DESCRIPTION

Title of Invention: GUANIDINE COMPOUND

Technical Field

[0001]

The present invention relates to a guanidine compound which is useful as an active ingredient of a pharmaceutical composition, in particular, a pharmaceutical composition for preventing and/or treating vascular adhesion protein-1 (hereinafter abbreviated as VAP-1)-related diseases.

Background Art

[0002]

VAP-1 is an amine oxidase (semicarbazide-sensitive amine oxidase, SSAO) which is abundant in human plasma (Non-Patent Document 1), and shows remarkably increased expression in vascular endothelium and vascular smooth muscle of inflammatory regions. While the physiological role of VAP-1 has not been clarified until recently, VAP-1 gene was cloned in 1998, and VAP-1 has been reported to be a membrane protein that regulates rolling and migration of lymphocytes and NK cells as an adhesion molecule under regulation of expression by inflammatory cytokines. Although the amine acting as a substrate is unknown, it is considered to be methylamine generated in any part of a living body. It is also known that hydrogen peroxide and aldehydes produced due to the amine oxidase activity in the molecule are important factors of adhesion activity.

[0003]

A recent report has demonstrated that the VAP-1 enzyme activity in plasma increases in patients with diabetes mellitus, whether type I or type II, and the increase is particularly remarkable in patients with diabetes mellitus suffering from retinopathy complications (Non-Patent Documents 2 and 3).

[0004]

In addition, it has been reported that VAP-1 is related to the following diseases:

(1) cirrhosis, essential stabilized hypertension, diabetes mellitus, and arthrosis (Patent Documents 1 and 2);

(2) endothelium damage (in diabetes mellitus, arterosclerosis, and hypertension), cardiovascular diseases related to diabetes mellitus and uremia, pain related to gout and arthritis, and retinopathy (in diabetes mellitus patients) (Patent Document 3);

(3) inflammatory diseases or conditions (of connective tissue) (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and osteoarthritis or degenerative joint disease, Reiter's syndrome, Sjogren's syndrome, Behcet's syndrome, relapsing

polychondritis, systemic lupus erythematosus, discoid lupus erythematosus, systemic sclerosis, eosinophilic fasciitis, polymyositis, dermatomyositis, polymyalgia rheumatica, vasculitis, temporal arteritis, polyarteritis nodosa, Wegener's granulomatosis, mixed connective tissue disease, and juvenile rheumatoid arthritis); gastrointestinal inflammatory diseases or conditions [Crohn's disease, ulcerative colitis, irritable bowel syndrome (spastic colon), fibrotic conditions of the liver, inflammation of the oral mucosa (stomatitis), and recurrent aphtous stomatitis]; central nervous system inflammatory diseases or conditions (multiple sclerosis, Alzheimer's disease, and ischemia-reperfusion injury related to ischemic stroke); pulmonary inflammatory diseases or conditions (asthma, adult respiratory distress syndrome, and chronic obstructive pulmonary disease); (chronic) skin inflammatory diseases or conditions (psoriasis, allergic lesions, lichen planus, pityriasis rosea, contact dermatitis, atopic dermatitis, and pityriasis rubra pilaris); diseases related to carbohydrate metabolism (diabetes mellitus and complications from diabetes mellitus) including microvascular and macrovascular diseases (arterosclerosis, vascular retinopathies, retinopathy, nephropathy, nephrotic syndrome and neuropathy (polyneuropathy, mononeuropathies and autonomic neuropathy), foot ulcers, joint problems, and increased risk of infection); diseases related to aberrations in adipocyte differentiation or function or smooth muscle cell function (arterosclerosis and obesity); vascular diseases [atheromatous arterosclerosis, nonatheromatous arterosclerosis, ischemic heart disease including myocardial infarction and peripheral arterial occlusion, Raynaud's disease and phenomenon, and thromboangiitis obliterans (Buerger's disease)]; chronic arthritis; inflammatory bowel diseases; and skin dermatoses (Patent Documents 4, 5, and 6, and Non-Patent Documents 4 and 5);

(4) diabetes mellitus (Patent Document 7);

(5) SSAO-mediated complications [diabetes mellitus (insulin dependent diabetes mellitus (IDDM) and non-insulin dependent diabetes mellitus (NIDDM)) and vascular complications (heart attack, angina, strokes, amputations, blindness, and renal insufficiency)], and macular edema (for example, diabetic and non-diabetic macular edema) (Patent Documents 8 and 9); and

(6) hepatitis, transplantation, and the like.

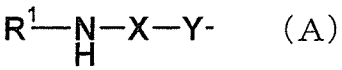
[0005]

Accordingly, the compounds acting on a VAP-1 enzyme may be used as an agent for preventing and/or treating the above-described diseases.

[0006]

On the other hand, in Patent Document 9, it is disclosed that a compound represented by the formula (A) has a VAP-1 inhibitory activity.

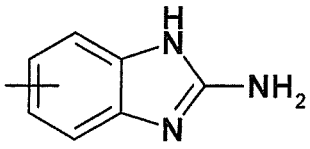
[Chem. 19]



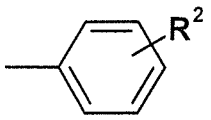
(A)

(wherein Z represents

[Chem. 20]



or

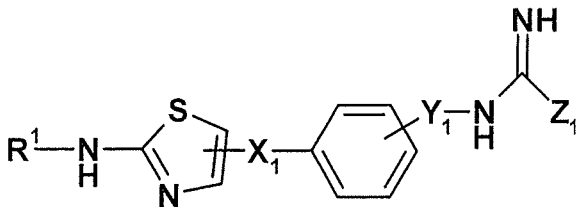


For the other symbols in the formula, refer to the corresponding patent publications)

[0007]

Further, in Patent Document 10, it is disclosed that a compound represented by the formula (B) has a VAP-1 inhibitory activity.

[Chem. 21]



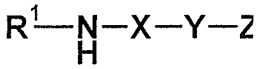
(B)

(For the symbols in the formula, refer to the corresponding patent publications)

[0008]

In Patent Document 11, it is disclosed that a compound represented by the formula (C) has a VAP-1 inhibitory activity and is effective in applications for treatment of VAP-1-related diseases, in particular, macular edema.

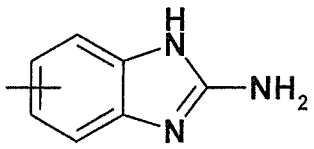
[Chem. 22]



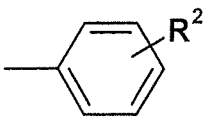
(C)

(wherein Z represents

[Chem. 23]



or

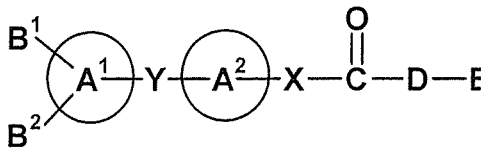


For the other symbols in the formula, refer to the corresponding patent publications)

[0009]

In addition, in Patent Document 12, it is disclosed that a compound represented by the formula (D) has a VAP-1 inhibitory activity.

[Chem. 24]



(D)

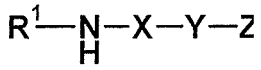
(wherein

D represents $-NR^3$ and E represents amino which may be substituted (optionally substituted amino), for the other symbols, refer to the corresponding patent publications)

[0010]

In Patent Document 13, it is disclosed that a compound represented by the formula (E) has a VAP-1 inhibitory activity.

[Chem. 25]



(E)

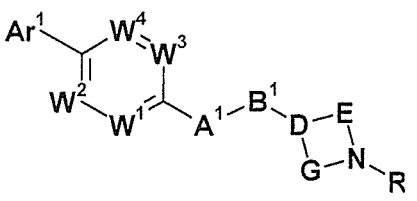
(wherein

X represents a divalent residue derived from thiazole which may be substituted (divalent residue derived from optionally substituted thiazole),

Z represents A-B-D-E, A represents a divalent residue derived from benzene which may be substituted (divalent residue derived from optionally substituted benzene) or a divalent residue derived from thiophene which may be substituted (divalent residue derived from optionally substituted thiophene), B represents $-(CH_2)_l-NR^2-CO-$, D represents $-NR^3$, and E represents amino which may be substituted (optionally substituted amino), for the other symbols, refer to the corresponding patent publications)

In Patent Document 14, it is disclosed that a compound represented by the formula (F) has a GPR119 agonistic activity, and is thus useful for, for example, treatment of diabetes mellitus or the like.

[Chem. 26]

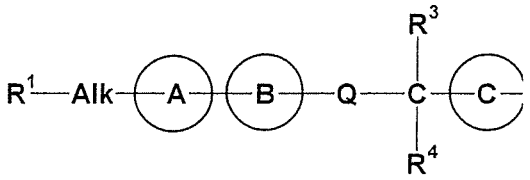


(F)

(For the symbols in the formula, refer to the corresponding patent publications)

In Patent Document 15, it is disclosed that a compound represented by the formula (G) has a GPR119 agonistic activity, and is thus useful for, for example, treatment of diabetes mellitus or the like.

[Chem. 27]

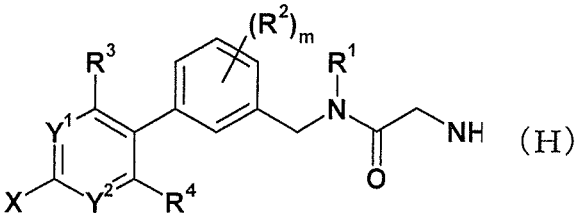


(G)

(For the symbols in the formula, refer to the corresponding patent publications)

In Patent Document 16, which is a patent application published after the filing date of the application which forms the basis of the priority of the present application, it is disclosed that a compound represented by the formula (H) has a VAP-1 activity.

[Chem. 28]



(H)

Related Art

Patent Document

[0011]

Patent Document 1: JP-A-61-239891

Patent Document 2: U. S. Patent No. 4,888,283

Patent Document 3: Pamphlet of International Publication WO 93/23023

Patent Document 4: Pamphlet of International Publication WO 02/02090

Patent Document 5: Pamphlet of International Publication WO 02/02541

Patent Document 6: US Patent Application Publication No. 2002/0173521

Patent Document 7: Pamphlet of International Publication WO 02/38152

Patent Document 8: Pamphlet of International Publication WO 02/38153

Patent Document 9: Pamphlet of International Publication WO 04/067521

Patent Document 10: Pamphlet of International Publication WO 06/011631

Patent Document 11: Pamphlet of International Publication WO 04/087138

Patent Document 12: Pamphlet of International Publication WO 09/145360

Patent Document 13: Pamphlet of International Publication WO 09/096609

Patent Document 14: Pamphlet of International Publication WO 08/025800

Patent Document 15: Pamphlet of International Publication WO 08/070692

Patent Document 16: Pamphlet of International Publication WO 11/034078

Non-Patent Document

[0012]

Non-Patent Document 1: J Neural Transm, Vol. 114, pp. 747-749, 2007

Non-Patent Document 2: Diabetologia, Vol. 42, pp. 233-237, 1999

Non-Patent Document 3: Diabetic Medicine, Vol. 16, pp. 514-521, 1999

Non-Patent Document 4: Diabetologia, Vol. 40, pp. 1243-1250, 1997

Non-Patent Document 5: J Neural Transm, Vol. 114, pp. 841-843, 2007

Disclosure of Invention

Problems to Be Solved by the Invention

[0013]

The present invention provides a compound which is useful as an active ingredient of a pharmaceutical composition, in particular, a pharmaceutical composition for preventing and/or treating VAP-1-related diseases.

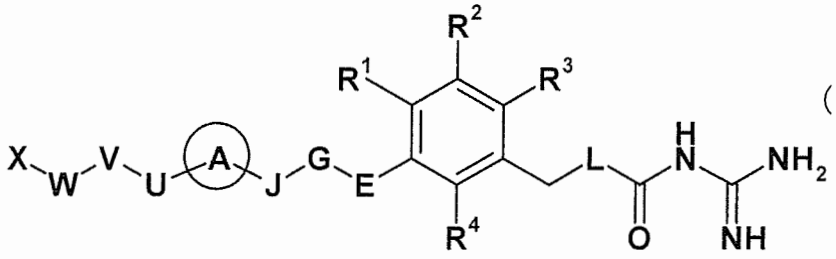
Means for Solving the Problems

[0014]

The present inventors have conducted intensive studies on a compound having a VAP-1 inhibitory activity, and as a result, they have found that a compound of the formula (I) or a salt thereof exhibits an excellent VAP-1 inhibitory activity and is useful for preventing and/or treating VAP-1-related diseases, in particular, diabetic nephropathy or diabetic macular edema, thereby completing the present invention.

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

[Chem. 29]



(I)

(wherein

A is aryl which may be substituted, or a hetero ring group which may be substituted,

R^1, R^2, R^3 and R^4 are the same as or different from each other, and are H, halogen, or lower alkyl which may be substituted,

E is a single bond, or lower alkylene which may be substituted,

G is a single bond, O, NH, or N(lower alkyl which may be substituted),

J is a single bond, or lower alkylene which may be substituted,

L is O, NH, or N(lower alkyl which may be substituted),

U is a single bond, O, NH, N(lower alkyl which may be substituted), SO_2, or lower alkylene which may be substituted,

V is a single bond, O, NH, N(lower alkyl which may be substituted), or lower alkylene which may be substituted,

W is a single bond, SO, SO_2, or lower alkylene which may be substituted,

X is H, OH, NH_2, lower alkyl which may be substituted, O-(lower alkyl which may be substituted), NH(lower alkyl which may be substituted), N(lower alkyl which may be substituted)$_2$, NH-SO_2-(lower alkyl which may be substituted), N(lower alkyl which may be substituted)-SO_2-(lower alkyl which may be substituted), cycloalkyl which may be substituted, O-(cycloalkyl which may be substituted), cycloalkenyl which may be substituted, aryl which may be substituted, O-(aryl which may be substituted), a hetero ring group which may be substituted, or O-(hetero ring group which may be substituted).)

Furthermore, unless specified otherwise, in the case where the symbols of the chemical formulae in the present specification are also used in other chemical formulae, the same symbols denote the same meanings.

[0015]

The present invention relates to a pharmaceutical composition comprising the compound of the formula (I) or a salt thereof, and an excipient.

Furthermore, the present invention relates to a pharmaceutical composition, in particular, a pharmaceutical composition for preventing and/or treating VAP-1-related diseases, which comprises the compound of the formula (I) or a salt thereof, and an excipient.

In addition, 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 and/or treating VAP-1-related diseases, use of the compound of the formula (I) or a salt thereof for preventing and/or treating VAP-1-related diseases, the compound of the formula (I) or a salt thereof for preventing and/or treating VAP-1-related diseases, and a method for preventing and/or treating VAP-1-related diseases, comprising administering to a patient an effective amount of the compound of the formula (I) or a salt thereof.

Effects of the Invention

[0016]

The compound of the formula (I) or a salt thereof has a VAP-1 inhibitory action, and can be used as an agent for preventing and/or treating VAP-1-related diseases.

Further, the VAP-1-related diseases refer to diseases selected from the group consisting of:

(1) cirrhosis, essential stabilized hypertension, diabetes mellitus, and arthrosis;

(2) endothelium damage (in diabetes mellitus, arterosclerosis, and hypertension), cardiovascular diseases related to diabetes mellitus and uremia, pain related to gout and arthritis, and retinopathy (in diabetes mellitus patients);

(3) (connective tissue) inflammatory diseases or conditions (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and osteoarthritis or degenerative joint disease, Reiter's syndrome, Sjogren's syndrome, Behcet's syndrome, relapsing polychondritis, systemic lupus erythematosus, discoid lupus erythematosus, systemic sclerosis, eosinophilic fasciitis, polymyositis, dermatomyositis, polymyalgia rheumatica, vasculitis, temporal arteritis, polyarteritis nodosa, Wegener's granulomatosis, mixed connective tissue disease, and juvenile rheumatoid arthritis); gastrointestinal inflammatory diseases or conditions [Crohn's disease, ulcerative colitis, irritable bowel syndrome (spastic colon), fibrotic conditions of the liver, inflammation of the oral mucosa (stomatitis), and recurrent aphtous stomatitis]; central nervous system inflammatory diseases or conditions (multiple sclerosis, Alzheimer's disease, and ischemia-reperfusion injury related to ischemic stroke); pulmonary inflammatory diseases or conditions (asthma, adult respiratory distress syndrome, and chronic obstructive pulmonary disease); (chronic) skin inflammatory diseases or conditions (psoriasis, allergic lesions, lichen planus, pityriasis rosea, contact dermatitis, atopic dermatitis, and pityriasis rubra pilaris); diseases related to carbohydrate metabolism (diabetes mellitus and complications from diabetes mellitus) including microvascular and macrovascular diseases (arterosclerosis, vascular retinopathies, retinopathy, nephropathy, nephrotic syndrome and neuropathy (polyneuropathy, mononeuropathies and autonomic neuropathy), foot ulcers, joint problems, and increased risk of infection); diseases related to aberrations in adipocyte differentiation or function or smooth muscle cell function (arterosclerosis and obesity); vascular diseases [atheromatous arterosclerosis, nonatheromatous arterosclerosis, ischemic heart disease including myocardial infarction and peripheral arterial occlusion, Raynaud's disease and phenomenon, and thromboangiitis obliterans (Buerger's disease)]; chronic arthritis; inflammatory bowel diseases; and skin dermatoses;

(4) diabetes mellitus;

(5) SSAO-mediated complications [diabetes mellitus (insulin dependent diabetes mellitus (IDDM) and non-insulin dependent diabetes mellitus (NIDDM)) and vascular complications (heart attack, angina, strokes, amputations, blindness, and renal

insufficiency)], macular edema (for example, diabetic and non-diabetic macular edema); and

(6) hepatitis and transplantation.

Embodiments for Carrying Out the Invention

[0017]

Hereinafter, the present invention will be described in detail.

[0018]

In the present specification, the "lower alkyl" refers to linear or branched alkyl having 1 to 6 carbon atoms (which is hereinafter simply referred to as C_{1-6}), for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl, or the like. In another embodiment, it is C_{1-4} alkyl, and in still another embodiment, C_{1-3} alkyl.

[0019]

The "lower alkenyl" refers to linear or branched C_{2-6} alkenyl, for example, vinyl, propenyl, butenyl, pentenyl, 1-methylvinyl, 1-methyl-2-propenyl, 1,3-butadienyl, 1,3-pentadienyl, or the like. In another embodiment, it is C_{2-4} alkenyl, and in still another embodiment, C_{2-3} alkenyl.

[0020]

The "lower alkylene" refers to linear or branched C_{1-6} alkylene, for example, methylene, dimethylene, trimethylene, or the like. In another embodiment, it is C_{1-4} alkylene, and in still another embodiment, C_{1-3} alkylene.

[0021]

The "cycloalkyl" refers to a C_{3-10} saturated hydrocarbon ring group, which may have a bridge. It is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, adamantyl, or the like. In another embodiment, it is C_{3-8} cycloalkyl, and in still another embodiment, C_{3-6} cycloalkyl.

[0022]

The "cycloalkenyl" refers to a C_{3-10} unsaturated hydrocarbon ring group, not including an aromatic hydrocarbon ring group. It is, for example, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, or the like. In another embodiment, it is C_{3-8} cycloalkenyl, and in still another embodiment, C_{3-6} cycloalkenyl.

[0023]

The "aryl" refers to a C_{6-14} monocyclic to tricyclic aromatic hydrocarbon ring group, and includes a ring group fused with C_{5-8} cycloalkene at its double bond site. It is, for example, phenyl, naphthyl, 5-tetrahydronaphthyl, 4-indenyl, 1-fluorenyl, or the like. In another embodiment, it is phenyl.

[0024]

The "hetero ring" means a ring group selected from i) a monocyclic 3- to 8-membered, and in another embodiment, a 5- to 7-membered hetero ring, containing 1 to 4 hetero atoms selected from oxygen, sulfur, and nitrogen, and ii) a bi- to tricyclic hetero ring containing 1 to 5 hetero atoms selected from oxygen, sulfur, and nitrogen, formed by ring-fusion of said monocyclic hetero ring with one or two rings which is selected from the group consisting of a monocyclic hetero ring, a benzene ring, C_{5-8} cycloalkane, and C_{5-8} cycloalkene. The ring atom, sulfur or nitrogen, may be oxidized to form an oxide or a dioxide.

[0025]

Examples of the "hetero ring" group include the following embodiments:

(1) Monocyclic saturated hetero ring groups

(a) those containing 1 to 4 nitrogen atoms, for example, azepanyl, diazepanyl, aziridinyl, azetidinyl, pyrrolidinyl, imidazolidinyl, piperidyl, pyrazolidinyl, piperazinyl, azocanyl, hexamethyleneimino, homopiperazinyl, and the like;

(b) those containing 1 to 3 nitrogen atoms and 1 to 2 sulfur atoms and/or 1 to 2 oxygen atoms, for example, thiomorpholinyl, thiazolidinyl, isothiazolidinyl, oxazolidinyl, morpholinyl, oxazepanyl, and the like;

(c) those containing 1 to 2 sulfur atoms, for example, tetrahydrothiopyranyl and the like;

(d) those containing 1 to 2 sulfur atoms and 1 to 2 oxygen atoms, for example, oxathiolanyl and the like;

(e) those containing 1 to 2 oxygen atoms, for example, oxiranyl, oxetanyl, dixolanyl, tetrahydrofuranyl, tetrahydropyranyl, 1,4-dioxanyl, and the like;

[0026]

(2) Monocyclic unsaturated hetero ring groups

(a) those containing 1 to 4 nitrogen atoms, for example, pyrrolyl, 2-pyrrolinyl, imidazolyl, 2-imidazolinyl, pyrazolyl, 2-pyrazolinyl, pyridyl, dihydropyridyl, tetrahydropyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl, tetrazolyl, triazinyl, dihydrotriazinyl, azepinyl, and the like;

(b) those containing 1 to 3 nitrogen atoms and 1 to 2 sulfur atoms and/or 1 to 2 oxygen atoms, for example, thiazolyl, isothiazolyl, thiadiazolyl, dihydrothiazinyl, oxazolyl, isoxazolyl, oxadiazolyl, oxazinyl, and the like;

(c) those containing 1 to 2 sulfur atoms, for example, thienyl, thiepinyl, dihydrodithiopyranyl, dihydrodithionyl, 2H-thiopyranyl, and the like;

(d) those containing 1 to 2 sulfur atoms and 1 to 2 oxygen atoms, for example, dihydroxathiopyranyl and the like;

(e) those containing 1 to 2 oxygen atoms, for example, furyl, dihydrofuryl, pyranyl, 2H-pyranyl, oxepinyl, dioxolyl, and the like;

[0027]

(3) Fused polycyclic saturated hetero ring groups

(a) those containing 1 to 5 nitrogen atoms, for example, quinuclidinyl, 7-azabicyclo[2.2.1]heptyl, 3-azabicyclo[3.2.2]nonanyl, and the like;

(b) those containing 1 to 4 nitrogen atoms and 1 to 3 sulfur atoms and/or 1 to 3 oxygen atoms, for example, trithiadiazaindenyl, dioxoloimidazolidinyl, and the like;

(c) those containing 1 to 3 sulfur atoms and/or 1 to 3 oxygen atoms, for example, 2,6-dioxabicyclo[3.2.2]oct-7-yl and the like;

[0028]

(4) Fused polycyclic unsaturated hetero ring groups

(a) those containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolinyl, indolidinyl, benzoimidazolyl, dihydrobenzoimidazolyl, tetrahydrobenzoimidazolyl, quinolyl, tetrahydroquinolyl, isoquinolyl, tetrahydroisoquinolyl, indazolyl, imidazopyridyl, dihydroimidazopyridyl, benzotriazolyl, tetrazolopyridazinyl, carbazolyl, acridinyl, quinoxalinyl, dihydroquinoxalinyl, tetrahydroquinoxalinyl, phthalazinyl, dihydroindazolyl, benzopyrimidinyl, naphthyridinyl, quinazolinyl, cinnolinyl, pyridopyrrolidinyl, triazolopiperidinyl, 9,10-dihydroacridine, and the like;

(b) those containing 1 to 4 nitrogen atoms and 1 to 3 sulfur atoms and/or 1 to 3 oxygen atoms, for example, benzothiazolyl, dihydrobenzothiazolyl, benzothiadiazolyl, imidazothiazolyl, imidazothiadiazolyl, benzoxazolyl, dihydrobenzoxazolyl, dihydrobenzoxadinyl, benzoxadiazolyl, benzoisothiazolyl, benzoisoxazolyl, thiazolopiperidinyl, 5,6-dihydro-4H-pyrrolo[3,4-d][1,3]thiazol-2-yl, 10H-phenothiazine, and the like;

(c) those containing 1 to 3 sulfur atoms, for example, benzothienyl, benzodithiopyranyl, chromanyl, dibenzo[b,d]thienyl, and the like;

(d) those containing 1 to 3 sulfur atoms and 1 to 3 oxygen atoms, for example, benzoxathiopyranyl, phenoxazinyl, and the like;

(e) those containing 1 to 3 oxygen atoms, for example, benzodioxolyl, benzofuranyl, dihydrobenzofuranyl, isobenzofuranyl, chromanyl, chromenyl, isochromenyl, dibenzo[b,d]furanyl, methylenedioxyphenyl, ethylenedioxyphenyl, xanthenyl, and the like;

etc.

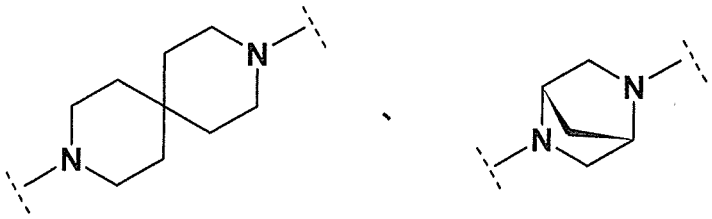
[0029]

Further, the "hetero ring" group in (1) to (4) above is described as a monovalent group, but this may represent a divalent or higher group in some cases.

[0030]

The "hetero ring" group includes a bicyclic hetero ring group having a spiro bond or a hetero ring group having a bridge structure, and it may be, for example, a ring group as shown below.

[Chem. 30]



[0031]

The "monocyclic hetero ring" group refers to a hetero ring group having one ring structure which is not fused with other rings as in (1) and (2), among the "hetero ring" groups above.

[0032]

The "monocyclic saturated hetero ring" group refers to a hetero ring group which is saturated as in (1), among the "monocyclic hetero ring" groups above.

[0033]

The "nitrogen-containing hetero ring" group refers to one containing at least one nitrogen atom, as in (1)(a), (1)(b), (2)(a), (2)(b), (3)(a), (3)(b), (4)(a), (4)(b), and the like, among the "hetero rings" above.

[0034]

The "nitrogen-containing monocyclic hetero ring" group refers to one containing at least one nitrogen atom, as in (1)(a), (1)(b), (2)(a), (2)(b), and the like, among the "monocyclic hetero ring" groups above.

[0035]

The "nitrogen-containing monocyclic unsaturated hetero ring" group refers to an unsaturated hetero ring group, as in (2)(a), (2)(b), and the like, among the "nitrogen-containing monocyclic hetero ring" groups above.

[0036]

The "nitrogen-containing monocyclic saturated hetero ring" group refers to a saturated hetero ring group, as in (1)(a), (1)(b), and the like, among the "nitrogen-containing monocyclic hetero ring" groups above.

[0037]

The "halogen" means F, Cl, Br, or I.

[0038]

In the present specification, the expression "which may be substituted" represents non-substitution or substitution with 1 to 5 substituents". Further, if it has a plurality of substituents, the substituents may be the same as or different from one other.

[0039]

Examples of the acceptable substituent used in the present specification include the groups shown in (a) to (n) below, which may be chemically acceptable groups. Further, in another embodiment, the substituents may be the groups shown in (a) to (m) below.

(a) halogen.

(b) OH, O-(lower alkyl) (in which the lower alkyl may be substituted with OH, COOH, COO-(lower alkyl), O-(lower alkyl), aryl, hetero ring group(s) (in which the hetero ring group may be substituted with OH, cycloalkyl, or lower alkyl which may be substituted with oxo (=O)), or oxo (=O)), O-(hetero ring group), or O-(aryl) (in which the aryl may be substituted with O-(lower alkyl)); in another embodiment, OH, O-(lower alkyl) (in which the lower alkyl may be substituted with COOH, COO-(lower alkyl), O-(lower alkyl), or aryl), or O-(aryl) (in which the aryl may be substituted with O-(lower alkyl)); in still another embodiment, OH, O-(lower alkyl), or O-(aryl); and in further still another embodiment, OH, or O-(lower alkyl).

(c) amino which may be substituted with one or two lower alkyl group(s) (in which the lower alkyl may be substituted with one or more oxo (=O), OH, O-(lower alkyl), or aryl), SO_2-lower alkyl, cycloalkyl, aryl (in which the aryl may be substituted with COOH or COO-(lower alkyl)) or hetero ring group(s), or nitro; in another embodiment, amino which may be substituted with one or two lower alkyl group(s) (in which the lower alkyl may be substituted with one or more oxo (=O), OH, O-(lower alkyl), or aryl), SO_2-lower alkyl, aryl (in which the aryl may be substituted with COOH) or hetero ring group(s), or nitro; in another embodiment, amino which may be substituted with one or two lower alkyl group(s), SO_2-lower alkyl, aryl or hetero ring group(s), or nitro.

(d) CHO, CO-(lower alkyl) (in which the lower alkyl may be substituted with OH, O-(lower alkyl), or oxo (=O)), CO-(cycloalkyl) (in which the cycloalkyl may be substituted with OH), CO-(aryl), CO-(hetero ring group) (in which the hetero ring group may be substituted with O-(lower alkyl)), or cyano; and in another embodiment, CHO, CO-(lower alkyl), CO-(cycloalkyl), CO-(aryl), CO-(hetero ring group), or cyano.

(e) aryl or cycloalkyl; further, this group may be substituted with halogen, OH, COOH, COO-(lower alkyl which may be substituted with aryl), lower alkyl (in which the lower alkyl may be substituted with hetero ring group(s) which may be substituted with oxo (=O), OH, O-(lower alkyl), COOH, COO-(lower alkyl), or oxo (=O)), O-(lower alkyl) (in which the lower alkyl may be substituted with hetero ring group(s)), amino which may be substituted with one or two lower alkyl group(s) (in which the lower alkyl may be

substituted with one or more oxo (=O) group(s)), $NHSO_2$-(lower alkyl), or SO_2-(lower alkyl); and in another embodiment, the group may be substituted with COOH, lower alkyl (in which the lower alkyl may be substituted with hetero ring group(s) which may be substituted with oxo (=O), OH or COOH), O-(lower alkyl) (in which the lower alkyl may be substituted with hetero ring group(s)), amino which may be substituted with one or two lower alkyl group(s) (in which the lower alkyl may be substituted with one or more oxo (=O) group(s)), $NHSO_2$-(lower alkyl), or SO_2-(lower alkyl).

(f) hetero ring group(s); and in another embodiment, monocyclic hetero ring group(s); further, these hetero ring group and monocyclic hetero ring group may be substituted with halogen, OH, oxo (=O), lower alkyl (in which the lower alkyl may be substituted with OH, O-(lower alkyl), or oxo (=O)), O-(lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O)), aryl (in which the aryl may be substituted with halogen or COOH), NHCO-(lower alkyl) or hetero ring group(s) (in which the hetero ring group may be substituted with COOH or O-(lower alkyl)); and in another embodiment, the groups may be substituted with halogen, OH, oxo (=O), lower alkyl (in which the lower alkyl may be substituted with O-(lower alkyl) or oxo (=O)), O-(lower alkyl), aryl (in which the aryl may be substituted with halogen or COOH), NHCO-(lower alkyl) or hetero ring group(s) (in which the hetero ring group may be substituted with COOH, O-(lower alkyl)).

(g) COOH or COO-(lower alkyl); further, the lower alkyl in COO-(lower alkyl) may be substituted with aryl.

(h) $CONH_2$ or CONH(lower alkyl may be substituted with OH), CON(lower alkyl)$_2$; in another embodiment, $CONH_2$, CONH(lower alkyl), or CON(lower alkyl)$_2$.

(i) O-CO-(lower alkyl) or O-COO-(lower alkyl).

(j) oxo (=O).

(k) SO-(lower alkyl) (in which the lower alkyl may be substituted with O-(lower alkyl)), SO-(cycloalkyl), SO-(hetero ring group), SO-(aryl), SO_2-(lower alkyl) (in which the lower alkyl may be substituted with O-(lower alkyl)), SO_2-(cycloalkyl), SO_2-(hetero ring group), SO_2-(aryl), or sulfamoyl which may be substituted with one or two lower alkyl group(s); in another embodiment, SO-(lower alkyl), SO-(cycloalkyl), SO-(hetero ring), SO-(aryl), SO_2-(lower alkyl), SO_2-(cycloalkyl), SO_2-(hetero ring group), SO_2-(aryl), or sulfamoyl which may be substituted with one or two lower alkyl group(s).

