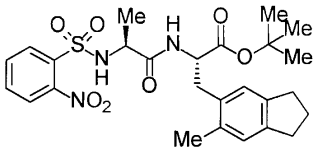
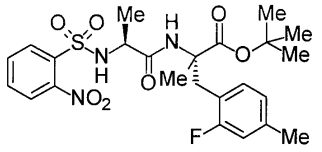
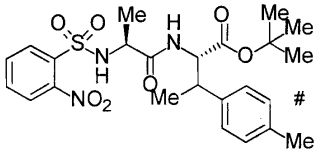
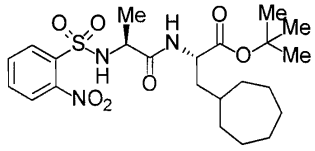
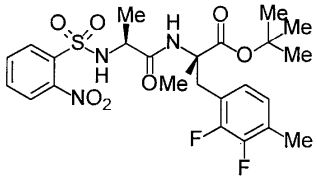
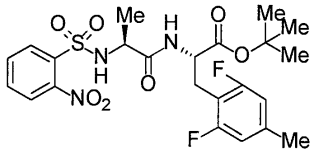
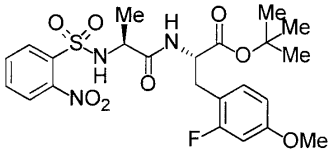
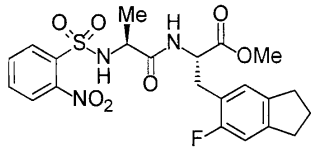
[0206]

[Table 31]

PEx	Str	PEx	Str
251		256	
252		257	
253		258	
254		259	
255		260	

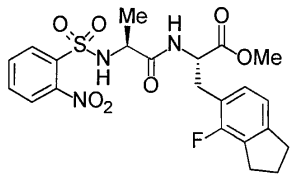
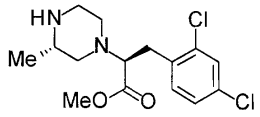
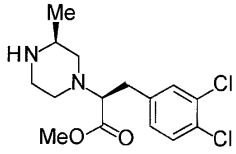
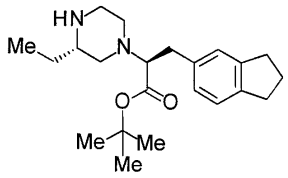
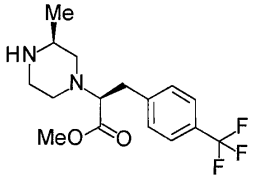
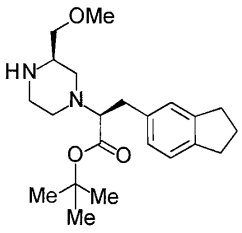
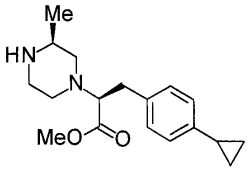
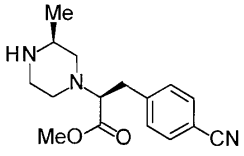
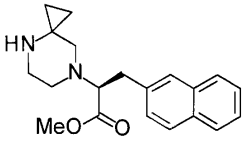
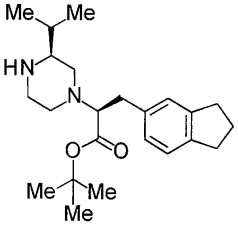
[0207]

[Table 32]

PEx	Str	PEx	Str
261		266	
262		267	
263		268	
264		269	
265		270	

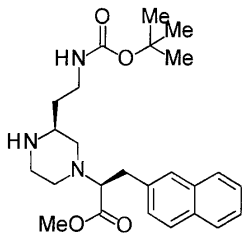
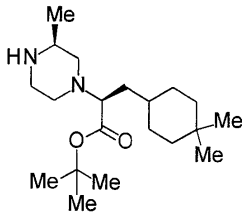
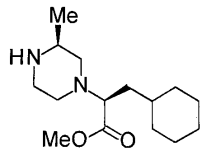
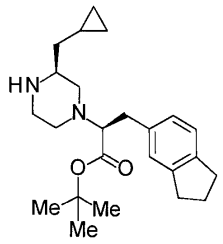
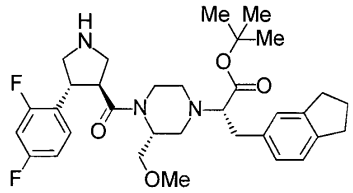
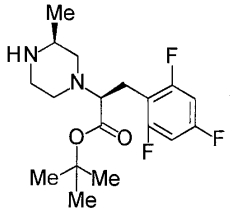
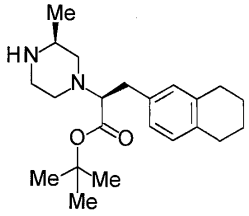
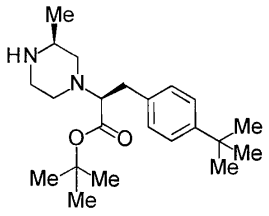
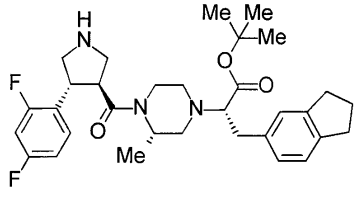
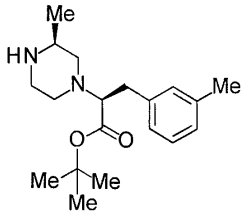
[0208]

[Table 33]

PEx	Str	PEx	Str
271		276	
272		277	
273		278	
274		279	
275		280	

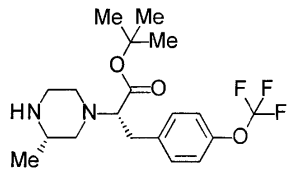
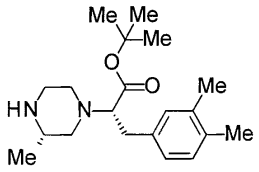
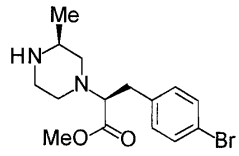
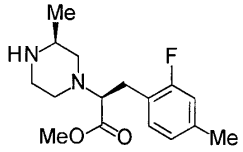
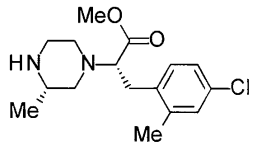
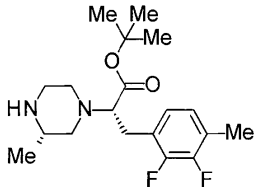
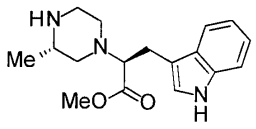
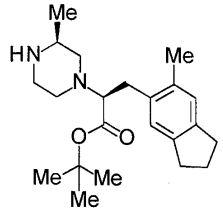
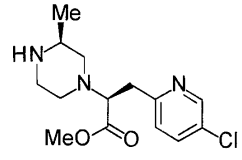
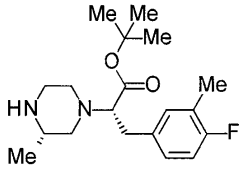
[0209]

[Table 34]

PEx	Str	PEx	Str
281		286	
282		287	
283		288	
284		289	
285		290	

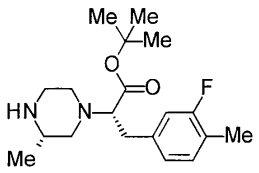
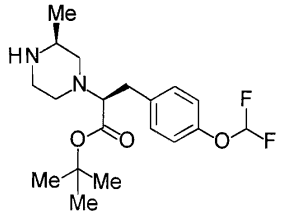
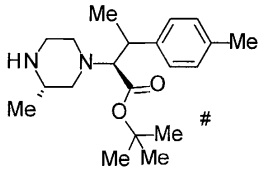
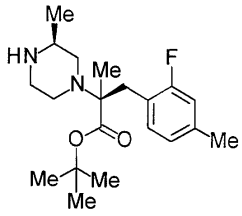
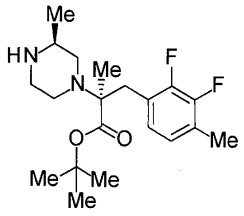
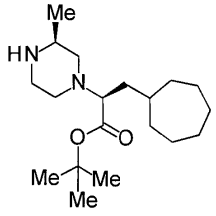
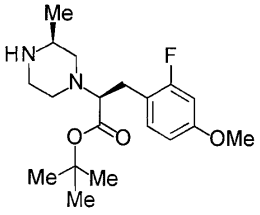
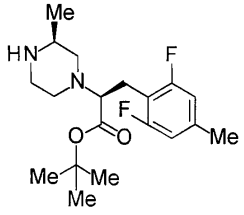
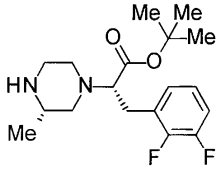
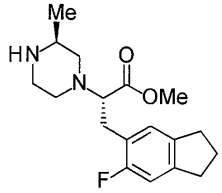
[0210]

[Table 35]

PEx	Str	PEx	Str
291		296	
292		297	
293		298	
294		299	
295		300	

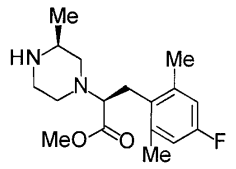
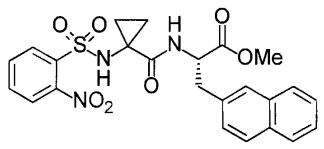
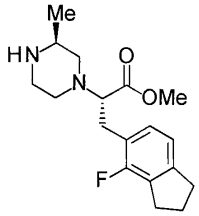
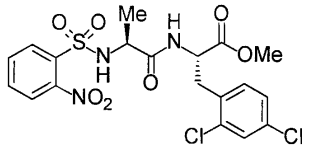
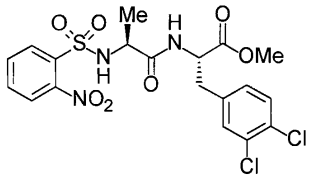
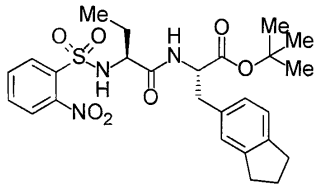
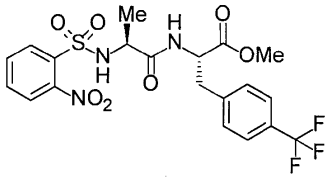
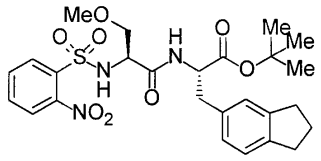
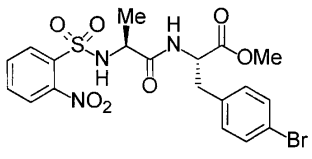
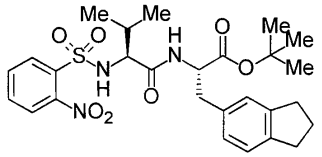
[0211]

[Table 36]

PEx	Str	PEx	Str
301		306	
302		307	
303		308	
304		309	
305		310	

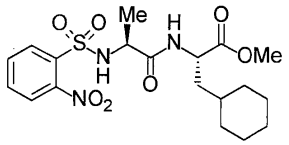
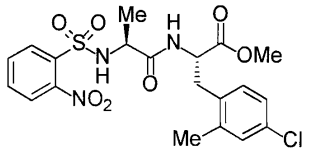
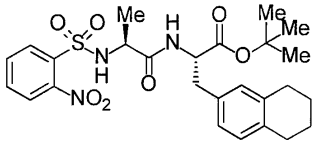
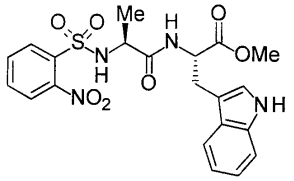
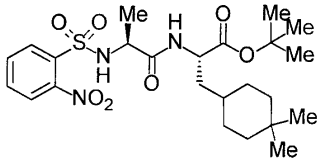
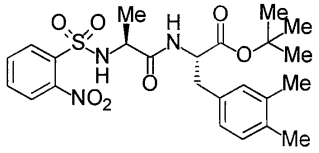
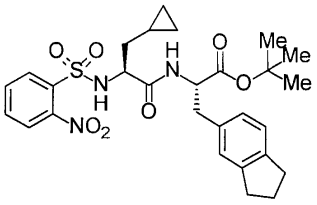
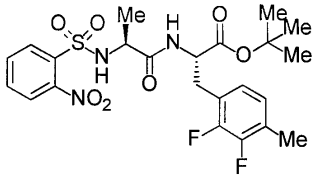
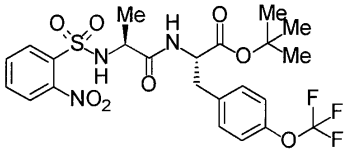
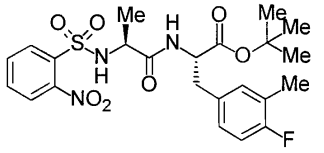
[0212]