(l) SO_2-NH_2, SO_2-NH(lower alkyl), or SO_2-N(lower alkyl)$_2$.

(m) lower alkyl group(s) which may each be substituted with one or more group(s) selected from the substituents shown in (a) to (k) above, or lower alkenyl group(s) which may each be substituted with one or more groups selected from the substituents shown in (a) to (k) above; in another embodiment, lower alkyl group(s) which may be

substituted with one or more group(s) selected from the substituents shown in (a) to (k) above.

(n) lower alkyl group(s) which may each be substituted with one or more group(s) selected from the substituents shown in (a) to (l) above, or lower alkenyl group(s) which may each be substituted with one or more group(s) selected from the substituents shown in (a) to (l) above; in another embodiment, lower alkyl group(s) which may be substituted with one or more group(s) selected from the substituents shown in (a) to (l) above.

[0040]

Examples of the acceptable substituent of the "aryl which may be substituted" and the "hetero ring group which may be substituted" in A include the groups exemplified in (a) to (n) above, in another embodiment, the groups exemplified in (a) to (m) above, in still another embodiment, the groups exemplified in (b), (c), and (m) above, and in further still another embodiment, the groups exemplified in (b) and (c) above.

[0041]

Examples of the acceptable substituent of the "lower alkyl which may be substituted" in R^1, R^2, R^3, and R^4 include the groups exemplified in (a) to (n) above, in another embodiment, the groups exemplified in (a) to (m) above, and in still another embodiment, the groups exemplified in (a) and (m) above.

[0042]

Examples of the acceptable substituent of the "lower alkylene which may be substituted" in E and J include the groups exemplified in (a) to (n) above, in another embodiment, the groups exemplified in (a) to (m) above, and in still another embodiment, the groups exemplified in (j) above.

[0043]

Examples of the acceptable substituent of the "lower alkyl which may be substituted" in G include the groups exemplified in (a) to (n) above, and in another embodiment, the groups exemplified in (a) to (m) above.

[0044]

Examples of the acceptable substituent of the "lower alkyl which may be substituted" in L include the groups exemplified in (a) to (n) above, and in another embodiment, the groups exemplified in (a) to (m) above.

[0045]

Examples of the acceptable substituent of the "lower alkylene which may be substituted" in U, V, and W include the groups exemplified in (a) to (n) above, in another embodiment, the groups exemplified in (a) to (m) above, and in still another embodiment, the groups exemplified in (j) above.

[0046]

Examples of the acceptable substituent of the "lower alkyl which may be substituted" in U and V include the groups exemplified in (a) to (n) above, in another embodiment, the groups exemplified in (a) to (m) above, and in still another embodiment, the groups exemplified in (b) and (c) above.

[0047]

Examples of the acceptable substituent of the "lower alkyl which may be substituted" in X include the groups exemplified in (a) to (n) above, in another embodiment, the groups exemplified in (a) to (m) above, and in still another embodiment, the groups exemplified in (a) above.

[0048]

Examples of the acceptable substituent of the "cycloalkyl which may be substituted" in X include the groups exemplified in (a) to (n) above, in another embodiment, the groups exemplified in (a) to (m) above, and in still another embodiment, the groups exemplified in (b) above.

Examples of the acceptable substituent of the "cycloalkenyl which may be substituted" in X include the groups exemplified in (a) to (n) above, in another embodiment, the groups exemplified in (a) to (m) above, and in still another embodiment, the groups exemplified in (b) above.

[0049]

Examples of the acceptable substituent of the "aryl which may be substituted" in X include the groups exemplified in (a) to (n) above, in another embodiment, the groups exemplified in (a) to (m) above, and in still another embodiment, the groups exemplified in (b), (f), and (l) above.

[0050]

Examples of the acceptable substituent of the "hetero ring group which may be substituted" in X include the groups exemplified in (a) to (n) above, and in another embodiment, the groups exemplified in (a) to (m) above.

[0051]

Examples of the acceptable substituent of the "lower alkyl which may be substituted" in R^{Q11}, R^{Q12}, R^{Q13}, R^{Q21}, R^{Q22}, R^{Q23}, R^{Q31}, R^{Q41}, R^{Q42}, R^{Q43}, R^{Q51}, R^{Q52}, R^{Q53}, and R^{Q61} include the groups exemplified in (a) to (n) above, and in another embodiment, the groups exemplified in (a) to (m) above.

[0052]

Examples of the acceptable substituent of the "lower alkyl which may be substituted" in R^{T11}, R^{T12}, R^{T13}, R^{T21}, R^{T22}, R^{T23}, R^{T31}, R^{T41}, R^{T42}, R^{T43}, R^{T51}, R^{T52}, R^{T53}, R^{T61}, R^{T62}, and R^{T63} include the groups exemplified in (a) to (n) above, in another embodiment, the groups exemplified in (a) to (m) above, and in still another embodiment, the groups exemplified in (b), (c), (e), (f), (g), and (j) above.

[0053]

Examples of the acceptable substituent of the "cycloalkyl which may be substituted" in R^{T11}, R^{T12}, R^{T13}, R^{T21}, R^{T22}, R^{T23}, R^{T31}, R^{T41}, R^{T42}, R^{T43}, R^{T51}, R^{T52}, R^{T53}, R^{T61}, R^{T62}, and R^{T63} include the groups exemplified in (a) to (n) above, in another embodiment, the groups exemplified in (a) to (m) above, and in still another embodiment, the groups exemplified in (m) above.

[0054]

Examples of the acceptable substituent of the "aryl which may be substituted" in R^{T11}, R^{T12}, R^{T13}, R^{T21}, R^{T22}, R^{T23}, R^{T31}, R^{T41}, R^{T42}, R^{T43}, R^{T51}, R^{T52}, R^{T53}, R^{T61}, R^{T62}, and R^{T63} include the groups exemplified in (a) to (n) above, in another embodiment, the groups exemplified in (a) to (m) above, and in still another embodiment, the groups exemplified in (a), (g), and (m) above.

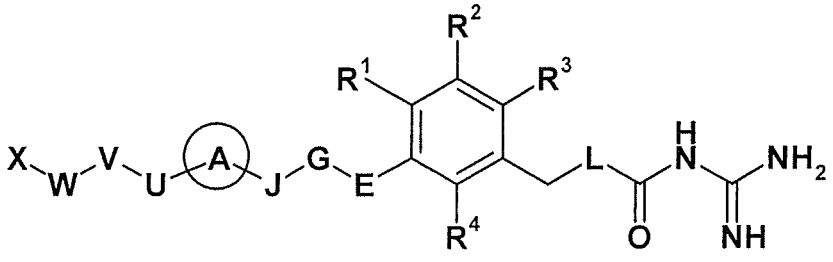
[0055]

Examples of the acceptable substituent of the "hetero ring group which may be substituted" in R^{T11}, R^{T12}, R^{T13}, R^{T21}, R^{T22}, R^{T23}, R^{T31}, R^{T41}, R^{T42}, R^{T43}, R^{T51}, R^{T52}, R^{T53}, R^{T61}, R^{T62}, and R^{T63} include the groups exemplified in (a) to (n) above, in another embodiment, the groups exemplified in (a) to (m) above, and in still another embodiment, the groups exemplified in (a), (b), (d), (g), and (m) above.

[0056]

In another embodiment of the present invention, a compound represented by the formula (I') or a salt thereof is provided.

[Chem. 31]



(I')

(wherein

A is aryl which may be substituted or a hetero ring group which may be substituted,

R^1, R^2, R^3, and R^4 are the same as or different from each other, and are H, halogen, or lower alkyl which may be substituted,

E is a single bond, or lower alkylene which may be substituted,

G is a single bond, O, NH, or N(lower alkyl which may be substituted),

J is a single bond, or lower alkylene which may be substituted,

L is O, NH, or N(lower alkyl which may be substituted),

U is a single bond, O, NH, N(lower alkyl which may be substituted), SO_2, or lower alkylene which may be substituted,

V is a single bond, O, NH, N(lower alkyl which may be substituted), or lower alkylene which may be substituted,

W is a single bond, SO_2, or lower alkylene which may be substituted, and

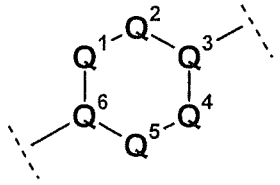
X is H, OH, NH_2, lower alkyl which may be substituted, O-(lower alkyl which may be substituted), NH(lower alkyl which may be substituted), N(lower alkyl which may be substituted)$_2$, cycloalkyl which may be substituted, O-(cycloalkyl which may be substituted), aryl which may be substituted, O-(aryl which may be substituted), a hetero ring group which may be substituted, or O-(hetero ring group which may be substituted)).

[0057]

Embodiments of the groups of the present invention are described below.

(1) A is

[Chem. 32]

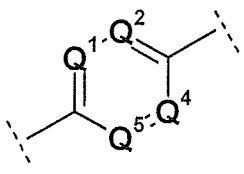


,

Q^1 is a single bond, $CR^{Q11}R^{Q12}$, or NR^{Q13}, Q^2 is $CR^{Q21}R^{Q22}$, or NR^{Q23}, Q^3 is CR^{Q31} or N, Q^4 is $CR^{Q41}R^{Q42}$ or NR^{Q43}, Q^5 is a single bond, $CR^{Q51}R^{Q52}$, or NR^{Q53}, Q^6 is CR^{Q61} or N, R^{Q11}, R^{Q12}, R^{Q13}, R^{Q21}, R^{Q22}, R^{Q23}, R^{Q31}, R^{Q41}, R^{Q42}, R^{Q43}, R^{Q51}, R^{Q52}, R^{Q53} and R^{Q61} are the same as or different from each other, and are H, lower alkyl which may be substituted, or O-(lower alkyl which may be substituted), or R^{Q11} and R^{Q21}, R^{Q11} and R^{Q23}, R^{Q13} and R^{Q21}, R^{Q13} and R^{Q23}, R^{Q13} and R^{Q23}, R^{Q31} and R^{Q41}, R^{Q31} and R^{Q43}, R^{Q51} and R^{Q61}, or R^{Q53} and R^{Q61} may be combined with each other to form a new bond, or R^{Q11} and R^{Q61}, R^{Q13} and R^{Q61}, R^{Q21} and R^{Q31}, R^{Q41} and R^{Q51}, R^{Q43} and R^{Q51}, R^{Q41} and R^{Q53}, or R^{Q43} and R^{Q53} may be combined with each other to form a new bond, or R^{Q11} and R^{Q12}, R^{Q21} and R^{Q22}, R^{Q41} and R^{Q42}, R^{Q51} and R^{Q52} may be combined with each other to form oxo (=O).

(2) A is

[Chem. 33]

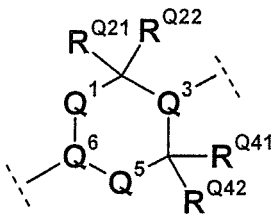


,

Q^1 is CR^{Q12} or N, Q^2 is CR^{Q22} or N, Q^4 is CR^{Q42} or N, Q^5 is CR^{Q52} or N, and R^{Q12}, R^{Q22}, R^{Q42} and R^{Q52} are the same as or different from each other, and are H, lower alkyl which may be substituted, or O-(lower alkyl which may be substituted).

(3) A is

[Chem. 34]



,

Q^1 is a single bond or $CR^{Q11}R^{Q12}$, Q^3 is CR^{Q31} or N, Q^5 is a single bond or $CR^{Q51}R^{Q52}$, Q^6 is CR^{Q61} or N, in which either one of Q^3 and Q^6 is N, R^{Q11}, R^{Q12}, R^{Q21}, R^{Q22}, R^{Q31}, R^{Q41}, R^{Q42}, R^{Q51}, R^{Q52} and R^{Q61} are the same as or different from each other, and are H, lower alkyl which may be substituted, or O-(lower alkyl which may be substituted), or R^{Q51} and R^{Q61} may be combined with each other to form a new bond, or R^{Q11} and R^{Q12}, R^{Q21} and R^{Q22}, R^{Q41} and R^{Q42}, or R^{Q51} and R^{Q52} may be combined with each other to form oxo (=O).

(4) R^{Q12}, R^{Q22}, R^{Q42} and R^{Q52} are H.

(5) R^{Q11}, R^{Q12}, R^{Q21}, R^{Q22}, R^{Q31}, R^{Q41}, R^{Q42}, R^{Q51}, R^{Q52} and R^{Q61} are the same as or different from each other, and are H, or R^{Q51} and R^{Q61} may be combined with each other to form a new bond, or R^{Q11} and R^{Q12} may be combined with each other to form oxo (=O); and in another embodiment, R^{Q11}, R^{Q12}, R^{Q21}, R^{Q22}, R^{Q31}, R^{Q41}, R^{Q42}, R^{Q51}, R^{Q52} and R^{Q61} are H.

(6) Q^1 is N, Q^2 is CR^{Q22}, Q^4 is CR^{Q42}, and Q^5 is N.

(7) Q^1 is CR^{Q12}, Q^2 is CR^{Q22}, Q^4 is CR^{Q42}, and Q^5 is N.

(8) Q^1 is $CR^{Q11}R^{Q12}$, Q^3 is N, Q^5 is $CR^{Q51}R^{Q52}$, and Q^6 is CR^{Q61} or N.

(9) Q^1 is $CR^{Q11}R^{Q12}$, Q^3 is N, Q^5 is $CR^{Q51}R^{Q52}$, and Q^6 is N.

(10) Q^1 is $CR^{Q11}R^{Q12}$, Q^3 is N, Q^5 is $CR^{Q51}R^{Q52}$, and Q^6 is CR^{Q61}.

(11) Q^1 is $CR^{Q11}R^{Q12}$, Q^3 is CR^{Q31}, Q^5 is $CR^{Q51}R^{Q52}$, and Q^6 is N.

(12) Q^1 is a single bond, Q^3 is N, Q^5 is a single bond, and Q^6 is CR^{Q61}.

(13) R^1, R^2, R^3 and R^4 are the same as or different from each other, and are H or halogen; in another embodiment, R^1, R^2 and R^3 are H, and R^4 is halogen; and in still another embodiment, R^1, R^2 and R^3 are H, and R^4 is F.

(14) E is a single bond.

(15) E is lower alkylene which may be substituted with oxo (=O).

(16) G is a single bond.

(17) G is O.

(18) G is NH.

(19) J is a single bond.

(20) J is lower alkylene which may be substituted.

(21) L is O.

(22) L is NH.

(23) U is a single bond.

(24) U is O.

(25) U is NH or N(lower alkyl which may be substituted).

(26) V is a single bond.

(27) V is lower alkylene which may be substituted with oxo (=O).

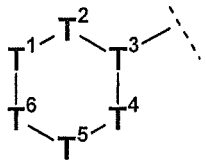
(28) W is a single bond.

(29) W is lower alkylene which may be substituted.

(30) X is H, OH, or NH_2.

(31) X is

[Chem. 35]

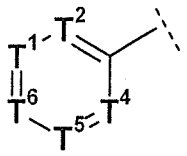


,

T^1 is a single bond, $CR^{T11}R^{T12}$, or NR^{T13}, T^2 is $CR^{T21}R^{T22}$ or NR^{T23}, T^3 is CR^{T31} or N, T^4 is $CR^{T41}R^{T42}$ or NR^{T43}, T^5 is a single bond, $(CR^{T51}R^{T52})_m$, or NR^{T53}, T^6 is $CR^{T61}R^{T62}$, O, or NR^{T63}, R^{T11}, R^{T12}, R^{T13}, R^{T21}, R^{T22}, R^{T23}, R^{T31}, R^{T41}, R^{T42}, R^{T43}, R^{T51}, R^{T52}, R^{T53}, R^{T61}, R^{T62} and R^{T63} are the same as or different from each other, and are H, OH, halogen, lower alkyl which may be substituted, aryl which may be substituted, cycloalkyl which may be substituted, a hetero ring group which may be substituted, O-(lower alkyl which may be substituted), NH(lower alkyl which may be substituted), N(lower alkyl which may be substituted)$_2$, NH(aryl which may be substituted), N(aryl which may be substituted)$_2$, SO_2-(lower alkyl which may be substituted), or SO_2-(cycloalkyl which may be substituted), or R^{T11} and R^{T61}, R^{T11} and R^{T63}, R^{T13} and R^{T61}, R^{T13} and R^{T63}, R^{T21} and R^{T31}, R^{T23} and R^{T31}, R^{T41} and R^{T51}, R^{T43} and R^{T51}, R^{T41} and R^{T53}, or R^{T43} and R^{T53} may be combined with each other to form a new bond, or R^{T11} and R^{T12}, R^{T21} and R^{T22}, R^{T41} and R^{T42}, R^{T51} and R^{T52}, or R^{T61} and R^{T62} may be combined with each other to form oxo (=O), and m is 1 or 2.

(32) X is

[Chem. 36]



,

T^1 is CR^{T12} or N, T^2 is CR^{T22} or N, T^4 is CR^{T42} or N, T^5 is CR^{T52} or N, T^6 is CR^{T62} or N, R^{T12}, R^{T22}, R^{T42}, R^{T52} and R^{T62} are the same as or different from each other, and are H, OH, halogen, lower alkyl which may be substituted, aryl which may be substituted, cycloalkyl which may be substituted, a hetero ring group which may be substituted, -O-(lower alkyl which may be substituted), NH-(lower alkyl which may be substituted), N(lower alkyl which may be substituted)$_2$, NH-(aryl which may be substituted), N(aryl which may be substituted)$_2$, SO_2-(lower alkyl which may be substituted), or SO_2-(cycloalkyl which may be substituted).

(33) R^{T11}, R^{T12}, R^{T21}, R^{T22}, R^{T31}, R^{T41}, R^{T42}, R^{T51} and R^{T52} are the same as or different from each other, and are H, halogen, or lower alkyl which may be substituted; and in another embodiment, R^{T11}, R^{T12}, R^{T21}, R^{T22}, R^{T31}, R^{T41}, R^{T42}, R^{T51} and R^{T52} are H; and in still another embodiment, R^{T11}, R^{T12}, R^{T21}, R^{T22}, R^{T31}, R^{T41}, R^{T42}, R^{T51} and R^{T52} are the same as or different from each other, and are H or OH.

(34) R^{T13}, R^{T23}, R^{T43}, R^{T53} are H.

(35) R^{T12}, R^{T22}, R^{T42} and R^{T52} are the same as or different from each other, and are H, halogen, lower alkyl which may be substituted, or O-(lower alkyl which may be substituted); in another embodiment, R^{T12}, R^{T22}, R^{T42} and R^{T52} are the same as or different from each other, and are H, lower alkyl which may be substituted with O-(lower alkyl), or O-(lower alkyl which may be substituted with O-(lower alkyl)); in still another embodiment, R^{T12}, R^{T22}, R^{T42} and R^{T52} are the same as or different from each other, and are H, methyl, methoxymethyl, or 2-methoxyethoxy; and in further still another embodiment, R^{T12}, R^{T22}, R^{T42} and R^{T52} are H.

(36) R^{T62} is H.

(37) R^{T62} is halogen, OH, lower alkyl which may be substituted, or O-(lower alkyl which may be substituted).

(38) R^{T62} is OH, lower alkyl (in which the lower alkyl may be substituted with O-(lower alkyl) or COOH), or O-(lower alkyl which may be substituted with O-(lower alkyl)).

(39) R^{T63} is CO-(C_{1-5} alkyl which may be substituted), CO-(cycloalkyl which may be substituted), CO-(aryl which may be substituted), CO-(nitrogen-containing monocyclic unsaturated hetero ring group which may be substituted), CON(lower alkyl which may be substituted)$_2$, or SO_2-(lower alkyl which may be substituted); in another embodiment, R^{T63}

is CO-(C_{1-5} alkyl which may be substituted with O-(lower alkyl) or nitrogen-containing monocyclic unsaturated hetero ring(s)), CO-(cycloalkyl), CO-(aryl), CO-(nitrogen-containing monocyclic unsaturated hetero ring group), CON(lower alkyl)$_2$, or SO_2-(lower alkyl); in still another embodiment, R^{T63} is CO-(C_{1-5} alkyl which may be substituted with O-(lower alkyl)), CO-(cycloalkyl), CO-(aryl), CO-(nitrogen-containing monocyclic unsaturated hetero ring group), CON(lower alkyl)$_2$, or SO_2-(lower alkyl); in further still another embodiment, R^{T63} is CO-(C_{1-5} lower alkyl which may be substituted with O-(lower alkyl), CO-(cycloalkyl), or SO_2-(lower alkyl); in further still another embodiment, R^{T63} is acetyl, propionyl, isobutyryl, pivaloyl, 2-ethoxy-1-oxoethyl, 2-methoxy-1-oxoethyl, 3-methoxy-1-oxopropyl, 3-methoxy-2,2-dimethyl-1-oxopropyl, cyclopropylcarbonyl, benzoyl, pyridin-3-ylcarbonyl, dimethylaminocarbonyl, methylsulfonyl, or ethylsulfonyl; in further still another embodiment, R^{T63} is acetyl, propionyl, isobutyryl, pivaloyl, 2-ethoxy-1-oxoethyl, 2-methoxy-1-oxoethyl, 3-methoxy-1-oxopropyl, cyclopropylcarbonyl, benzoyl, pyridin-3-ylcarbonyl, dimethylaminocarbonyl, methylsulfonyl, or ethylsulfonyl; and in further still another embodiment, R^{T63} is acetyl, propionyl, isobutyryl, pivaloyl, 2-ethoxy-1-oxoethyl, cyclopropylcarbonyl, benzoyl, pyridin-3-ylcarbonyl, dimethylaminocarbonyl, or methylsulfonyl.

(40) T^1 is a single bond, $CR^{T11}R^{T12}$, or NR^{T13}, T^2 is $CR^{T21}R^{T22}$, T^3 is CR^{T31} or N, T^4 is $CR^{T41}R^{T42}$, T^5 is a single bond, $(CR^{T51}R^{T52})_m$, or NR^{T53}, T^6 is $CR^{T61}R^{T62}$, O, or NR^{T63}, R^{T21} and R^{T31} may be combined with each other to form a new bond, or R^{T11} and R^{T12} may be combined with each other to form oxo (=O).

(41) T^1 is a single bond or $CR^{T11}R^{T12}$, T^2 is $CR^{T21}R^{T22}$, T^3 is CR^{T31} or N, T^4 is $CR^{T41}R^{T42}$, T^5 is a single bond or $(CR^{T51}R^{T52})_m$, and T^6 is NR^{T63}.

(42) T^1 is $CR^{T11}R^{T12}$, T^2 is $CR^{T21}R^{T22}$, T^3 is CR^{T31}, T^4 is $CR^{T41}R^{T42}$, T^5 is $(CR^{T51}R^{T52})_m$, and T^6 is NR^{T63}.

(43) T^1 is $CR^{T11}R^{T12}$, T^2 is $CR^{T21}R^{T22}$, T^3 is CR^{T31}, T^4 is $CR^{T41}R^{T42}$, T^5 is $(CR^{T51}R^{T52})_m$, and T^6 is O.

(44) T^1 is a single bond, T^2 is $CR^{T21}R^{T22}$, T^3 is CR^{T31}, T^4 is $CR^{T41}R^{T42}$, T^5 is $(CR^{T51}R^{T52})_m$, and T^6 is O.

(45) T^1 is $CR^{T11}R^{T12}$, T^2 is $CR^{T21}R^{T22}$, T^3 is N, T^4 is $CR^{T41}R^{T42}$, T^5 is $(CR^{T51}R^{T52})_m$, and T^6 is O.

(46) T^1 is $CR^{T11}R^{T12}$, T^2 is $CR^{T21}R^{T22}$, T^3 is N, T^4 is $CR^{T41}R^{T42}$, T^5 is $(CR^{T51}R^{T52})_m$, and T^6 is $CR^{T61}R^{T62}$.

(47) T^1 is a single bond, T^2 is $CR^{T21}R^{T22}$, T^3 is N, T^4 is $CR^{T41}R^{T42}$, T^5 is a single bond, and T^6 is $CR^{T61}R^{T62}$.

(48) T^1 is a single bond, T^2 is $CR^{T21}R^{T22}$, T^3 is N, T^4 is $CR^{T41}R^{T42}$, T^5 is $(CR^{T51}R^{T52})_m$, and T^6 is $CR^{T61}R^{T62}$.

(49) T^1 is $CR^{T11}R^{T12}$, T^2 is $CR^{T21}R^{T22}$, T^3 is N, T^4 is $CR^{T41}R^{T42}$, T^5 is $(CR^{T51}R^{T52})_m$, and T^6 is NR^{T63}.

(50) T^1 is $CR^{T11}R^{T12}$, T^2 is $CR^{T21}R^{T22}$, T^3 is CR^{T31}, T^4 is $CR^{T41}R^{T42}$, T^5 is $(CR^{T51}R^{T52})_m$, and T^6 is $CR^{T61}R^{T62}$.

(51) T^1 is N, T^2 is CR^{T22}, T^4 is CR^{T42}, T^5 is N, and T^6 is CR^{T62}.

(52) T^1 is CR^{T12}, T^2 is CR^{T22}, T^4 is N, T^5 is CR^{T52}, and T^6 is CR^{T62}.

(53) T^1 is CR^{T12}, T^2 is CR^{T22}, T^4 is CR^{T42}, T^5 is N, and T^6 is CR^{T62}.

(54) T^1 is CR^{T12}, T^2 is CR^{T22}, T^4 is CR^{T42}, T^5 is CR^{T52}, and T^6 is N.

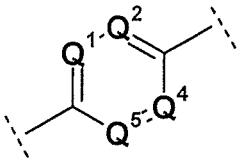
(55) m is 1.

(56) m is 2.

Other embodiments of the present invention are described below.

(57) A is

[Chem. 37]

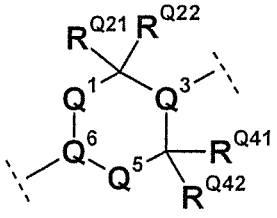


,

Q^1 is CR^{Q12} or N, Q^2 is CR^{Q22} or N, Q^4 is CR^{Q42} or N, Q^5 is CR^{Q52} or N, R^{Q12}, R^{Q22}, R^{Q42} and R^{Q52} are the same as or different from each other, and are H, lower alkyl, O-(lower alkyl), or $N(\text{lower alkyl})_2$, or

A is

[Chem. 38]



,

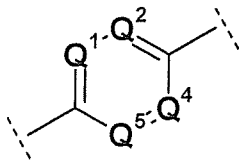
Q^1 is a single bond or $CR^{Q11}R^{Q12}$, Q^3 is CR^{Q31} or N, Q^5 is a single bond or $(CR^{Q51}R^{Q52})_a$, Q^6 is CR^{Q61} or N, in which either one of Q^3 and Q^6 is N,

R^{Q11}, R^{Q12}, R^{Q21}, R^{Q22}, R^{Q31}, R^{Q41}, R^{Q42}, R^{Q51}, R^{Q52} and R^{Q61} are the same as or different from each other, and are H, OH, lower alkyl, or R^{Q51} and R^{Q61} may be combined with each other to form a new bond, or R^{Q11} and R^{Q12} may be combined with each other to form oxo (=O), and a is 1 or 2.

(58)

(58-1) A is

[Chem. 39]



,

Q^1 is CR^{Q12} or N, Q^2 is CR^{Q22} or N, Q^4 is CR^{Q42} or N, Q^5 is CR^{Q52} or N, and R^{Q12}, R^{Q22}, R^{Q42} and R^{Q52} are the same as or different from each other, and are H, lower alkyl, O-(lower alkyl), or N(lower alkyl)$_2$.

(58-2) In (57) and (58-1), R^{Q12}, R^{Q22}, R^{Q42} and R^{Q52} are H.

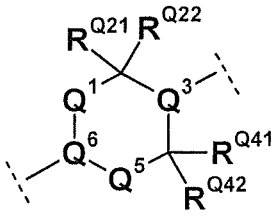
(58-3) In (57) and (58-1) to (58-2), Q^1 is N, Q^2 is CR^{Q22}, Q^4 is CR^{Q42}, and Q^5 is N.

(58-4) In (57) and (58-1) to (58-2), Q^1 is CR^{Q12}, Q^2 is CR^{Q22}, Q^4 is CR^{Q42}, and Q^5 is N.

(59)

(59-1) A is

[Chem. 40]



,

Q^1 is a single bond or $CR^{Q11}R^{Q12}$, Q^3 is CR^{Q31} or N, Q^5 is a single bond or $(CR^{Q51}R^{Q52})_a$, Q^6 is CR^{Q61} or N, in which either one of Q^3 and Q^6 is N,

R^{Q11}, R^{Q12}, R^{Q21}, R^{Q22}, R^{Q31}, R^{Q41}, R^{Q42}, R^{Q51}, R^{Q52} and R^{Q61} are the same as or different from each other, and are H, OH, or lower alkyl, or R^{Q51} and R^{Q61} may be combined with each other to form a new bond, or R^{Q11} and R^{Q12} may be combined with each other to form oxo (=O), and a is 1 or 2.

(59-2) In (57) and (59-1), a is 1.

(59-3) In (57) and (59-1) to (59-2), R^{Q11}, R^{Q12}, R^{Q21}, R^{Q22}, R^{Q31}, R^{Q41}, R^{Q42}, R^{Q51}, R^{Q52} and R^{Q61} are the same as or different from each other, and are H, or R^{Q51} and R^{Q61} may be combined with each other to form a new bond, or R^{Q11} and R^{Q12} may be combined with each other to form oxo (=O).

(59-4) In (57) and (59-1) to (59-3), Q^1 is $CR^{Q11}R^{Q12}$, Q^3 is N, Q^5 is $CR^{Q51}R^{Q52}$, and Q^6 is CR^{Q61}, or N.

(59-5) In (57) and (59-1) to (59-3), Q^1 is $CR^{Q11}R^{Q12}$, Q^3 is N, Q^5 is $CR^{Q51}R^{Q52}$, and Q^6 is N.

(59-6) In (57) and (59-1) to (59-3), Q^1 is $CR^{Q11}R^{Q12}$, Q^3 is N, Q^5 is $CR^{Q51}R^{Q52}$, and Q^6 is CR^{Q61}.

(59-7) In (57) and (59-1) to (59-3), Q^1 is $CR^{Q11}R^{Q12}$, Q^3 is CR^{Q31}, Q^5 is $CR^{Q51}R^{Q52}$, and Q^6 is N.

(59-8) In (57) and (59-1) to (59-3), Q^1 is a single bond, Q^3 is N, Q^5 is a single bond, and Q^6 is CR^{Q61}.

(60)

(60-1) X is

H,

OH,

NH_2,

lower alkyl which may be substituted with halogen,

O-(lower alkyl which may be substituted with OH),

NH(lower alkyl which may be substituted with oxo (=O)),

N(lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O))$_2$,

NH-SO_2-(lower alkyl),

N(lower alkyl)-SO_2-(lower alkyl),

cycloalkyl which may be substituted with group(s) selected from Group G^{XA1} below,

O-(cycloalkyl),

cycloalkenyl which may be substituted with group(s) selected from Group G^{XA1} below,

aryl which may be substituted with group(s) selected from Group G^{XA1} below,

O-(aryl which may be substituted with O-(lower alkyl)), or

a hetero ring group which may be substituted with group(s) selected from Group G^{XA1} below, and

Group G^{XA1} is

i) halogen,

ii) OH,

iii) lower alkyl which may be substituted with group(s) selected from the group consisting of halogen; OH; O-(lower alkyl which may be substituted with OH, aryl, O-(lower alkyl), or oxo (=O)); NH_2; NH(lower alkyl which may be substituted with OH); N(lower alkyl)$_2$; NH(cycloalkyl); NH(hetero ring group); cycloalkyl which may be substituted with OH; aryl which may be substituted with O-(lower alkyl), COOH, or COO-(lower alkyl which may be substituted with aryl); hetero ring group(s) which may be substituted with O-(lower alkyl), oxo (=O), NH(lower alkyl which may be substituted with oxo (=O)), or lower alkyl; and oxo (=O),

iv) O-(lower alkyl which may be substituted with OH, O-(lower alkyl), aryl, hetero ring group(s) (in which the hetero ring group may be substituted with lower alkyl which may be substituted with cycloalkyl or oxo (=O)), or oxo (=O)),

v) NH-(lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O)),

vi) N(lower alkyl which may be substituted with oxo (=O))$_2$,

vii) NH-(aryl which may be substituted with COOH or COO-(lower alkyl)),

viii) cycloalkyl which may be substituted with group(s) selected from the group consisting of lower alkyl which may be substituted with OH; COOH; and COO-(lower alkyl),

ix) aryl which may be substituted with group(s) selected from the group consisting of halogen; lower alkyl (in which the lower alkyl may be substituted with COOH or COO-(lower alkyl)); O-(lower alkyl); COOH; and COO-(lower alkyl),

x) hetero ring group(s) which may be substituted with group(s) selected from the group consisting of OH; halogen; lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl which may be substituted with O-(lower alkyl)); and oxo (=O),

xi) O-(hetero ring group),

xii) SO_2-(lower alkyl which may be substituted with O-(lower alkyl)),

xiii) SO_2-(cycloalkyl),

xiv) SO_2-(aryl),

xv) $NHSO_2$-(lower alkyl), or

xvi) oxo (=O).

(60-2) X is

H,

OH,

NH_2,

lower alkyl which may be substituted with halogen,

O-(lower alkyl which may be substituted with OH),

NH(lower alkyl which may be substituted with oxo (=O)),

N(lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O))$_2$,

NH-SO_2-(lower alkyl),

N(lower alkyl)-SO_2-(lower alkyl),

cycloalkyl which may be substituted with group(s) selected from Group G^{XA2} below,

O-(cycloalkyl),

cycloalkenyl which may be substituted with group(s) selected from Group G^{XA2} below,

aryl which may be substituted with group(s) selected from Group G^{XA2} below,

O-(aryl which may be substituted with O-(lower alkyl)), or

a hetero ring group which may be substituted with group(s) selected from Group G^{XA2} below,

G^{XA2} is

i) halogen,

ii) OH,

iii) lower alkyl which may be substituted with group(s) selected from the group consisting of halogen; OH; O-(lower alkyl which may be substituted with OH, phenyl, O-(lower alkyl), or oxo (=O)); NH_2; NH(lower alkyl which may be substituted with OH); N(lower alkyl)$_2$; NH(cycloalkyl); NH(nitrogen-containing monocyclic hetero ring group); cycloalkyl which may be substituted with OH; phenyl which may be substituted with O-(lower alkyl), COOH, or COO-(lower alkyl which may be substituted with phenyl); monocyclic hetero ring group(s) which may be substituted with O-(lower alkyl), oxo (=O), NH(lower alkyl which may be substituted with oxo (=O)) or lower alkyl; and oxo (=O),

iv) O-(lower alkyl which may be substituted with OH, O-(lower alkyl), phenyl, nitrogen-containing monocyclic hetero ring group(s) (in which the nitrogen-containing monocyclic hetero ring group may be substituted with lower alkyl which may be substituted with cycloalkyl or oxo (=O)), or oxo (=O)),

v) NH-(lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O)),

vi) N(lower alkyl which may be substituted with oxo (=O))$_2$,

vii) NH-(aryl which may be substituted with COOH or COO-(lower alkyl)),

viii) cycloalkyl which may be substituted with group(s) selected from the group consisting of lower alkyl which may be substituted with OH; COOH; and COO-(lower alkyl),

ix) aryl which may be substituted with group(s) selected from the group consisting of halogen; lower alkyl (in which the lower alkyl may be substituted with COOH or COO-(lower alkyl)); O-(lower alkyl); COOH; and COO-(lower alkyl),

x) hetero ring group(s) which may be substituted with group(s) selected from the group consisting of OH; halogen; lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl which may be substituted with O-(lower alkyl)); and oxo (=O),

xi) O-(monocyclic saturated hetero ring group),

xii) SO_2-(lower alkyl which may be substituted with O-(lower alkyl)),

xiii) SO_2-(cycloalkyl),

xiv) SO_2-(phenyl),

xv) $NHSO_2$-(lower alkyl), or

xvi) oxo (=O).

(60-3) X is

H,

OH,

NH_2,

lower alkyl which may be substituted with halogen,

O-(lower alkyl which may be substituted with OH),

NH(lower alkyl which may be substituted with oxo (=O)),

N(lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O))$_2$,

NH-SO_2-(lower alkyl),

N(lower alkyl)-SO_2-(lower alkyl),

cycloalkyl which may be substituted with group(s) selected from Group G^{XA3} below,

O-(cycloalkyl),

cycloalkenyl which may be substituted with group(s) selected from Group G^{XA3} below,

phenyl which may be substituted with group(s) selected from Group G^{XA3} below,

O-(phenyl which may be substituted with O-(lower alkyl)), or

a hetero ring group which may be substituted with group(s) selected from Group G^{XA3} below, and

Group G^{XA3} is

i) halogen,

ii) OH,

iii) lower alkyl which may be substituted with group(s) selected from the group consisting of halogen; OH; O-(lower alkyl which may be substituted with OH, phenyl, O-(lower alkyl), or oxo (=O)); NH_2; NH(lower alkyl which may be substituted with OH); N(lower alkyl)$_2$; NH(cycloalkyl); NH(thiazolyl); cycloalkyl which may be substituted with OH; phenyl which may be substituted with O-(lower alkyl), COOH, or COO-(lower alkyl which may be substituted with phenyl); tetrahydropyranyl, furanyl, thiazolyl, morphonyl, azetidinyl, oxazolidinyl, or pyridyl, each of which may be substituted with O-(lower alkyl), oxo (=O), NH(lower alkyl which may be substituted with oxo (=O)) or lower alkyl; and oxo (=O),

iv) O-(lower alkyl which may be substituted with OH, O-(lower alkyl), phenyl, piperidinyl or morphonyl (in which the piperidinyl or morphonyl group may be substituted with lower alkyl which may be substituted with cycloalkyl or oxo (=O)), or oxo (=O)),

v) NH-(lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O)),

vi) N(lower alkyl which may be substituted with oxo (=O))$_2$,

vii) NH-(phenyl which may be substituted with COOH or COO-(lower alkyl)),

viii) cycloalkyl which may be substituted with group(s) selected from the group consisting of lower alkyl which may be substituted with OH; COOH; and COO-(lower alkyl),

ix) phenyl which may be substituted with group(s) selected from the group consisting of halogen; lower alkyl (in which the lower alkyl may be substituted with COOH or COO-(lower alkyl)); O-(lower alkyl); COOH; and COO-(lower alkyl),

x) hetero ring group(s) which may be substituted with group(s) selected from the group consisting of OH; halogen; lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl which may be substituted with O-(lower alkyl)); and oxo (=O),

xi) O-(tetrahydropyranyl)

xii) SO_2-(lower alkyl which may be substituted with O-(lower alkyl)),

xiii) SO_2-(cycloalkyl),

xv) SO_2-(phenyl),

xv) $NHSO_2$-(lower alkyl), or

xvi) oxo (=O).

(60-4) X is

H,

OH,

NH_2,

lower alkyl which may be substituted with halogen,

O-(lower alkyl which may be substituted with OH),

NH(lower alkyl which may be substituted with oxo (=O)),

N(lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O))$_2$,

NH-SO_2-(lower alkyl),

N(lower alkyl)-SO_2-(lower alkyl),

cycloalkyl which may be substituted with OH or O-(lower alkyl which may be substituted with aryl or oxo (=O)),

O-(cycloalkyl),

cycloalkenyl which may be substituted with OH or O-(lower alkyl which may be substituted with aryl or oxo (=O)),

aryl which may be substituted with group(s) selected from the group consisting of lower alkyl which may be substituted with OH, O-(lower alkyl), hetero ring group(s) (in which the hetero ring group may be substituted with oxo (=O)) or oxo (=O); O-(lower alkyl which may be substituted with hetero ring group(s)); hetero ring group(s); NH(lower alkyl which may be substituted with oxo (=O)); N(lower alkyl which may be substituted with oxo (=O))$_2$; $NHSO_2$-(lower alkyl); and SO_2-(lower alkyl),

O-(aryl which may be substituted with O-(lower alkyl)), or

a hetero ring group which may be substituted with group(s) selected from Group G^{XA4} below, and

Group G^{XA4} is

i) halogen,

ii) OH,

iii) lower alkyl which may be substituted with group(s) selected from the group consisting of halogen; OH; O-(lower alkyl which may be substituted with OH, aryl, O-(lower alkyl), or oxo (=O)); NH_2; NH(lower alkyl which may be substituted with OH); N(lower alkyl)$_2$; NH(cycloalkyl); NH(hetero ring group); cycloalkyl which may be substituted with OH; arly which may be substituted with O-(lower alkyl), COOH, or COO-(lower alkyl which may be substituted with aryl); hetero ring group(s) which may be substituted with O-(lower alkyl), NH(lower alkyl which may be substituted with oxo (=O)), or lower alkyl; and oxo (=O),

iv) O-(lower alkyl which may be substituted with OH, O-(lower alkyl), aryl, hetero ring group(s) (in which the hetero ring group may be substituted with lower alkyl which may be substituted with cycloalkyl or oxo (=O)), or oxo (=O)),

v) NH-(lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O)),

vi) NH-(aryl which may be substituted with COOH or COO-(lower alkyl)),

vii) cycloalkyl which may be substituted with group(s) selected from the group consisting of lower alkyl which may be substituted with OH; COOH; and COO-(lower alkyl),

viii) aryl which may be substituted with group(s) selected from the group consisting of halogen; lower alkyl (in which the lower alkyl may be substituted with COOH or COO-(lower alkyl)); O-(lower alkyl); COOH; and COO-(lower alkyl),

ix) hetero ring group(s) which may be substituted with group(s) selected from the group consisting of OH; halogen; lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl which may be substituted with O-(lower alkyl)); and oxo (=O),

x) O-(hetero ring group),

xi) SO_2-(lower alkyl which may be substituted with O-(lower alkyl)),

xii) SO_2-(cycloalkyl),

xiii) SO_2-(aryl), or

xiv) oxo (=O).

(60-5) X is

H,

OH,

NH_2,

lower alkyl which may be substituted with halogen,

O-(lower alkyl which may be substituted with OH),

NH(lower alkyl which may be substituted with oxo (=O)),

N(lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O))$_2$,

NH-SO_2-(lower alkyl),

N(lower alkyl)-SO_2-(lower alkyl),

cycloalkyl which may be substituted with OH or O-(lower alkyl which may be substituted with phenyl or oxo (=O)),

O-(cycloalkyl),

cycloalkenyl which may be substituted with OH or O-(lower alkyl which may be substituted with phenyl or oxo (=O)),

aryl which may be substituted with group(s) selected from the group consisting of lower alkyl which may be substituted with OH, O-(lower alkyl), nitrogen-containing monocyclic hetero ring group(s) (in which the nitrogen-containing monocyclic hetero ring group may be substituted with oxo (=O)) or oxo (=O); O-(lower alkyl which may be substituted with nitrogen-containing monocyclic hetero ring group(s)); nitrogen-containing monocyclic hetero ring group(s); NH(lower alkyl which may be substituted with oxo (=O)); N(lower alkyl which may be substituted with oxo (=O))$_2$; $NHSO_2$-(lower alkyl); and SO_2-(lower alkyl),

O-(aryl which may be substituted with O-(lower alkyl)), or

a hetero ring group which may be substituted with group(s) selected from Group G^{XA5} below, and

Group G^{XA5} is

i) halogen,

ii) OH,

iii) lower alkyl which may be substituted with group(s) selected from the group consisting of halogen; OH; O-(lower alkyl which may be substituted with OH, phenyl, O-(lower alkyl), or oxo (=O)); NH_2; NH(lower alkyl which may be substituted with OH); N(lower alkyl)$_2$; NH(cycloalkyl); NH(nitrogen-containing monocyclic hetero ring group); cycloalkyl which may be substituted with OH; phenyl which may be substituted with O-(lower alkyl), COOH, or COO-(lower alkyl which may be substituted with phenyl); monocyclic hetero ring group(s) which may be substituted with O-(lower alkyl), NH(lower alkyl which may be substituted with oxo (=O)) or lower alkyl; and oxo (=O),

iv) O-(lower alkyl which may be substituted with OH, O-(lower alkyl), phenyl, nitrogen-containing monocyclic hetero ring group(s) (in which the nitrogen-containing monocyclic hetero ring group may be substituted with lower alkyl which may be substituted with cycloalkyl or oxo (=O)), or oxo (=O)),

v) NH-(lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O)),

vi) NH-(aryl which may be substituted with COOH or COO-(lower alkyl)),

vii) cycloalkyl which may be substituted with group(s) selected from the group consisting of lower alkyl which may be substituted with OH; COOH; and COO-(lower alkyl),

viii) aryl which may be substituted with group(s) selected from the group consisting of halogen; lower alkyl (in which the lower alkyl may be substituted with COOH or COO-(lower alkyl)); O-(lower alkyl); COOH; and COO-(lower alkyl),

ix) hetero ring group(s) which may be substituted with group(s) selected from the group consisting of OH; halogen; lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl which may be substituted with O-(lower alkyl)); and oxo (=O),

x) O-(monocyclic saturated hetero ring group),

xi) SO_2-(lower alkyl which may be substituted with O-(lower alkyl)),

xii) SO_2-(cycloalkyl),

xiii) SO_2-(phenyl), or

xiv) oxo (=O).

(60-6) X is

H,

OH,

NH_2,

lower alkyl which may be substituted with halogen,

O-(lower alkyl which may be substituted with OH),

NH(lower alkyl which may be substituted with oxo (=O)),

N(lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O))$_2$,

NH-SO_2-(lower alkyl),

N(lower alkyl)-SO_2-(lower alkyl),

cycloalkyl which may be substituted with OH or O-(lower alkyl which may be substituted with phenyl or oxo (=O)),

O-(cycloalkyl),

cycloalkenyl which may be substituted with OH or O-(lower alkyl which may be substituted with phenyl or oxo (=O)),

phenyl which may be substituted with group(s) selected from the group consisting of lower alkyl which may be substituted with OH, O-(lower alkyl), oxazolidinyl (in which the oxazolidinyl group may be substituted with oxo (=O)) or oxo (=O); O-(lower alkyl which may be substituted with morphonyl); pyridyl; morphonyl; NH(lower alkyl which may be substituted with oxo (=O)); N(lower alkyl which may be substituted with oxo (=O))$_2$; NHSO$_2$-(lower alkyl); and SO_2-(lower alkyl),

O-(phenyl which may be substituted with O-(lower alkyl)), or

a hetero ring group which may be substituted with group(s) selected from Group G^{XA6} below, and

Group G^{XA6} is

i) halogen,

ii) OH,

iii) lower alkyl which may be substituted with group(s) selected from the group consisting of halogen; OH; O-(lower alkyl which may be substituted with OH, phenyl, O-(lower alkyl), or oxo (=O)); NH_2; NH(lower alkyl which may be substituted with OH); N(lower alkyl)$_2$; NH(cycloalkyl); NH(thiazolyl); cycloalkyl which may be substituted with OH; phenyl which may be substituted with O-(lower alkyl), COOH, or COO-(lower alkyl which may be substituted with phenyl); tetrahydropyranyl, furanyl, thiazolyl, morphonyl, azetidinyl, or pyridyl, each of which may be substituted with O-(lower alkyl), NH(lower alkyl which may be substituted with oxo (=O)) or lower alkyl; and oxo (=O),

iv) O-(lower alkyl which may be substituted with OH, O-(lower alkyl), phenyl, piperidinyl or morphonyl (in which the piperidinyl or morphonyl group may be substituted with lower alkyl which may be substituted with cycloalkyl or oxo (=O)), or oxo (=O)),

v) NH-(lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O)),

vi) NH-(phenyl which may be substituted with COOH or COO-(lower alkyl)),

vii) cycloalkyl which may be substituted with group(s) selected from the group consisting of lower alkyl which may be substituted with OH; COOH; and COO-(lower alkyl),

viii) phenyl which may be substituted with group(s) selected from the group consisting of halogen; lower alkyl (in which the lower alkyl may be substituted with COOH or COO-(lower alkyl)); O-(lower alkyl); COOH; and COO-(lower alkyl),

ix) hetero ring group(s) which may be substituted with group(s) selected from the group consisting of OH; halogen; lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl which may be substituted with O-(lower alkyl)); and oxo (=O),

x) O-(tetrahydropyranyl)

xi) SO_2-(lower alkyl which may be substituted with O-(lower alkyl)),

xii) SO_2-(cycloalkyl),

xiii) SO_2-(phenyl), or

xiv) oxo (=O).

(61)

(61-1) X is H,

lower alkyl, O-(lower alkyl), O-(cycloalkyl),

cycloalkyl which may be substituted with group(s) selected from Group G^{XB1} below,

cycloalkenyl which may be substituted with group(s) selected from Group G^{XB1} below,

aryl which may be substituted with group(s) selected from Group G^{XB1} below, or

a hetero ring group which may be substituted with group(s) selected from Group G^{XB1} below, and

Group G^{XB1} is

i) OH,

ii) lower alkyl which may be substituted with group(s) selected from the group consisting of OH; O-(lower alkyl which may be substituted with aryl); NH(lower alkyl); N(lower alkyl)$_2$; NH(cycloalkyl); cycloalkyl which may be substituted with OH; aryl; hetero ring group(s) which may be substituted with lower alkyl; and oxo (=O),

iii) O-(lower alkyl which may be substituted with O-(lower alkyl), aryl, hetero ring group(s) (in which the hetero ring group may be substituted with lower alkyl which may be substituted with cycloalkyl or oxo (=O)) or oxo (=O)),

iv) NH-(lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O)),

v) cycloalkyl which may be substituted with COOH or COO-(lower alkyl),

vi) hetero ring group(s) which may be substituted with group(s) selected from the group consisting of OH; halogen; lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl which may be substituted with O-(lower alkyl)); and oxo (=O),

vii) O-(hetero ring group),

viii) SO_2-(lower alkyl),

ix) SO_2-(cycloalkyl), or

x) oxo (=O).

(61-2) X is H,

lower alkyl, O-(lower alkyl), O-(cycloalkyl),

cycloalkyl which may be substituted with group(s) selected from Group G^{XB2} below,

cycloalkenyl which may be substituted with group(s) selected from Group G^{XB2} below,

aryl which may be substituted with group(s) selected from Group G^{XB2} below, or

a hetero ring group which may be substituted with group(s) selected from Group G^{XB2} below, and

Group G^{XB2} is

i) OH,

ii) lower alkyl which may be substituted with group(s) selected from the group consisting of OH; O-(lower alkyl which may be substituted with phenyl); NH(lower alkyl);

N(lower alkyl)$_2$; NH(cycloalkyl); cycloalkyl which may be substituted with OH; phenyl; monocyclic hetero ring group(s) which may be substituted with lower alkyl; and oxo (=O),

iii) O-(lower alkyl which may be substituted with O-(lower alkyl), phenyl, nitrogen-containing monocyclic saturated hetero ring group(s) (in which the nitrogen-containing monocyclic saturated hetero ring group may be substituted with lower alkyl which may be substituted with cycloalkyl or oxo (=O)) or oxo (=O)),

iv) NH-(lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O)),

v) cycloalkyl which may be substituted with COOH or COO-(lower alkyl),

vi) monocyclic hetero ring group(s) which may be substituted with group(s) selected from the group consisting of OH; halogen; lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl which may be substituted with O-(lower alkyl)); and oxo (=O),

vii) O-(monocyclic saturated hetero ring group),

viii) SO_2-(lower alkyl),

ix) SO_2-(cycloalkyl), or

x) oxo (=O).

(61-3) In (61-2), vi) is

vi) nitrogen-containing monocyclic hetero ring group(s) which may be substituted with group(s) selected from the group consisting of OH; halogen; lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl which may be substituted with O-(lower alkyl)); and oxo (=O).

(61-4) X is H,

lower alkyl, O-(lower alkyl), O-(cycloalkyl),

cycloalkyl which may be substituted with group(s) selected from Group G^{XB3} below,

cycloalkenyl which may be substituted with group(s) selected from Group G^{XB3} below,

phenyl which may be substituted with group(s) selected from Group G^{XB3} below, or

tetrahydropyranyl, tetrahydrofuranyl, 1,2-dihydropyridyl, thiazolyl, azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, imidazo[1,2-a]pyridyl, or benzothiazolyl, which may substituted with group(s) selected from Group G^{XB3} below, and

Group G^{XB3} is

i) OH,

ii) lower alkyl which may be substituted with group(s) selected from the group consisting of OH; O-(lower alkyl which may be substituted with phenyl); NH(lower alkyl);

N(lower alkyl)$_2$; NH(cycloalkyl); cycloalkyl which may be substituted with OH; phenyl; pyridyl which may be substituted with lower alkyl; tetrahydropyranyl; and oxo (=O),

iii) O-(lower alkyl which may be substituted with O-(lower alkyl), phenyl, piperidinyl (in which piperidinyl group may be substituted with lower alkyl which may be substituted with cycloalkyl or oxo (=O)) or oxo (=O)),

iv) NH-(lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O)),

v) cycloalkyl which may be substituted with COOH or COO-(lower alkyl),

vi) 1,2-dihydropyridyl, pyridyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, oxazepanyl, or tetrahydropyranyl, each of which may be substituted with group(s) selected from the group consisting of OH; halogen; lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl which may be substituted with O-(lower alkyl)); and oxo (=O),

vii) O-(tetrahydropyranyl),

viii) SO_2-(lower alkyl),

ix) SO_2-(cycloalkyl), or

x) oxo (=O).

(61-5) X is H,

lower alkyl, O-(lower alkyl), O-(cycloalkyl),

cycloalkyl which may be substituted with group(s) selected from Group G^{XB4} below,

cycloalkenyl which may be substituted with group(s) selected from Group G^{XB4} below,

phenyl which may be substituted with group(s) selected from Group G^{XB4} below, or

azetidinyl, pyrrolidinyl, piperidinyl, pyridyl, tetrahydrofuranyl, tetrahydropyranyl, or morpholinyl, each of which may be substituted with group(s) selected from Group G^{XB4} below, and

Group G^{XB4} is

i) OH,

ii) lower alkyl which may be substituted with group(s) selected from the group consisting of OH; O-(lower alkyl which may be substituted with phenyl); NH(lower alkyl); N(lower alkyl)$_2$; NH(cycloalkyl); cycloalkyl which may be substituted with OH; phenyl; pyridyl which may be substituted with lower alkyl; tetrahydropyranyl; and oxo (=O),

iii) O-(lower alkyl which may be substituted with O-(lower alkyl), phenyl, piperidinyl (in which the piperidinyl group may be substituted with lower alkyl which may be substituted with cycloalkyl or oxo (=O)), or oxo (=O)),

iv) NH-(lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O)),

v) cycloalkyl which may be substituted with COOH or COO-(lower alkyl),

vi) 1,2-dihydropyridyl, pyridyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or oxazepanyl, each of which may be substituted with group(s) selected from the group consisting of OH; halogen; lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl which may be substituted with O-(lower alkyl)); and oxo (=O)

vii) O-(tetrahydropyranyl),

viii) SO_2-(lower alkyl),

ix) SO_2-(cycloalkyl), or

x) oxo (=O).

(61-6) X is H,

lower alkyl, O-(lower alkyl), O-(cycloalkyl),

cycloalkyl which may be substituted with group(s) selected from Group G^{XB4} above,

cycloalkenyl which may be substituted with group(s) selected from Group G^{XB4} above,

phenyl which may be substituted with group(s) selected from Group G^{XB4} above, or

tetrahydropyranyl, tetrahydrofuranyl, 1,2-dihydropyridyl, thiazolyl, azetidinyl, piperidinyl, morpholinyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, imidazo[1,2-a]pyridyl, or benzothiazolyl, each of which may be substituted with group(s) selected from Group G^{XB4} above.

(61-7) X is H,

lower alkyl, O-(lower alkyl), O-(cycloalkyl),

cycloalkyl which may be substituted with OH or O-(lower alkyl which may be substituted with aryl or oxo (=O)),

cycloalkenyl which may be substituted with OH or O-(lower alkyl which may be substituted with aryl or oxo (=O)),

aryl which may be substituted with group(s) selected from the group consisting of lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl); and hetero ring group(s), or

a hetero ring group which may be substituted with group(s) selected from Group G^{XB5} below, and

Group G^{XB5} is

i) OH,

ii) lower alkyl which may be substituted with group(s) selected from the group consisting of OH; O-(lower alkyl which may be substituted with aryl); NH(lower alkyl); N(lower alkyl)$_2$; NH(cycloalkyl); cycloalkyl which may be substituted with OH; aryl; hetero ring group(s) which may be substituted with lower alkyl; and oxo (=O),

iii) O-(lower alkyl which may be substituted with O-(lower alkyl) or hetero ring group(s) (in which the hetero ring group may be substituted with lower alkyl which may be substituted with cycloalkyl or oxo (=O))),

iv) NH-(lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O)),

v) cycloalkyl which may be substituted with COOH or COO-(lower alkyl),

vi) hetero ring group(s) which may be substituted with group(s) selected from the group consisting of OH; halogen; lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl which may be substituted with O-(lower alkyl)); and oxo (=O),

vii) O-(hetero ring group),

viii) SO_2-(lower alkyl),

ix) SO_2-(cycloalkyl), or

x) oxo (=O).

(61-8) X is H,

lower alkyl, O-(lower alkyl), O-(cycloalkyl),

cycloalkyl which may be substituted with OH or O-(lower alkyl which may be substituted with phenyl or oxo (=O)),

cycloalkenyl which may be substituted with OH or O-(lower alkyl which may be substituted with phenyl or oxo (=O)),

aryl which may be substituted with group(s) selected from the group consisting of lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl); and nitrogen-containing monocyclic unsaturated hetero ring group(s), or

a hetero ring group which may be substituted with group(s) selected from Group G^{XB6} below,

Group G^{XB6} is

i) OH,

ii) lower alkyl which may be substituted with group(s) selected from the group consisting of OH; O-(lower alkyl which may be substituted with phenyl); NH(lower alkyl); N(lower alkyl)$_2$; NH(cycloalkyl); cycloalkyl which may be substituted with OH; phenyl; monocyclic hetero ring group(s) which may be substituted with lower alkyl; and oxo (=O),

iii) O-(lower alkyl which may be substituted with O-(lower alkyl) or nitrogen-containing monocyclic saturated hetero ring group(s) (in which the nitrogen-containing monocyclic saturated hetero ring group may be substituted with lower alkyl which may be substituted with cycloalkyl or oxo (=O))),

iv) NH-(lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O)),

v) cycloalkyl which may be substituted with COOH or COO-(lower alkyl),

vi) monocyclic hetero ring group(s) which may be substituted with group(s) selected from the group consisting of OH; halogen; lower alkyl which may be substituted

with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl which may be substituted with O-(lower alkyl)); and oxo (=O),

vii) O-(monocyclic saturated hetero ring group),

viii) SO_2-(lower alkyl),

ix) SO_2-(cycloalkyl), or

x) oxo (=O).

(61-9) In (61-8), vi) is

vi) nitrogen-containing monocyclic hetero ring group(s) which may be substituted with group(s) selected from the group consisting of OH; halogen; lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl which may be substituted with O-(lower alkyl)); and oxo (=O).

(61-10) X is H,

lower alkyl, O-(lower alkyl), O-(cycloalkyl),

cycloalkyl which may be substituted with OH or O-(lower alkyl which may be substituted with phenyl or oxo (=O)),

cycloalkenyl which may be substituted with OH or O-(lower alkyl which may be substituted with phenyl or oxo (=O)),

phenyl which may be substituted with group(s) selected from the group consisting of lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl); and pyridyl, or

tetrahydropyranyl, tetrahydrofuranyl, 1,2-dihydropyridyl, thiazolyl, azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, imidazo[1,2-a]pyridyl, or benzothiazolyl, each of which may be substituted with group(s) selected from Group G^{XB7} below, and

Group G^{XB7} is

i) OH,

ii) lower alkyl which may be substituted with group(s) selected from the group consisting of OH; O-(lower alkyl which may be substituted with phenyl); NH(lower alkyl); $N(\text{lower alkyl})_2$; NH(cycloalkyl); cycloalkyl which may be substituted with OH; phenyl; pyridyl which may be substituted with lower alkyl; tetrahydropyranyl; and oxo (=O),

iii) O-(lower alkyl which may be substituted with O-(lower alkyl) or piperidinyl (in which the piperidinyl group may be substituted with lower alkyl which may be substituted with cycloalkyl or oxo (=O))),

iv) NH-(lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O)),

v) cycloalkyl which may be substituted with COOH or COO-(lower alkyl),

vi) 1,2-dihydropyridyl, pyridyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, oxazepanyl, or tetrahydropyranyl, each of which may be substituted with group(s) selected from the group consisting of OH; halogen; lower alkyl which may be

substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl which may be substituted with O-(lower alkyl)); and oxo (=O),

vii) O-(tetrahydropyranyl),

viii) SO_2-(lower alkyl),

ix) SO_2-(cycloalkyl), or

x) oxo (=O).

(61-11) X is H,

lower alkyl, O-(lower alkyl), O-(cycloalkyl),

cycloalkyl which may be substituted with OH or O-(lower alkyl which may be substituted with phenyl or oxo (=O)),

cycloalkenyl which may be substituted with OH or O-(lower alkyl which may be substituted with phenyl or oxo (=O)),

phenyl which may be substituted with group(s) selected from the group consisting of lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl); and pyridyl, or

azetidinyl, pyrrolidinyl, piperidinyl, pyridyl, tetrahydrofuranyl, tetrahydropyranyl, or morpholinyl, each of which may be substituted with group(s) selected from Group G^{XB8} below, and

Group G^{XB8} is

i) OH,

ii) lower alkyl which may be substituted with group(s) selected from the group consisting of OH; O-(lower alkyl which may be substituted with phenyl); NH(lower alkyl); N(lower alkyl)$_2$; NH(cycloalkyl); cycloalkyl which may be substituted with OH; phenyl; pyridyl which may be substituted with lower alkyl; tetrahydropyranyl; and oxo (=O),

iii) O-(lower alkyl which may be substituted with O-(lower alkyl) or piperidinyl (in which the piperidinyl group may be substituted with lower alkyl which may be substituted with cycloalkyl or oxo (=O))),

iv) NH-(lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O)),

v) cycloalkyl which may be substituted with COOH or COO-(lower alkyl),

vi) 1,2-dihydropyridyl, pyridyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or oxazepanyl, each of which may be substituted with group(s) selected from the group consisting of OH; halogen; lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl which may be substituted with O-(lower alkyl)); and oxo (=O)

vii) O-(tetrahydropyranyl),

viii) SO_2-(lower alkyl),

ix) SO_2-(cycloalkyl), or

x) oxo (=O).

(61-12) X is H,

lower alkyl, O-(lower alkyl), O-(cycloalkyl),

cycloalkyl which may be substituted with OH or O-(lower alkyl which may be substituted with phenyl or oxo (=O)),

cycloalkenyl which may be substituted with OH or O-(lower alkyl which may be substituted with phenyl or oxo (=O)),

phenyl which may be substituted with group(s) selected from the group consisting of lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl); and pyridyl, or

tetrahydropyranyl, tetrahydrofuranyl, 1,2-dihydropyridyl, thiazolyl, azetidinyl, piperidinyl, morpholinyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, imidazo[1,2-a]pyridyl, or benzothiazolyl, each of which may be substituted with group(s) selected from Group G^{XB8} above.

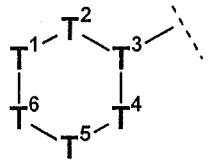
(62)

(62-1) X is OH, NH_2, lower alkyl which may be substituted with halogen,

O-(lower alkyl which may be substituted with OH), NH(lower alkyl which may be substituted with oxo (=O)), N(lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O))$_2$, NH-SO_2-(lower alkyl), N(lower alkyl)-SO_2-(lower alkyl), O-(cycloalkyl), or O-(aryl which may be substituted with O-(lower alkyl)), or

X is

[Chem. 41]



,

T^1 is a single bond, $CR^{T11}R^{T12}$, O, or NR^{T13}, T^2 is $CR^{T21}R^{T22}$, O, or NR^{T23}, T^3 is CR^{T31} or N, T^4 is $CR^{T41}R^{T42}$ or O, T^5 is a single bond, $(CR^{T51}R^{T52})_m$, or NR^{T53}, T^6 is $CR^{T61}R^{T62}$, O, S, SO_2, or NR^{T63},

R^{T11}, R^{T12}, R^{T21}, R^{T22}, R^{T31}, R^{T41}, R^{T42}, R^{T51} and R^{T52} are the same as or different from each other, and are

H, OH, lower alkyl (in which the lower alkyl may be substituted with OH, NH_2, NH(lower alkyl which may be substituted with OH), O-(lower alkyl), or oxo (=O)), O-(lower alkyl), or nitrogen-containing monocyclic saturated hetero ring group(s),

R^{T13}, R^{T23} and R^{T53} are the same as or different from each other, and are H or lower alkyl (in which the lower alkyl may be substituted with O-(lower alkyl) or oxo (=O)),

R^{T61} is H, OH, or halogen,

R^{T62} is H, OH, halogen, lower alkyl (in which the lower alkyl may be substituted with OH, halogen, O-(lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O)), NH_2, NH(lower alkyl which may be substituted with OH), nitrogen-containing monocyclic saturated hetero ring group(s) which may be substituted with O-(lower alkyl), or oxo (=O)), O-(lower alkyl which may be substituted with OH, O-(lower alkyl), aryl, or oxo (=O)), NH(lower alkyl which may be substituted with oxo (=O)), NH(aryl which may be substituted with COOH or COO-(lower alkyl)), SO_2-(lower alkyl), SO_2-(aryl), or a hetero ring group (in which the hetero ring group may be substituted with lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O), or oxo (=O)),

R^{T63} is H,

lower alkyl which may be substituted with group(s) selected from the group consisting of OH; O-(lower alkyl); aryl (in which the aryl may be substituted with O-(lower alkyl), COOH, or COO-(lower alkyl which may be substituted with aryl); NH_2; NH(lower alkyl); N(lower alkyl)$_2$; NH(cycloalkyl); cycloalkyl which may be substituted with OH; monocyclic hetero ring group(s) which may be substituted with NH(lower alkyl which may be substituted with oxo (=O)); NH(nitrogen-containing monocyclic unsaturated hetero ring group); and oxo (=O),

a nitrogen-containing monocyclic unsaturated hetero ring group which may be substituted with lower alkyl,

cycloalkyl which may be substituted with group(s) selected from the group consisting of lower alkyl which may be substituted with OH; COOH; and COO-(lower alkyl),

aryl which may be substituted with group(s) selected from the group consisting of halogen; lower alkyl (in which the lower alkyl may be substituted with COOH or COO-(lower alkyl)); O-(lower alkyl); COOH; and COO-(lower alkyl),

SO_2-(lower alkyl which may be substituted with O-(lower alkyl)), or

SO_2-(cycloalkyl), or

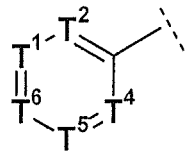
R^{T21} and R^{T31} may be combined with each other to form a new bond, or

R^{T11} and R^{T12}, R^{T21} and R^{T22}, R^{T41} and R^{T42}, R^{T51} and R^{T52}, or R^{T61} and R^{T62} may be combined with each other to form oxo (=O), and

m is 1 or 2, or

X is

[Chem. 42]



,

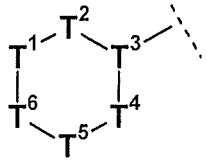
T^1 is CR^{T12} or N, T^2 is CR^{T22} or N, T^4 is CR^{T42} or N, T^5 is CR^{T52} or N, T^6 is CR^{T62} or N, and

R^{T12}, R^{T22}, R^{T42}, R^{T52} and R^{T62} are the same as or different from each other, and are H, lower alkyl which may be substituted with OH or oxazolidinyl (in which the oxazolidinyl group may be substituted with oxo (=O)), O-(lower alkyl which may be substituted with nitrogen-containing monocyclic saturated hetero ring group(s)), NH(lower alkyl which may be substituted with oxo (=O)), N(lower alkyl which may be substituted with oxo (=O))$_2$, NH-SO_2-(lower alkyl), SO_2-(lower alkyl), or a nitrogen-containing monocyclic saturated hetero ring group.