[Table 37]

PEx	Str	PEx	Str
311		316	
312		317	
313		318	
314		319	
315		320	

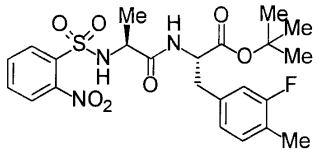
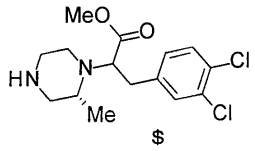
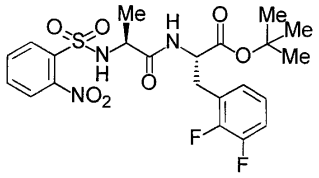
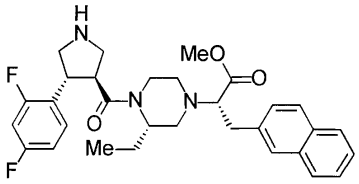
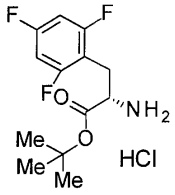
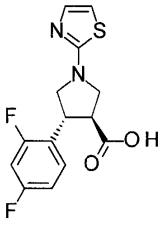
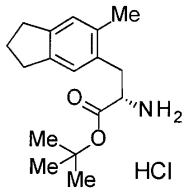
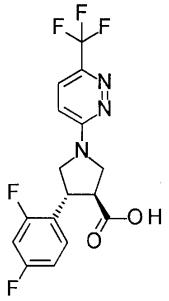
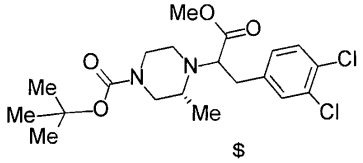
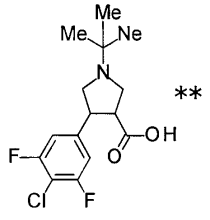
[0213]

[Table 38]

PEx	Str	PEx	Str
321		326	
322		327	
323		328	
324		329	
325		330	

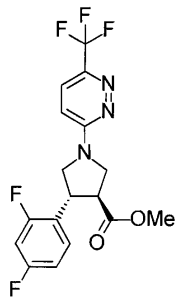
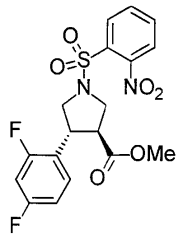
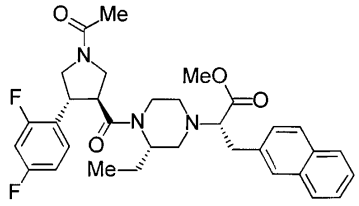
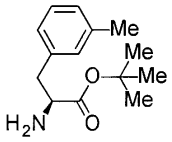
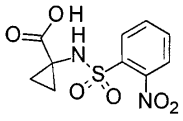
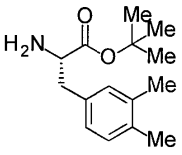
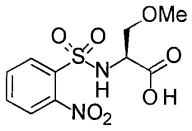
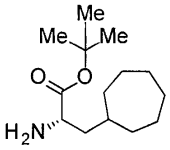
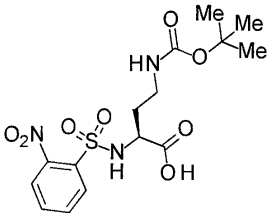
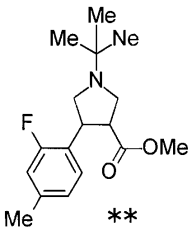
[0214]

[Table 39]

PEx	Str	PEx	Str
331		336	 $
332		337	
333	 HCl	338	
334	 HCl	339	
335	 $	340	 **

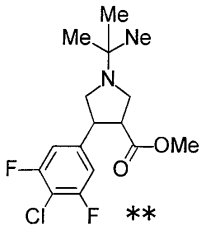
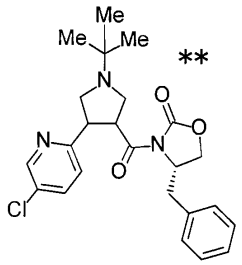
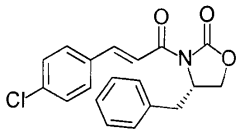
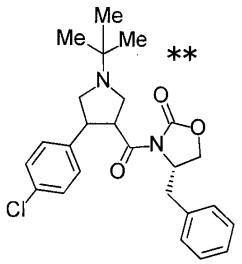
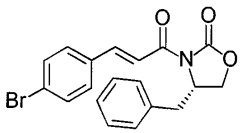
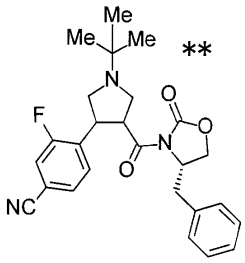
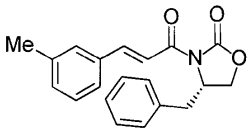
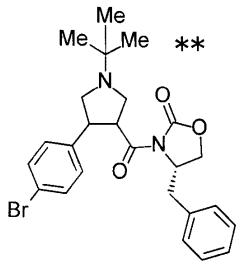
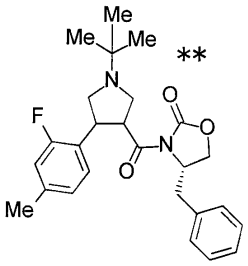
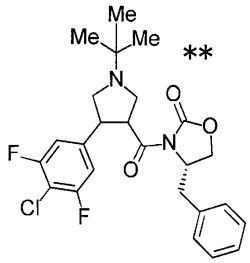
[0215]

[Table 40]

PEx	Str	PEx	Str
341		346	
342		347	
343		348	
344		349	
345		350	

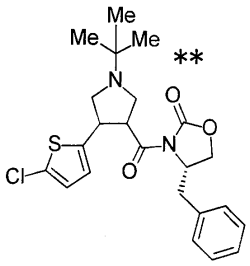
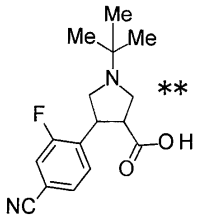
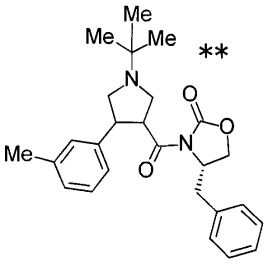
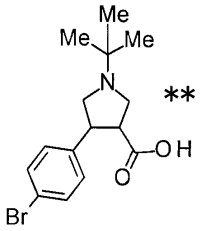
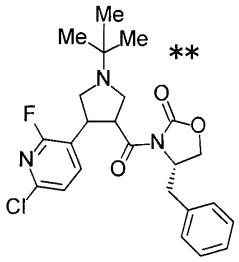
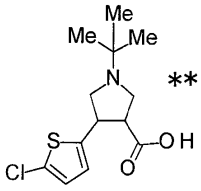
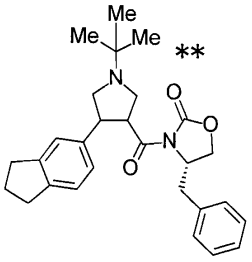
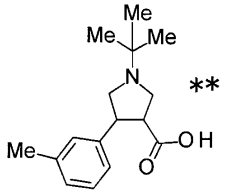
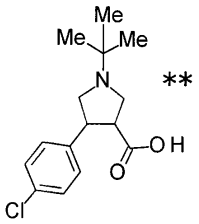
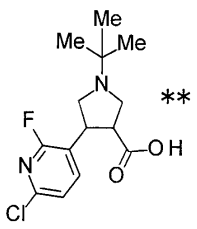
[0216]

[Table 41]

PEx	Str	PEx	Str
351		356	
352		357	
353		358	
354		359	
355		360	

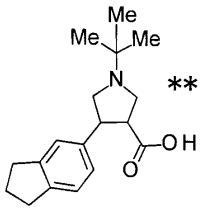
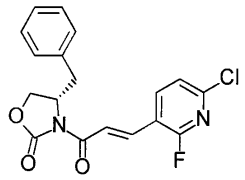
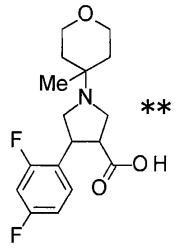
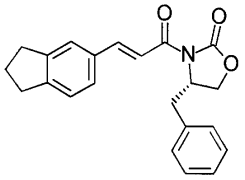
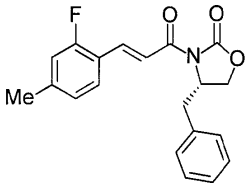
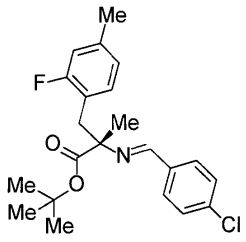
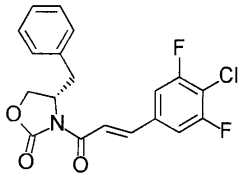
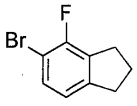
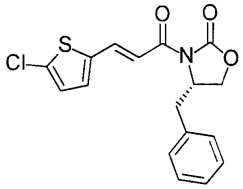
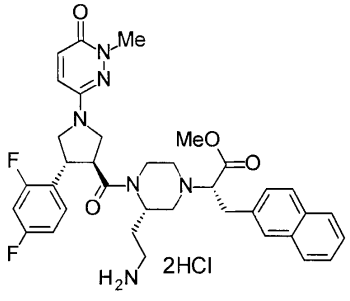
[0217]

[Table 42]

PEx	Str	PEx	Str
361		366	
362		367	
363		368	
364		369	
365		370	

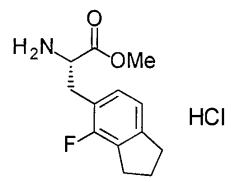
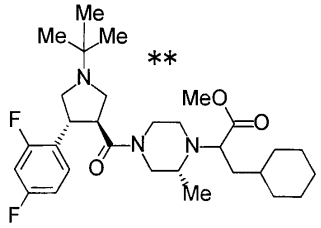
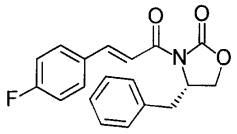
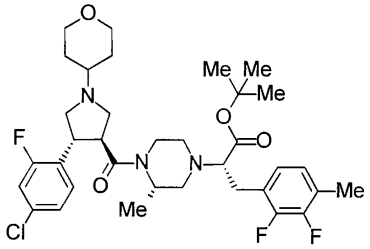
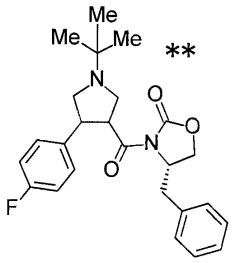
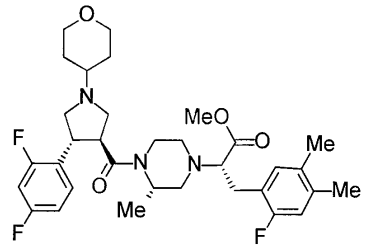
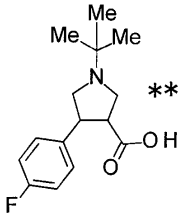
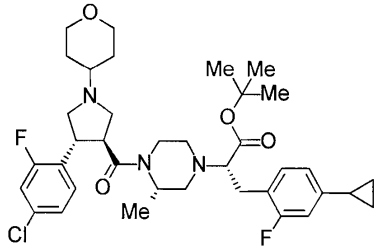
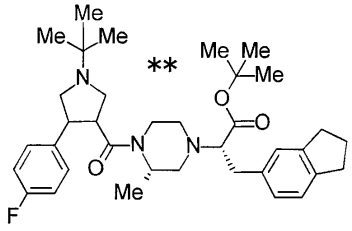
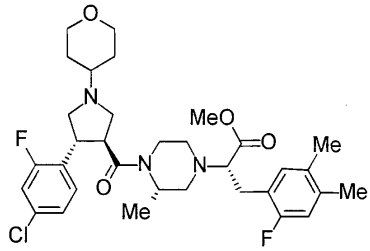
[0218]

[Table 43]