(62-2) X is OH, NH_2, lower alkyl which may be substituted with halogen, O-(lower alkyl which may be substituted with OH), NH(lower alkyl which may be substituted with oxo (=O)), N(lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O))$_2$, NH-SO_2-(lower alkyl), N(lower alkyl)-SO_2-(lower alkyl), O-(cycloalkyl), or O-(phenyl which may be substituted with O-(lower alkyl)), or

X is

[Chem. 43]



,

T^1 is a single bond, $CR^{T11}R^{T12}$, O, or NR^{T13}, T^2 is $CR^{T21}R^{T22}$, O, or NR^{T23}, T^3 is CR^{T31} or N, T^4 is $CR^{T41}R^{T42}$ or O, T^5 is a single bond, $(CR^{T51}R^{T52})_m$, or NR^{T53}, T^6 is $CR^{T61}R^{T62}$, O, S, SO_2, or NR^{T63},

R^{T11}, R^{T12}, R^{T21}, R^{T22}, R^{T31}, R^{T41}, R^{T42}, R^{T51} and R^{T52} are the same as or different from each other, and are

H, OH, lower alkyl (in which the lower alkyl may be substituted with OH, NH_2, NH(lower alkyl which may be substituted with OH), O-(lower alkyl), or oxo (=O)), O-(lower alkyl), or morpholinyl,

R^{T13}, R^{T23} and R^{T53} are the same as or different from each other, and are H or lower alkyl (in which the lower alkyl may be substituted with O-(lower alkyl) or oxo (=O)),

R^{T61} is H, OH, or halogen,

R^{T62} is H, OH, halogen, lower alkyl (in which the lower alkyl is OH, halogen, O-(lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O)), NH_2, NH(lower alkyl which may be substituted with OH), azetidinyl which may be substituted with O-(lower alkyl), morpholinyl, or oxo (=O)), O-(lower alkyl which may be substituted with OH, O-(lower alkyl), phenyl, or oxo (=O)), NH(lower alkyl which may be substituted with oxo (=O)), NH(phenyl which may be substituted with COOH or COO-(lower alkyl)),

SO_2-(lower alkyl), SO_2-(phenyl), or tetrahydropyranyl, piperidinyl, morpholinyl, pyridyl, dihydrobenzoimidazolinyl, or dihydroimidazopyridyl, each of which may be substituted with lower alkyl (in which the lower alkyl may be substituted with OH, O-(lower alkyl), or oxo (=O)) or oxo (=O),

R^{T63} is H,

lower alkyl which may be substituted with group(s) selected from the group consisting of OH; O-(lower alkyl); phenyl (in which the phenyl may be substituted with O-(lower alkyl), COOH, or COO-(lower alkyl which may be substituted with phenyl); NH_2; NH(lower alkyl); N(lower alkyl)$_2$; NH(cycloalkyl); cycloalkyl which may be substituted with OH; tetrahydropyranyl, thiazolyl, pyridyl, or furanyl, each of which may be substituted with NH(lower alkyl which may be substituted with oxo (=O)); NH(thiazolyl); and oxo (=O),

pyridyl which may be substituted with lower alkyl,

cycloalkyl which may be substituted with group(s) selected from the group consisting of lower alkyl which may be substituted with OH; COOH; and COO-(lower alkyl),

phenyl which may be substituted with group(s) selected from the group consisting of halogen; lower alkyl (in which the lower alkyl may be substituted with COOH or COO-(lower alkyl)); O-(lower alkyl); COOH; and COO-(lower alkyl),

SO_2-(lower alkyl which may be substituted with O-(lower alkyl)), or

SO_2-(cycloalkyl), or

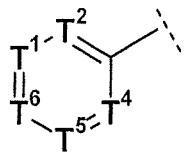
R^{T21} and R^{T31} may be combined with each other to form a new bond, or

R^{T11} and R^{T12}, R^{T21} and R^{T22}, R^{T41} and R^{T42}, R^{T51} and R^{T52}, or R^{T61} and R^{T62} may be combined with each other to form oxo (=O),

m is 1 or 2, or

X is

[Chem. 44]



,

T^1 is CR^{T12} or N, T^2 is CR^{T22} or N, T^4 is CR^{T42} or N, T^5 is CR^{T52} or N, T^6 is CR^{T62} or N, and

R^{T12}, R^{T22}, R^{T42}, R^{T52} and R^{T62} are the same as or different from each other, and are H, lower alkyl which may be substituted with OH, or oxazolidinyl (in which the oxazolidinyl group may be substituted with oxo (=O)), O-(lower alkyl which may be substituted with morpholinyl), NH(lower alkyl which may be substituted with oxo (=O)),

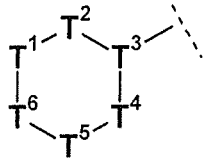
N(lower alkyl which may be substituted with oxo (=O))$_2$, NH-SO_2-(lower alkyl), SO_2-(lower alkyl), or morpholinyl.

(63)

(63-1) X is lower alkyl, O-(lower alkyl), or O-(cycloalkyl), or

X is

[Chem. 45]



,

T^1 is a single bond or $CR^{T11}R^{T12}$, T^2 is $CR^{T21}R^{T22}$, O, or NR^{T23}, T^3 is CR^{T31} or N, T^4 is $CR^{T41}R^{T42}$, T^5 is a single bond or $(CR^{T51}R^{T52})_m$, T^6 is $CR^{T61}R^{T62}$, O, or NR^{T63},

R^{T11}, R^{T12}, R^{T21}, R^{T22}, R^{T31}, R^{T41}, R^{T42}, R^{T51} and R^{T52} are the same as or different from each other, and are H, or OH,

R^{T23} is H, or CO-(C_{1-5} alkyl),

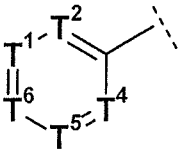
R^{T61} is H,

R^{T62} is H,

R^{T63} is cycloalkyl which may be substituted with COOH or COO-(lower alkyl), CO-(C_{1-5} alkyl which may be substituted with OH, oxo (=O), O-(lower alkyl) or nitrogen-containing monocyclic unsaturated hetero ring(s)), CO-(cycloalkyl which may be substituted with OH), CO-(aryl), CO-(nitrogen-containing monocyclic unsaturated hetero ring group), CO-O-(C_{1-5} alkyl), CONH (lower alkyl), CON(lower alkyl)$_2$, CONH (cycloalkyl), SO_2-(lower alkyl), or SO_2-(cycloalkyl), and m is 1 or 2, or

X is

[Chem. 46]



,

T^1 is CR^{T12} or N, T^2 is CR^{T22} or N, T^4 is CR^{T42} or N, T^5 is CR^{T52} or N, T^6 is CR^{T62} or N, and

R^{T12}, R^{T22}, R^{T42}, R^{T52} and R^{T62} are the same as or different from each other, and are H, or O-(lower alkyl).

(63-2)

(63-2-1) In (63-1),

R^{T63} is CO-(C_{1-5} alkyl which may be substituted with O-(lower alkyl) or nitrogen-containing monocyclic unsaturated hetero ring(s)), CO-(cycloalkyl), CO-(aryl),

CO-(nitrogen-containing monocyclic unsaturated hetero ring group), CON(lower alkyl)$_2$, or SO_2-(lower alkyl).

(63-2-2) In (63-1), R^{T63} is CO-(C_{1-5} alkyl which may be substituted with O-(lower alkyl)), CO-(cycloalkyl), CO-(aryl), CO-(nitrogen-containing monocyclic unsaturated hetero ring group), CON(lower alkyl)$_2$, or SO_2-(lower alkyl).

(63-2-3) In (63-1), R^{T63} is CO-(C_{1-5} lower alkyl which may be substituted with O-(lower alkyl)), CO-(cycloalkyl), or SO_2-(lower alkyl).

(63-2-4) In (63-1), R^{T63} is acetyl, propionyl, isobutyryl, pivaloyl, 2-ethoxy-1-oxoethyl, 2-methoxy-1-oxoethyl, 3-methoxy-1-oxopropyl, 3-methoxy-2,2-dimethyl-1-oxopropyl, cyclopropylcarbonyl, benzoyl, pyridin-3-ylcarbonyl, dimethylaminocarbonyl, methylsulfonyl, or ethylsulfonyl.

(63-2-5) In (63-1), R^{T63} is acetyl, propionyl, isobutyryl, pivaloyl, 2-ethoxy-1-oxoethyl, 2-methoxy-1-oxoethyl, 3-methoxy-1-oxopropyl, cyclopropylcarbonyl, benzoyl, pyridin-3-ylcarbonyl, dimethylaminocarbonyl, methylsulfonyl, or ethylsulfonyl.

(63-2-6) In (63-1), R^{T63} is acetyl, propionyl, isobutyryl, pivaloyl, 2-ethoxy-1-oxoethyl, cyclopropylcarbonyl, benzoyl, pyridin-3-ylcarbonyl, dimethylaminocarbonyl, or methylsulfonyl.

(63-3)

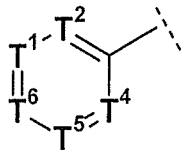
(63-3-1) In (63-1) to (63-2), R^{T11}, R^{T12}, R^{T21}, R^{T22}, R^{T31}, R^{T41}, R^{T42}, R^{T51} and R^{T52} are the same as or different from each other, and are H or OH.

(63-3-2) In (63-1) to (63-2), R^{T11}, R^{T12}, R^{T21}, R^{T22}, R^{T31}, R^{T41}, R^{T42}, R^{T51} and R^{T52} are H.

(63-4) In (63-1) to (63-3), R^{T23} is H.

(63-5) In (63-1) to (63-4), X is

[Chem. 47]



,

T^1 is CR^{T12}, T^2 is CH, T^4 is CH, T^5 is CR^{T52} or N, T^6 is CH, and R^{T12} and R^{T52} are the same as or different from each other, and are H or O-(lower alkyl).

(63-6)

(63-6-1) In (63-1) to (63-5), T^1 is a single bond or $CR^{T11}R^{T12}$, T^2 is $CR^{T21}R^{T22}$, T^3 is CR^{T31} or N, T^4 is $CR^{T41}R^{T42}$, T^5 is a single bond or $(CR^{T51}R^{T52})_m$, and T^6 is NR^{T63}.

(63-6-2) In (63-1) to (63-5), T^1 is $CR^{T11}R^{T12}$, T^2 is $CR^{T21}R^{T22}$, T^3 is CR^{T31}, T^4 is $CR^{T41}R^{T42}$, T^5 is $(CR^{T51}R^{T52})_m$, and T^6 is NR^{T63}.

(63-7) In (63-1) to (63-6), m is 1.

(64)

(64-1) X is H,

lower alkyl, O-(lower alkyl),

cycloalkyl which may be substituted with group(s) selected from Group G^{XC1} below,

cycloalkenyl which may be substituted with group(s) selected from Group G^{XC1} below,

aryl which may be substituted with group(s) selected from Group G^{XC1} below, or

a hetero ring group which may be substituted with group(s) selected from Group G^{XC1} below, and

Group G^{XC1} is

i) OH,

ii) lower alkyl which may be substituted with group(s) selected from the group consisting of OH; O-(lower alkyl which may be substituted with aryl); N(lower alkyl)$_2$; cycloalkyl; hetero ring group(s) which may be substituted with lower alkyl; and oxo (=O),

iii) O-(lower alkyl which may be substituted with O-(lower alkyl), aryl, hetero ring group(s) (in which the hetero ring group may be substituted with lower alkyl which may be substituted with cycloalkyl or oxo (=O)), or oxo (=O)),

iv) NH-(lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O)),

v) cycloalkyl,

vi) hetero ring group(s) which may be substituted with group(s) selected from the group consisting of OH; halogen; lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl which may be substituted with O-(lower alkyl)); and oxo (=O),

vii) O-(hetero ring group),

viii) SO_2-(lower alkyl),

ix) SO_2-(cycloalkyl), or

x) oxo (=O).

(64-2) X is H,

lower alkyl, O-(lower alkyl),

cycloalkyl which may be substituted with group(s) selected from Group G^{XC2} below,

cycloalkenyl which may be substituted with group(s) selected from Group G^{XC2} below,

aryl which may be substituted with group(s) selected from Group G^{XC2} below, or

a hetero ring group which may be substituted with group(s) selected from Group G^{XC2} below, and

Group G^{XC2} is

i) OH,

ii) lower alkyl which may be substituted with group(s) selected from the group consisting of OH; O-(lower alkyl which may be substituted with phenyl); N(lower alkyl)$_2$; cycloalkyl; monocyclic hetero ring group(s) which may be substituted with lower alkyl; and oxo (=O),

iii) O-(lower alkyl which may be substituted with O-(lower alkyl), phenyl, nitrogen-containing monocyclic saturated hetero ring group(s) (in which the nitrogen-containing monocyclic saturated hetero ring group may be substituted with lower alkyl which may be substituted with cycloalkyl or oxo (=O)),

iv) NH-(lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O)),

v) cycloalkyl,

vi) monocyclic hetero ring group(s) which may be substituted with group(s) selected from the group consisting of OH; halogen; lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl which may be substituted with O-(lower alkyl)); and oxo (=O),

vii) O-(tetrahydropyranyl),

viii) SO_2-(lower alkyl),

ix) SO_2-(cycloalkyl), or

x) oxo (=O).

(64-3) In (64-2), vi) of Group G^{XC2} is

vi) nitrogen-containing monocyclic hetero ring group(s) which may be substituted with group(s) selected from the group consisting of OH; halogen; lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl which may be substituted with O-(lower alkyl)); and oxo (=O).

(64-4) X is H,

lower alkyl, O-(lower alkyl),

cycloalkyl which may be substituted with group(s) selected from Group G^{XC3} below,

cycloalkenyl which may be substituted with group(s) selected from Group G^{XC3} below

phenyl which may be substituted with group(s) selected from Group G^{XC3} below, or

tetrahydropyranyl, tetrahydrofuranyl, 1,2-dihydropyridyl, thiazolyl, piperidinyl, morpholinyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, imidazo[1,2-a]pyridyl, or

benzothiazolyl, each of which may be substituted with group(s) selected from Group G^{XC3} below, and

G^{XC3} is

i) OH,

ii) lower alkyl which may be substituted with group(s) selected from the group consisting of OH; O-(lower alkyl which may be substituted with phenyl); N(lower alkyl)$_2$; cycloalkyl; pyridyl which may be substituted with lower alkyl; tetrahydropyranyl; and oxo (=O),

iii) O-(lower alkyl which may be substituted with O-(lower alkyl), phenyl, piperidinyl (in which the piperidinyl group may be substituted with lower alkyl which may be substituted with cycloalkyl or oxo (=O)), or oxo (=O)),

iv) NH-(lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O)),

v) cycloalkyl,

vi) 1,2-dihydropyridyl, pyridyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, oxazepanyl, or tetrahydropyranyl, each of which may be substituted with group(s) selected from the group consisting of OH; halogen; lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl which may be substituted with O-(lower alkyl)); and oxo (=O),

vii) O-(tetrahydropyranyl),

viii) SO_2-(lower alkyl),

ix) SO_2-(cycloalkyl), or

x) oxo (=O).

(64-5) X is H,

lower alkyl, O-(lower alkyl),

cycloalkyl which may be substituted with group(s) selected from Group G^{XC4} below,

cycloalkenyl which may be substituted with group(s) selected from Group G^{XC4}

phenyl which may be substituted with group(s) selected from Group G^{XC4}, or

tetrahydropyranyl, tetrahydrofuranyl, 1,2-dihydropyridyl, piperidinyl, pyridyl, pyrimidinyl, or imidazo[1,2-a]pyridyl, each of which may be substituted with group(s) selected from Group G^{XC4}, and

G^{XC4} is

i) OH,

ii) lower alkyl which may be substituted with group(s) selected from the group consisting of OH; O-(lower alkyl which may be substituted with phenyl); N(lower alkyl)$_2$; cycloalkyl; pyridyl which may be substituted with lower alkyl; tetrahydropyranyl; and oxo (=O),

iii) O-(lower alkyl which may be substituted with O-(lower alkyl), phenyl, piperidinyl (in which the piperidinyl group may be substituted with lower alkyl which may be substituted with cycloalkyl or oxo (=O)), or oxo (=O)),

iv) NH-(lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O)),

v) cycloalkyl,

vi) 1,2-dihydropyridyl, pyridyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or oxazepanyl, each of which may be substituted with group(s) selected from the group consisting of OH; halogen; lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl which may be substituted with O-(lower alkyl)); and oxo (=O),

vii) O-(tetrahydropyranyl),

viii) SO_2-(lower alkyl),

ix) SO_2-(cycloalkyl), or

x) oxo (=O).

(64-6) X is H,

lower alkyl, O-(lower alkyl),

cycloalkyl which may be substituted with OH or O-(lower alkyl which may be substituted with aryl or oxo (=O)),

cycloalkenyl which may be substituted with OH or O-(lower alkyl which may be substituted with aryl or oxo (=O)),

aryl which may be substituted with group(s) selected from the group consisting of lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl); and hetero ring group(s), or

a hetero ring group which may be substituted with group(s) selected from Group G^{XC5} below, and

G^{XC5} is

i) lower alkyl which may be substituted with group(s) selected from the group consisting of OH; O-(lower alkyl which may be substituted with aryl); N(lower alkyl)$_2$; cycloalkyl; hetero ring group(s) which may be substituted with lower alkyl; and oxo (=O),

ii) O-(lower alkyl which may be substituted with O-(lower alkyl) or hetero ring group(s) (in which the hetero ring group may be substituted with lower alkyl which may be substituted with cycloalkyl or oxo (=O))),

iii) NH-(lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O)),

iv) cycloalkyl,

v) hetero ring group(s) which may be substituted with group(s) selected from the group consisting of OH; halogen; lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl which may be substituted with O-(lower alkyl)); and oxo (=O),

vi) O-(hetero ring group),

vii) SO_2-(lower alkyl),

viii) SO_2-(cycloalkyl), or

ix) oxo (=O).

(64-7) X is H,

lower alkyl, O-(lower alkyl),

cycloalkyl which may be substituted with OH or O-(lower alkyl which may be substituted with phenyl or oxo (=O)),

cycloalkenyl which may be substituted with OH or O-(lower alkyl which may be substituted with phenyl or oxo (=O)),

aryl which may be substituted with group(s) selected from the group consisting of lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl); and nitrogen-containing monocyclic unsaturated hetero ring group(s), or

a hetero ring group which may be substituted with group(s) selected from Group G^{XC6} below, and

G^{XC6} is

i) lower alkyl which may be substituted with group(s) selected from the group consisting of OH; O-(lower alkyl which may be substituted with phenyl); $N(\text{lower alkyl})_2$; cycloalkyl; monocyclic hetero ring group(s) which may be substituted with lower alkyl; and oxo (=O),

ii) O-(lower alkyl which may be substituted with O-(lower alkyl) or nitrogen-containing monocyclic saturated hetero ring group(s) (in which the nitrogen-containing monocyclic saturated hetero ring group may be substituted with lower alkyl which may be substituted with cycloalkyl or oxo (=O))),

iii) NH-(lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O)),

iv) cycloalkyl,

v) monocyclic hetero ring group(s) which may be substituted with group(s) selected from the group consisting of OH; halogen; lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl which may be substituted with O-(lower alkyl)); and oxo (=O),

vi) O-(tetrahydropyranyl),

vii) SO_2-(lower alkyl),

viii) SO_2-(cycloalkyl), or

ix) oxo (=O).

(64-8) In (64-7), v) of Group G^{XC6} is

v) nitrogen-containing monocyclic hetero ring group(s) which may be substituted with group(s) selected from the group consisting of OH; halogen; lower alkyl which may

be substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl which may be substituted with O-(lower alkyl)); and oxo (=O).

(64-9) X is H,

lower alkyl, O-(lower alkyl),

cycloalkyl which may be substituted with OH or O-(lower alkyl which may be substituted with phenyl or oxo (=O)),

cycloalkenyl which may be substituted with OH or O-(lower alkyl which may be substituted with phenyl or oxo (=O)),

phenyl which may be substituted with group(s) selected from the group consisting of lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl); and pyridyl, or

tetrahydropyranyl, tetrahydrofuranyl, 1,2-dihydropyridyl, thiazolyl, azetidinyl, piperidinyl, morpholinyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, imidazo[1,2-a]pyridyl, or benzothiazolyl, each of which may be substituted with group(s) selected from Group G^{XC7} below, and

G^{XC7} is

i) lower alkyl which may be substituted with group(s) selected from the group consisting of OH; O-(lower alkyl which may be substituted with phenyl); N(lower alkyl)$_2$; cycloalkyl; pyridyl which may be substituted with lower alkyl; tetrahydropyranyl; and oxo (=O),

ii) O-(lower alkyl which may be substituted with O-(lower alkyl) or piperidinyl (in which the piperidinyl group may be substituted with lower alkyl which may be substituted with cycloalkyl or oxo (=O))),

iii) NH-(lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O)),

iv) cycloalkyl,

v) 1,2-dihydropyridyl, pyridyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, oxazepanyl, or tetrahydropyranyl, each of which may be substituted with group(s) selected from the group consisting of OH; halogen; lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl which may be substituted with O-(lower alkyl)); and oxo (=O),

vi) O-(tetrahydropyranyl),

vii) SO_2-(lower alkyl),

viii) SO_2-(cycloalkyl), or

ix) oxo (=O).

(64-10) X is H,

lower alkyl, O-(lower alkyl),

cycloalkyl which may be substituted with OH or O-(lower alkyl which may be substituted with phenyl or oxo (=O)),

cycloalkenyl which may be substituted with OH or O-(lower alkyl which may be substituted with phenyl or oxo (=O)),

phenyl which may be substituted with group(s) selected from the group consisting of lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl); and pyridyl, or

tetrahydropyranyl, tetrahydrofuranyl, 1,2-dihydropyridyl, azetidinyl, piperidinyl, pyridyl, pyrimidinyl, or imidazo[1,2-a]pyridyl, each of which may be substituted with group(s) selected from Group G^{XC8} below, and

G^{XC8} is

i) lower alkyl which may be substituted with group(s) selected from the group consisting of OH; O-(lower alkyl which may be substituted with phenyl); N(lower alkyl)$_2$; cycloalkyl; pyridyl which may be substituted with lower alkyl; tetrahydropyranyl; and oxo (=O),

ii) O-(lower alkyl which may be substituted with O-(lower alkyl) or piperidinyl (in which the piperidinyl group may be substituted with lower alkyl which may be substituted with cycloalkyl or oxo (=O))),

iii) NH-(lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O)),

iv) cycloalkyl,

v) 1,2-dihydropyridyl, pyridyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or oxazepanyl, each of which may be substituted with group(s) selected from the group consisting of OH; halogen; lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl which may be substituted with O-(lower alkyl)); and oxo (=O),

vi) O-(tetrahydropyranyl),

vii) SO_2-(lower alkyl),

viii) SO_2-(cycloalkyl), or

ix) oxo (=O).

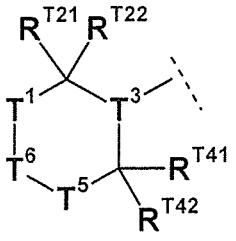
(65)

(65-1) X is

H, lower alkyl, or O-(lower alkyl), or

X is

[Chem. 48]



,

T^1 is a single bond, $CR^{T11}R^{T12}$, or NR^{T13}, T^3 is CR^{T31} or N, T^5 is a single bond or $CR^{T51}R^{T52}$, T^6 is a single bond, $CR^{T61}R^{T62}$, O, or NR^{T63},

R^{T11}, R^{T12}, R^{T13}, R^{T21}, R^{T22}, R^{T31}, R^{T41}, R^{T42}, R^{T51}, R^{T52}, R^{T61}, R^{T62} and R^{T63} are the same as or different from each other, and are

H,

OH,

lower alkyl which may be substituted with group(s) selected from the group consisting of O-(lower alkyl which may be substituted with aryl); $N(\text{lower alkyl})_2$; cycloalkyl; hetero ring group(s) which may be substituted with lower alkyl; and oxo (=O),

O-(lower alkyl which may be substituted with aryl or oxo (=O)),

a hetero ring group which may be substituted with group(s) selected from the group consisting of lower alkyl which may be substituted with OH or oxo (=O); and oxo (=O),

SO_2-(lower alkyl), or

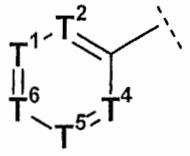
SO_2-(cycloalkyl), or

R^{T21} and R^{T31}, or R^{T41} and R^{T51} may be combined with each other to form a new bond, or

R^{T61} and R^{T62} may be combined with each other to form oxo (=O), or

X is

[Chem. 49]



,

T^1 is CR^{T12} or N, T^2 is CR^{T22} or N, T^4 is CR^{T42} or N, T^5 is CR^{T52} or N, T^6 is CR^{T62} or N,

R^{T12}, R^{T22}, R^{T42}, R^{T52} and R^{T62} are the same as or different from each other, and are

H,

lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O),

O-(lower alkyl which may be substituted with O-(lower alkyl) or hetero ring group(s) (in which the hetero ring group may be substituted with lower alkyl which may be substituted with cycloalkyl or oxo (=O))),

NH-(lower alkyl which may be substituted with O-(lower alkyl)),

cycloalkyl,

a hetero ring group which may be substituted with group(s) selected from the group consisting of OH; halogen; lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O); and O-(lower alkyl which may be substituted with O-(lower alkyl)), or

O-(hetero ring group), or

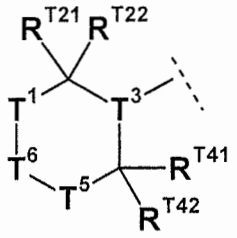
X is thiazolyl which may be substituted with morpholinyl or NH(lower alkyl which may be substituted with oxo (=O)), benzothiazolyl, or imidazo[1,2-a]pyridyl which may be substituted with lower alkyl.

(65-2) X is

H, lower alkyl, or O-(lower alkyl), or

X is

[Chem. 50]



,

T^1 is a single bond, $CR^{T11}R^{T12}$, or NR^{T13}, T^3 is CR^{T31} or N, T^5 is a single bond or $CR^{T51}R^{T52}$, T^6 is a single bond, $CR^{T61}R^{T62}$, O, or NR^{T63},

R^{T11}, R^{T12}, R^{T13}, R^{T21}, R^{T22}, R^{T31}, R^{T41}, R^{T42}, R^{T51}, R^{T52}, R^{T61}, R^{T62} and R^{T63} are the same as or different from each other, and are

H,

OH,

lower alkyl which may be substituted with group(s) selected from the group consisting of O-(lower alkyl which may be substituted with phenyl); N(lower alkyl)$_2$; cycloalkyl, monocyclic hetero ring group(s) which may be substituted with lower alkyl; and oxo (=O),

O-(lower alkyl which may be substituted with phenyl or oxo (=O)),

a monocyclic hetero ring group which may be substituted with group(s) selected from the group consisting of lower alkyl which may be substituted with OH or oxo (=O); and oxo (=O),

SO_2-(lower alkyl), or

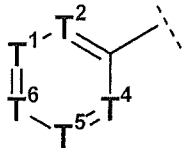
SO_2-(cycloalkyl), or

R^{T21} and R^{T31}, or R^{T41} and R^{T51} may be combined with each other to form a new bond, or

R^{T61} and R^{T62} may be combined with each other to form oxo (=O), or

X is

[Chem. 51]



,

T^1 is CR^{T12} or N, T^2 is CR^{T22} or N, T^4 is CR^{T42} or N, T^5 is CR^{T52} or N, T^6 is CR^{T62} or N,

R^{T12}, R^{T22}, R^{T42}, R^{T52} and R^{T62} are the same as or different from each other, and are

H,

lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O),

O-(lower alkyl which may be substituted with O-(lower alkyl) or nitrogen-containing monocyclic saturated hetero ring group(s) (in which the nitrogen-containing monocyclic saturated hetero ring group may be substituted with lower alkyl which may be substituted with cycloalkyl or oxo (=O))),

NH-(lower alkyl which may be substituted with O-(lower alkyl)),

cycloalkyl,

a monocyclic hetero ring group which may be substituted with group(s) selected from the group consisting of OH; halogen; lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O); and O-(lower alkyl which may be substituted with O-(lower alkyl)), or

O-(monocyclic hetero ring group), or

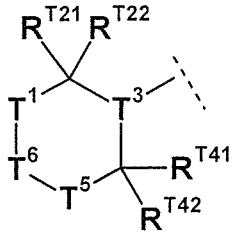
X is thiazolyl which may be substituted with morpholinyl or NH(lower alkyl which may be substituted with oxo (=O)), benzothiazolyl, or imidazo[1,2-a]pyridyl which may be substituted with lower alkyl.

(65-3) X is

H, lower alkyl, or O-(lower alkyl), or

X is

[Chem. 52]



,

T^1 is a single bond, $CR^{T11}R^{T12}$, or NR^{T13}, T^3 is CR^{T31} or N, T^5 is a single bond or $CR^{T51}R^{T52}$, T^6 is a single bond, $CR^{T61}R^{T62}$, O, or NR^{T63},

R^{T11}, R^{T12}, R^{T13}, R^{T21}, R^{T22}, R^{T31}, R^{T41}, R^{T42}, R^{T51}, R^{T52}, R^{T61}, R^{T62} and R^{T63} are the same as or different from each other, and are

H,

OH,

lower alkyl which may be substituted with group(s) selected from the group consisting of O-(lower alkyl which may be substituted with phenyl); N(lower alkyl)$_2$; cycloalkyl; monocyclic hetero ring group(s) which may be substituted with lower alkyl; and oxo (=O),

O-(lower alkyl which may be substituted with phenyl or oxo (=O)),

a nitrogen-containing monocyclic hetero ring group which may be substituted with group(s) selected from the group consisting of lower alkyl which may be substituted with OH or oxo (=O); and oxo (=O),

SO_2-(lower alkyl), or

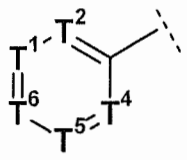
SO_2-(cycloalkyl), or

R^{T21} and R^{T31}, or R^{T41} and R^{T51} may be combined with each other to form a new bond, or

R^{T61} and R^{T62} may be combined with each other to form oxo (=O), or

X is

[Chem. 53]



,

T^1 is CR^{T12} or N, T^2 is CR^{T22} or N, T^4 is CR^{T42} or N, T^5 is CR^{T52} or N, T^6 is CR^{T62} or N,

R^{T12}, R^{T22}, R^{T42}, R^{T52} and R^{T62} are the same as or different from each other, and are

H,

lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O),

O-(lower alkyl which may be substituted with O-(lower alkyl) or nitrogen-containing monocyclic saturated hetero ring group(s) (in which the nitrogen-containing monocyclic saturated hetero ring group may be substituted with lower alkyl which may be substituted with cycloalkyl or oxo (=O))),

NH-(lower alkyl which may be substituted with O-(lower alkyl)),

cycloalkyl,

a nitrogen-containing monocyclic hetero ring group which may be substituted with group(s) selected from the group consisting of OH; halogen; lower alkyl which may

be substituted with O-(lower alkyl) or oxo (=O); and O-(lower alkyl which may be substituted with O-(lower alkyl)), or

O-(monocyclic saturated hetero ring group), or

X is thiazolyl which may be substituted with morpholinyl or NH(lower alkyl which may be substituted with oxo (=O)), benzothiazolyl, or imidazo[1,2-a]pyridyl which may be substituted with lower alkyl.

(65-4) X is

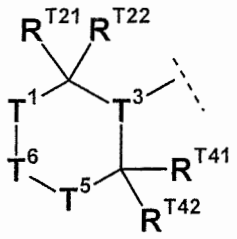
H,

lower alkyl, or

O-(lower alkyl), or

X is

[Chem. 54]



,

T^1 is a single bond, $CR^{T11}R^{T12}$, or NR^{T13}, T^3 is CR^{T31} or N, T^5 is a single bond or $CR^{T51}R^{T52}$, T^6 is a single bond, $CR^{T61}R^{T62}$, O, or NR^{T63},

R^{T11}, R^{T12}, R^{T13}, R^{T21}, R^{T22}, R^{T31}, R^{T41}, R^{T42}, R^{T51}, R^{T52}, R^{T61}, R^{T62} and R^{T63} are the same as or different from each other, and are

H,

OH,

lower alkyl which may be substituted with group(s) selected from the group consisting of O-(lower alkyl which may be substituted with phenyl); N(lower alkyl)$_2$; cycloalkyl; pyridyl which may be substituted with lower alkyl; tetrahydropyranyl; and oxo (=O),

O-(lower alkyl which may be substituted with phenyl or oxo (=O)),

1,2-dihydropyridyl, pyridyl, or tetrahydropyranyl, each of which may be substituted with group(s) selected from the group consisting of lower alkyl which may be substituted with OH or oxo (=O); and oxo (=O),

SO_2-(lower alkyl), or

SO_2-(cycloalkyl), or

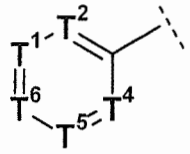
R^{T21} and R^{T31}, or R^{T41} and R^{T51} may be combined with each other to form a new bond, or

R^{T61} and R^{T62} may be combined with each other to form oxo (=O),

or,

X is

[Chem. 55]



,

T^1 is CR^{T12} or N, T^2 is CR^{T22} or N, T^4 is CR^{T42} or N, T^5 is CR^{T52} or N, T^6 is CR^{T62} or N,

R^{T12}, R^{T22}, R^{T42}, R^{T52} and R^{T62} are the same as or different from each other, and are

H,

lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O),

O-(lower alkyl which may be substituted with O-(lower alkyl) or piperidinyl (in which the piperidinyl group may be substituted with lower alkyl which may be substituted with cycloalkyl or oxo (=O))),

NH-(lower alkyl which may be substituted with O-(lower alkyl)),

cycloalkyl,

pyridyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or oxazepanyl, each of which may be substituted with group(s) selected from the group consisting of OH; halogen; lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O); and O-(lower alkyl which may be substituted with O-(lower alkyl)), or

O-(tetrahydropyranyl), or

X is thiazolyl which may be substituted with morpholinyl or NH(lower alkyl which may be substituted with oxo (=O)), benzothiazolyl, or imidazo[1,2-a]pyridyl which may be substituted with lower alkyl.

(65-5) X is

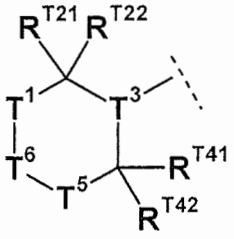
H,

lower alkyl, or

O-(lower alkyl), or

X is

[Chem. 56]



,

T^1 is a single bond, $CR^{T11}R^{T12}$, or NR^{T13}, T^3 is CR^{T31} or N, T^5 is a single bond or $CR^{T51}R^{T52}$, T^6 is a single bond, $CR^{T61}R^{T62}$, O, or NR^{T63},

R^{T11}, R^{T12}, R^{T13}, R^{T21}, R^{T22}, R^{T31}, R^{T41}, R^{T42}, R^{T51}, R^{T52}, R^{T61}, R^{T62} and R^{T63} are the same as or different from each other, and are

H,

OH,

lower alkyl which may be substituted with group(s) selected from the group consisting of O-(lower alkyl which may be substituted with phenyl); N(lower alkyl)$_2$; cycloalkyl; pyridyl which may be substituted with lower alkyl; tetrahydropyranyl; and oxo (=O),

O-(lower alkyl which may be substituted with phenyl or oxo (=O)),

1,2-dihydropyridyl or pyridyl, each of which may be substituted with group(s) selected from the group consisting of lower alkyl which may be substituted with OH or oxo (=O); and oxo (=O),

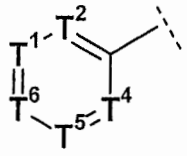
SO_2-(lower alkyl), or

SO_2-(cycloalkyl), or

R^{T21} and R^{T31}, or R^{T41} and R^{T51} may be combined with each other to form a new bond, or R^{T61} and R^{T62} may be combined with each other to form oxo (=O), or

X is

[Chem. 57]



,

T^1 is CR^{T12} or N, T^2 is CR^{T22} or N, T^4 is CR^{T42} or N, T^5 is CR^{T52} or N, T^6 is CR^{T62} or N,

R^{T12}, R^{T22}, R^{T42}, R^{T52} and R^{T62} are the same as or different from each other, and are

H,

lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O),

O-(lower alkyl which may be substituted with O-(lower alkyl) or piperidinyl (in which the piperidinyl group may be substituted with lower alkyl which may be substituted with cycloalkyl or oxo (=O))),

NH-(lower alkyl which may be substituted with O-(lower alkyl)),

cycloalkyl,

pyridyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or oxazepanyl, each of which may be substituted with group(s) selected from the group

consisting of OH; halogen; lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O); and O-(lower alkyl which may be substituted with O-(lower alkyl)), or

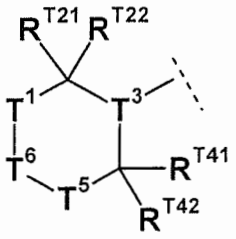
O-(tetrahydropyranyl), or

X is thiazolyl which may be substituted with morpholinyl or NH(lower alkyl which may be substituted with oxo (=O)), benzothiazolyl, or imidazo[1,2-a]pyridyl which may be substituted with lower alkyl.

(66)

(66-1) In (65-1) to (65-5), X is

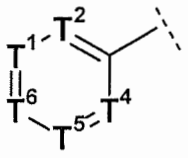
[Chem. 58]



, or

X is

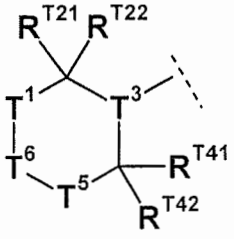
[Chem. 59]



.

(66-2) In (65-1) to (65-5), X is

[Chem. 60]



.

(66-3) In (66-1) to (66-2),

R^{T11}, R^{T12}, R^{T13}, R^{T21}, R^{T22}, R^{T31}, R^{T41}, R^{T42}, R^{T51}, R^{T52}, R^{T61}, R^{T62} and R^{T63} are the same as or different from each other, and are

H,

OH,

lower alkyl which may be substituted with group(s) selected from the group consisting of O-(lower alkyl which may be substituted with phenyl); N(lower alkyl)$_2$;

cycloalkyl; monocyclic hetero ring group(s) which may be substituted with lower alkyl; and oxo (=O),

O-(lower alkyl which may be substituted with phenyl or oxo (=O)),

a monocyclic hetero ring group which may be substituted with group(s) selected from the group consisting of lower alkyl which may be substituted with OH or oxo (=O); and oxo (=O),

SO_2-(lower alkyl), or

SO_2-(cycloalkyl), or

R^{T21} and R^{T31}, or R^{T41} and R^{T51} may be combined with each other to form a new bond, or

R^{T61} and R^{T62} may be combined with each other to form oxo (=O).

(66-4) In (66-1) to (66-2),

R^{T11}, R^{T12}, R^{T13}, R^{T21}, R^{T22}, R^{T31}, R^{T41}, R^{T42}, R^{T51}, R^{T52}, R^{T61}, R^{T62} and R^{T63} are the same as or different from each other, and are

H,

OH,

lower alkyl which may be substituted with group(s) selected from the group consisting of O-(lower alkyl which may be substituted with phenyl); $N(\text{lower alkyl})_2$; cycloalkyl; pyridyl which may be substituted with lower alkyl; tetrahydropyranyl; and oxo (=O),

O-(lower alkyl which may be substituted with phenyl or oxo (=O)),

1,2-dihydropyridyl or pyridyl, each of which may be substituted with group(s) selected from the group consisting of lower alkyl which may be substituted with OH or oxo (=O); and oxo (=O),

SO_2-(lower alkyl), or

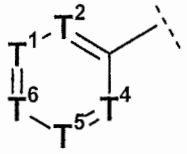
SO_2-(cycloalkyl), or

R^{T21} and R^{T31}, or R^{T41} and R^{T51} may be combined with each other to form a new bond, or

R^{T61} and R^{T62} may be combined with each other to form oxo (=O).

(66-5) In (65-1) to (65-5), X is

[Chem. 61]



(67)

(67-1) In (66-1) to (66-4),

T^1 is $CR^{T11}R^{T12}$ or NR^{T13}, T^3 is CR^{T31}, T^5 is $CR^{T51}R^{T52}$, T^6 is $CR^{T61}R^{T62}$, or NR^{T63},

R^{T11}, R^{T12}, R^{T13}, R^{T21}, R^{T22}, R^{T31}, R^{T41}, R^{T42}, R^{T51}, R^{T52}, R^{T61} and R^{T62} are the same as or different from each other, and are

H, or lower alkyl, or

R^{T61} and R^{T62} may be combined with each other to form oxo (=O),

R^{T63} is lower alkyl which may be substituted with group(s) selected from the group consisting of O-(lower alkyl); N(lower alkyl)$_2$; cycloalkyl; hetero ring group(s) which may be substituted with lower alkyl; and oxo (=O),

a monocyclic hetero ring group which may be substituted with group(s) selected from the group consisting of lower alkyl which may be substituted with OH or oxo (=O); and oxo (=O),

SO_2-(lower alkyl), or

SO_2-(cycloalkyl), or

R^{T21} and R^{T31}, or R^{T41} and R^{T51} may be combined with each other to form a new bond.

(67-2) In (67-1),

R^{T63} is lower alkyl which may be substituted with group(s) selected from the group consisting of O-(lower alkyl); N(lower alkyl)$_2$; cycloalkyl; nitrogen-containing monocyclic unsaturated hetero ring group(s) which may be substituted with lower alkyl; monocyclic saturated hetero ring group(s); and oxo (=O),

a nitrogen-containing monocyclic hetero ring group which may be substituted with group(s) selected from the group consisting of lower alkyl which may be substituted with OH or oxo (=O); and oxo (=O),

SO_2-(lower alkyl), or

SO_2-(cycloalkyl).

(67-3) In (67-1) to (67-2),

R^{T63} is lower alkyl which may be substituted with group(s) selected from the group consisting of O-(lower alkyl); N(lower alkyl)$_2$; cyclopropyl; pyridyl which may be substituted with lower alkyl; tetrahydropyranyl; and oxo (=O),

1,2-dihydropyridyl or pyridyl, each of which may be substituted with group(s) selected from the group consisting of lower alkyl which may be substituted with OH or oxo (=O); and oxo (=O),

SO_2-(lower alkyl), or

SO_2-(cyclopropyl).

(67-4)

(67-4-1) In (66-1) to (66-4), and (67-1) to (67-3),

R^{T11}, R^{T12}, R^{T21}, R^{T22}, R^{T31}, R^{T41} and R^{T42} are H,

R^{T51} and R^{T52} are the same as or different from each other, and are H, lower alkyl, or O-(lower alkyl),

R^{T61} and R^{T62} are the same as or different from each other, and are H, OH, O-(lower alkyl which may be substituted with aryl or oxo (=O)), or a monocyclic hetero ring group,

R^{T13} is H or lower alkyl, or

R^{T61} and R^{T62} may be combined with each other to form oxo (=O), or

R^{T21} and R^{T31}, or R^{T41} and R^{T51} may be combined with each other to form a new bond.

(67-4-2) In (66-1) to (66-4), and (67-1) to (67-3),

R^{T11}, R^{T12}, R^{T21}, R^{T22}, R^{T31}, R^{T41} and R^{T42} are H,

R^{T51} and R^{T52} are the same as or different from each other, and are H, lower alkyl, or O-(lower alkyl),

R^{T61} and R^{T62} are the same as or different from each other, and are H, OH, O-(lower alkyl which may be substituted with phenyl or oxo (=O)), or a monocyclic saturated hetero ring group,

R^{T13} is H or lower alkyl, or

R^{T61} and R^{T62} may be combined with each other to form oxo (=O), or

R^{T21} and R^{T31}, or R^{T41} and R^{T51} may be combined with each other to form a new bond.

(67-4-3) In (66-1) to (66-4), and (67-1) to (67-3),

R^{T11}, R^{T12}, R^{T21}, R^{T22}, R^{T31}, R^{T41} and R^{T42} are H,

R^{T51} and R^{T52} are the same as or different from each other, and are H, lower alkyl, or O-(lower alkyl),

R^{T61} and R^{T62} are the same as or different from each other, and are H, OH, O-(lower alkyl which may be substituted with phenyl or oxo (=O)), or tetrahydropyranyl,

R^{T13} is H or lower alkyl, or

R^{T61} and R^{T62} may be combined with each other to form oxo (=O), or

R^{T21} and R^{T31}, or R^{T41} and R^{T51} may be combined with each other to form a new bond.

(67-5) In (67-1) to (67-3),

R^{T11}, R^{T12}, R^{T21}, R^{T22}, R^{T31}, R^{T41}, R^{T42}, R^{T51}, R^{T52}, R^{T61} and R^{T62} are H,

R^{T13} is H or lower alkyl, or

R^{T61} and R^{T62} may be combined with each other to form oxo (=O), or

R^{T21} and R^{T31}, or R^{T41} and R^{T51} may be combined with each other to form a new bond.

(67-6) In (67-1) to (67-5),

T^1 is $CR^{T11}R^{T12}$, T^3 is CR^{T31}, T^5 is $CR^{T51}R^{T52}$, and T^6 is NR^{T63}.

(67-7) In (67-1) to (67-5),

T^1 is NR^{T13}, T^3 is CR^{T31}, T^5 is $CR^{T51}R^{T52}$, and T^6 is $CR^{T61}R^{T62}$.

(68) E is a single bond, or lower alkylene which may be substituted with oxo (=O).

(69)

(69-1) G is a single bond, O, NH, or N(lower alkyl).

(69-2) G is a single bond, O, or NH.

(70) J is a single bond or lower alkylene.

(71)

(71-1) L is O, NH, or N(lower alkyl).

(71-2) L is O or NH.

(72)

(72-1) U is a single bond, O, NH, N(lower alkyl which may be substituted with O-(lower alkyl)), SO_2, or lower alkylene which may be substituted with oxo (=O).

(72-2) U is a single bond, O, NH, N(lower alkyl), SO_2, or lower alkylene which may be substituted with oxo (=O).

(72-3) U is a single bond, O, or lower alkylene.

(72-4) U is a single bond, O, NH, or N(lower alkyl which may be substituted with O-(lower alkyl)).

(72-5) U is a single bond or O.

(73)

(73-1) V is a single bond, O, NH, N(lower alkyl), or lower alkylene which may be substituted with OH, O-(lower alkyl), or oxo (=O).

(73-2) V is a single bond, O, N(lower alkyl), or lower alkylene which may be substituted with oxo (=O).

(73-3) V is a single bond, O, or lower alkylene.

(73-4) V is a single bond or lower alkylene which may be substituted with OH, O-(lower alkyl), or oxo (=O).

(73-5) V is a single bond, O, or lower alkylene which may be substituted with oxo (=O).

(73-6) V is a single bond, or lower alkylene which may be substituted with oxo (=O).

(74)

(74-1) W is a single bond, SO, SO_2, or lower alkylene.

(74-2) W is a single bond, SO, or SO_2.

(74-3) W is a single bond or lower alkylene.

(74-4) W is a single bond.

(75) R^1, R^2, R^3 and R^4 are the same as or different from each other, and are H, halogen, or lower alkyl.

(76) R^{T61} is H.

[0058]

Furthermore, other embodiments of the compound (I) of the present invention include compounds or salts thereof including a consistent combination of two or more groups among the groups described in (1) to (56) above, and specifically, the following compounds or salts thereof.

(77) The compound of the formula (I), wherein A is as described in (1).

(78) The compound of the formula (I), wherein A is as described in (2).

(79) The compound as described in (77) to (78), wherein R^{Q12}, R^{Q22}, R^{Q42} and R^{Q52} are as described in (4).

(80) The compound as described in (77) to (79), wherein Q^1, Q^2, Q^4 and Q^5 are as described in (6).

(81) The compound as described in (77) to (80), wherein R^1, R^2, R^3 and R^4 are as described in (13).

(82) The compound as described in (77) to (81), wherein E is as described in (14).

(83) The compound as described in (77) to (82), wherein G is as described in (16).

(84) The compound as described in (77) to (83), wherein J is as described in (19).

(85) The compound as described in (77) to (84), wherein L is as described in (21).

(86) The compound as described in (77) to (85), wherein U is as described in (24).

(87) The compound as described in (77) to (86), wherein V is as described in (27).

(88) The compound as described in (77) to (87), wherein W is as described in (28).

(89) The compound as described in (77) to (88), wherein X is as described in (31).

(90) The compound as described in (89), wherein R^{T11}, R^{T12}, R^{T21}, R^{T22}, R^{T31}, R^{T41}, R^{T42}, R^{T51} and R^{T52} are as described in (33).

(91) The compound as described in (89) to (90), wherein R^{T63} is as described in (39).

(92) The compound as described in (89) to (91), wherein T^1, T^2, T^3, T^4, T^5 and T^6 are as described in (40).

(93) The compound as described in (89) to (91), wherein T^1, T^2, T^3, T^4, T^5 and T^6 are as described in (41).

(94) The compound as described in (89) to (91), wherein T^1, T^2, T^3, T^4, T^5 and T^6 are as described in (42).

(95) The compound as described in (89) to (91), wherein T^1, T^2, T^3, T^4, T^5 and T^6 are as described in (43).

(96) The compound as described in (89) to (95), wherein m is as described in (55).

(97) The compound as described in (89) to (95), wherein m is as described in (56).

(98) The compound of the formula (I), wherein A is as described in (3).

(99) The compound as described in (77) or (98), wherein R^{Q11}, R^{Q12}, R^{Q13}, R^{Q31}, R^{Q51}, R^{Q52}, R^{Q53} and R^{Q61} are as described in (5).

(100) The compound as described in (77), or (98) to (99), wherein Q^1, Q^3, Q^5 and Q^6 are as described in (9).

(101) The compound as described in (77), or (98) to (99), wherein Q^1, Q^3, Q^5 and Q^6 are as described in (12).

(102) The compound as described in (98) to (101), wherein R^1, R^2, R^3 and R^4 are as described in (13).

(103) The compound as described in (98) to (102), wherein E is as described in (14).

(104) The compound as described in (98) to (103), wherein G is as described in (16).

(105) The compound as described in (98) to (104), wherein J is as described in (19).

(106) The compound as described in (98) to (105), wherein L is as described in (21).

(107) The compound as described in (98) to (106), wherein U is as described in (23).

(108) The compound as described in (98) to (107), wherein V is as described in (26).

(109) The compound as described in (98) to (108), wherein W is as described in (28).

(110) The compound as described in (98) to (109), wherein X is as described in (31).

(111) The compound as described in (110), wherein R^{T11}, R^{T12}, R^{T21}, R^{T22}, R^{T31}, R^{T41}, R^{T42}, R^{T51} and R^{T52} are as described in (33).

(112) The compound as described in (110) to (111), wherein R^{T63} is as described in (39).

(113) The compound as described in (110) to (112), wherein T^1, T^2, T^3, T^4, T^5 and T^6 are as described in (40).

(114) The compound as described in (110) to (112), wherein T^1, T^2, T^3, T^4, T^5 and T^6 are as described in (41).

(115) The compound as described in (110) to (112), wherein T^1, T^2, T^3, T^4, T^5 and T^6 are as described in (42).

(116) The compound as described in (110) to (115), wherein m is as described in (55).

(117) The compound as described in (110) to (115), wherein m is as described in (56).

In addition, still other embodiments of the compound (I) of the present invention include compounds or salts thereof including a consistent combination of two or more groups, among the groups described in (1) to (56) and (76) above, and specifically, the following compounds or salts thereof.

(118) The compound as described in (77) to (117), wherein R^{T61} is as described in (76).

(119) The compound as described in (77) to (117), or (118), wherein R^{T62} is as described in (36) to (38).

[0059]

In addition, further still other embodiments of the compound (I) of the present invention include compounds or salts thereof including a consistent combination of two or more groups, among the groups described in (1) to (76) above, and specifically, the following compounds or salts thereof.

(120) The compound of the formula (I), wherein A is as described in (1) or (57).

(121) The compound of the formula (I), wherein A is as described in (2) or (58).

(122) The compound as described in (120) to (121), wherein R^1, R^2, R^3 and R^4 are as described in (13) or (75).

(123) The compound as described in (120) to (122), wherein E is as described in (14), (15), or (68).

(124) The compound as described in (120) to (123), wherein G is as described in (16), (17), (18), or (69).

(125) The compound as described in (120) to (124), wherein J is as described in (19), (20), or (70).

(126) The compound as described in (120) to (125), wherein L is as described in (21), (22), or (71).

(127) The compound as described in (120) to (126), wherein U is as described in (23), (24), (25), or (72).

(128) The compound as described in (120) to (127), wherein V is as described in (26), (27), or (73).

(129) The compound as described in (120) to (128), wherein W is as described in (28), (29), or (74).

(130) The compound as described in (120) to (129), wherein X is as described in (60) or (61).

(131) The compound as described in (120) to (129), wherein X is as described in (31), or (62) to (63).

(132) The compound as described in (131), wherein R^{T11}, R^{T12}, R^{T21}, R^{T22}, R^{T31}, R^{T41}, R^{T42}, R^{T51} and R^{T52} are as described in (33).

(133) The compound as described in (131) to (132), wherein R^{T61} is as described in (76).

(134) The compound as described in (131) to (133), wherein R^{T62} is as described in (36) to (38).

(135) The compound as described in (131) to (134), wherein R^{T63} is as described in (39).

(136) The compound as described in (131) to (135), wherein T^1, T^2, T^3, T^4, T^5 and T^6 are as described in (40).

(137) The compound as described in (131) to (135), wherein T^1, T^2, T^3, T^4, T^5 and T^6 are as described in (41).

(138) The compound as described in (131) to (135), wherein T^1, T^2, T^3, T^4, T^5 and T^6 are as described in (42).

(139) The compound as described in (131) to (135), wherein T^1, T^2, T^3, T^4, T^5 and T^6 are as described in (43).

(140) The compound as described in (131) to (139), wherein m is as described in (55).

(141 The compound as described in (131) to (139), wherein m is as described in (56).

(142) The compound as described in (I), wherein A is as described in (3) or (59).

(143) The compound as described in (120), or (142), wherein R^1, R^2, R^3 and R^4 are as described in (13) or (75).

(144) The compound as described in (120), or (142) to (143), wherein E is as described in (14), (15), or (68).

(145) The compound as described in (120), or (142) to (144), wherein G is as described in (16), (17), (18), or (69).

(146) The compound as described in (120), or (142) to (145), wherein J is as described in (19), (20), or (70).

(147) The compound as described in (120), or (142) to (146), wherein L is as described in (21), (22), or (71).

(148) The compound as described in (120), or (142) to (147), wherein U is as described in (23), (24), (25), or (72).

(149) The compound as described in (120), or (142) to (148), wherein V is as described in (26), (27), or (73).

(150) The compound as described in (120), or (142) to (149), wherein W is as described in (28), (29), or (74).

(151) The compound as described in (120), or (142) to (150), wherein X is as described in (60), (61), or (64).

(152) The compound as described in (120), or (142) to (150), wherein X is as described in (31), (65) to (67).

(153) The compound as described in (152), wherein R^{T11}, R^{T12}, R^{T21}, R^{T22}, R^{T31}, R^{T41}, R^{T42}, R^{T51} and R^{T52} are as described in (33).

(154) The compound as described in (152) to (153), wherein R^{T61} is as described in (76).

(155) The compound as described in (152) to (154), wherein R^{T62} is as described in (36) to (38).

(156) The compound as described in (152) to (155), wherein R^{T63} is as described in (39).

(157) The compound as described in (152) to (156), wherein T^1, T^2, T^3, T^4, T^5 and T^6 are as described in (40).

(158) The compound as described in (152) to (156), wherein T^1, T^2, T^3, T^4, T^5 and T^6 are as described in (41).

(159) The compound as described in (152) to (156), wherein T^1, T^2, T^3, T^4, T^5 and T^6 are as described in (42).

(160) The compound as described in (152) to (159), wherein m is as described in (55).

(161) The compound as described in (152) to (159), wherein m is as described in (56).

[0060]

Specific examples of the compound encompassed by the present invention include the following compounds or salts thereof:

1-carbamimidoyl-3-{3-[2-(morpholin-4-yl)pyrimidin-5-yl)benzyl}urea,

2-fluoro-3-[2-(morpholin-4-yl)pyrimidin-5-yl]benzyl carbamimidoylcarbamate,

3-{2-[(3S)-3-fluoropyrrolidin-1-yl]pyrimidin-5-yl}benzyl carbamimidoylcarbamate,

N-{4-[2-(3-{[(carbamimidoylcarbamoyl)amino]methyl}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide,

2-fluoro-3-[2-(3-methoxyazetidin-1-yl)pyrimidin-5-yl]benzyl carbamimidoylcarbamate,

2-fluoro-3-[4-(pyridin-4-yl)piperidin-1-yl]benzyl carbamimidoylcarbamate,

3-(4-{4-[5-(3-{[(carbamimidoylcarbamoyl)oxy]methyl}-2-fluorophenyl)pyrimidin-2-yl]piperazin-1-yl}phenyl)propanoic acid,

2-fluoro-3-{4-[2-(3-methoxyazetidin-1-yl)pyrimidin-5-yl]piperazin-1-yl}benzyl carbamimidoylcarbamate,
2-fluoro-3-{4-[2-(4-hydroxy-4-methylpiperidin-1-yl)pyrimidin-5-yl]piperazin-1-yl}benzyl carbamimidoylcarbamate,
2-fluoro-3-(4-{2-[(3R)-3-fluoropyrrolidin-1-yl]pyrimidin-5-yl}piperazin-1-yl)benzyl carbamimidoylcarbamate,
2-fluoro-3-[4-(2-methoxypyrimidin-5-yl)piperazin-1-yl]benzyl carbamimidoylcarbamate,
3-{2-[(1-acetylpiperidin-4-yl)methoxy]pyrimidin-5-yl}-2-fluorobenzyl carbamimidoylcarbamate,
3-(2-{[1-(cyclopropylcarbonyl)piperidin-4-yl]methoxy}pyrimidin-5-yl)-2-fluorobenzyl carbamimidoylcarbamate,
2-fluoro-3-(2-{[1-(pyridin-3-ylcarbonyl)piperidin-4-yl]methoxy}pyrimidin-5-yl)benzyl carbamimidoylcarbamate,
2-fluoro-3-{4-[(trans-4-methoxycyclohexyl)carbonyl]piperazin-1-yl}benzyl carbamimidoylcarbamate,
2-fluoro-3-[4-(tetrahydro-2H-pyran-4-ylacetyl)piperazin-1-yl]benzyl carbamimidoylcarbamate,
3-[4-(ethylsulfonyl)piperazin-1-yl]-2-fluorobenzyl carbamimidoylcarbamate,
3-{4-[(1-acetylpiperidin-4-yl)oxy]piperidin-1-yl}-2-fluorobenzyl carbamimidoylcarbamate,
1-(3-{2-[(1-acetylpiperidin-4-yl)methoxy]pyrimidin-5-yl}-2-fluorobenzyl)-3-carbamimidoylurea,
2-fluoro-3-[4-(pyridin-3-yl)piperazin-1-yl]benzyl carbamimidoylcarbamate,
2-fluoro-3-[4-(6-methylpyridin-3-yl)piperazin-1-yl]benzyl carbamimidoylcarbamate,
2-fluoro-3-[3-oxo-4-(pyridin-3-yl)piperazin-1-yl]benzyl carbamimidoylcarbamate,
2-fluoro-3-{3-[(1-propionylpiperidin-4-yl)oxy]azetidin-1-yl}benzyl carbamimidoylcarbamate,
2-fluoro-3-{3-[(6-methylpyridin-3-yl)oxy]azetidin-1-yl}benzyl carbamimidoylcarbamate,
2-fluoro-3-(3-{[6-(methoxymethyl)pyridin-3-yl]oxy}azetidin-1-yl)benzyl carbamimidoylcarbamate,
3-{3-[(2,6-dimethylpyridin-4-yl)methoxy]azetidin-1-yl}-2-fluorobenzyl carbamimidoylcarbamate,
2-fluoro-3-{4-[6-(methoxymethyl)pyridin-3-yl]piperazin-1-yl}benzyl carbamimidoylcarbamate,
2-fluoro-3-[4-(imidazo[1,2-a]pyridin-7-yl)piperazin-1-yl]benzyl carbamimidoylcarbamate,

2-fluoro-3-{3-[(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)oxy]azetidin-1-yl}benzyl carbamimidoylcarbamate,
2-fluoro-3-{4-[5-(methoxymethyl)pyridin-3-yl)piperazin-1-yl}benzyl carbamimidoylcarbamate,
2-fluoro-3-{4-[2-(2-methoxyethoxy)pyridin-4-yl]piperazin-1-yl}benzyl carbamimidoylcarbamate,
3-[3-(1-acetylpiperidin-4-yl)azetidin-1-yl]-2-fluorobenzyl carbamimidoylcarbamate,
2-fluoro-3-[3-(1-propionylpiperidin-4-yl)azetidin-1-yl]benzyl carbamimidoylcarbamate,
3-{3-[1-(cyclopropylcarbonyl)piperidin-4-yl]azetidin-1-yl}-2-fluorobenzyl carbamimidoylcarbamate,
2-fluoro-3-{3-[1-(methoxyacetyl)piperidin-4-yl]azetidin-1-yl}benzyl carbamimidoylcarbamate,
2-fluoro-3-{3-[1-(3-methoxypropanoyl)piperidin-4-yl]azetidin-1-yl}benzyl carbamimidoylcarbamate,
2-fluoro-3-{3-[1-(methylsulfonyl)piperidin-4-yl]azetidin-1-yl}benzyl carbamimidoylcarbamate, or
2-fluoro-3-{4-[2-(methoxymethyl)pyridin-4-yl]piperazin-1-yl}benzyl carbamimidoylcarbamate.

[0061]

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 form of isomer, yet the present invention includes other isomers, an isolated form of the isomers, or a mixture thereof.

In addition, the compound of the formula (I) may have asymmetric carbon atoms or axial asymmetry in some cases, and correspondingly, it may exist in the form of optical isomers based thereon. The present invention includes both an isolated form of the optical isomers of the compound of the formula (I) or a mixture thereof.

[0062]

Moreover, the present invention also includes a pharmaceutically acceptable prodrug of the compound represented by 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, Drug Design, 163-198.

[0063]

Furthermore, 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, phosphoric acid, and the like, 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, glutamic acid, and the like, and salts with inorganic bases such as sodium, potassium, magnesium, calcium, aluminum, and the like or organic bases such as methylamine, ethylamine, ethanolamine, lysine, ornithine, and the like, salts with various amino acids or amino acid derivatives such as acetylleucine and the like, ammonium salts, etc.

[0064]

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

[0065]

(Preparation Methods)

The compound of the formula (I) and 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 (4^{th} 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.

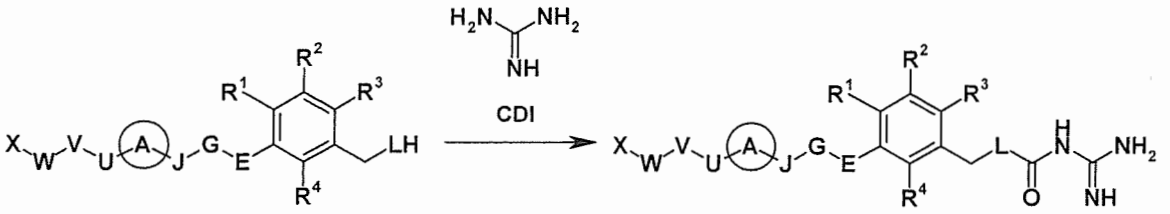
In addition, the prodrug of the compound of the formula (I) can be prepared by introducing a specific group at the stage from a starting material to an intermediate, as in the case of the above-mentioned protective group, or by carrying out the reaction using the obtained compound of the formula (I).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

Hereinbelow, the representative preparation methods for the compound of the formula (I) will be described. Each of the production processes 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 as shown below. Further, depending on the compounds, the preparation method can be carried out while changing the sequence of the production processes.