PEx	Str	PEx	Str
371		376	
372		377	
373		378	
374		379	
375		380	

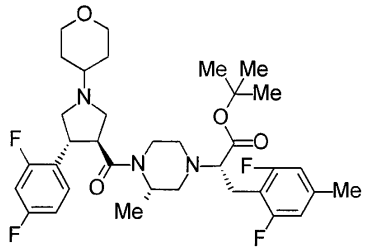
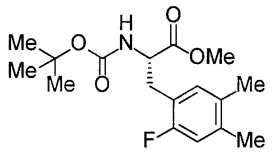
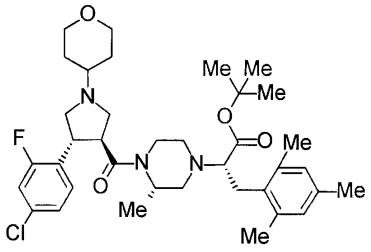
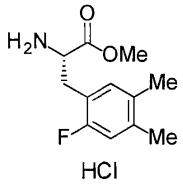
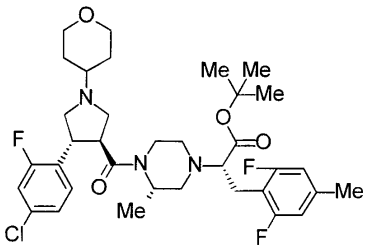
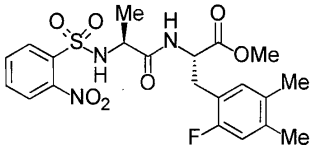
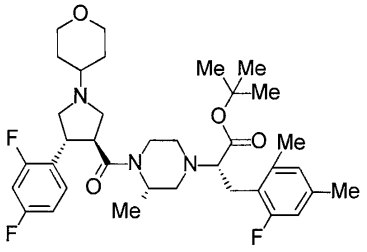
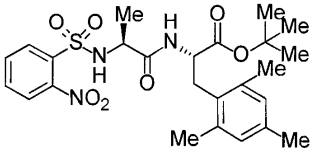
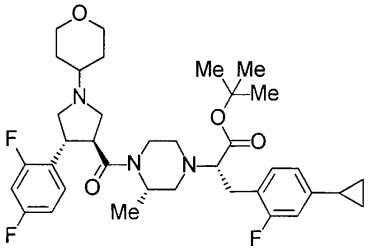
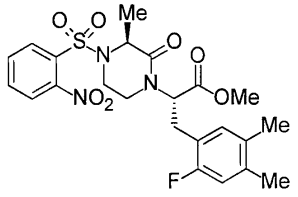
[0219]

[Table 44]

PEx	Str	PEx	Str
381		386	
382		387	
383		388	
384		389	
385		390	

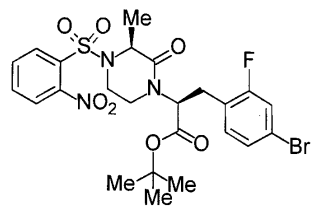
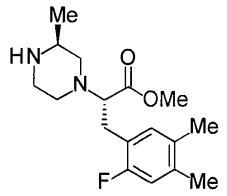
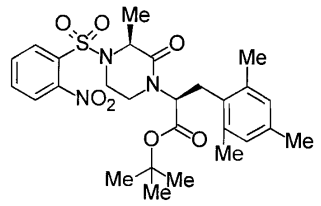
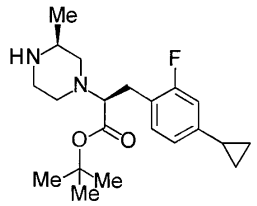
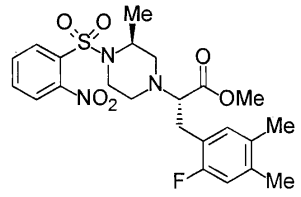
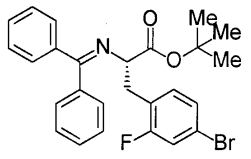
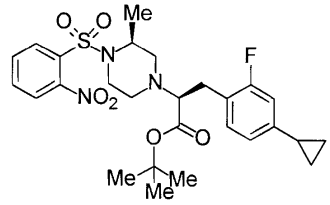
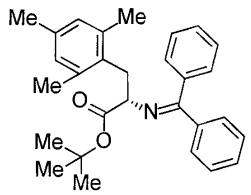
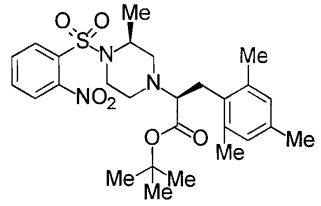
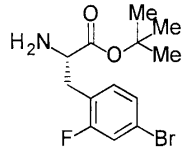
[0220]

[Table 45]

PEx	Str	PEx	Str
391		396	
392		397	
393		398	
394		399	
395		400	

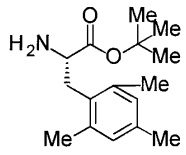
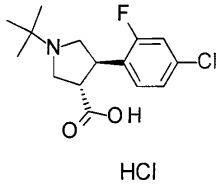
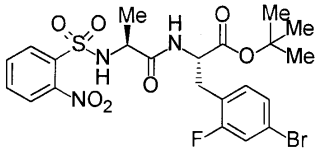
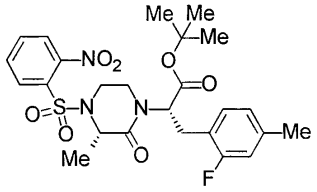
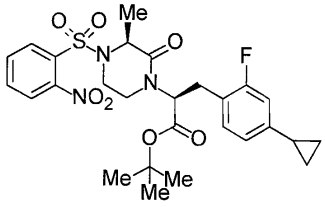
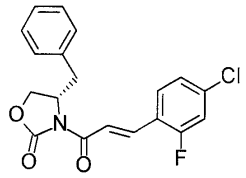
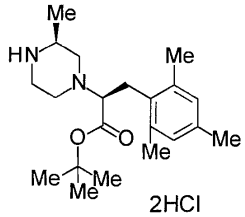
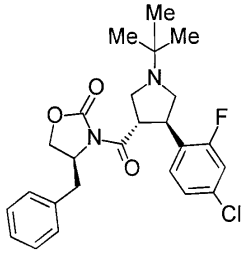
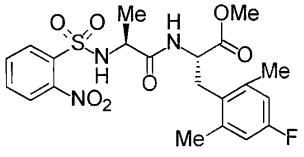
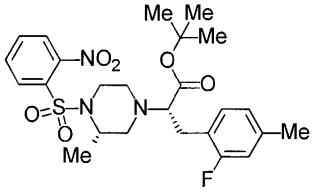
[0221]

[Table 46]

PEx	Str	PEx	Str
401		406	
402		407	
403		408	
404		409	
405		410	

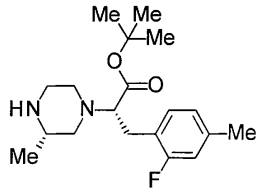
[0222]

[Table 47]

PEx	Str	PEx	Str
411		416	 HCl
412		417	
413		418	
414	 2HCl	419	
415		420	

[0223]

[Table 48]

PEx	Str
421	

[0224]

[Table 49]

PEx	PSyn	DAT
1	1	EI: 208
2	2	ESI+: 274
3	3	ESI+: 327
4	4	ESI+: 309
5	5	ESI+: 328
6	6	ESI+: 334 [M+Na]+
7	7	APCI/ESI+: 468
8	8	APCI/ESI+: 494
9	9	APCI/ESI+: 480
10	10	APCI/ESI+: 295
11	11	APCI/ESI+: 604
12	12	^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 2.30 (3H, s) 2.38 (3H, s) 4.55 (2H, d, *J*=1.2 Hz) 6.73 (1H, d, *J*=10.8 Hz) 6.80 (1H, s)
13	13	ESI+: 432
14	14	ESI+: 268
15	15	ESI+: 546[M+Na]+
16	16	ESI+: 305
17	17	ESI-: 476
18	18	ESI+: 262
19	19	ESI+: 502
20	20	ESI+: 327
21	21	ESI+: 431
22	22	ESI+: 299 [M-OMe]+
23	23	ESI+: 473
24	24	ESI+: 688
25	25	ESI+: 355
26	26	ESI+: 413
27	27	ESI+: 678
28	28	ESI+: 325
29	29	ESI+: 256
30	30	ESI+: 622
31	31	ESI+: 315
32	32	ESI+: 278
33	33	APCI/ESI+: 606
34	34	ESI+: 343

[0225]

[Table 50]

PEx	PSyn	DAT
35	35	ESI+: 297
36	36	ESI+: 283
37	37	ESI+: 338
38	38	ESI+: 437
39	39	ESI+: 278
40	40	^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 1.23 (3H, d, *J*=6.4 Hz) 1.34 (9H, s) 1.94-2.03 (2H, m) 2.50-2.63 (1H, m) 2.76-3.06 (9H, m) 3.14-3.28 (3H, m) 3.34-3.52 (1H, m) 6.95 (1H, d, *J*=7.5 Hz) 7.06 (1H, s) 7.12 (1H, d, *J*=7.6 Hz)
41	41	APCI/ESI+: 351
42	42	ESI+: 228
43	43	ESI+: 408
44	44	^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 2.75 (1H, dd, *J*=5.5, 2.7 Hz) 3.17 (1H, dd, *J*=5.7, 4.1 Hz) 4.09 (1H, dd, *J*=3.9, 2.7 Hz) 7.06-7.14 (3H, m)
45	45	ESI+: 244
46	46	EI: 214, 216
47	47	ESI+: 238
48	48	ESI+: 269
49	49	ESI+: 485
50	8	ESI+: 572 [M+Na]+
51	9	ESI+: 536
52	16	ESI+: 351
53	11	ESI+: 660
54	8	ESI+: 504
55	9	ESI+: 490
56	11	ESI+: 586
57	9	ESI+: 526
58	16	ESI+: 341
59	11	ESI+: 606
60	17	APCI/ESI-: 516
61	8	ESI+: 544
62	9	APCI/ESI+: 530
63	16	APCI/ESI+: 345
64	11	APCI/ESI+: 610

[0226]

[Table 51]

PEx	PSyn	DAT
65	17	ESI+: 464
66	8	ESI+: 490
67	9	ESI+: 476
68	16	ESI+: 291
69	11	ESI+: 573
70	15	ESI+: 492
71	8	ESI+: 518
72	9	ESI+: 504
73	16	ESI+: 319
74	11	ESI+: 600
75	11	ESI+: 576
76	3	APCI/ESI+: 297
77	4	APCI/ESI+: 279
78	5	APCI/ESI+: 298
79	6	ESI+: 360[M+Na]+
80	6	^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 1.19-1.42 (9H, m) 2.33 (6H, s) 2.93-3.09 (2H, m) 3.60-3.77 (3H, br) 4.40-4.59 (1H, m) 5.00-5.12 (1H, m) 6.72 (2H, d, *J*=9.4 Hz)
81	6	ESI+: 360 [M+Na]+
82	8	ESI+: 552 [M+Na]+
83	8	ESI+: 530
84	8	ESI+: 540
85	8	ESI+: 524
86	8	ESI+: 530
87	8	ESI+: 580 [M+Na]+
88	8	ESI+: 574
89	8	ESI+: 594 [M+Na]+
90	8	ESI+: 663 [M+Na]+
91	8	ESI+: 468
92	8	ESI+: 558
93	8	ESI+: 560 [M+Na]+
94	8	ESI+: 606 [M+Na]+
95	8	ESI+: 580 [M+Na]+
96	8	ESI+: 582 [M+Na]+
97	8	ESI+: 518

[0227]

[Table 52]

PEx	PSyn	DAT
98	8	ESI+: 610 [M+Na]+
99	8	ESI+: 510
100	8	ESI+: 501
101	8	ESI+: 497
102	8	ESI+: 554 [M+Na]+
103	8	ESI+: 554
104	8	ESI+: 558
105	8	ESI+: 536
106	8	ESI+: 536
107	8	ESI+: 554 [M+Na]+
108	8	ESI+: 590 [M+Na]+
109	8	ESI+: 574 [M+Na]+
110	8	ESI+: 540
111	8	ESI+: 592 [M+Na]+
112	8	ESI+: 572 [M+Na]+
113	8	ESI+: 546 [M+Na]+
114	8	ESI+: 554
115	8	ESI+: 542 [M+Na]+
116	8	APCI/ESI+: 508
117	8	ESI+: 542 [M+Na]+
118	9	ESI+: 516
119	9	ESI+: 516
120	9	ESI+: 488
121	9	ESI+: 510
122	9	ESI+: 516
123	9	ESI+: 544
124	9	ESI+: 560
125	9	ESI+: 526, 528
126	9	ESI+: 558
127	9	ESI+: 627
128	9	ESI+: 454
129	9	ESI+: 544
130	9	ESI+: 524
131	9	ESI+: 570
132	9	ESI+: 544

[0228]

[Table 53]

PEx	PSyn	DAT
133	9	ESI+: 546
134	9	ESI+: 504
135	9	ESI+: 574
136	9	APCI/ESI+: 496
137	9	ESI+: 487
138	9	ESI+: 483
139	9	ESI+: 518
140	9	ESI+: 540
141	9	ESI+: 544
142	9	ESI+: 522
143	9	ESI+: 522
144	9	ESI+: 518
145	9	ESI+: 554
146	9	ESI+: 538
147	9	ESI+: 526
148	9	ESI+: 556
149	9	ESI+: 536
150	9	ESI+: 510
151	9	ESI+: 540
152	9	ESI+: 506
153	9	APCI/ESI+: 494
154	9	ESI+: 506
155	11	ESI+: 596
156	11	ESI+: 596
157	11	ESI+: 568
158	11	ESI+: 596
159	11	ESI+: 590
160	11	ESI+: 596
161	11	ESI+: 625
162	11	ESI+: 640
163	11	ESI+: 553
164	11	ESI+: 638
165	11	ESI+: 663
166	11	ESI+: 760
167	11	ESI+: 535

[0229]

[Table 54]

PEx	PSyn	DAT
168	11	ESI+: 682
169	11	ESI+: 769
170	11	ESI+: 626
171	11	ESI+: 637
172	11	ESI+: 638
173	11	ESI+: 624
174	11	ESI+: 740
175	11	ESI+: 700
176	11	ESI+: 604
177	11	ESI+: 651
178	11	ESI+: 625
179	11	ESI+: 596
180	11	ESI+: 627
181	11	ESI+: 610
182	11	ESI+: 609
183	11	ESI+: 584
184	11	ESI+: 655
185	11	ESI+: 605
186	11	ESI+: 628
187	11	APCI/ESI+: 617
188	11	ESI+: 606
189	11	ESI+: 626
190	11	ESI+: 636
191	11	ESI+: 652,654
192	11	ESI+: 645
193	11	ESI+: 576
194	11	ESI+: 567
195	11	ESI+: 563
196	11	APCI/ESI+: 614
197	11	ESI+: 614
198	11	ESI+: 550
199	11	ESI+: 560
200	11	ESI+: 620
201	11	ESI+: 625
202	11	ESI+: 618

[0230]

[Table 55]

PEx	PSyn	DAT
203	11	ESI+: 618
204	11	ESI+: 636
205	11	ESI+: 588
206	11	ESI+: 654
207	11	ESI+: 627
208	11	ESI+: 598
209	11	ESI+: 650
210	11	ESI+: 624
211	11	ESI+: 634
212	11	ESI+: 624
213	11	ESI+: 614
214	11	ESI+: 652
215	11	ESI+: 616
216	11	ESI+: 644
217	11	ESI+: 606
218	11	ESI+: 636
219	11	ESI+: 586
220	11	ESI+: 642
221	11	APCI/ESI+: 590
222	11	ESI+: 678
223	11	ESI+: 639
224	11	ESI+: 630
225	11	ESI+: 615
226	11	ESI+: 645
227	12	CI+: 203, 205
228	12	CI+: 224, 226 (M+)
229	13	ESI+: 426
230	13	ESI+: 440
231	13	ESI+: 418
232	13	ESI+: 440
233	13	APCI/ESI+: 470
234	13	ESI+: 436
235	13	ESI+: 440
236	13	ESI+: 418
237	13	ESI+: 418

[0231]

[Table 56]

PEx	PSyn	DAT
238	13	ESI+: 414
239	13	ESI+: 434
240	13	ESI+: 422
241	13	ESI+: 452
242	13	ESI+: 436
243	14	ESI+: 262
244	14	ESI+: 276
245	14	ESI+: 254
246	14	ESI+: 306
247	14	ESI+: 272
248	14	ESI+: 254
249	14	ESI+: 254
250	14	ESI+: 250
251	14	ESI+: 286
252	14	ESI+: 270
253	14	ESI+: 258
254	14	ESI+: 288
255	14	ESI+: 268
256	14	ESI+: 294 [M+Na]+
257	17	ESI+: 637 [M+Na]+
258	15	ESI-: 530
259	15	ESI+: 556 [M+Na]+
260	15	ESI+: 492
261	15	ESI+: 471
262	15	ESI+: 554 [M+Na]+
263	15	ESI+: 528 [M+Na]+
264	15	ESI+: 564 [M+Na]+
265	15	ESI-: 524
266	15	ESI+: 566 [M+Na]+
267	15	ESI+: 546 [M+Na]+
268	15	ESI+: 520 [M+Na]+
269	15	ESI+: 550 [M+Na]+
270	15	ESI+: 516 [M+Na]+
271	15	ESI+: 494
272	16	ESI+: 331

[0232]

[Table 57]

PEx	PSyn	DAT
273	16	ESI+: 331
274	16	ESI+: 303
275	16	ESI+: 325
276	16	ESI+: 331
277	16	ESI+: 359
278	16	ESI+: 375
279	16	ESI+: 288
280	16	ESI+: 373
281	16	ESI+: 442
282	16	ESI+: 269
283	16	ESI+: 584
284	16	ESI+: 359
285	16	ESI+: 554
286	16	ESI+: 339
287	16	ESI+: 385
288	16	ESI+: 359
289	16	ESI+: 361
290	16	ESI+: 319
291	16	ESI+: 389
292	16	ESI+: 341
293	16	ESI+: 311
294	16	ESI+: 302
295	16	ESI+: 298
296	16	ESI+: 333
297	16	APCI/ESI+: 295
298	16	ESI+: 355
299	16	ESI+: 359
300	16	ESI+: 337
301	16	ESI+: 337
302	16	ESI+: 333
303	16	ESI+: 369
304	16	ESI+: 353
305	16	ESI+: 341
306	16	ESI+: 371
307	16	ESI+: 351

[0233]

[Table 58]

PEx	PSyn	DAT
308	16	ESI+: 325
309	16	ESI+: 355
310	16	ESI+: 321
311	16	APCI/ESI+: 309
312	16	ESI+: 321
313	17	ESI+: 504
314	17	ESI+: 504
315	17	ESI-: 514
316	15	ESI+: 498
317	17	ESI+: 504
318	17	ESI+: 532
319	17	ESI+: 570 [M+Na]+
320	17	ESI-: 544
321	17	ESI+: 442
322	17	ESI+: 554 [M+Na]+
323	17	ESI-: 510
324	17	ESI-: 557
325	17	ESI+: 584 [M+Na]+
326	17	APCI/ESI+: 484
327	17	ESI+: 475
328	17	ESI+: 528 [M+Na]+
329	17	ESI+: 550 [M+Na]+
330	17	ESI+: 532 [M+Na]+
331	17	ESI+: 532 [M+Na]+
332	17	ESI+: 536 [M+Na]+
333	18	ESI+: 276
334	18	ESI+: 276
335	21	ESI+: 431
336	22	ESI+: 331
337	22	ESI+: 536
338	26	ESI+: 311
339	26	ESI+: 374
340	26	ESI+: 318
341	28	ESI+: 388
342	30	ESI+: 578

[0234]

[Table 59]

PEx	PSyn	DAT
343	31	ESI+: 287
344	31	ESI+: 305
345	31	ESI+: 426 [M+Na]+
346	31	ESI+: 427
347	32	^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 1.43 (9H, s) 2.33 (3H, s) 3.22 (1H, dd, *J*=14.4, 6.4 Hz) 3.30 (1H, dd, *J*=14.4, 5.6 Hz) 4.28 (1H, t, *J*=6.2 Hz) 7.02-7.07 (2H, m) 7.11 (1H, d, *J*=7.6 Hz) 7.20-7.27 (1H, m)
348	32	^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 1.34 (9H, s) 2.19 (6H, s) 2.86-3.03 (2H, m) 4.00-4.06 (1H, m) 6.95 (1H, dd, *J*=7.4, 1.6 Hz) 6.98-7.02 (1H, m) 7.09 (1H, d, *J*=7.4 Hz)
349	32	ESI+: 242
350	35	ESI+: 294
351	35	ESI+: 332
352	37	ESI+: 342
353	37	ESI+: 386, 388
354	37	ESI+: 322
355	38	ESI+: 439
356	38	ESI+: 442
357	38	ESI+: 441
358	38	APCI/ESI+: 450
359	38	ESI+: 485, 487
360	38	ESI+: 477
361	38	APCI/ESI+: 447
362	38	ESI+: 421
363	38	APCI/ESI+: 460
364	38	ESI+: 447
365	39	ESI+: 282
366	39	APCI/ESI+: 291
367	39	ESI+: 326, 328
368	39	APCI/ESI+: 288
369	39	ESI+: 262
370	39	ESI+: 301
371	39	ESI+: 288
372	39	ESI+: 326

[0235]

[Table 60]

PEx	PSyn	DAT
373	41	ESI+: 340
374	41	ESI+: 400 [M+Na]+
375	41	APCI/ESI+: 348
376	41	APCI/ESI+: 361
377	41	ESI+: 348
378	43	ESI+: 390
379	46	EI: 214, 216
380	47	ESI+: 659
381	47	ESI+: 238
382	37	ESI+: 326
383	38	ESI+: 425
384	39	ESI+: 266
385	11	ESI+: 593
386	11	ESI+: 534
387	11	ESI+: 664
388	11	ESI+: 603
389	11	APCI/ESI+: 672
390	11	ESI+: 618
391	11	ESI+: 649
392	11	ESI+: 656
393	11	ESI+: 664
394	11	ESI+: 644
395	11	ESI+: 656
396	6	ESI+: 348 [M+Na]+
397	47	ESI+: 226
398	15	ESI+: 504 [M+Na]+
399	15	ESI+: 542 [M+Na]+
400	8	ESI+: 530 [M+Na]+
401	8	ESI+: 622,624 [M+Na]+
402	8	ESI+: 546
403	9	ESI+: 494
404	9	ESI+: 548
405	9	ESI+: 532
406	16	ESI+: 309
407	16	ESI+: 363

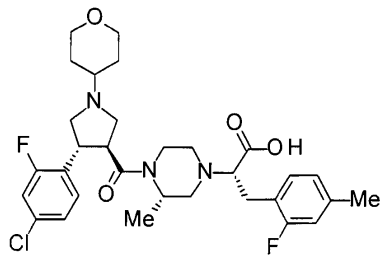
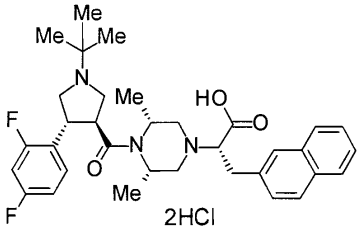
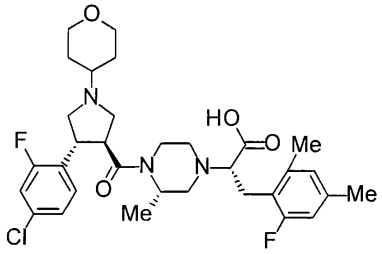
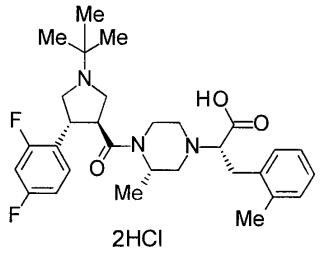
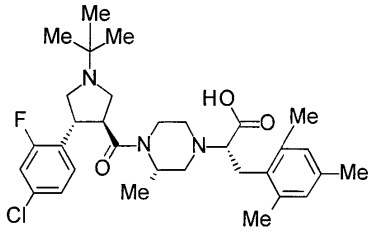
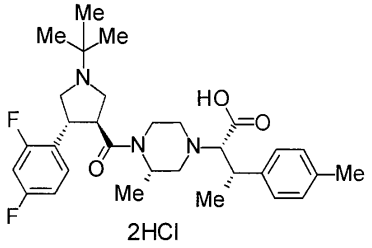
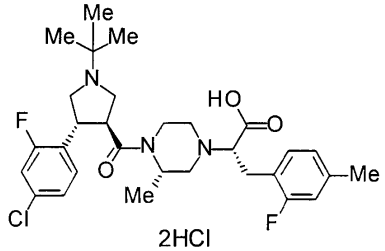
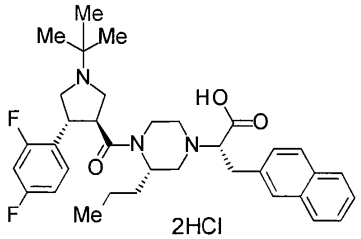
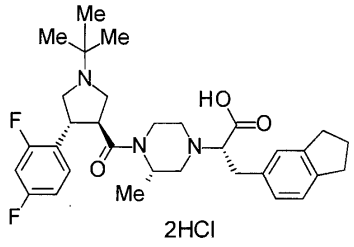
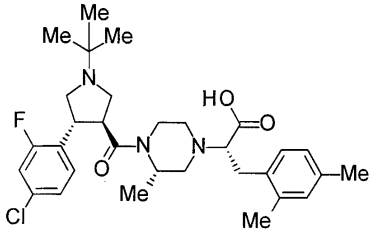
[0236]

[Table 61]