[0066]

(Production Process 1)

[Chem. 62]



(29) (I)

The compound (I) of the present invention can be obtained by the condensation of the compound (29) with guanidine in the presence of 1,1'-carbonyldiimidazole (CDI).

In this reaction, the compound (29) and guanidine in an equivalent amount or an excess amount are used, and a mixture thereof is stirred in a range of from cooling to heating, preferably at -20°C to 60°C, usually for about 0.1 hours to 5 days, in a solvent which is inert to the reaction, in the presence of CDI. The solvent as used herein is not particularly limited, but examples thereof 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, dimethoxyethane, and the like, DMF, DMSO, EtOAc, acetonitrile, or water, and a mixture thereof. It may be in some cases advantageous for smooth progress of the reaction to carry out the reaction in the presence of organic bases such as triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, DBU, and the like, or inorganic bases such as sodium hydride, potassium carbonate, sodium carbonate, potassium hydroxide, and the like.

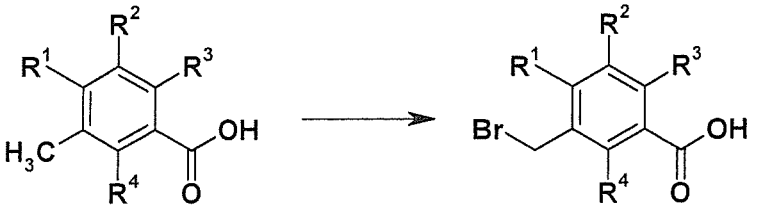
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Synthesis 2006, 4, 629-632

[0067]

(Starting Material Synthesis 1)

[Chem. 63]



(1) (2)

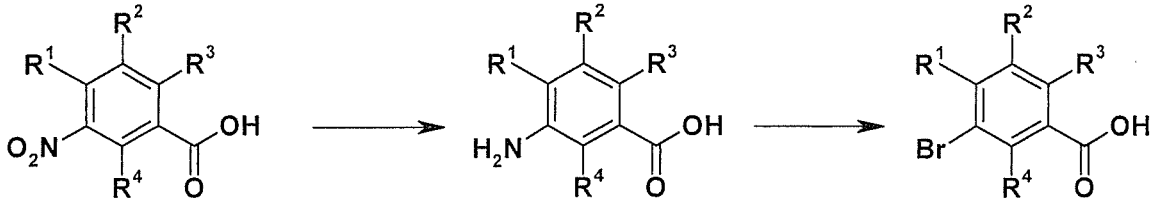
The compound (2) can be obtained by the bromination reaction of the compound (1).

For the bromination reaction, the compound (1) and a brominating agent in an equivalent amount or an excess amount are used, and a mixture thereof is stirred in a range of from cooling to heating and refluxing, preferably at -20°C to 200°C, and more preferably at a temperature from -10°C to 150°C, usually for about 0.1 hours to 5 days, without a solvent or in a solvent which is inert to the reaction. The solvent as used herein is not particularly limited, but examples thereof include alcohols such as methanol, ethanol, tert-butanol, and the like, ethers such as diethyl ether, tetrahydrofuran, dioxane, dimethoxyethane, and the like, halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, chloroform, and the like, N,N-dimethylformamide, dimethylsulfoxide, and a mixture thereof. It may be in some cases advantageous for smooth progress of the reaction to carry out the reaction in the presence of a Lewis acid such as aluminum chloride ($AlCl_3$), boron trifluoride (BF_3), and the like, or a radical initiator such as α,α'-azobisisobutyronitrile (AIBN) and the like. Examples of the brominating reagent include N-bromosuccinimide, in addition to bromine (Br_2).

[0068]

(Starting Material Synthesis 2)

[Chem. 64]



(3) (4) (42)

The compound (4) can be obtained by the reduction reaction of a compound (3).

In this reaction, the compound (3) is treated by using a reducing agent in an equivalent amount or an excess amount, or a metallic catalyst in a catalytic amount or an excess amount in a range of from cooling to heating, preferably at -20°C to 80°C, usually for about 0.1 hours to 3 days, in a solvent which is inert to the reaction. The solvent as

used herein is not particularly limited, but examples thereof include ethers such as diethyl ether, tetrahydrofuran, dioxane, dimethoxyethane, and the like, alcohols such as methanol, ethanol, 2-propanol, and the like, aromatic hydrocarbons such as benzene, toluene, xylene, and the like, N,N-dimethylformamide, dimethylsulfoxide, ethyl acetate, and a mixture thereof. As the reducing agent, metal reducing agents such as zinc, iron, tin, and the like, and reducing agents described in the documents below are suitably used. Alternatively, in the reaction using a metal catalyst such as palladium, platinum, and the like, hydrogen gas atmosphere or ammonium formate is used as a hydrogen source.

[Documents]

M. Hudlicky, "Reductions in Organic Chemistry, 2nd Ed. (ACS Monograph: 188)", ACS, 1996

R. C. Larock, "Comprehensive Organic Transformations", 2nd Ed., VCH Publishers, Inc., 1999

T. J. Donohoe, "Oxidation and Reduction in Organic Synthesis (Oxford Chemistry Primers 6)", Oxford Science Publications, 2000

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

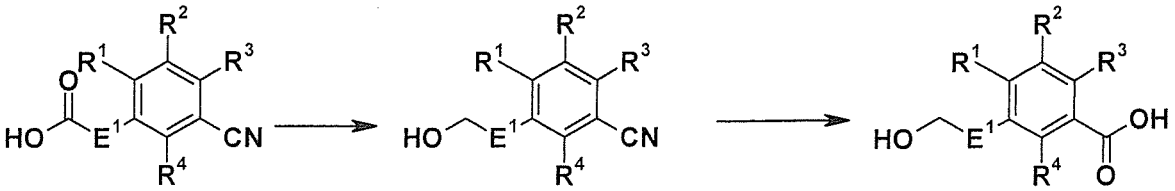
The compound (42) can be obtained by subjecting the compound (4) to a Sandmeyer's Reaction.

In this reaction, the compound (4) is converted into a diazonium salt by reaction of the compound (4) in the presence of hydrogen halide and sodium nitrite in an equivalent amount or an excess amount, in a range of from cooling to heating, preferably at -20°C to 80°C, usually for about 0.1 hours to 3 days, in a solvent which is inert to the reaction. The solvent as used herein is not particularly limited, but examples thereof include ethers such as diethyl ether, tetrahydrofuran, dioxane, dimethoxyethane, and the like, alcohols such as methanol, ethanol, 2-propanol, and the like, aromatic hydrocarbons such as benzene, toluene, xylene, and the like, N,N-dimethylformamide, dimethylsulfoxide, ethyl acetate, and a mixture thereof. Next, the compound (42) can be obtained by reaction of the obtained diazonium salt of the compound (4) in the presence of copper (I) halide in an equivalent amount or an excess amount, in a range of from room temperature to heating, preferably at -20°C to 80°C, usually for about 0.1 hours to 3 days, in a solvent which is inert to the reaction. The solvent as used herein is not particularly limited, but examples thereof include ethers such as diethyl ether, tetrahydrofuran, dioxane, dimethoxyethane, and the like, alcohols such as methanol, ethanol, 2-propanol, and the like, aromatic hydrocarbons such as benzene, toluene, xylene, and the like, N,N-dimethylformamide, dimethylsulfoxide, ethyl acetate, and a mixture thereof. Further, examples of the copper (I) halide as used herein include copper (I) chloride and copper (I) bromide.

[0069]

(Starting Material Synthesis 3)

[Chem. 65]



(5) (6) (7)

(wherein E^1 represents lower alkylene which may be substituted having a number of carbon atoms one less than that of carbon atoms in lower alkylene which may be substituted in E).

The compound (6) can be obtained by the reduction reaction of the compound (5).

In this reduction reaction, the compound (5) is converted into an ester or treated with CDI, and then treated with a reducing agent in an equivalent amount or an excess amount in a range of from cooling to heating, preferably at -78°C to 120°C, usually for about 0.1 hours to 3 days, in a solvent which is inert to the reaction. The solvent as used herein is not particularly limited, but examples thereof include ethers such as diethyl ether, tetrahydrofuran, dioxane, dimethoxyethane, and the like, aromatic hydrocarbons such as benzene, toluene, xylene, and the like, and a mixture thereof. As the reducing agent, sodium borohydride, diisobutylaluminum hydride, or the like is suitably used.

A compound (7) can be obtained by the hydrolysis reaction of a compound (6).

In this hydrolysis reaction, the compound (6) is treated with an acid or base in an equivalent amount or an excess amount in a range of from cooling to heating, preferably at 25°C to 120°C, usually for about 0.1 hours to 3 days, in a solvent which is inert to the reaction. The solvent as used herein is not particularly limited, but examples thereof include ethers such as diethyl ether, tetrahydrofuran, dioxane, dimethoxyethane, and the like, aromatic hydrocarbons such as benzene, toluene, xylene, and the like, N,N-dimethylformamide, dimethylsulfoxide, water, and a mixture thereof. As the acid, for example, hydrochloric acid, sulfuric acid, or the like is suitably used. As the base, sodium hydroxide, lithium hydroxide, or the like is suitably used, and the reaction is carried out in the presence of hydrogen peroxide, it maybe advantageous in the reaction to proceed smoothly.

[Documents]

B. M. Trost, "Comprehensive Organic Synthesis", Vol. 7, 1991

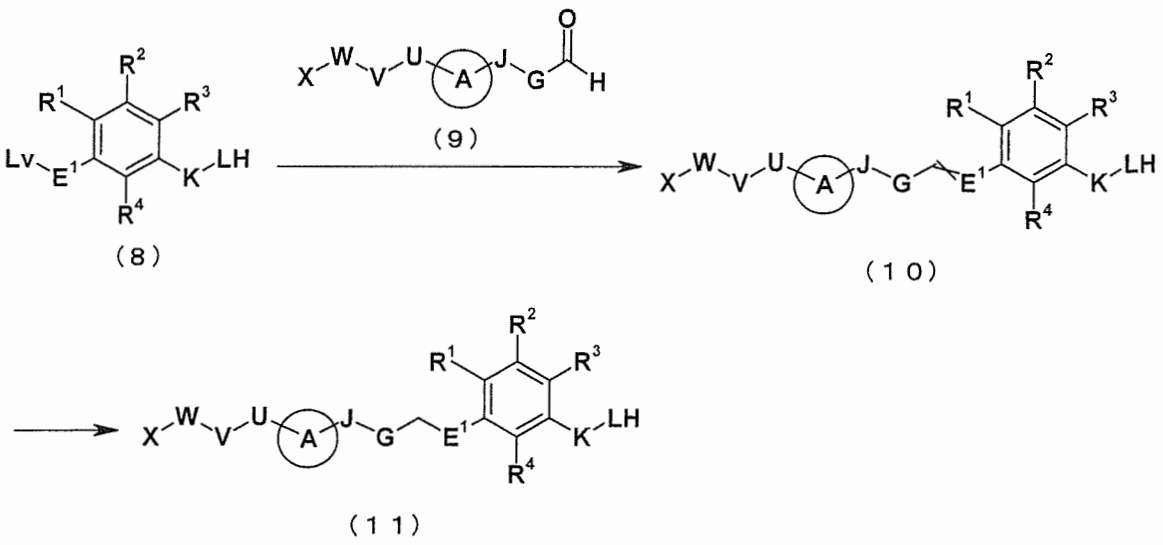
M. Hudlicky, "Oxidation in Organic Chemistry (ACS Monograph: 186)", ACS, 1990

"Jikken Kagaku Koza" (Courses in Experimental Chemistry) (5th Edition), edited by The Chemical Society of Japan, Vol. 17 (2005) (Maruzen)

[0070]

(Starting Material Synthesis 4)

[Chem. 66]



(8) (9) (10) (11)

(wherein Lv represents a leaving group, K represents CH_2 or C(=O), and when K is C(=O), L represents O).

A compound (10) can be synthesized by subjecting the compound (8) to a Wittig reaction. Here, examples of the leaving group, Lv, include halogen, a methanesulfonyloxy group, a p-toluenesulfonyloxy group, and the like.

In this reaction, the compound (8) is converted into a phosphonium salt in the presence of a phosphorous compound in an equivalent amount or in an excess amount in a range of from cooling to heating, preferably at -20°C to 150°C, usually for about 0.1 hours to 3 days, in a solvent which is inert to the reaction. The solvent as used herein is not particularly limited, but examples thereof include ethers such as diethyl ether, tetrahydrofuran, dioxane, dimethoxyethane, and the like, aromatic hydrocarbons such as benzene, toluene, xylene, and the like, N,N-dimethylformamide, dimethylsulfoxide, and a mixture thereof. As the phosphorous compound, for example, an alkyltriphenylphosphonium salt is suitably used, and specific examples thereof include (methoxymethyl)triphenylphosphonium chloride, (methylthiomethyl)triphenylphosphonium chloride, and the like. Thereafter, the phosphonium salt of the compound (8) and the compound (9) are converted into the compound (10) by treating them in a range of from cooling to heating, preferably at -20°C to 80°C, usually for about 0.1 hours to 3 days, in a solvent which is inert to the reaction. The solvent as used herein is not particularly limited, but examples thereof include ethers such as diethyl ether, tetrahydrofuran, dioxane, dimethoxyethane, and the like, aromatic hydrocarbons such as benzene, toluene, xylene, and the like, N,N-dimethylformamide, dimethylsulfoxide, and a mixture thereof. It may be in some cases advantageous for

smooth progress of the reaction to carry out the reaction in the presence of a base such as sodium bis(trimethylsilyl)amide, n-butyllithium, potassium tert-butoxide, sodium ethoxide, sodium methoxide, and the like.

The compound (11) can be obtained by the hydrogenation reaction of the compound (10).

In this reaction, the compound (10) is stirred under hydrogen atmosphere, preferably at normal pressure to 3 atm., in a range of from cooling to heating, preferably at room temperature to 50°C, usually for about 1 hour to 5 days, in the presence of a metallic catalyst, in a solvent which is inert to the reaction. The solvent as used herein is not particularly limited, but examples thereof include alcohols such as methanol, ethanol, 2-propanol, and the like, ethers such as diethyl ether, tetrahydrofuran, dioxane, dimethoxyethane, and the like, water, ethyl acetate, N,N-dimethylformamide, dimethylsulfoxide, and a mixture thereof. As the metal catalyst, palladium catalysts such as palladium carbon, palladium black, palladium hydroxide, and the like, platinum catalysts such as a platinum plate, platinum oxide, and the like, nickel catalysts such as reduced nickel, Raney nickel, and the like, rhodium catalysts such as tetrakistriphenylphosphine chlororhodium, and the like, or iron catalysts such as reduced iron and the like are suitably used. Instead of the hydrogen gas, formic acid or ammonium formate in an equivalent amount or an excess amount may also be used as a hydrogen source, relative to the compound (10).

[Documents]

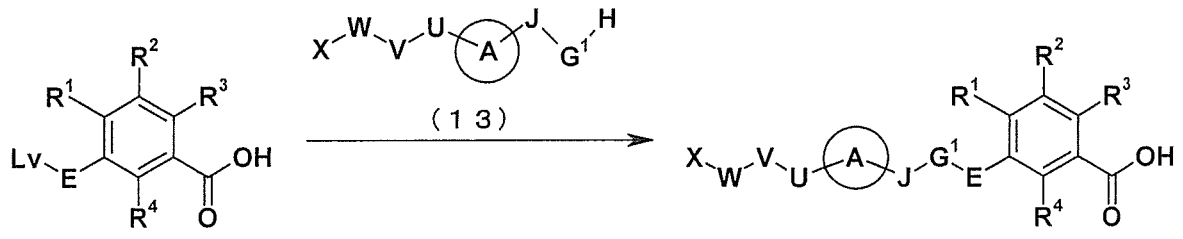
M. Hudlicky, "Reductions in Organic Chemistry, 2nd ed (ACS Monograph: 188)", ACS, 1996

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

[0071]

(Starting Material Synthesis 5)

[Chem. 67]



(wherein G^1 represents O, NH, N(lower alkyl which may be substituted)).

The compound (14) can be obtained by the substitution reaction of the compound (12) and the compound (13).

In this reaction, the compound (12) and the compound (13) in an equivalent amount or an excess amount are used, a mixture thereof is stirred in a range of from cooling to heating and refluxing, preferably at 0°C to 200°C, and more preferably at 60°C to 150°C, usually for 0.1 hours to 5 days in a solvent which is inert to the reaction or without a solvent. It is in some cases advantageous for smooth progress of the reaction to carry out the reaction under irradiation with microwaves. The solvent used herein is not particularly limited, but examples thereof include alcohols such as methanol, ethanol, tert-butanol, and the like, aromatic hydrocarbons such as benzene, toluene, xylene, and the like, ethers such as diethyl ether, tetrahydrofuran, dioxane, 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. It may be advantageous in some cases for the smooth progress of the reaction to carry out the reaction in the presence of an organic base such as triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, and the like, or an inorganic base such as sodium tert-butoxide, potassium carbonate, sodium bis(methylsilyl)amide, sodium carbonate, potassium hydroxide, and the like.

Furthermore, the reaction may be carried out by using a catalyst which is not particularly limited, but includes catalysts used for Ullmann reaction, a Buchwald-Hartwig reaction, or the like. The catalyst as used herein is not particularly limited, but a suitable combination of tris(dibenzylideneacetone)palladium, tetrakis(triphenylphosphine)palladium, or the like with 4,5-bis(diphenylphosphino)-9,9'-dimethylxanthene (Xantphos), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (XPhos), and the like can be used.

[Documents]

S. R. Sandler and W. Karo, "Organic Functional Group Preparations", 2nd Ed., Vol. 1, Academic Press Inc., 1991

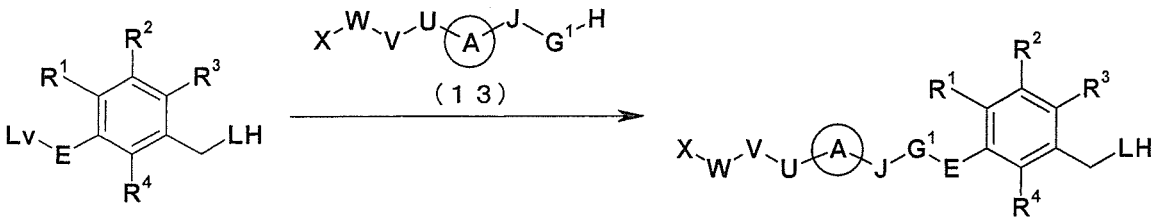
"Jikken Kagaku Koza" (Courses in Experimental Chemistry) (5th Edition), edited by The Chemical Society of Japan, Vol. 14 (2005) (Maruzen)

Synthesis 2006, 4, 629 to 632

[0072]

(Starting Material Synthesis 6)

[Chem. 68]



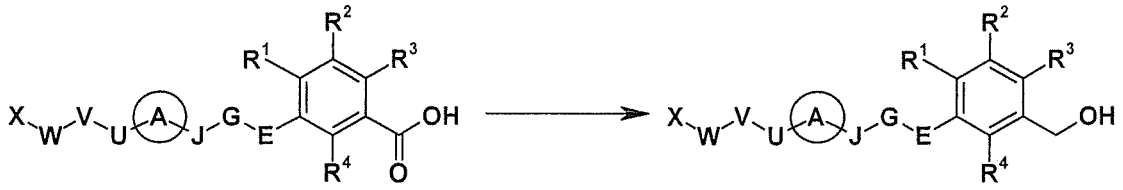
(15) (13) (16)

The compound (16) can be obtained by the substitution reaction of the compound (15) and the compound (13). This reaction can be carried out using the same conditions as for the substitution reaction in Starting Material Synthesis 5.

[0073]

(Starting Material Synthesis 7)

[Chem. 69]



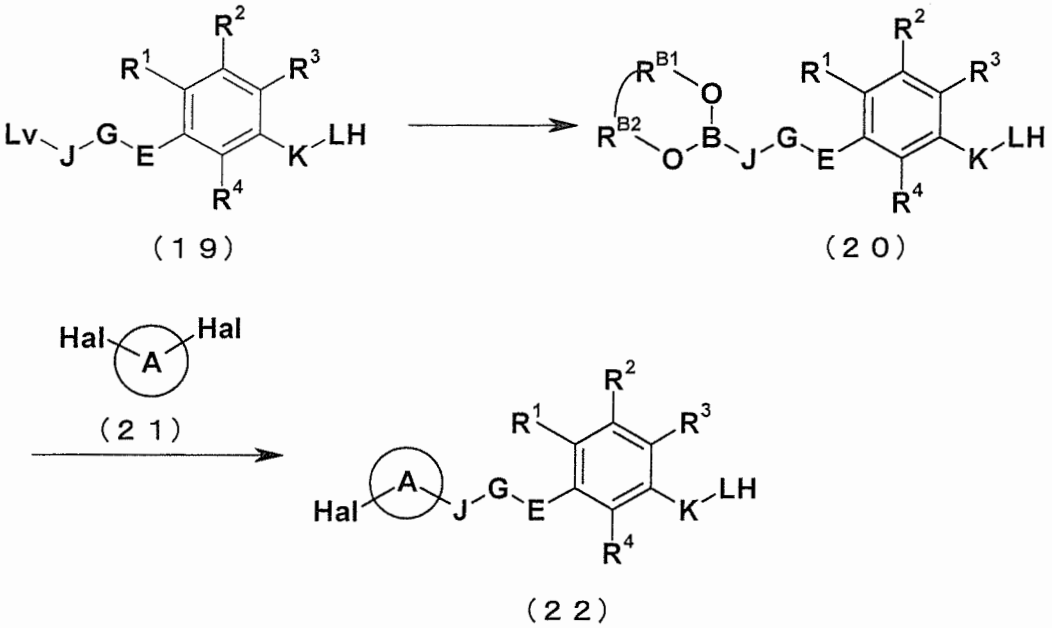
(17) (18)

The compound (18) can be obtained by the reduction reaction of the compound (17). The present reaction can be carried out using the same reaction conditions in Starting Material Synthesis 3. As the reducing agent in the present reaction, lithium aluminum hydride, borane, sodium borohydride, diisobutylaluminum hydride, or the like can be used.

[0074]

(Starting Material Synthesis 8)

[Chem. 70]



(19) (20)

(21) (22)

(R^{B1} and R^{B2} are the same as or different from each other, and are H or lower alkyl, or R^{B1} and R^{B2} are combined with each other to represent lower alkylene).

The compound (20) can be obtained by formation reaction of boronate ester of the compound (19).

For the reaction, a mixture of the compound (19) and the reagent for the formation of boronate ester in an equivalent amount or an excess amount is stirred in a range of from cooling to heating, preferably at -20°C to 60°C, usually for about 0.1 hours to 5 days, in a solvent which is inert to the reaction, in the presence of an organic metal compound. The solvent as used herein is not particularly limited, but examples thereof 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, dimethoxyethane, and the like, DMF, DMSO, EtOAc, acetonitrile, water, and a mixture thereof. Examples of the reagent for the formation of boronate ester include triisopropyl borate, tributyl borate, and the like. Examples of the organic metal compound as used in the present reaction include organic lithium compounds such as n-butyl lithium and the like.

Furthermore, the compound (22) can be obtained by the coupling reaction of the compound (20) and the compound (21).

In this reaction, a mixture of the compound (20) and the compound (21) in an equivalent amount or an excess amount is stirred in a range of from cooling to heating and refluxing, and preferably 0°C to 80°C, in a solvent which is inert to the reaction or without a solvent, usually for 0.1 hours to 5 days. The solvent as used herein is not particularly limited, but examples thereof include aromatic hydrocarbons such as benzene, toluene,

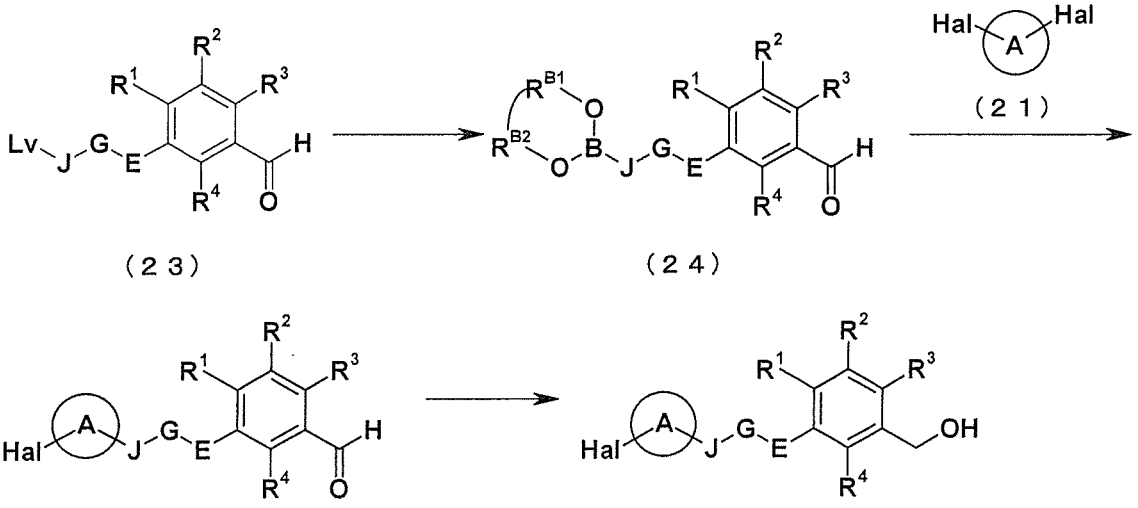
xylene, and the like, ethers such as dimethyl ether, diethyl ether, tetrahydrofuran, dioxane, dimethoxyethane, and the like, halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, chloroform, and the like, N,N-dimethylformamide, dimethylsulfoxide, ethyl acetate, acetonitrile and a mixture thereof. It may be in some cases advantageous for smooth progress of the reaction to carry out the reaction in the presence of organic bases such as triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, and the like, or inorganic bases such as potassium carbonate, sodium carbonate, potassium phosphate, potassium hydroxide, and the like.

Furthermore, the reaction can also be carried out using, for example, a catalyst used for the Suzuki-Miyaura cross-coupling reaction, but is not limited thereto. The catalyst as used herein is not particularly limited, but tetrakis(triphenylphosphine)palladium (0), palladium acetate (II), dichloro[1,1'-bis(diphenylphosphenylphosphino)ferrocene]palladium (II), bistriphenylphosphine palladium chloride (II), or the like can be used. Further, the coupling reaction can also be carried out using metal palladium (0).

[0075]

(Starting Material Synthesis 9)

[Chem. 71]



The compound (24) can be prepared by foramtion reaction of boronate ester of the compound (23). This reaction can be carried out using the same reaction conditions as in Starting Material Synthesis 8 as described above.

The compound (25) can be obtained by the coupling reaction of the compound (24) and the compound (21). This reaction can be carried out using the same reaction conditions as in Starting Material Synthesis 8 as described above.

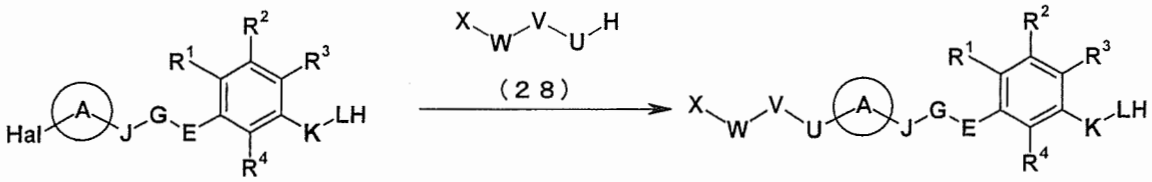
Furthermore, a compound (26) can be obtained by the reduction reaction of the compound (25). In this reduction reaction, the compound (25) is treated with a reducing

agent in an equivalent amount or an excess amount in a range of from cooling to heating, preferably at -78°C to 120°C, usually for about 0.1 hours to 3 days, in a solvent which is inert to the reaction. The solvent as used herein is not particularly limited, but examples thereof include ethers such as diethyl ether, tetrahydrofuran, dioxane, dimethoxyethane, and the like, aromatic hydrocarbons such as benzene, toluene, xylene, and the like, and a mixture thereof. As the reducing agent, sodium borohydride, diisobutylaluminum hydride, or the like is suitably used.

[0076]

(Starting Material Synthesis 10)

[Chem. 72]



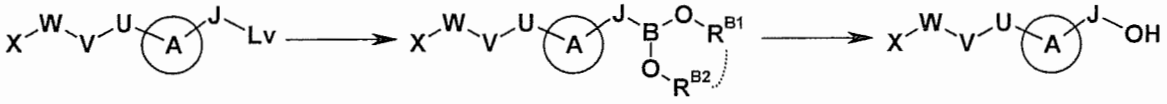
(27) (29)

The compound (29) can be obtained by the substitution reaction of the compound (27) and the compound (28). This reaction can be carried out using the same reaction conditions in Starting Material Synthesis 5.

[0077]

(Starting Material Synthesis 11)

[Chem. 73]



(29) (30) (31)

The compound (30) can be prepared by the boronic acid esterification reaction of the compound (29). This reaction can be carried out using the same reaction conditions as in Starting Material Synthesis 8 as described above.

The compound (31) can be obtained by the hydrolysis reaction of the compound (30).

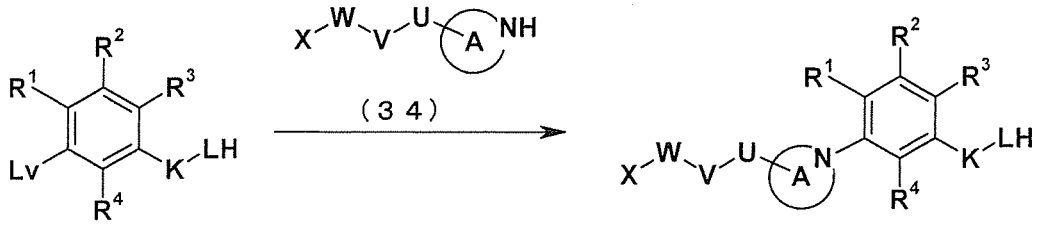
In this reaction, a mixture of the compound (30) and water in an equivalent amount or an excess amount is stirred in a range of from cooling to heating and refluxing, preferably at 0°C to 80°C, usually for about 0.1 hours to 5 hours, in a solvent which is inert to the reaction or without a solvent. The solvent as used herein is not particularly limited, but examples thereof include aromatic hydrocarbons such as benzene, toluene, xylene, and the like, ethers such as dimethyl ether, diethyl ether, tetrahydrofuran, dioxane, 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 oxidant include sodium perborate·hexahydrate, aqueous hydrogen peroxide, and the like.

[0078]

(Starting Material Synthesis 12)

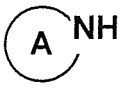
[Chem. 74]



(33) (35)

(wherein

[Chem. 75]



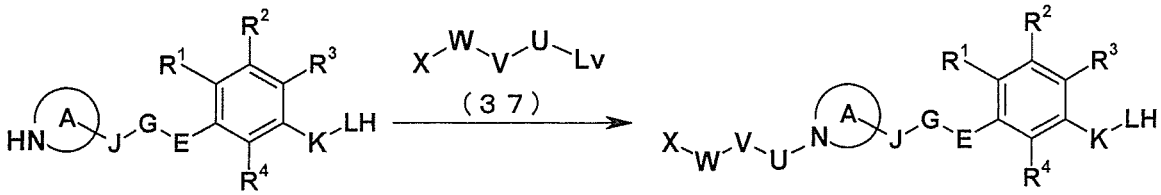
represents a nitrogen-containing hetero ring group which may be substituted, and the substituent represents an acceptable substituent in the hetero ring group which may be substituted in A).

The compound (35) can be obtained by the substitution reaction of the compound (33) and the compound (34). This reaction can be carried out using the same conditions as for the substitution reaction in Starting Material Synthesis 5.