PEx	PSyn	DAT
408	13	ESI+: 482, 484
409	13	ESI+: 428
410	14	ESI+: 318, 320
411	14	ESI+: 264
412	17	ESI+: 596, 598 [M+Na]+
413	19	ESI+: 562
414	10	ESI+: 347
415	7	APCI/ESI+: 482
416	416	ESI+: 300
417	417	ESI+: 558 [M+Na]+
418	37	ESI+: 360
419	38	ESI+: 459
420	9	ESI+: 522
421	16	ESI+: 337

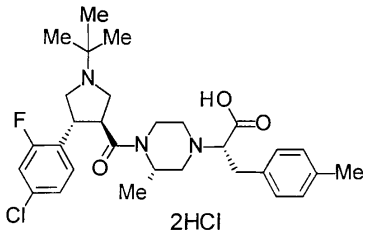
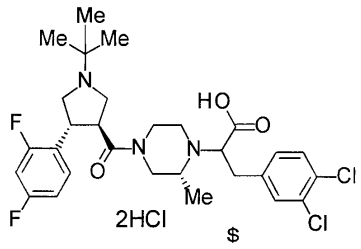
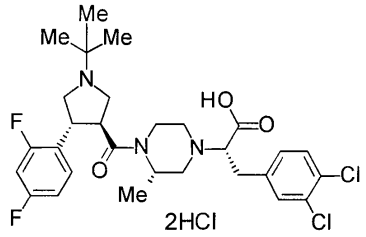
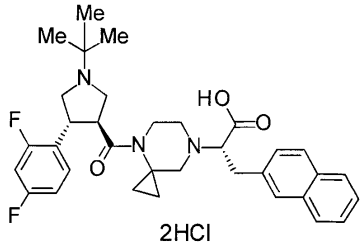
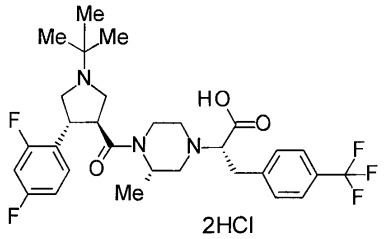
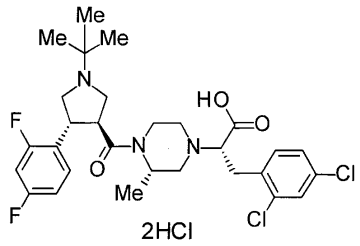
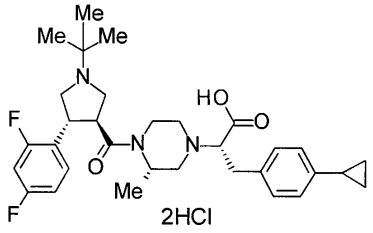
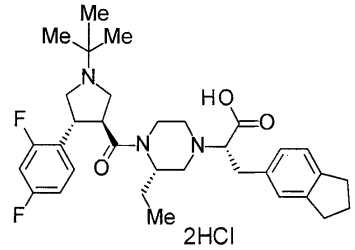
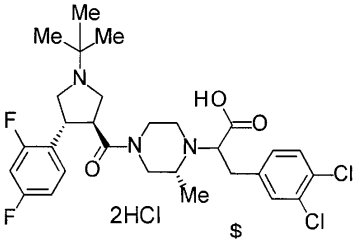
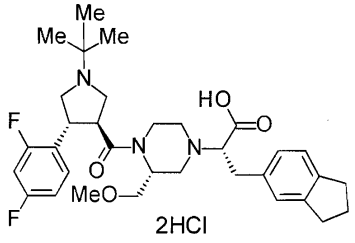
[0237]

[Table 62]

Ex	Str	Ex	Str
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2		7	
3		8	
4		9	
5		10	

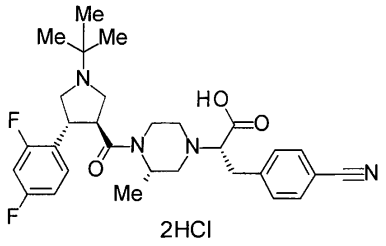
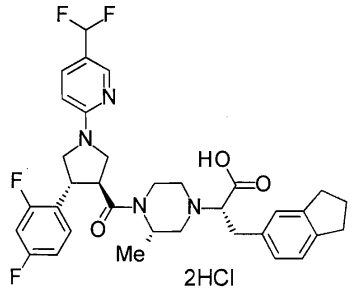
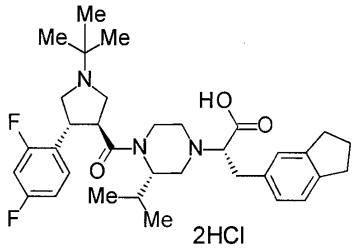
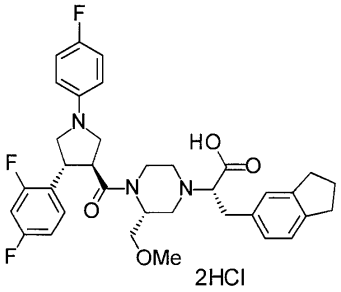
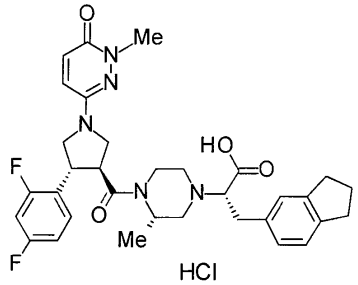
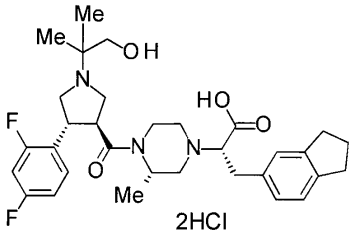
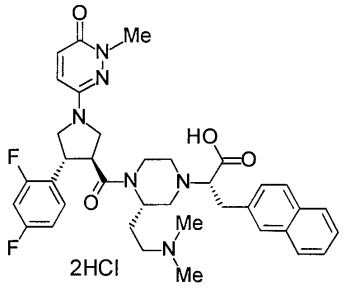
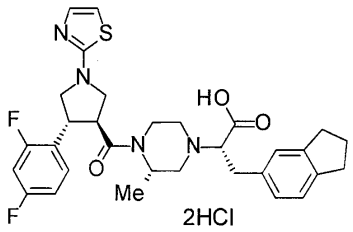
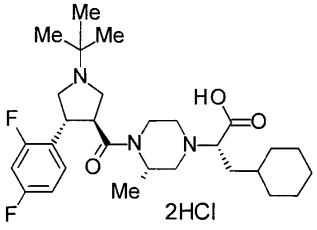
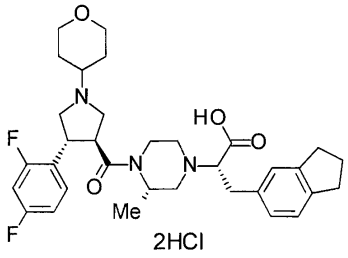
[0238]

[Table 63]

Ex	Str	Ex	Str
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12		17	
13		18	
14		19	
15		20	

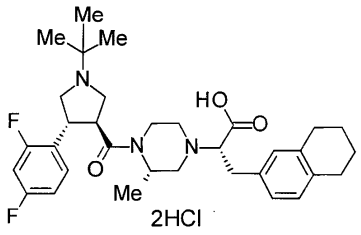
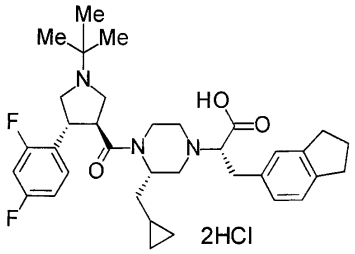
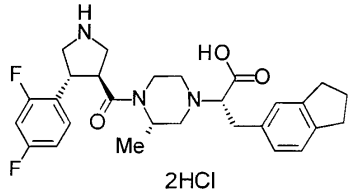
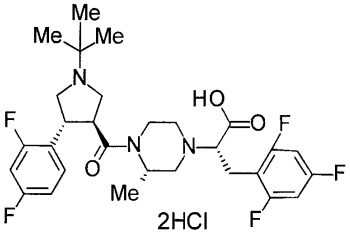
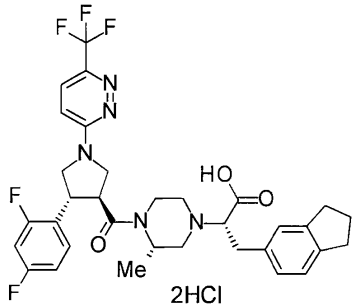
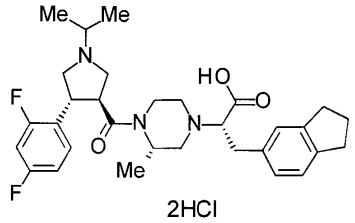
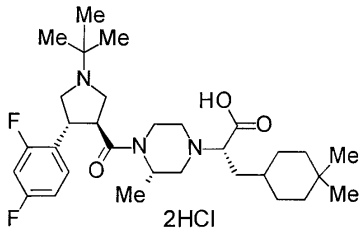
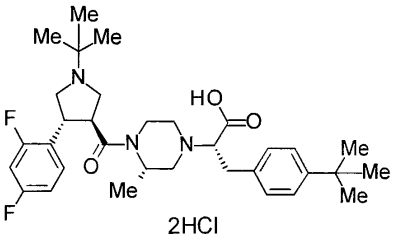
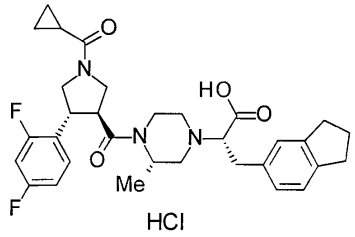
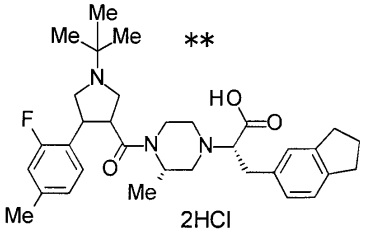
[0239]

[Table 64]

Ex	Str	Ex	Str
21	 2HCl	26	 2HCl
22	 2HCl	27	 2HCl
23	 HCl	28	 2HCl
24	 2HCl	29	 2HCl
25	 2HCl	30	 2HCl

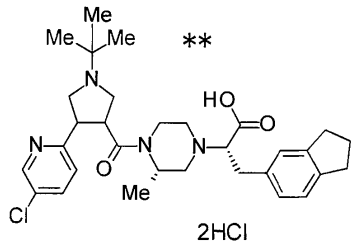
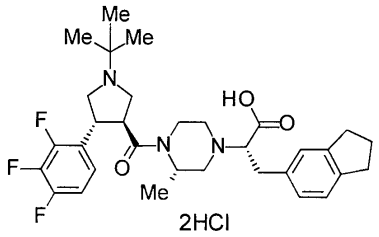
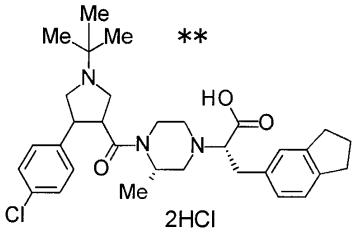
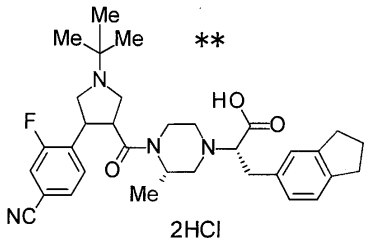
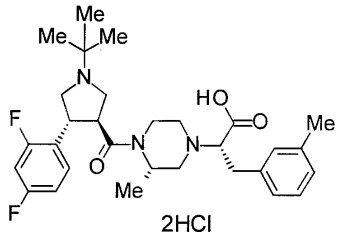
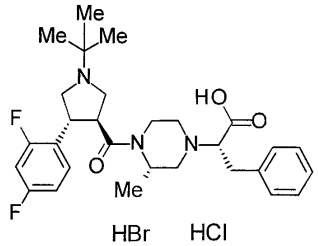
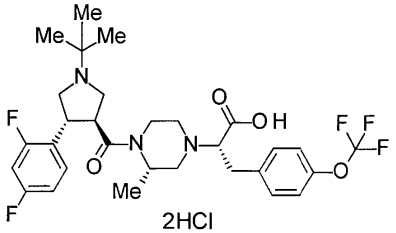
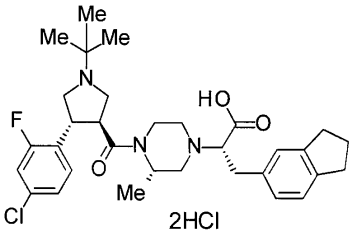
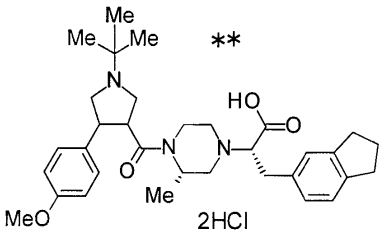
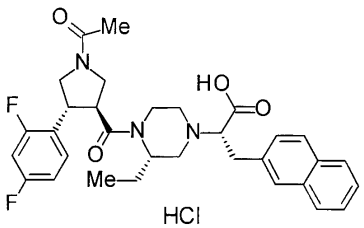
[0240]

[Table 65]

Ex	Str	Ex	Str
31		36	
32		37	
33		38	
34		39	
35		40	

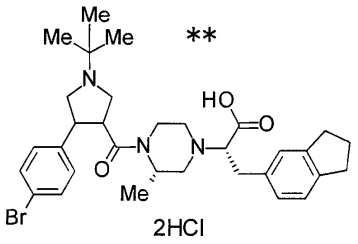
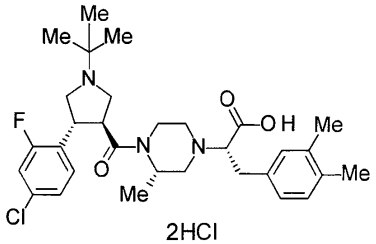
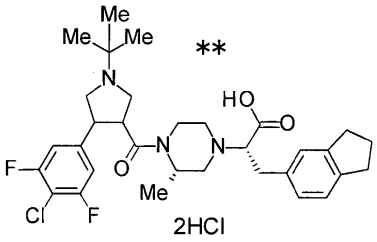
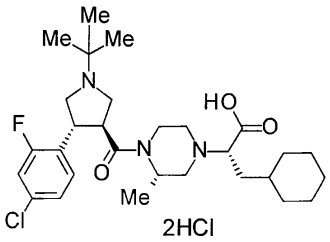
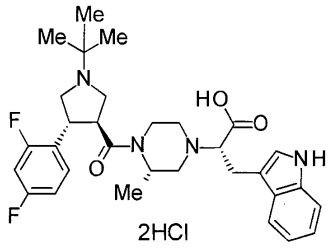
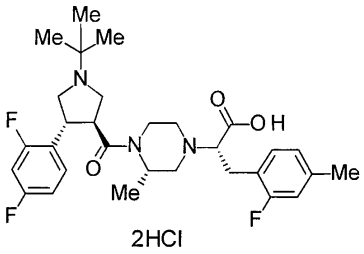
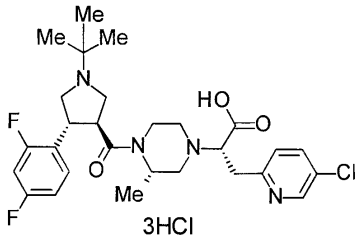
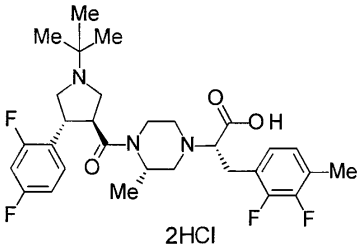
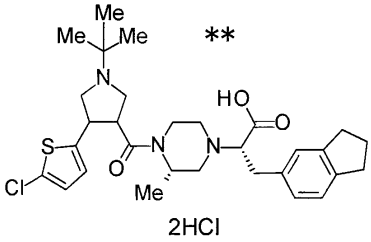
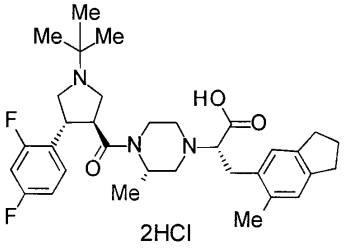
[0241]

[Table 66]

Ex	Str	Ex	Str
41	 2HCl	46	 2HCl
42	 2HCl	47	 2HCl
43	 2HCl	48	 HBr HCl
44	 2HCl	49	 2HCl
45	 2HCl	50	 HCl

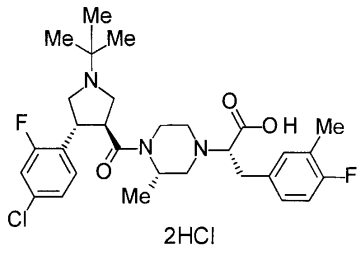
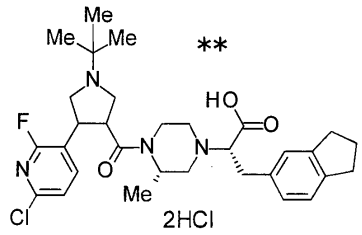
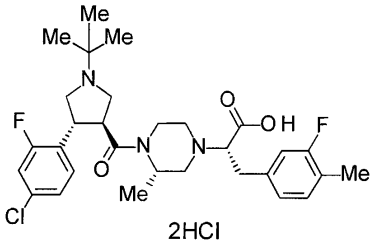
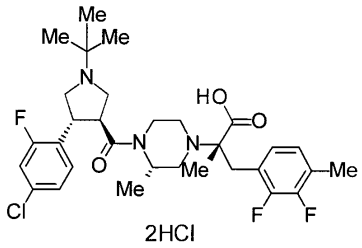
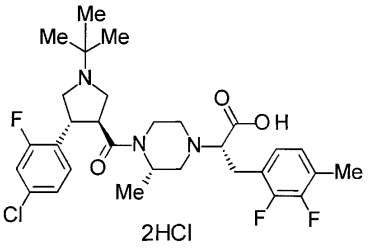
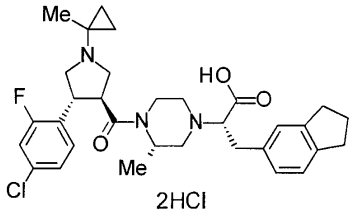
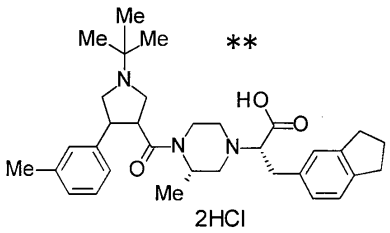
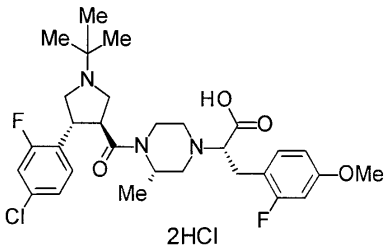
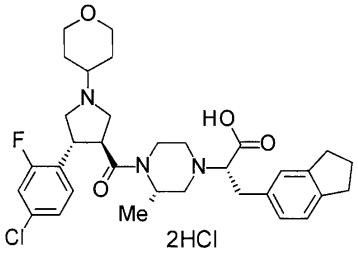
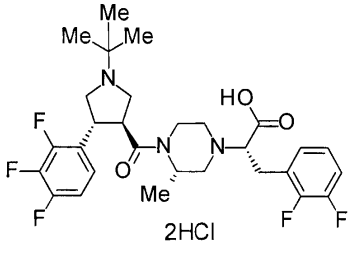
[0242]

[Table 67]

Ex	Str	Ex	Str
51	 2HCl	56	 2HCl
52	 2HCl	57	 2HCl
53	 2HCl	58	 2HCl
54	 3HCl	59	 2HCl
55	 2HCl	60	 2HCl

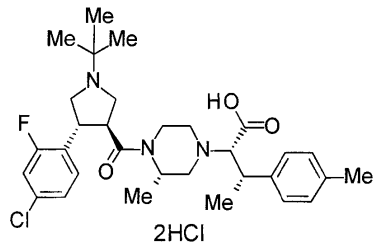
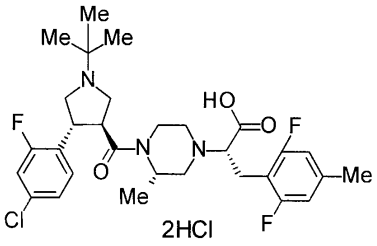
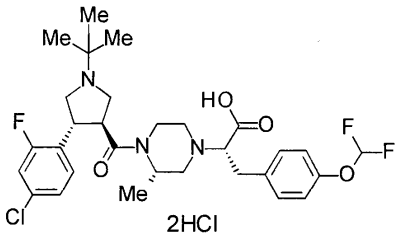
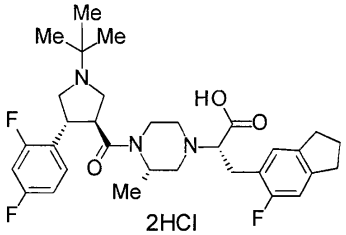
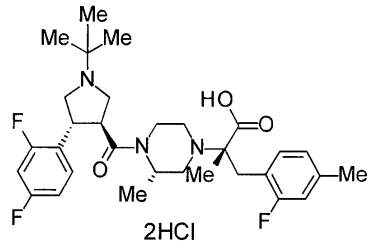
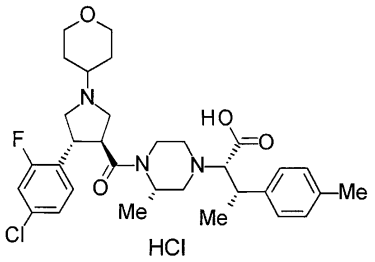
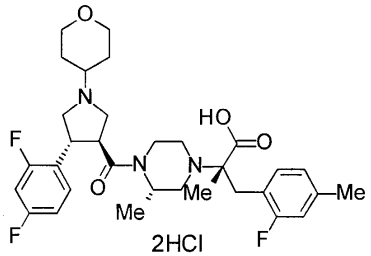
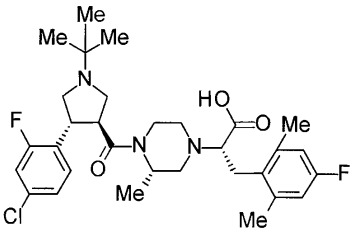
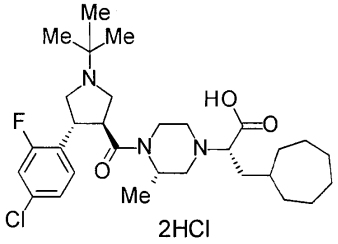
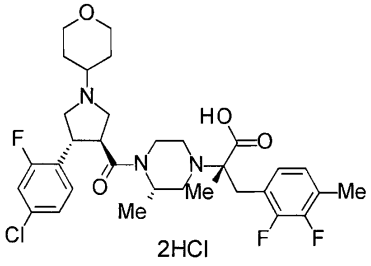
[0243]

[Table 68]

Ex	Str	Ex	Str
61	 2HCl	66	 2HCl
62	 2HCl	67	 2HCl
63	 2HCl	68	 2HCl
64	 2HCl	69	 2HCl
65	 2HCl	70	 2HCl

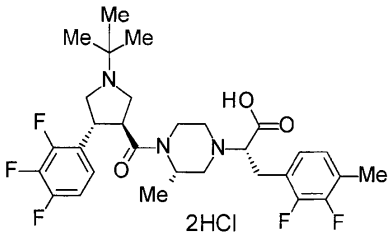
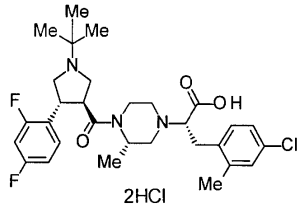
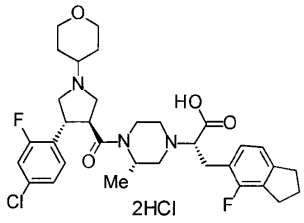
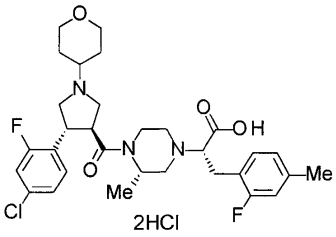
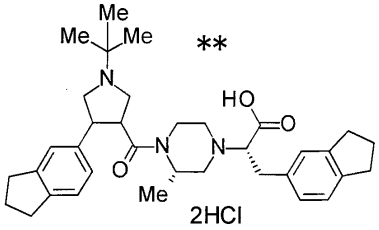
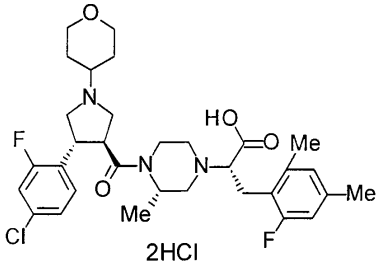
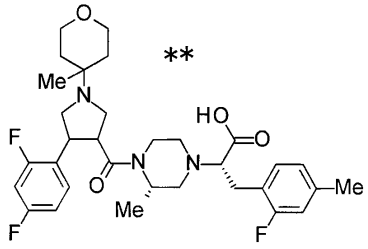
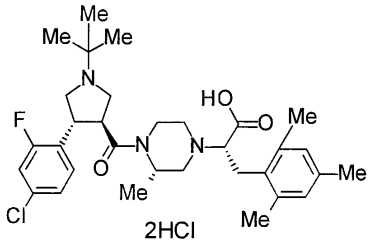
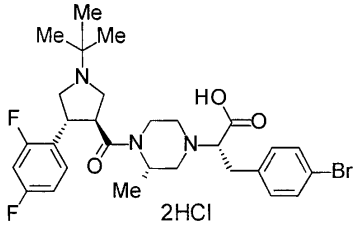
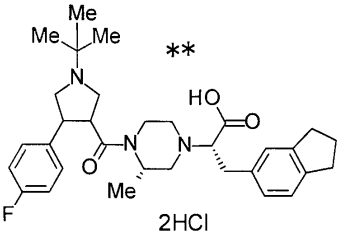
[0244]