[0079]

(Starting Material Synthesis 13)

[Chem. 76]



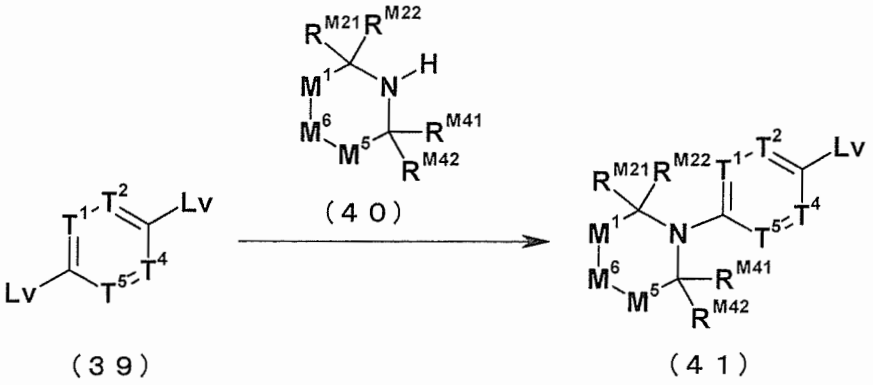
(36) (38)

The compound (38) can be obtained by the substitution reaction of the compound (36) and the compound (37). This reaction can be carried out using the same conditions as for the substitution reaction in Starting Material Synthesis 5.

[0080]

(Starting Material Synthesis 14)

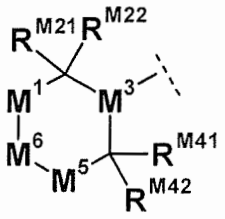
[Chem. 77]



(39) (40) (41)

(wherein in the formula:

[Chem. 78]



,

M^1 is a single bond or $CR^{M11}R^{M12}$, M^3 is CR^{M31} or N, M^5 is a single bond or $(CR^{M51}R^{M52})_n$, M^6 is $CR^{M61}R^{M62}$, O, or NR^{M63}, wherein either one of M^3 and M^6 is N, R^{M11}, R^{M12}, R^{M21}, R^{M22}, R^{M31}, R^{M41}, R^{M42}, R^{M51}, R^{M52}, R^{M61}, R^{M62} and R^{M63} are the same as or different from each other, and are H, OH, halogen, lower alkyl which may be substituted, O-(lower alkyl which may be substituted), or SO_2-(lower alkyl which may be substituted), or R^{M21} and R^{M31} may be combined with each other to form a new bond, or R^{M11} and R^{M12}, R^{M21} and R^{M22}, R^{M41} and R^{M42}, R^{M51} and R^{M52}, or R^{M61} and R^{M62} may be combined with each other to form oxo (=O), and n is 1 or 2).

The compound (41) among the compounds (37) can be obtained by the substitution reaction of the compound (39) and the compound (40). This reaction can be carried out using the same conditions as for the substitution reaction in Starting Material Synthesis 5.

[0081]

The compounds of the formula (I) can be isolated and purified as their free compounds, salts, hydrates, solvates, or polymorphic crystalline substances thereof. The salts of the compound of the formula (I) can be prepared by carrying out the treatment of a conventional salt forming reaction.

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

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

[0082]

The pharmacological activity of the compound of the formula (I) was confirmed by the tests shown below.

[0083]

Test Example 1: Inhibitory Effect on Human VAP-1 Enzyme (SSAO) Activity

A human VAP-1 enzyme (SSAO) (reference: J Exp Med. 1998 Jul 6; 188(1): 17 to 27) activity was measured by a radiochemistry-enzymatic assay using ^{14}C-benzylamine as an artificial substrate. After homogenizing CHO (Chinese Hamster Ovary) cells stably expressing a human VAP-1 enzyme (SSAO) in a 50 mM phosphate buffer containing 1% NP-40, an enzyme suspension was obtained by taking the supernatant obtained by centrifugation. The enzyme suspension was preincubated with the compound of the present invention in a 96-well microplate at room temperature for 30 minutes. Subsequently, the enzyme suspension was incubated with ^{14}C-benzylamine (a final concentration of 1×10^{-5} mol/L) to a final volume of 50 mL at 37°C for 1 hour. The enzymatic reaction was stopped by the addition of 2 mol/L (50 μL) of citric acid. The oxidation products were extracted directly into a 200μL toluene scintillator, and the radioactivity was measured with a scintillation spectrometer.

Test Example 2: Inhibitory Effect on Rat VAP-1 Enzyme (SSAO) Activity

A rat VAP-1 enzyme (SSAO) (reference: Biol Pharm Bull. 2005 Mar; 28(3): 413-8) activity was measured by a radiochemistry-enzymatic assay using ^{14}C-benzylamine as an artificial substrate. After homogenizing CHO (Chinese Hamster Ovary) cells stably expressing a rat VAP-1 enzyme (SSAO) in a 50 mM phosphate buffer containing 1% NP-40, an enzyme suspension was obtained by taking the supernatant obtained by centrifugation. The enzyme suspension was preincubated with the compound of the present invention in a 96-well microplate at room temperature for 30 minutes. Subsequently, the enzyme suspension was incubated with ^{14}C-benzylamine (a final concentration of 1×10^{-5} mol/L) to a final volume of 50 mL at 37°C for 1 hour. The enzymatic reaction was stopped by the addition of 2 mol/L (50 μL) of citric acid. The oxidation products were extracted directly in a 200μL toluene scintillator, and the radioactivity was measured with a scintillation spectrometer.

The results are shown in Table 1. In addition, the inhibitory activity is expressed as an IC_{50} (nmol/L) value. Further, Ex in the tables represents Example No.

[0084]

[Table 1]

Ex	human (nM)	rat (nM)
11	5.2	2.2
29	7.2	1.9
52	23	1.7
63	3.4	1.1
74	5.3	1.8
81	9.7	3.9
83	25	1.9
105	14	2.6
110	32	1.4
118	29	1.7
126	15	0.53
157	49	2.1
178	33	4.4
220	25	1
273	19	0.95
293	19	0.97
300	19	1.7
304	34	6.6
316	11	0.9

Ex	human (nM)	rat (nM)
322	51	22
335	11	2
551	14	1.8
552	25	5.5
553	20	3
554	21	0.97
555	20	3.5
556	2.7	1.3
557	11	1.6
558	23	1.2
559	4.3	0.81
560	9	1.4
561	9.6	1.6
562	14	1.4
563	20	1.5
564	19	1.5
565	19	2.5
566	6.3	1.2
567	4.3	0.81

[0085]

From these test, it was confirmed that the compound of the present invention has an extremely high inhibitory activity on human and rat VAP-1.

Test Example 3: Inhibitory Effect on Rat VAP-1 Enzyme (SSAO) Activity in Rat Plasma

Eight-week to twelve-week Wistar male rats were fasted for 20 hours, and orally administered with a test drug (0.3 mg/1 kg). Heparin blood collection from the tail vein was performed immediately before the administration, and at 1 h, 3 h, 6 h, 12 h, or 24 h after the administration. The resulting blood was subjected to centrifugation at 14000 rpm for 5 minutes to separate plasma, and the VAP-1 enzyme activity in the resulting plasma was measured by a radio-enzyme assay method.

For the radio-enzyme assay method, ^{14}C-benzylamine which is a synthetic substrate (10 μM) was reacted with the resulting plasma at 37°C, and the resulting metabolite was extracted with a mixture of toluene/ethyl acetate. The radioactivity was measured and taken as a VAP-1 enzyme activity in the plasma. The effect of the test drug was calculated from the inhibitory ratio (%) of the VAP-1 activity after the administration of the test drug relative to the VAP-1 activity in the plasma immediately before the administration. Further, Ex in the tables represents Example No.

Reference Document: Diabetologia (1997) 40 1243-1250

[0086]

[Table 2]

Ex	Inhibition Ratio (%)				
	1h	3h	6h	12h	24h
11	64	70	63		12
29	46	60	58		22
52	90	68	52	37	
63	83	87	80	68	
74	79	74	81		40
81	78	78	78	53	
83	34	66	86	53	
105	22	38	31		6
110	96	96	95		75
118	87	86	88		59
126	98	97	97		69
157	95	91	80		39
178	63	73	67	80	
220	80	80	84		27
273	55	74	54		19
293	59	83	72		60
300	92	93	88		85
304	52	56	56		18
316	91	99	98	91	
322	40	55	50	38	
335	82	84	86	83	
551	68	59	51		5
552	93	81	75		24
553	67	57	50		40
554	99	100	87		72
555	67	69	54		27
556	55	70	46		19
557	53	71	56		22
558	84	87	81		62
559	86	89	82		59
560	89	91	84		58
561	91	92	85		64
562	79	81	78		37
563	69	77	70		43
564	89	90	85		59
565	77	83	71		47
566	75	74	70		38
567	86	89	82		59

Test Example 4: Effect on Albuminuria in Rats with Diabetes Mellitus

Seven- to eight-week SD rats (having weights up to 200 to 250 g during fasting) were used and fasted for 20 hours, and then intraperitoneally administered with 60 mg/ml/kg of streptozotocin (STZ) prepared with a 2 mmol/l citric acid buffer (pH 4.5). At the same time, the control rats were injected with the same amount of a 2 mmol/l citric acid buffer (pH 4.5). The blood glucose value was measured using a colorimetric method, and the rats that had showed a value of 350 mg/dl blood glucose levels on day 3 after the treatment with STZ were diagnosed with diabetes mellitus.

The test substance was given daily for 4 weeks after the treatment with STZ. After 4 weeks of the treatment with the test substance, 24-hour urine collection was performed using metabolic cages.

The amounts of urinary albunmin excretion after 4 weeks were 67 (mg/gCr) and 236 (mg/gCr) with the control group and the STZ-treated group, respectively, and the amount of urinary albunmin excretion of the STZ-treated group increased 3.5 times than that of the control group. On the other hand, as a result of the oral administration of the compound of Example 11 in the amount of 0.3 mg/kg once daily, an amount of urinary albunmin excretion was 103 (mg/gCr), which was decreased to 1.5 times than that of the control group.

Furthermore, in the test with the compound of Example 557, the amount of urinary albunmin excretion after 4 weeks were 45 (mg/gCr) and 234 (mg/gCr) with the control group and the STZ-treated group, respectively, and the amount of urinary albunmin excretion of the STZ-treated group was increased to 5.2 times than that of the control group. On the other hand, as a result of the oral administration of the compound of Example 557 in the amount of 0.3 mg/kg once daily, amount of urinary albunmin excretion was 105 (mg/gCr), which was decreased to 2.3 times than that of the control group.

Test Example 5: Effect on Eye Permeability in Rats with Diabetes Mellitus

Seven-week Long-Evans rats (having weights up to 200 to 250 g during fasting) were used and fasted for 20 hours, and then intraperitoneally administered with 60 mg/ml/kg of streptozotocin (STZ) prepared with a 2 mmol/l citric acid buffer (pH 4.5). At the same time, the control rats were injected with the same amount of a 2 mmol/l citric acid buffer (pH 4.5). The blood glucose value was measured using a colorimetric method, and the rats that had showed a value of 350 mg/dl blood glucose levels on day 3 after the treatment with STZ were diagnosed with diabetes mellitus.

The test substance was given daily for 2 weeks after the treatment with STZ. After 2 weeks of the treatment with the test substance, the retinal vascular permeability was examined after 24 hours from the date of the final administration. The retinal permeability was examined on the basis of the dye leakage into the retina after 2 h from the tail vein administration of 40 mg/ml/kg of Evans Blue Dye solution. The permeability as an index of the evaluation was expressed in the ratio of the retinal concentration/plasma

concentration of the Evans Blue Dye. Measurement of the Evans Blue Dye concentration was carried out by measuring the absorbance using a plate reader.

[0087]

After the result of the tests above, it was confirmed that some of the compounds of the formula (I) constantly exhibit a VAP-1 activity in blood in the oral administration test with rats. Therefore, the compounds can be used for treatment of VAP-1-related diseases or the like.

[0088]

In the present specification, the thermal analysis measurement was carried out in the following order.

(Differential Scanning Calorimetry (DSC Analysis))

The DSC analysis was carried out using a Q1000 manufactured by TA Instruments. Approximately 2 mg of a sample was charged in an exclusively-used aluminum-made sample pan, and the change in heat amount generated between the sample and a reference (an empty aluminum sample pan), with a measurement range from room temperature to 300°C under nitrogen atmosphere (50 mL/min) and a temperature elevating rate of 10°C/min were continuously measured and recorded. Furthermore, the devices including data processing was handled in accordance to the methods and procedures as instructed in each device.

[0089]

Furthermore, the term "around" as used in the values of the endothermic onset temperature in DSC largely means the values of the temperature of the endothermic onset (extrapolation initiation), preferably, it means that the values be not more or less than the values by 2°C, and more preferably, it means that the values be not more or less than the values by 1°C.

[0090]

A pharmaceutical composition containing one or two 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 preparations, carriers for pharmaceutical preparations, 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, ophthalmic solutions, eye ointments, transdermal liquid preparations, ointments, transdermal patches, transmucosal liquid preparations, transmucosal patches, inhalers, and the like.

[0091]

The solid composition for use in the oral administration is used in the form of tablets, powders, granules, or the like. In such a solid composition, 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 a lubricant, a disintegrating agent, a stabilizer, or a solubilization assisting agent. If necessary, tablets or pills may be coated with sugar or a film of a gastric or enteric coating substance.

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

[0092]

The injections for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions and emulsions. The aqueous solvent includes, for example, distilled water for injection and physiological saline. Examples of the non-aqueous solvent include alcohols such as ethanol. Such a composition may further contain a tonicity agent, an antiseptic, a moistening agent, an emulsifying agent, a dispersing agent, a stabilizer, or a solubilizing aid. These are sterilized, for example, by filtration through a bacteria retaining filter, by blending a bactericide, or irradiation. In addition, these can also be used by preparing a sterile solid composition, and dissolving or suspending it in sterile water or a sterile solvent for injection prior to its use.

[0093]

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

[0094]

As the transmucosal agents such as an inhaler, a transnasal agent, and the like, those in the form of a solid, liquid, or semi-solid state are used, and can be prepared in accordance with a conventionally known method. For example, a known excipient, and also a pH adjusting agent, an antiseptic, a surfactant, a lubricant, a stabilizer, a thickening agent, or the like may be appropriately added thereto. For their administration, an appropriate device 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 a pharmaceutically acceptable carrier, using a known device or sprayer, such as a measured administration inhalation device, and the like. A dry powder inhaler or the like may be for single or multiple administration use, and a dry powder or a

powder-containing capsule may be used. Alternatively, this may be in a form such as a pressurized aerosol spray which uses an appropriate ejection agent, for example, a suitable gas such as chlorofluoroalkane, carbon dioxide, and the like.

[0095]

In oral administration, the daily dose is generally from about 0.001 to 100 mg/kg, preferably from 0.1 to 30 mg/kg, and more preferably 0.1 to 10 mg/kg, per body weight, administered in one portion or in 2 to 4 separate portions. In the case of intravenous administration, the daily dose is suitably administered from about 0.0001 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 to 100 mg/kg per body weight, once a day or two or more times a day. The dose is appropriately decided upon in response to the individual case by taking the symptoms, the age, and the gender, and the like into consideration.

[0096]

The compound of the formula (I) can be used in combination with various therapeutic or prophylactic agents for 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 blend, or may be prepared individually.

Examples

[0097]

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 only the preparation methods of the specific Examples and Preparation Examples are shown below, but the compound of the formula (I) can be prepared by any combination of the preparation methods or the methods that are apparent to a person skilled in the art.

[0098]

Furthermore, the following abbreviations may be used in some cases in the Examples, Preparation Examples, and Tables below.

Rf: Preparation Example No.,

Ex: Example No.,

Data: Physicochemical data,

ESI+: representing m/z values in ESI-MS (positive ions), and representing $[M+H]^+$ peaks unless otherwise specified,

APCI/ESI+: representing m/z values in APCI-MS (positive ions) and ESI-MS (positive ions), and representing $[M+H]^+$ peaks unless otherwise specified,

FAB+: representing m/z values in FAB-MS (positive ions), and representing $[M+H]^+$ peaks unless otherwise specified,

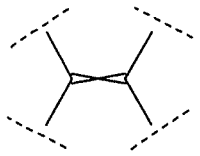
EI: representing m/z values in EI-MS (positive ions), and representing [M] peaks unless otherwise specified,

NMR-DMSO-d_6: δ (ppm) in ^{1}H-NMR in DMSO-d_6,

NMR-$CDCl_3$: δ (ppm) in ^{1}H-NMR in $CDCl_3$,

in the present specification, in the formula:

[Chem. 79]



,

the double bond indicates that a mixture of isomers of E isomers and Z isomers exists,

Structure: Structural formula (A case where HCl, PA, or L-TA is described in the structural formula means that the compound forms a salt with the acid. Further, a case where a numeral is present before the acid means that the compound forms a salt having a valence with that number, for example, 2HCl means formation of dihydrochloride).

cis: indicating that a steric structure in the structural formula is in the cis configuration,

trans: indicating that a steric structure in the structural formula is in the trans configuration,

Syn: preparation method (in which the numeral alone shows that the compound is prepared by the same preparation method as the compound having the Example No. and R prefixed before the numeral shows that the compound is prepared by the same preparation method as the compound having the Preparation Example No.),

L-TA: L-tartaric acid,

HCl: hydrochloric acid,

PA: phosphoric acid,

Boc: tert-butoxycarbonyl group,

CDI: 1,1'-carbonyldiimidazole

DMSO: dimethylsulfoxide,

THF: tetrahydrofuran,

EtOAc: ethyl acetate,

$MgSO_4$: anhydrous magnesium sulfate,

DMF: N,N-dimethylformamide,

Na_2SO_4: anhydrous sodium sulfate,

MeOH: methanol,

EtOH: ethanol

$CHCl_3$: chloroform,
NMP: N-methyl-2-pyrrolidone,
WSC: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide,
HOBt: 1-hydroxybenzotriazole,
TEA: triethylamine,
DIPEA: diisopropylethylamine,
MeCN: acetonitrile,
TFA: trifluoroacetic acid,
DME: 1,2-dimethoxyethane,
DBU: diazabicycloundecene,
TBAF: tetrabutylammonium fluoride,
BINAP: 1,1'-binaphthalene-2,2'-diylbis(diphenylphosphine),
$Pd_2(dba)_3$: tris(dibenzylideneacetone)dipalladium,
$NaBH_4$: sodium borohydride,
DIAD: diisopropyl azodicarboxylate,
DCE: 1,2-dichloroethane,
MsCl: methanesulfonyl chloride,
TBSCl: tert-butyldimethylchlorosilane,
Boc_2O: di-tert-butyldicarbonate,
DMAP: 4-(dimethylamino)pyridine,
$iPrNH_2$: isopropylamine,
NaH: sodium hydride (55% suspended in oil),
NaOH: sodium hydroxide,
IPA: isopropyl alcohol,
$NaHCO_3$: sodium hydrogen carbonate,
CH_2Cl_2: dichloromethane,
NH_3: ammonia,
M: mol/L.

[0099]

Preparation Example 12

Tetrakis(triphenylphosphine)palladium (36 mg) and sodium carbonate (330 mg) were added to a mixture of 4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxoboran-2-yl)phenyl]morpholine (300 mg), (3-bromophenyl)methanol (233 mg), DME (6 ml), and water (3 ml), followed by stirring at 80°C overnight, and then the reaction mixture was concentrated under reduced pressure. Water and $CHCl_3$ were added to the obtained residue, and the organic layer was dried over $MgSO_4$, and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (EtOAc/hexane/$CHCl_3$) to obtain [4'-(morpholin-4-yl)biphenyl-3-yl]methanol (242 mg).

[0100]

Preparation Example 32

Under argon atmosphere, sodium carbonate (1000 mg) and tetrakis(triphenylphosphine)palladium (170 mg) were added to a mixture of (2-fluoro-3-formylphenyl)boranic acid (700 mg), tert-butyl 4-{[(trifluoromethyl)sulfonyl]oxy}-3,6-dihydropyridine-1(2H)-carboxylate (100 mg), toluene (15 ml), and EtOH (5 ml), followed by stirring at 80°C overnight. The reaction mixture was concentrated under reduced pressure, and $CHCl_3$ and a saturated aqueous sodium hydrogen carbonate solution were then added thereto. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/EtOAc). The purified product thus obtained was mixed with EtOH, and $NaBH_4$ (120 mg) was added thereto, followed by stirring at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure, and then EtOAc and water were added thereto. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/EtOAc) to obtain tert-butyl 4-[2-fluoro-3-(hydroxymethyl)phenyl]-3,6-dihydropyridine-1(2H)-carboxylate (637 mg).

[0101]

Preparation Example 33

(3-Bromophenyl)methanol (10 g) was mixed with dioxane (100 ml), and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (15 g), bis(triphenylphosphine)palladium chloride (1.2 g), and potassium acetate (15.8 g) were added thereto, followed by stirring at 80°C for 1 day. The reaction mixture was concentrated under reduced pressure, and $CHCl_3$ and a saturated aqueous sodium hydrogen carbonate solution were added thereto. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/EtOAc) to obtain [3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol (12.5 g).

[0102]

Preparation Example 38

A mixture of 4-(5-bromopyrimidin-2-yl)morpholine (2 g), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (2.5 g), bis(triphenylphosphine)palladium chloride (180 mg), potassium acetate (2.5 g), and dioxane (20 ml) was stirred at 80°C overnight under argon atmosphere. Water and EtOAc were added to the reaction mixture, and the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The obtained residue was mixed with THF (10 ml) and water (10 ml), and sodium perborate·trihydrate (3.5 g) was added thereto, followed by stirring at room temperature overnight. Then, a saturated aqueous ammonium chloride

solution was added thereto. The aqueous layer was extracted with EtOAc, and the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/EtOAc) to obtain 2-(morpholin-4-yl)pyrimidin-5-ol (610 mg).

[0103]

Preparation Example 39

Calcium carbonate (11 g) was added to a mixture of ethyl [3-(bromomethyl)phenyl]acetate (4.56 g), dioxane (70 ml) and water (10 ml), followed by stirring at 80°C for 6 hours. EtOAc and water were added to the reaction mixture, and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/EtOAc). The purified product thus obtained was mixed with EtOH (50 ml), and a 1 M aqueous NaOH solution (35 ml) was added thereto, followed by stirring at room temperature for 1 hour. 1 M hydrochloric acid (35 ml) was added to the reaction mixture, followed by concentration under reduced pressure. MeOH and Na_2SO_4 were added to the obtained residue, and the insoluble matter was removed by filtration. The filtrate was concentrated under reduced pressure to obtain [3-(hydroxymethyl)phenyl]acetic acid (1.9 g).

[0104]

Preparation Example 41

Using [(3-bromo-2-fluorobenzyl)oxy](tert-butyl)dimethylsilane (6.5 g) as a starting material and cesium carbonate as a base under the same reaction conditions as in Preparation Example 228, 1-[3-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]piperidin-4-yl benzoate (4.5 g) was prepared.

[0105]

Preparation Example 42

Under argon atmosphere, [(3-bromo-2-fluorobenzyl)oxy](tert-butyl)dimethylsilane (2 g) and ethyl piperidine-4-carboxylate (16 g) were mixed with toluene (30 ml), and $Pd_2(dba)_3$ (150 mg), BINAP (300 mg), and cesium carbonate (3.2 g) were added thereto, followed by stirring at 100°C for 1 hour. The reaction mixture was cooled to room temperature, and EtOAc was added thereto, followed by filtration using Celite as a filtration adjuvant. The filtrate was concentrated under reduced pressure, the residue was then mixed with THF (30 ml), and a 1 M TBAF/THF solution (12 ml) was added thereto, followed by stirring at room temperature for 1 hour. To the reaction mixture were added EtOAc and water, and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/EtOAc) to obtain ethyl 1-[2-fluoro-3-(hydroxymethyl)phenyl]piperidine-4-carboxylate (1.02 g).

[0106]

Preparation Example 44

tert-Butyl [(3-ethynyl-2-fluorobenzyl)oxy]dimethylsilane (1 g) was mixed with THF (20 ml), and a 1.65 M n-butyl lithium/hexane solution (2.5 ml) was added dropwise thereto at -78°C, followed by stirring at -78°C for 30 minutes. Benzyl chloroformate (774 mg) was added dropwise thereto at the same temperature, followed by stirring overnight while raising the temperature to room temperature. A saturated aqueous ammonium chloride solution was added thereto at 0°C, followed by extraction with $CHCl_3$. The organic layer was washed with water and saturated brine, and dried over Na_2SO_4, and the solvent was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (EtOAc/hexane) to obtain benzyl 3-[3-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]prop-2-ionate (1.41 g).

[0107]

Preparation Example 45

tert-Butyl{2-[(chloroacetyl)(tetrahydro-2H-pyran-4-yl)amino]ethyl}carbamate (6.86 g) was mixed with THF (70 ml), and sodium hydride (55% suspended in oil) (1.4 g) was added thereto at 0°C, followed by stirring at room temperature overnight. To the reaction mixture was added a saturated aqueous ammonium chloride solution at 0°C, followed by extraction with $CHCl_3$. The organic layer was washed with water and saturated brine, and dried over Na_2SO_4, and the solvent was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (EtOAc/hexane/MeOH) to obtain tert-butyl 3-oxo-4-(tetrahydro-2H-pyran-4-yl)piperazine-1-carboxylate (5.25 g).

[0108]

Preparation Example 48

Using ({1-[(benzyloxy)carbonyl]piperidin-4-yl}methyl)(triphenyl)phosphonium iodide (6.0 g) as a starting material and lithium bis(trimethylsilyl)amide as a base under the same conditions as in Preparation Example 581, benzyl tert-butyl 4,4'-(Z)-ethene-1,2-diyldipiperidine-1-carboxylate (2.5 g) was prepared.

[0109]

Preparation Example 50

1-Benzyl-4-(tetrahydro-2H-pyran-4-ylmethoxy)pyridinium bromide (1.9 g) was mixed with MeOH (35 ml), and $NaBH_4$ (850 mg) was added thereto, followed by stirring at room temperature for 1 hour. Acetone (6 ml) was added to the reaction mixture, followed by stirring at room temperature for 30 minutes, and then activated carbon (1 g) was added thereto, followed by stirring at room temperature for 30 minutes and filtering using Celite as a filtration adjuvant. The filtrate was concentrated under reduced pressure. EtOAc and a saturated aqueous sodium hydrogen carbonate solution were added to the obtained

residue, and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was mixed with MeOH (35 ml), and ammonium formate (3 g) and 10% palladium carbon (400 mg) were added thereto, followed by stirring at 50°C for 4 hours and filtering using Celite, and the filtrate was concentrated under reduced pressure. EtOAc and a saturated aqueous sodium hydrogen carbonate solution were added to the residue, and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by basic silica gel column chromatography ($CHCl_3$/MeOH) to obtain 4-(tetrahydro-2H-pyran-4-ylmethoxy)piperidine (1.01 g).

[0110]

Preparation Example 54

4-(Tetrahydro-2H-pyran-4-ylmethoxy)pyridine (1.1 g) was mixed with THF (12 ml), and benzyl bromide (1.4 g) was added thereto, followed by stirring at room temperature overnight. The precipitated solid was collected by filtration to obtain 1-benzyl-4-(tetrahydro-2H-pyran-4-ylmethoxy)pyridinium bromide (1.9 g).

[0111]

Preparation Example 57

2-Fluoro-3-methylbenzoic acid (4 g), THF (55 ml), and tert-butanol (55 ml) were mixed, and Boc_2O (7.5 g) and DMAP (1.0 g) were added thereto at room temperature, followed by stirring at room temperature overnight. The solvent was concentrated under reduced pressure, and EtOAc and water were added thereto. The organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/EtOAc) to obtain tert-butyl 2-fluoro-3-methylbenzoate (5.46 g).

[0112]

Preparation Example 58

tert-Butyl 3-hydroxyazetidine-1-carboxylate (4.0 g) and pyridin-4-ol (1.8 g) were mixed with THF (50 ml), and triphenylphosphine (6.23 g) was added thereto. A 1.9 M DIAD/toluene solution (12.5 ml) was added dropwise, followed by stirring at 55°C overnight. Triphenylphosphine (5 g) and a 1.9 M DIAD/toluene solution (10 ml) were added to the reaction mixture, followed by stirring at 55°C overnight. The reaction mixture was concentrated under reduced pressure, and a liquid separation operation was carried out by the addition of EtOAc and 0.5 M hydrochloric acid. The aqueous layer was adjusted to a pH of around 10 by the addition of a 4 M aqueous NaOH solution, and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography ($CHCl_3$/MeOH) to obtain tert-butyl 3-(pyridin-4-yloxy)azetidine-1-carboxylate (4.2 g).

[0113]

Preparation Example 60

1-[3-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]piperidin-4-ol (200 mg) and pyridin-4-ol (65 mg) were mixed with THF (3 ml), and triphenylphosphine (250 mg) was added thereto. A 1.9 M DIAD/toluene solution (0.5 ml) was added dropwise to the reaction mixture, followed by stirring at 55°C overnight. Then, a 1 M TBAF/THF solution (1 ml) was added to the reaction mixture, followed by stirring at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, and diethyl ether and 1 M hydrochloric acid were added thereto. The organic layer was separated by a liquid separation operation, and the aqueous layer was washed with diethyl ether twice again. The aqueous layer was adjusted to a pH of around 10 by the addition of a 4 M aqueous NaOH solution, and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography ($CHCl_3$/MeOH) to obtain {2-fluoro-3-[4-(pyridin-4-yloxy)piperidin-1-yl]phenyl}methanol (84 mg).

[0114]

Preparation Example 62

tert-Butyl 3-hydroxyazetidine-1-carboxylate (3.0 g) was mixed with THF (30 ml), and sodium hydride (55% suspended in oil) (600 mg) was added thereto, followed by stirring at room temperature for 10 minutes. Benzyl bromide (2.5 ml) was added thereto, followed by stirring at room temperature for 3 hours. Water and EtOAc were added to the reaction mixture, and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was mixed with DCE (30 ml), and TFA (15 g) was added thereto, followed by stirring at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure and purified by basic silica gel column chromatography ($CHCl_3$/MeOH) to obtain 3-(benzyloxy)azetidine (2.2 g).

[0115]

Preparation Example 63

tert-Butyl 4-[(methylsulfonyl)oxy]piperidine-1-carboxylate (1.1 g), 2-methylpyridin-3-ol (500 mg), potassium carbonate (1.7 g), and DMF (10 ml) were mixed, followed by stirring at 100°C for 6 hours. The reaction mixture was concentrated under reduced pressure, and $CHCl_3$ and a saturated aqueous sodium hydrogen carbonate solution were then added thereto. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography ($CHCl_3$/MeOH). The purified product thus obtained was mixed with DCE (10 ml), and TFA (4.5 g) was added thereto, followed by stirring at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure, and $CHCl_3$ and a 1 M aqueous NaOH solution were the added thereto, and the organic

layer was dried over Na_2SO_4 and concentrated under reduced pressure to obtain 2-methyl-3-(piperidin-4-yloxy)pyridine (355 mg).

[0116]

Preparation Example 67

1-[3-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]piperazine (500 mg) was mixed with dioxane (15 ml), and methyl 5-bromopyridine-2-carboxylate (399 mg), palladium acetate (35 mg), 2-dicyclohexylphosphino-2',4',6'-tri-isopropyl-1,1'-biphenyl (147 mg), and potassium phosphate (981 mg) were added thereto, followed by stirring at 100°C for 48 hours. The reaction mixture was cooled to room temperature, and filtered by the addition of $CHCl_3$ and Celite, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (EtOAc/hexane) to obtain methyl 5-{4-[3-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]piperazin-1-yl}pyridine-2-carboxylate (310 mg).

[0117]

Preparation Example 69

1-[3-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]-4-(pyridin-3-yl)piperidin-4-ol (908 mg) was mixed with dichloromethane (15 ml), and TEA (1.1 g), DMAP (799 mg), and MsCl (749 mg) were added thereto at 0°C, followed by stirring at room temperature overnight. Water and EtAOc were added to the reaction mixture, and the organic layer was washed with water and saturated brine, and dried over anhydrous sodium carbonate. The solvent was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (EtOAc/hexane) to obtain 1'-[3-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]-1',2',3',6'-tetrahydro-3,4'-bipyridine (477 mg).

[0118]

Preparation Example 70

Dioxane (12 ml) was added to a mixture of 5-iodo-2-(3-methoxyazetidin-1-yl)pyrimidine (1.14 g), tert-butyl 3-oxopiperazine-1-carboxylate (941 mg), rel-(1R,2R)-N,N'-dimethyl cyclohexane-1,2-diamine (223 mg), copper iodide (149 mg), and potassium phosphate (2.5 g), followed by stirring at 100°C overnight. The reaction mixture was cooled to room temperature and then filtered by the addition of $CHCl_3$ and Celite, and the filtrate was concentrated. The obtained residue was purified by basic silica gel column chromatography (EtOAc/hexane) to obtain tert-butyl 4-[2-(3-methoxyazetidin-1-yl)pyrimidin-5-yl]-3-oxopiperazine-1-carboxylate (867 mg).

[0119]

Preparation Example 81

2-Fluoro-4'-(morpholin-4-yl)biphenyl-3-carboaldehyde (288 mg) was mixed with THF (3 ml), and $NaBH_4$ (40 mg) was added thereto. MeOH (3 ml) was added to the reaction mixture dropwise, followed by stirring at room temperature for 30 minutes. EtOAc and 1 M hydrochloric acid were added to the reaction mixture, and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/EtOAc) to obtain [2-fluoro-4'-(morpholin-4-yl)biphenyl-3-yl]methanol (290 mg).