[Table 69]

Ex	Str	Ex	Str
71		76	
72		77	
73		78	
74		79	
75		80	

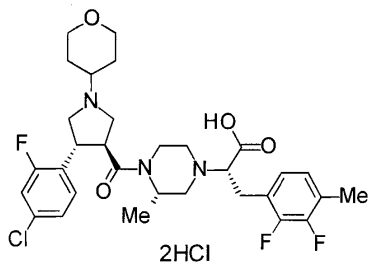
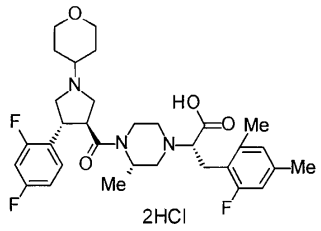
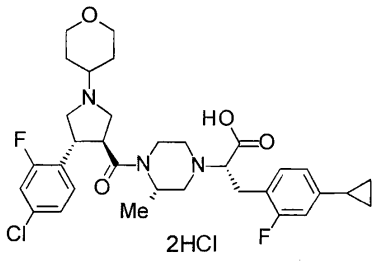
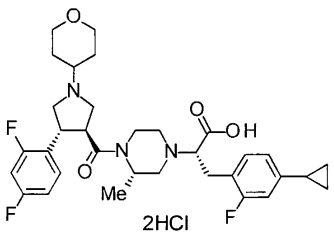
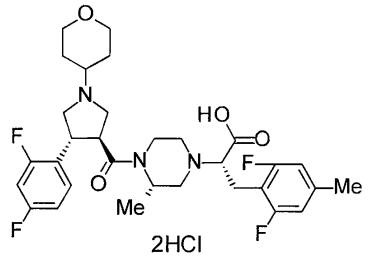
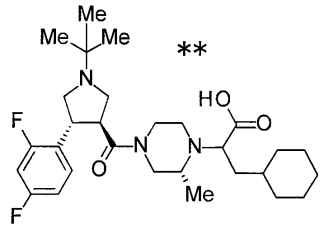
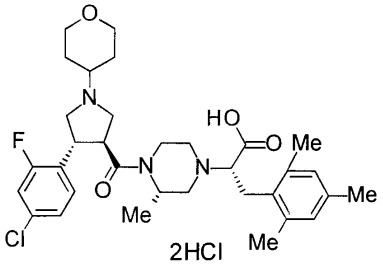
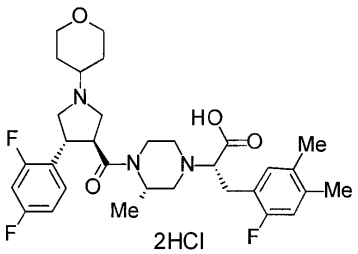
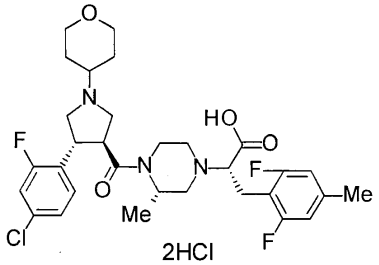
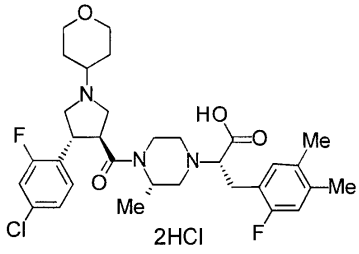
[0245]

[Table 70]

Ex	Str	Ex	Str
81		86	
82		87	
83		88	
84		89	
85		90	

[0246]

[Table 71]

Ex	Str	Ex	Str
91		96	
92		97	
93		98	
94		99	
95		100	

[0247]

[Table 72]

Ex	Syn	DAT
1	1	ESI+: 590 ^{1}H-NMR (500 MHz, pyridine-d5, 90°C) δ ppm 1.10 (3H, d, *J*=6.7 Hz) 1.49-1.63 (2H, m) 1.66-1.75 (2H, m) 2.18 (3H, s) 2.31-2.40 (1H, m) 2.54-2.64 (1H, m) 2.66-2.73 (1 H, m)2.87-3.14 (6H, m) 3.17-3.29 (3H, m) 3.31-3.40 (2H, m) 3.42-3.52 (1H, m) 3.73-3.78 (1H, m) 3.87-3.98 (2H, m) 4.21-4.29 (1H, m) 6.84-6.90 (2H, m) 7.08-7.16 (2H, m) 7.24-7.29 (1H, m) 7.49-7.58 (1H, m) 2θ (°)=9.1, 12.7, 13.7, 14.1, 15.5, 15.9, 18.3, 19.5, 21.7, 28.8
2	2	ESI+: 605 ^{1}H-NMR (500 MHz, pyridine-d5, 90°C) δ ppm 1.09 (3H, d, *J*=6.7 Hz) 1.50-1.63 (2H, m) 1.66-1.75 (2H, m) 2.15 (3H, s) 2.31-2.39 (1H, m) 2.35 (3H, s) 2.58-2.71 (2 H, m) 2.87-3.05 (4H, m) 3.08-3.19 (2H, m) 3.20-3.29 (3H, m) 3.30-3.39 (2H, m) 3.43-3.52 (1H, m) 3.69-3.75 (1H, m) 3.87-3.98 (2H, m) 4.22-4.30 (1H, m) 6.72-6.78 (2H, m) 7.07-7.17 (2H, m) 7.51-7.57 (1H, m) 2θ (°)=8.2, 9.0, 12.6, 13.9, 15.1, 15.9, 18.9, 21.3, 22.9, 28.3
3	3	ESI+: 572 ^{1}H-NMR (500 MHz, pyridine-d5, 90°C) δ ppm 1.08 (9H, s) 1.20 (3H, d, *J*=6.7 Hz) 2.17 (3H, s) 2.40 (6H, s) 2.62-2.70 (1H, m) 2.71-2.76 (1H, m) 2.82-2.88 (1H, m) 2.89 (1H, dd, *J*=8.7, 6.3 Hz) 3.04-3.21 (5H, m) 3.28 (1H, t, *J*=8.2 Hz) 3.37 (1H, dd, *J*=14.3, 7.3 Hz) 3.46-3.54 (1H, m) 3.59 (1H, dd, *J*=7.7, 6.5 Hz) 4.18-4.25 (1H, m) 6.82 (2H, s) 7.08-7.16 (2H, m) 7.53-7.58 (1H, m) 2θ (°)=5.4, 8.5, 10.8, 12.1, 12.6, 13.8, 14.2, 15.6, 17.9, 19.6
4	4	ESI+: 562 ^{1}H-NMR (500 MHz, pyridine-d5, 90°C) δ ppm 0.84-1.15 (3H, brs), 1.40 (9H, m) 2.18 (3H, s) 2.38-2.51 (1H, m) 2.53-2.68 (1 H, m) 2.77-2.90 (1 H, m) 2.91-3.03 (1 H, m) 3.08-3.16 (1H, m) 3.16-3.24 (1H, m) 3.57-3.71 (3H, m) 3.71-3.79 (1H, m) 3.85 (1H, dd, *J*=10.4, 6.4 Hz) 4.25-4.33(1H, m) 4.34-4.46 (1H, m) 6.82-6.88 (2H, m) 7.10-7.23 (3H, m) 8.08-8.18(1H, m)
5	5	ESI+: 554 ^{1}H-NMR (500 MHz, pyridine-d5, 90°C) δ ppm 1.08 (3H, brs) 1.40 (9H, s) 1.84-1.95 (2H, m) 2.38-2.56 (1H, m) 2.59-2.80 (5H, m) 2.80-2.92 (1H, m) 2.93-3.06 (2H, m) 3.20-3.26 (1H, m)3.57-3.78 (4H, m) 3.82-3.91 (1H, m) 4.23-4.33 (1H, m) 4.34-4.45 (1H, m) 6.83-6.97 (2H, m) 7.09-7.14 (2H, m) 7.18 (1H, s) 8.09-8.26 (1H, m)
6	6	ESI+: 578

[0248]

[Table 73]

Ex	Syn	DAT
7	7	ESI+: 528
8	8	ESI+: 542
9	4	ESI+: 592 ^{1}H-NMR (500 MHz, pyridine-d5, 90°C) δ ppm 0.45-1.61 (7H, m) 1.40 (9H, s)2.03-2.69 (2H, m) 2.71-3.12 (3H, m) 3.21 (1H, dd, *J*=14.0, 8.6 Hz) 3.32-3.45 (1H, m) 3.47-3.87 (6H, m) 4.18-4.85 (3H, m) 6.86-6.92 (1H, m) 6.93-6.99 (1H, m) 7.31-7.49 (3H, m) 7.76-7.82 (4H, m) 8.01-8.35 (1H, m)
10	1	ESI+: 558
11	5	ESI+: 544 ^{1}H-NMR (500 MHz, pyridine-d5, 90°C) δ ppm 0.93-1.17 (3H, brs) 1.41 (9H, s) 2.20 (3H, s) 2.39-2.53 (1H, m) 2.58-2.71 (1H, m) 2.80-3.04 (2H, m) 3.00 (1H, dd, *J*=14.1, 7.3 Hz) 3.20 (1H, dd, *J*=14.1, 7.3 Hz) 3.57-3.71 (3H, m) 3.72-3.79 (1H, m) 3.86 (1H, dd, *J*=10.9, 6.4 Hz) 4.25-4.35 (1H, m) 4.35-4.45 (1H, m) 7.03-7.23 (6H, m) 8.08-8.18 (1H, m)
12	4	ESI+: 582
13	4	ESI+: 582
14	4	ESI+: 554
15	6	ESI+: 582
16	4	ESI+: 582
17	4	ESI+: 576
18	4	ESI+: 582
19	5	ESI+: 568
20	5	ESI+: 585
21	4	ESI+: 539
22	5	ESI+: 582
23	5	ESI+: 606
24	4	ESI+: 674
25	4	ESI+: 521
26	5	ESI+: 625
27	5	ESI+: 622
28	5	ESI+: 570
29	5	ESI+: 581
30	5	ESI+: 582

[0249]

[Table 74]

Ex	Syn	DAT
31	5	ESI+: 568
32	5	ESI+: 498
33	5	ESI+: 644
34	5	ESI+: 549
35	5	ESI+: 566
36	5	ESI+: 594
37	5	ESI+: 568
38	5	ESI+: 540
39	5	ESI+: 570
40	5	ESI+: 550
41	5	ESI+: 553
42	5	ESI+: 552
43	5	ESI+: 528
44	5	ESI+: 598
45	5	ESI+: 548
46	5	ESI+: 572
47	5	ESI+: 561
48	7	ESI+: 514
49	5	ESI+: 570
50	4	ESI+: 564
51	5	ESI+: 596, 598
52	5	ESI+: 588
53	4	ESI+: 553
54	4	ESI+: 549
55	5	ESI+: 558
56	5	ESI+: 558
57	4	ESI+: 536
58	4	ESI+: 546
59	5	ESI+: 564
60	5	ESI+: 569
61	5	ESI+: 562
62	5	ESI+: 562
63	5	ESI+: 580
64	5	ESI+: 532
65	5	ESI+: 598

[0250]

[Table 75]

Ex	Syn	DAT
66	5	ESI+: 571
67	5	ESI+: 594
68	5	ESI+: 568
69	5	ESI+: 578
70	5	ESI+: 568
71	8	ESI+: 558
72	5	ESI+: 596
73	5	ESI+: 560
74	5	ESI+: 588
75	5	ESI+: 550
76	5	ESI+: 580
77	4	ESI+: 572
78	8	ESI+: 586
79	1	ESI+: 576
80	5	ESI+: 622
81	5	ESI+: 582
82	4	ESI+: 616
83	5	ESI+: 558
84	2	ESI+: 588
85	4	ESI+: 592, 594
86	4	ESI+: 562
87	87	ESI+: 590 ^{1}H-NMR (500 MHz, pyridine-d5, 90°C) δ ppm 1.07 (3H, d, *J*=6.8 Hz) 1.76-1.90 (4H, m) 2.18 (3H, s) 2.48-2.58 (1H, m) 2.61-2.70 (1H, m) 2.70-2.84 (1H, m) 2.93-3.09 (2H, m) 3.14-3.37 (7H, m) 3.53-3.60 (1H, m) 3.70-3.76 (1H, m) 3.78-3.87 (1H, m) 3.92-3.99 (2H, m) 4.28-4.34 (1H, m) 6.83-6.90 (2H, m) 7.08-7.18 (2H, m) 7.22-7.27 (1H, m) 7.77-7.85 (1H, m)

[0251]

[Table 76]

Ex	Syn	DAT
88	5	ESI+: 604 ^{1}H-NMR (500 MHz, pyridine-d5, 90°C) δ ppm 1.03 (3H, d, *J*=6.1 Hz) 1.82-2.02 (4H, m) 2.15 (3H, s) 2.33 (3H, s) 2.48-2.66 (2H, m) 2.93-3.04 (2H, m) 3.05-3.12 (1H, m) 3.17-3.23 (2H, m) 3.24–3.34 (2H, m) 3.35-3.42 (1H, m) 3.43-3.51 (2H, m) 3.64-3.75 (2H, m) 3.90-3.98 (2H, m) 3.99-4.07 (1H, m) 4.30-4.39 (1H, m) 6.67–6.76 (2H, m) 7.09-7.19 (2H, m) 7.95 (1H, t. *J*=8.2 Hz)
89	87	ESI+: 572 ^{1}H-NMR (500 MHz, pyridine-d5, 90°C) δ ppm 1.01-1.21 (3H, m) 1.40 (9H, s) 2.16 (3H, s) 2.36 (6H, s) 2.49-2.61 (1H, m)2.61-2.73 (1H, m) 2.90-3.08 (3H, m) 3.32 (1H, dd, *J*=14.1, 7.5 Hz) 3.53 (1H, t, *J*=6.8 Hz) 3.58-3.70 (2H, m) 3.70-3.78 (1H, m) 3.86 (1H, dd, *J*=10.7, 6.7 Hz) 4.25-4.35 (1H, m) 4.35-4.46 (1H, m) 6.80 (2H, s) 7.11-7.21 (2H, m) 8.11-8.19 (1H, m)
90	5	ESI+: 536
91	5	ESI+: 608
92	5	ESI+: 616
93	5	ESI+: 592
94	5	ESI+: 600
95	5	ESI+: 608
96	5	ESI+: 588
97	5	ESI+: 600
98	3	ESI+: 520
99	4	ESI+: 588
100	4	ESI+: 604

Industrial Applicability

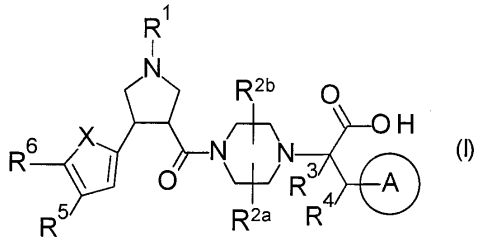
[0252]

The compound of the formula (I) or a salt thereof is a compound having an MC_4 receptor agonistic activity, and can be used as an active ingredient of a pharmaceutical composition for preventing or treating bladder and/or urinary tract diseases, in particular, , underactive bladder, hypotonic bladder, acontractile bladder, detrusor underactivity, neurogenic bladder, urethral relaxation failure, detrusor-external urethral sphincter dyssynergia, and voiding dysfunctions in benign prostatic hyperplasia.

Claims

[Claim 1] A compound of the formula (I) or a salt thereof:

[Chem. 18]



(I)

(In the formula,

R^1 is H, C_{1-6} alkyl which may be substituted with OH, C_{3-8} cycloalkyl which may be substituted with R^{00}, heterocycloalkyl which may be substituted with R^{00}, phenyl which may be substituted with R^{00}, heteroaryl which may be substituted with R^{00}, -CO-C_{1-6} alkyl, or -CO-C_{3-8} cycloalkyl, in which R^{00} represents substituents selected from the group consisting of C_{1-6} alkyl, halogeno-C_{1-6} alkyl, and halogen,

R^{2a} is C_{1-6} alkyl which may be substituted with R^{01}, in which R^{01} represents substituents selected from the group consisting of C_{3-8} cycloalkyl, -O-(C_{1-6} alkyl), -N(C_{1-6} alkyl)$_2$,
-NH(C_{1-6} alkyl), and -NH_2,

R^{2b} is H or C_{1-6} alkyl,

R^{2a} and R^{2b} may be combined with the same carbon atom in the piperazine ring to form C_{3-8} cycloalkyl,

R^3 is H or C_{1-6} alkyl,

R^4 is H or C_{1-6} alkyl,

X is *-CR^7=CR^8-, *-CR^7=N-, *-N=CR^8-, or S, in which * represents a bond with a carbon atom substituted with R^6,

R^5, R^6, and R^7 are the same as or different from each other, and are H, C_{1-6} alkyl, -O-(C_{1-6} alkyl), halogen, or CN,

R^5 and R^6 may be combined with each other to form C_{5-7} cycloalkenyl,

R^8 is H or F, and

the ring A is aryl which may be substituted with R^{02}, C_{5-7} cycloalkenyl-fused phenyl which may be substituted with R^{02}, heteroaryl which may be substituted with R^{02}, or C_{6-8} cycloalkyl which may be substituted with R^{02}, in which R^{02} represents substituents selected from the group consisting of C_{1-6} alkyl, halogeno-C_{1-6} alkyl, C_{3-8} cycloalkyl, -O-(C_{1-6} alkyl), -O-(halogeno-C_{1-6} alkyl), halogen, and -CN.)

[Claim 2] The compound or a salt thereof according to claim 1, wherein

R^1 is

i. tert-butyl which may be substituted with OH,

ii. C_{3-5} cycloalkyl which may be substituted with C_{1-6} alkyl,

iii. 4-tetrahydropyranyl which may be substituted with C_{1-6} alkyl,

iv. phenyl which may be substituted with halogen,

v. heteroaryl which may be substituted with substituents selected from the group consisting of C_{1-6} alkyl and halogeno-C_{1-6} alkyl,

vi. -CO-C_{1-6} alkyl, or

vii. -CO-C_{3-5} cycloalkyl,

R^{2a} is C_{1-6} alkyl which may be substituted with R^{03}, in which R^{03} represents substituents selected from the group consisting of C_{3-5} cycloalkyl, -O-(C_{1-6} alkyl), and -N(C_{1-6} alkyl)$_2$,

R^{2b} is H or C_{1-6} alkyl,

R^5, R^6, and R^7 are the same as or different from each other, and are H, C_{1-6} alkyl, or halogen, and

the ring A is

i. aryl which may be substituted with substituents selected from the group consisting of C_{1-6} alkyl, halogeno-C_{1-6} alkyl, C_{3-5} cycloalkyl, -O-(C_{1-6} alkyl), -O-(halogeno-C_{1-6} alkyl), halogen, and -CN,

ii. C_{5-7} cycloalkenyl-fused phenyl which may be substituted with substituents selected from the group consisting of C_{1-6} alkyl and halogen,

iii. heteroaryl which may be substituted with halogen, or

iv. C_{6-8} cycloalkyl which may be substituted with C_{1-6} alkyl.

[Claim 3] The compound or a salt thereof according to claim 2, wherein

R^1 is

i. tert-butyl,

ii. 4-tetrahydropyranyl,

iii. pyridyl which may be substituted with halogeno-C_{1-6} alkyl, or

iv. 1,6-dihydro-6-oxopyridazinyl which may be substituted with C_{1-6} alkyl,

R^{2a} is C_{1-6} alkyl,

R^{2b} is H,

R^3 is H or methyl,

R^4 is H or methyl,

X is *-CR^7=CR^8-, or *-N=CR^8-,

R^5 is H or halogen,

R^6 is halogen,

R^7 is H or halogen,

R^8 is F, and

the ring A is

i. phenyl which may be substituted with substituents selected from the group consisting of C_{1-6} alkyl, C_{3-5} cycloalkyl and halogen,

ii. naphthyl,

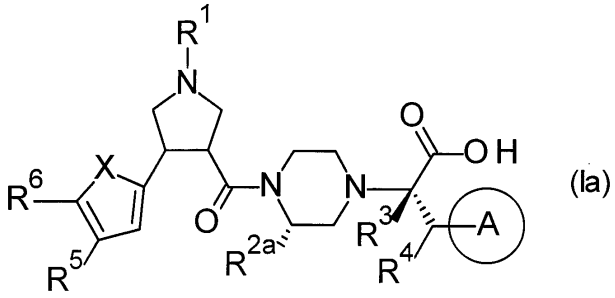
iii. 2,3-dihydro-1H-inden-5-yl which may be substituted with substituents selected from the group consisting of C_{1-6} alkyl and halogen,

iv. cyclohexyl which may be substituted with C_{1-6} alkyl, or

v. cycloheptyl which may be substituted with C_{1-6} alkyl.

[Claim 4] The compound or a salt thereof according to claim 3, wherein the formula (I) is the following formula (Ia):

[Chem. 19]



R^1 is

i. tert-butyl,

ii. 4-tetrahydropyranyl,

iii. pyridyl which may be substituted with difluoromethyl, or

iv. 1,6-dihydro-6-oxopyridazinyl which may be substituted with methyl,

R^{2a} is methyl, ethyl, or n-propyl,

X is *-CR^7=CR^8-,

R^5 is H,

R^6 is F or Cl,

R^7 is H, and

the ring A is

i. phenyl which may be substituted with substituents selected from the group consisting of C_{1-6} alkyl, C_{3-5} cycloalkyl, and halogen,

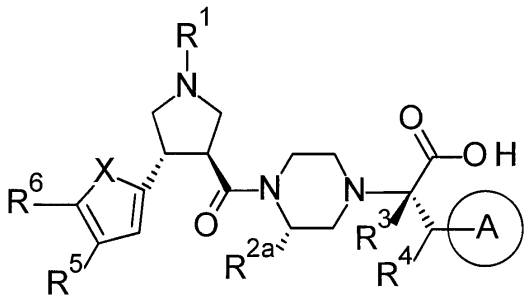
ii. naphthyl,

iii. 2,3-dihydro-1H-inden-5-yl which may be substituted with substituents selected from the group consisting of C_{1-6} alkyl and halogen, or

iv. cyclohexyl which may be substituted with C_{1-6} alkyl.

[Claim 5] The compound or a salt thereof according to claim 4, wherein the formula (Ia) is the following formula (Ib):

[Chem. 20]



(Ib)

R^1 is

i. tert-butyl or

ii. 4-tetrahydropyranyl,

R^3 is H,

R^4 is H, and

the ring A is

i. phenyl which may be substituted with substituents selected from the group consisting of C_{1-6} alkyl and halogen,

ii. naphthyl, or

iii. 2,3-dihydro-1H-inden-5-yl.

[Claim 6]

The compound or a salt thereof according to claim 1, wherein the compound is a compound selected from the group consisting of:

(2S)-2-[(3S)-4-{[(3S,4R)-4-(4-chloro-2-fluorophenyl)-1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-(2-fluoro-4-methylphenyl)propanoic acid,

(2S)-2-[(3S)-4-{[(3S,4R)-4-(4-chloro-2-fluorophenyl)-1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-(2-fluoro-4,6-dimethylphenyl)propanoic acid,

(2S)-2-[(3S)-4-{[(3S,4R)-1-tert-butyl-4-(4-chloro-2-fluorophenyl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-mesitylpropanoic acid,

(2S)-2-[(3S)-4-{[(3S,4R)-1-tert-butyl-4-(4-chloro-2-fluorophenyl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-(2-fluoro-4-methylphenyl)propanoic acid,

(2S)-2-[(3S)-4-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-(2,3-dihydro-1H-inden-5-yl)propanoic acid,

(2S)-2-[(3S)-4-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}-3-propylpiperazin-1-yl]-3-(2-naphthyl)propanoic acid, and

(2S)-2-[(3S)-4-{[(3S,4R)-1-tert-butyl-4-(4-chloro-2-fluorophenyl)pyrrolidin-3-yl]carbonyl}-3-methylpiperazin-1-yl]-3-(4-methylphenyl)propanoic acid.

[Claim 7] A pharmaceutical composition comprising the compound or a salt thereof according to claim 1, and a pharmaceutically acceptable excipient.

[Claim 8] The pharmaceutical composition according to claim 7, for preventing or treating bladder and/or urinary tract diseases.

[Claim 9] Use of the compound or a salt thereof according to claim 1 for the manufacture of a pharmaceutical composition for preventing or treating bladder and/or urinary tract diseases.

[Claim 10] Use of the compound or a salt thereof according to claim 1 for preventing or treating bladder and/or urinary tract diseases.

[Claim 11] The compound or a salt thereof according to claim 1 for preventing or treating bladder and/or urinary tract diseases.

[Claim 12] A method for preventing or treating bladder and/or urinary tract diseases, comprising administering an effective amount of the compound or a salt thereof according to claim 1 to a subject.