[0120]

Preparation Example 135

[3-(2-Chloropyrimidin-5-yl)phenyl]methanol (200 mg) was mixed with DMF (4 ml), and 4-methoxypiperidine hydrochloride (180 mg) and potassium carbonate (500 mg) were added thereto, followed by stirring at 70°C for 5 hours. The reaction mixture was concentrated under reduced pressure, and $CHCl_3$ and a saturated aqueous sodium hydrogen carbonate solution were then added thereto. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/EtOAc) to obtain {3-[2-(4-methoxypiperidin-1-yl)pyrimidin-5-yl]phenyl}methanol (249 mg).

[0121]

Preparation Example 159

5-{4-[3-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]piperazin-1-yl}pyrimidin-2-yltrifluoromethanesulfonate (200 mg) was mixed with DMF (4 ml), and 1-acetylpiperazine (72 mg) and potassium carbonate (300 mg) were added thereto, followed by stirring at 60°C overnight. The reaction mixture was concentrated under reduced pressure, and water and EtOAc were added to the residue. The organic layer was washed with saturated brine, then dried over Na_2SO_4, and concentrated under reduced pressure. The obtained residue was mixed with THF, and a 1 M TBAF/THF solution was added thereto, followed by stirring at room temperature for 3 hours. Water and EtOAc were added to the reaction mixture, and the organic layer was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (EtOAc/hexane/MeOH/$CHCl_3$) to obtain 1-[4-(5-{4-[2-fluoro-3-(hydroxymethyl)phenyl]piperazin-1-yl}pyrimidin-2-yl)piperazin-1-yl]ethanone (133 mg).

[0122]

Preparation Example 162

Ethyl 3-(2-ethoxy-2-oxoethyl)benzoate (1.41 g) was mixed with THF (20 ml), and lithium borohydride (260 mg) was added thereto at 0°C, followed by stirring at room temperature overnight. A saturated ammonium chloride solution and EtOAc were added to the reaction mixture at 0°C. The organic layer was washed with water and saturated

brine, dried over Na_2SO_4, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (EtOAc/hexane) to obtain ethyl 3-(2-hydroxyethyl)benzoate (824 mg).

[0123]

Preparation Example 163

2,5-Dibromo-1,3-thiazole (500 mg) was mixed with morpholine (2 ml), followed by stirring at 60°C for 5 hours. Water was added to the reaction mixture, followed by stirring for 1 hour, and the resulting insoluble matter was collected by filtration, followed by washing with water, to obtain 4-(5-bromo-1,3-thiazol-2-yl)morpholine (475 mg).

[0124]

Preparation Example 174

$CHCl_3$ and a saturated aqueous sodium hydrogen carbonate solution were added to [3-(piperazin-1-yl)phenyl]methanol dihydrochloride (240 mg) to carry out liquid separation. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The obtained residue was mixed with dichloromethane (5 ml), and tetrahydro-4H-pyran-4-one (100 mg) and acetic acid (168 mg) were added thereto, followed by stirring at room temperature for 15 minutes. Sodium triacetoxyborohydride (576 mg) was added to the reaction mixture at 0°C, followed by stirring at room temperature for 5 hours. Water and $CHCl_3$ were added to the reaction mixture, and the aqueous layer was adjusted to a pH of 8 to 9 by the addition of a saturated aqueous sodium hydrogen carbonate solution. The organic layer was washed with water, dried over $MgSO_4$, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH) to obtain {3-[4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl]phenyl}methanol (45 mg).

[0125]

Preparation Example 177

Ethyl 1-{5-[2-fluoro-3-(hydroxymethyl)phenyl]pyrimidin-2-yl}piperidine-4-carboxylate (1.4 g) was mixed with THF (10 ml) and EtOH (15 ml), and a 1 M aqueous NaOH solution (5.8 ml) was added thereto, followed by stirring at room temperature overnight. The insoluble matter was collected by filtration, and the filtrate was concentrated under reduced pressure. Water and 1 M hydrochloric acid (5.8 ml) were added to the obtained residue at 0°C, followed by stirring at 0°C for 30 minutes. The solid was collected by filtration, washed with water, and then dried at 50°C under reduced pressure to obtain 1-{5-[2-fluoro-3-(hydroxymethyl)phenyl]pyrimidin-2-yl}piperidine-4-carboxylic acid (1.29 g).

[0126]

Preparation Example 182

(3-Bromophenyl)methanol (500 mg) was mixed with DMF (10 ml), and sodium hydride (55% suspended in oil) was added thereto at 0°C, followed by stirring for 10 minutes under ice-cooling. 1-(Chloromethyl)-4-methoxybenzene (520 mg) was added to the reaction mixture, followed by stirring at room temperature for 2 hours. Water and EtOAc were added to the reaction mixture, and the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography ($CHCl_3$/hexane) to obtain 1-bromo-3-{[(4-methoxybenzyl)oxy]methyl}benzene (801 mg).

[0127]

Preparation Example 228

[(3-Bromo-2-fluorobenzyl)oxy](tert-butyl)dimethylsilane (300 mg) was mixed with toluene (6 ml), and 1-(2-methylpyridin-4-yl)piperazine (200 mg), $Pd_2(dba)_3$ (43 mg), BINAP (88 mg), and sodium tert-butoxide (135 mg) were added thereto, followed by stirring at 80°C for 5 hours. After cooling to room temperature, filtration was carried out by the addition of $CHCl_3$ and Celite, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (EtOAc/hexane/28% aqueous ammonia/MeOH/) to obtain 1-[3-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]-4-(2-methylpyridin-4-yl)piperazine (259 mg).

[0128]

Preparation Example 285

Under argon atmosphere, [(3-bromo-2-fluorobenzyl)oxy](tert-butyl)dimethylsilane (800 mg) and 4-(azetidin-3-yloxy)pyridine (268 mg) were mixed with toluene (6 ml), and $Pd_2(dba)_3$ (80 mg), BINAP (160 mg), and potassium tert-butoxide (300 mg) were added thereto, followed by stirring at 90°C for 3 hours. The reaction mixture was cooled to room temperature, and EtOAc was added thereto, followed by carrying out filtration using Celite as a filtration adjuvant. The filtrate was concentrated under reduced pressure, and then the residue was purified by silica gel column chromatography (hexane/EtOAc). The purified product thus obtained was mixed with THF (6 ml), and a 1 M TBAF/THF solution (3 ml) was added thereto, followed by stirring at room temperature for 1 hour. To the reaction mixture were added a saturated aqueous ammonium chloride solution and $CHCl_3$, and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/EtOAc) to obtain {2-fluoro-3-[3-(pyridin-4-yloxy)azetidin-1-yl]phenyl}methanol (335 mg).

[0129]

Preparation Example 290

Under argon atmosphere, 4-(5-bromopyrimidin-2-yl)morpholine (700 mg) and tert-butyl piperazine-1-carboxylate (800 mg) were mixed with toluene (10 ml), and

$Pd_2(dba)_3$ (130 mg), BINAP (260 mg), and potassium tert-butoxide (500 mg) were added thereto, followed by stirring at 90°C overnight. The reaction mixture was cooled to room temperature, the reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/EtOAc). The purified product thus obtained was mixed with EtOH (10 ml), and 4 M hydrogen chloride/dioxane (7 ml) was added thereto, followed by stirring at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and $CHCl_3$ and a saturated aqueous sodium hydrogen carbonate solution were then added thereto. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography ($CHCl_3$/MeOH) to obtain 4-[5-(piperazin-1-yl)pyrimidin-2-yl]morpholine (239 mg).

[0130]

Preparation Example 294

1-(3-{[(4-Methoxybenzyl)oxy]methyl}phenyl)-4-(pyridin-4-yl)piperazine (308 mg) was mixed with dichloromethane (2 ml), and TFA (1 ml) was added thereto. The reaction mixture was stirred at room temperature for 1 hour, and then the reaction mixture was concentrated under reduced pressure. To the obtained residue were added a saturated aqueous sodium hydrogen carbonate solution and $CHCl_3$, and the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The obtained residue was purified by basic silica gel column chromatography to obtain {3-[4-(pyridin-4-yl)piperazin-1-yl]phenyl}methanol (167 mg).

[0131]

Preparation Example 297

(3-Bromophenyl)methanol (5.0 g) was mixed with THF (60 ml), and TBSCl (5.0 g) and imidazole (3 g) were added thereto, followed by stirring at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and water and EtOAc were added thereto. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain [(3-bromobenzyl)oxy](tert-butyl)dimethylsilane (8.0 g).

[0132]

Preparation Example 301

[(3-Bromobenzyl)oxy](tert-butyl)dimethylsilane (860 mg) was mixed with THF (10 ml), followed by cooling to -78°C under argon atmosphere. A 1.60 M n-butyl lithium/hexane solution (1.8 ml) was added dropwise thereto, followed by stirring at -78°C for 10 minutes, and then 2-morpholin-4-ylpyrimidine-5-carboaldehyde (500 mg) was added thereto. The mixture was warmed to 0°C over 1 hour and then stirred again at 0°C for 1 hour. Water and EtOAc were added to the reaction mixture, and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue

was purified by silica gel column chromatography (hexane/EtOAc) to obtain [3-({[tert-butyl(dimethyl)silyl]oxy}methyl)phenyl][2-(morpholin-4-yl)pyrimidin-5-yl]methanol (914 mg).

[0133]

Preparation Example 302

[3-({[tert-Butyl(dimethyl)silyl]oxy}methyl)phenyl][2-(morpholin-4-yl)pyrimidin-5-yl]methanol (400 mg), trimethylsilane (364 mg), and TFA (4 ml) were mixed, followed by stirring at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and EtOAc and water were added to the obtained residue. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain (3-{[2-(morpholin-4-yl)pyrimidin-5-yl]methyl}phenyl)methanol (39 mg).

[0134]

Preparation Example 304

1-[3-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]piperazine (355 mg) was mixed with IPA (4.5 ml), and 4-chloro-pyrimidine hydrochloride (150 mg) and TEA (302 mg) were added thereto, followed by stirring at 60°C overnight. The reaction mixture was cooled to room temperature and then concentrated under reduced pressure, and the residue was purified by silica gel column chromatography ($MeOH/CHCl_3$) to obtain 4-{4-[3-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]piperazin-1-yl}pyrimidine (391 mg).

[0135]

Preparation Example 305

Ethyl 2-fluoro-3-({[2-(morpholin-4-yl)pyrimidin-5-yl]oxy}methyl)benzoate (375 mg) was mixed with toluene (5 ml), followed by cooling to 0°C. A 1.01 M diisobutylaluminum hydride/toluene solution (3 ml) was added dropwise thereto, followed by stirring at the same temperature for 1 hour. The reaction mixture was subjected to liquid separation by the addition of a 1 M aqueous NaOH solution and toluene. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/EtOAc) to obtain [2-fluoro-3-({[2-(morpholin-4-yl)pyrimidin-5-yl]oxy}methyl)phenyl]methanol (282 mg).

[0136]

Preparation Example 306

1-(6-Chloropyridazine-3-yl)azetidin-3-ol (599 mg) was mixed with DMF (6 ml), and sodium hydride (55% suspended in oil) (211 mg) was added thereto at 0°C, followed by stirring at 0°C for 10 minutes. Then, methyl iodide (916 mg) was added thereto at 0°C, followed by stirring at room temperature overnight. To the reaction mixture were added

water, EtOAc, and $CHCl_3$, and the organic layer was washed with water and saturated brine, then dried over anhydrous Na_2CO_3, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (EtOAc/hexane) to obtain 3-chloro-6-(3-methoxyazetidin-1-yl)pyridazine (323 mg).

[0137]

Preparation Example 307

tert-Butyl 4-hydroxypiperidine-1-carboxylate (1.0 g) was mixed with DMF (15 ml), and sodium hydride (55% suspended in oil) (300 mg) was added thereto, followed by stirring at room temperature for 10 minutes. To the reaction mixture was added 1-bromo-3-methoxypropane (1.0 g), followed by stirring at room temperature overnight. Water was added to the reaction mixture, and the reaction mixture was concentrated under reduced pressure. EtOAc and water were added to the obtained residue, and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/EtOAc). The purified product thus obtained was mixed with EtOH (10 ml), and a 4 M hydrogen chloride/dioxane (10 ml) was added thereto, followed by stirring at room temperature overnight. The reaction mixture was concentrated under reduced pressure to obtain 4-(3-methoxypropoxy)piperidine hydrochloride (302 mg).

[0138]

Preparation Example 309

2-Fluoro-3-methylbenzoic acid (8.0 g) was mixed with EtOH (100 ml), and concentrated sulfuric acid was added thereto, followed by stirring at 90°C overnight. The reaction mixture was concentrated under reduced pressure, and EtOAc and water were then added thereto. The organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution, then dried over Na_2SO_4, and concentrated under reduced pressure to obtain ethyl 2-fluoro-3-methylbenzoate (7.84 g).

[0139]

Preparation Example 336

1-[2-Fluoro-3-(hydroxymethyl)phenyl]piperidine-4-carboxylic acid (100 mg) and morpholine (50 mg) were mixed with DCE (3 ml), and WSC hydrochloride (140 mg) and HOBt (95 mg) were added thereto, followed by stirring at room temperature for 3 hours. A saturated aqueous sodium hydrogen carbonate solution and $CHCl_3$ were added to the reaction mixture, and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography ($CHCl_3$/MeOH) to obtain {1-[2-fluoro-3-(hydroxymethyl)phenyl]piperidin-4-yl}(morpholin-4-yl)methanone (126 mg).

[0140]

Preparation Example 341

(2-Fluoro-3-{4-[2-(piperidin-4-yl)ethyl]piperidin-1-yl}phenyl)methanol (200 mg) and acetic acid (63 mg) were mixed with DCE (3 ml), and WSC hydrochloride (220 mg) and HOBt (155 mg) were added thereto, followed by stirring at room temperature for 3 hours. A saturated aqueous sodium hydrogen carbonate solution and $CHCl_3$ were added to the reaction mixture, and the organic layer was liquid separation and concentrated under reduced pressure. The obtained residue was mixed with MeOH (3 ml), and a 1 M aqueous NaOH solution (1 ml) was added thereto, followed by stirring at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure, and $CHCl_3$ and a saturated aqueous sodium hydrogen carbonate solution were then added thereto. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography ($CHCl_3$/MeOH) to obtain 1-[4-(2-{1-[2-fluoro-3-(hydroxymethyl)phenyl]piperidin-4-yl}ethyl)piperidin-1-yl]ethanone (211 mg).

[0141]

Preparation Example 343

5-[3-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]-2-(piperidin-4-yloxy)pyrimidine (150 mg) and cyclohexane carboxylic acid (82 mg) were mixed with DCE (3.6 ml), and WSC hydrochloride (125 mg) and HOBt (85 mg) were added thereto, followed by stirring at room temperature for 3 hours. A saturated aqueous sodium hydrogen carbonate solution and $CHCl_3$ were added to the reaction mixture, and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was mixed with THF (3.6 ml), and a 1 M TBAF/THF solution (0.85 ml) was added thereto, followed by stirring at room temperature for 1 hour. EtOAc and an aqueous ammonium chloride solution were added to the reaction mixture, and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography ($CHCl_3$/MeOH) to obtain cyclohexyl[4-({5-[2-fluoro-3-(hydroxymethyl)phenyl]pyrimidin-2-yl}oxy)piperidin-1-yl]methanone (148 mg).

[0142]

Preparation Example 347

1-(3-Bromophenyl)methanamine (10 g) was mixed with THF (100 ml), and Boc_2O (12.9 g) was added thereto, followed by stirring at room temperature overnight. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane) to obtain tert-butyl (3-bromobenzyl)carbamate (15.0 g).

[0143]

Preparation Example 376

1-[3-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]-3-methoxyazetidine (121 mg) was mixed with THF (4 ml), and a 1 M TBAF/THF solution (0.8 ml) was added thereto, followed by stirring at room temperature for 1 hour. Water and EtOAc were added to the reaction mixture, and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain [2-fluoro-3-(3-methoxyazetidin-1-yl)phenyl]methanol (72 mg).

[0144]

Preparation Example 478

tert-Butyl 4-[2-(morpholin-4-yl)pyrimidin-5-yl]piperazine-1-carboxylate (1.42 g) was mixed with MeOH (20 ml) and THF (20 ml), and a 4 M hydrogen chloride/EtOAc (10 ml) was added thereto, followed by stirring at room temperature overnight and then stirring for 30 minutes under ice-cooling. The precipitated solid was collected by filtration and washed with EtOAc to obtain 4-[5-(piperazin-1-yl)pyrimidin-2-yl]morpholine dihydrochloride (1.15 g).

[0145]

Preparation Example 508

tert-Butyl 4-[2-fluoro-3-(hydroxymethyl)phenyl]piperidine-1-carboxylate (352 mg) was mixed with EtOH (5 ml), and 4 M hydrogen chloride/dioxane (3 ml) was added thereto, followed by stirring at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and then EtOH and potassium carbonate were added thereto, followed by stirring at 60°C for 5 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The reaction mixture was mixed with THF (5 ml), and TBSCl (450 mg) and imidazole (210 mg) were added thereto, followed by stirring at room temperature for 1 hour. EtOAc and water were added to the reaction mixture, and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography ($CHCl_3$/MeOH) to obtain 4-[3-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]piperidine (271 mg).

[0146]

Preparation Example 514

tert-Butyl 4-{5-[3-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]pyrimidin-2-yl}piperidine-1-carboxylate (170 mg) was mixed with MeOH (1.7 ml), and a 4 M hydrogen chloride/EtOAc (0.17 ml) was added thereto, followed by stirring at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and 10% MeOH/$CHCl_3$ and a saturated aqueous sodium hydrogen carbonate solution were added to

the residue. Then, the reaction mixture was concentrated under reduced pressure. 10% MeOH/$CHCl_3$ was added to the obtained residue, followed by stirring for 30 minutes. The filtrate was concentrated under reduced pressure to obtain {2-fluoro-3-[2-(piperidin-4-yl)pyrimidin-5-yl]phenyl}methanol (96 mg).

[0147]

Preparation Example 516

Methyl 3-(bromomethyl)benzoate (4.0 g) was mixed with toluene (40 ml), and triphenylphosphine (5.0 g) was added thereto, followed by stirring at 90°C overnight. The precipitated solid was collected by filtration to obtain [3-(methoxycarbonyl)benzyl](triphenyl)phosphonium bromide (8.2 g).

[0148]

Preparation Example 518

1-[3-({[tert-Butyl(dimethyl)silyl]oxy}methyl)phenyl]-4-(pyridin-2-yl)piperazine (240 mg) was mixed with THF (2 ml), and a 1 M hydrochloric acid (2 ml) was added thereto, followed by stirring at room temperature for 5 hours. A saturated aqueous sodium hydrogen carbonate solution and $CHCl_3$ were added to the reaction mixture, and the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/EtOAc) to obtain {3-[4-(pyridin-2-yl)piperazin-1-yl]phenyl}methanol (166 mg).

[0149]

Preparation Example 548

Benzyl 3-oxo-4-(pyridin-3-ylmethyl)piperazine-1-carboxylate (345 mg) was mixed with EtOH (7 ml), and 10% palladium carbon (70 mg) was added thereto under argon atmosphere to change the atmosphere to hydrogen atmosphere, followed by stirring at room temperature overnight. The reaction mixture was filtered using Celite as a filtration adjuvant, and the filtrate was concentrated under reduced pressure to obtain 1-(pyridin-3-ylmethyl)piperazin-2-one (190 mg).

[0150]

Preparation Example 563

tert-Butyl 4-hydroxypiperidine-1-carboxylate (2.0 g) was mixed with THF (20 ml), and TEA (3 ml) and benzoyl chloride (1.2 g) were added thereto, followed by stirring at room temperature for 1 hour. Water and EtOAc were added to the reaction mixture, and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/EtOAc) to obtain tert-butyl 4-(benzoyloxy)piperidine-1-carboxylate (2.45 g).

[0151]

Preparation Example 564

tert-Butyl 4-hydroxypiperidine-1-carboxylate (3.0 g) was mixed with DCE (30 ml), and TEA (3.0 ml) and benzoyl chloride (2.4 g) was added thereto, followed by stirring at room temperature for 1 hour. A saturated aqueous sodium hydrogen carbonate solution and EtOAc were added to the reaction mixture, and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was mixed with DCE (30 ml), and TFA (10 ml) was added thereto, followed by stirring at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure, and then the residue was purified by basic silica gel column chromatography ($CHCl_3$/MeOH) to obtain piperidin-4-yl benzoate (3.1 g).

[0152]

Preparation Example 568

Under argon atmosphere, ethynyl(trimethyl)silane (9.0 ml) was mixed with triethylamine (50 ml), and (3-bromo-2-fluorophenyl)methanol, bis(triphenylphosphine)palladium chloride (II) (1.54 g), and copper iodide (420 mg) were added thereto, followed by stirring at 90°C overnight. The reaction mixture was cooled to room temperature, and EtOAc was added thereto, followed by filtering using Celite as a filtration adjuvant. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/EtOAc) to obtain {2-fluoro-3-[(trimethylsilyl)ethynyl]phenyl}methanol (4.88 g).

[0153]

Preparation Example 572

tert-Butyl({2-fluoro-3-[(trimethylsilyl)ethynyl]benzyl}oxy)dimethylsilane (4.13 g) was mixed with EtOH (61 ml), and potassium carbonate (847 mg) was added thereto, followed by stirring at room temperature for 1 hour. Water and $CHCl_3$ were added to the reaction mixture at 0°C, and the organic layer was washed with water and saturated brine, dried over Na_2SO_4, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (EtOAc/hexane) to obtain tert-butyl[(3-ethynyl-2-fluorobenzyl)oxy]dimethylsilane (3.19 g).

[0154]

Preparation Example 573

H_2SO_4 (44 g) was added to water (18 ml) at 0°C, and (3-cyanophenyl)acetic acid (1.5 g) was added thereto at 0°C, followed by stirring at 100°C overnight, then warming to 130°C, and stirring for 5 hours. The reaction mixture was cooled to room temperature, and EtOH (190 ml) was then added thereto, followed by stirring at 90°C for 2 days. The reaction mixture was concentrated under reduced pressure, and EtOAc and water were added to the residue. Then, the organic layer was washed with water, a saturated aqueous sodium hydrogen carbonate solution, and saturated brine, dried over Na_2SO_4, and then

concentrated under reduced pressure to obtain ethyl 3-(2-ethoxy-2-oxoethyl)benzoate (1.41 g).

[0155]

Preparation Example 574

Ethyl 3-(2-hydroxyethyl)benzoate (824 mg) was mixed with dichloromethane (10 ml), DIPEA (1.5 ml) was added thereto, and methanesulfonyl chloride (972 mg) was added dropwise thereto at 0°C, followed by stirring for 1.5 hours while slowly warming to room temperature. Water was added to the reaction mixture, followed by stirring for 10 minutes, and then the organic layer was washed with water and saturated brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane) to obtain ethyl 3-{2-[(methylsulfonyl)oxy]ethyl}benzoate (1.12 g).

[0156]

Preparation Example 581

[3-(Methoxycarbonyl)benzyl](triphenyl)phosphonium bromide (930 mg) was mixed with DMF (6 ml), and potassium tert-butoxide (300 mg) was added thereto at 0°C, followed by stirring for 30 minutes. 2-(Morpholin-4-yl)pyrimidine-5-carboaldehyde (300 mg) was added to the reaction mixture, followed by stirring at 0°C for 1 hour, and stirring again at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, and EtOAc and a saturated aqueous sodium hydrogen carbonate solution were then added thereto. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/EtOAc) to obtain methyl 3-{2-[2-(morpholin-4-yl)pyrimidin-5-yl]vinyl}benzoate (377 mg).

[0157]

Preparation Example 582

Ethyl 3-{2-[(methylsulfonyl)oxy]ethyl}benzoate (170 mg) was mixed with MeCN (3.4 ml), and 1,2,3,4,5,6-hexahydro-[4,4']bipyridinyl (122 mg) and potassium carbonate (173 mg) were added thereto, followed by stirring at 60°C overnight. After cooling to room temperature, the insoluble matter was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($MeOH/CHCl_3$) to obtain ethyl 3-{2-[4-(pyridin-4-yl)piperidin-1-yl]ethyl}benzoate (121 mg).

[0158]

Preparation Example 584

Ethyl 3-{2-[4-morpholin-4-yl)piperidin-1-yl]ethyl}benzoate (337 mg) was mixed with THF (7 ml), and aluminum lithium hydride (74 mg) was added thereto at 0°C, followed by stirring at 0°C for 1 hour. Sodium sulfate decahydrate was added to the reaction mixture

at 0°C, followed by stirring at room temperature overnight, the insoluble matter was removed by filtration, and the filtrate was concentrated under reduced pressure to obtain (3-{2-[4-(morpholin-4-yl)piperidin-1-yl]ethyl}phenyl)methanol (281 mg).

[0159]

Preparation Example 589

Ethyl (3-methylphenyl)acetate (5.36 g) was mixed with carbon tetrachloride (80 ml), followed by heating at 90°C. N-Bromosuccinimide (5.62 g) and α,α'-azobisisobutyronitrile (250 mg) were added thereto, followed by stirring at 90°C for 5 hours. The reaction mixture was cooled to room temperature, and then the solid was removed by filtration. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/EtOAc) to obtain ethyl [3-(bromomethyl)phenyl]acetate (4.56 g).

[0160]

Preparation Example 592

2-Fluoro-3-formylphenyl)boronic acid (5.14 g) was mixed with THF (51 ml) and water (51 ml), and sodium perborate·trihydrate (17 g) was added thereto, followed by stirring at room temperature overnight. EtOAc and 1 M hydrochloric acid were added to the reaction mixture, and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was mixed with EtOH (50 ml), and $NaBH_4$ (1.4 g) was added thereto, followed by stirring at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, and EtOAc and 1 M hydrochloric acid were then added thereto. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/EtOAc) to obtain 2-fluoro-3-(hydroxymethyl)phenol (2.2 g).

[0161]

Preparation Example 593

2-(Morpholin-4-yl)pyrimidin-5-ol (300 mg) and ethyl 3-(bromomethyl)-2-fluorobenzoate (850 mg) were mixed with MeCN (5 ml), THF (2 ml) and DMF (1 ml), and potassium carbonate was added thereto, followed by stirring at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, and EtOAc and water were then added thereto. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/EtOAc) to obtain ethyl 2-fluoro-3-({[2-(morpholin-4-yl)pyrimidin-5-yl]oxy}methyl)benzoate (378 mg).

[0162]

Preparation Example 594

5-Bromo-2-chloropyridine (5.0 g) was mixed with N,N-dimethylacetamide (25 ml), and morpholine (23 ml) was added thereto, followed by stirring at 130°C for 2 days. The

reaction mixture was concentrated under reduced pressure, and water was added to the residue, followed by extraction with EtOAc, and the organic layer was washed with saturated brine and dried over Na_2SO_4. The organic layer was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/EtOAc) to obtain 4-(5-bromopyridin-2-yl)morpholine (6.07 g).

[0163]

Preparation Example 596

5-Bromo-2-fluoropyridine (1.7 g) was mixed with N,N-dimethylacetamide (5 ml), and 3-methoxyazetidine hydrochloride (335 mg) and potassium carbonate (1.5 g) were added thereto, followed by stirring at 100°C overnight. The reaction mixture was concentrated under reduced pressure, and $CHCl_3$ and water were then added thereto. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/EtOAc) to obtain 5-bromo-2-(3-methoxyazetidin-1-yl)pyridine (581 mg).

[0164]

Preparation Example 603

1'-[3-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]-1',2',3',6'-tetrahydro-3,4'-bipyridine (257 mg) was mixed with EtOH (5 ml), and 10% palladium carbon (55 mg) was added thereto under argon atmosphere, followed by stirring at room temperature overnight under hydrogen atmosphere. The reaction mixture was filtered using Celite as a filtration adjuvant, and the filtrate was concentrated under reduced pressure to obtain 3-{1-[3-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]piperidin-4-yl}pyridine (239 mg).

[0165]

Preparation Example 613

tert-Butyl 4-[2-(3-methoxyazetidin-1-yl)pyrimidin-5-yl]-3,6-dihydropyridine-1(2H)-carboxylate (483 mg) was mixed with EtOH (5 ml), and 10% palladium carbon (100 mg) was added thereto, followed by stirring at room temperature for 5 hours under hydrogen atmosphere. The reaction mixture was filtered using Celite as a filtration adjuvant, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc). The purified product thus obtained was mixed with EtOH (5 ml), and 4 M hydrogen chloride/dioxane (3.5 ml) was added thereto, followed by stirring at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and then mixed with EtOH (5 ml), and potassium carbonate (2.0 g) was added thereto, followed by stirring at 80°C for 2 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to obtain 2-(3-methoxyazetidin-1-yl)-5-(piperidin-4-yl)pyrimidine (143 mg).

[0166]

Preparation Example 614

4-(4-Methylpyrimidin-2-yl)morpholine (300 mg) was mixed with dichloromethane (4 ml), and N-bromosuccinimide (357 mg) was added thereto at 0°C, followed by stirring at room temperature for 1 hour. Hexane was added to the reaction mixture, followed by purification by silica gel column chromatography (EtOAc/hexane), to obtain 4-(5-bromo-4-methylpyrimidin-2-yl) morpholine (372 mg).

[0167]

Preparation Example 617

{2-Fluoro-3-[2-(morpholin-4-yl)pyrimidin-5-yl]phenyl}methanol (337 mg), 1H-isoindole-1,3(2H)-dione (257 mg) and triphenylphosphine (458 mg) were mixed with THF, and diethyl azodicarboxylate (40% toluene solution) (0.68 ml) was added thereto at 0°C, followed by stirring at room temperature overnight. The reaction mixture was stirred at 0°C for 30 minutes, then filtered, washed with ice-cooled THF, and dried at 50°C under reduced pressure to obtain 2-{2-fluoro-3-[2-(morpholin-4-yl)pyrimidin-5-yl]benzyl}-1H-isoindole-1,3(2H)-dione (452 mg).

[0168]

Preparation Example 631

4-(5-Bromo-4-methylpyrimidin-2-yl)morpholine (372 mg), (2-fluoro-3-formylphenyl)boronic acid (315 mg), and potassium phosphate (918 mg) were mixed with toluene (10 ml) and water (10 ml), and palladium acetate (16 mg) and dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (59 mg) were added thereto, followed by stirring at 100°C for 4 hours. (2-Fluoro-3-formylphenyl)boronic acid (315 mg), potassium phosphate (918 mg), palladium acetate (16 mg), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (59 mg), and water (1 ml) were added to the reaction mixture, followed by stirring at 100°C overnight. The reaction mixture was cooled to room temperature, $CHCl_3$ and water were then added thereto, and the insoluble matter was removed by filtration. The organic layer of the filtrate was washed with water and saturated brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (EtOAc/hexane/ $CHCl_3$) to obtain 2-fluoro-3-[4-methyl-2-(morpholin-4-yl)pyrimidin-5-yl]benzaldehyde (282 mg).

[0169]

Preparation Example 638

Tetrahydro-2H-pyran-4-ol (200 mg) was mixed with THF (5 ml), and sodium hydride (55% suspended in oil) (120 mg) was added thereto, followed by stirring at room temperature for 5 minutes. 5-Bromo-2-chloropyrimidine (460 mg) was added to the

reaction mixture, followed by stirring at room temperature. Water and EtOAc were added to the reaction mixture, and the organic layer was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/EtOAc) to obtain 5-bromo-2-(tetrahydro-2H-pyran-4-yloxy)pyrimidine (361 mg).

[0170]

Preparation Example 651

1-[4-(Hydroxymethyl)piperidin-1-yl]ethan-1-one (200 mg) and THF (4 ml) were mixed, and NaH (70 mg) was added thereto, followed by stirring at room temperature for 10 minutes. 5-[3-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]-2-chloropyrimidine (200 mg) was added to the reaction mixture, followed by stirring at room temperature for 1 hour, and then 1 M TBAF/THF (1.2 ml) was added thereto, followed by stirring at room temperature. Water and EtOAc were added to the reaction mixture, and the organic layer was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/EtOAc/$CHCl_3$/MeOH) to obtain 1-{4-[({5-[2-fluoro-3-(hydroxymethyl)phenyl]pyrimidin-2-yl}oxy)methyl]piperidin-1-yl}ethan-1-one (167 mg).

[0171]

Preparation Example 653

5-[3-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]-2-chloropyrimidine (200 mg) was mixed with THF (4 ml), and sodium ethoxide (132 mg) was added thereto, followed by stirring at room temperature for 3 hours, and then a 1 M TBAF/THF solution (1.2 ml) was added thereto, followed by stirring at room temperature for 1 hour. Water and EtOAc were added to the reaction mixture, and the organic layer was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/EtOAc) to obtain [3-(2-ethoxypyrimidin-5-yl)-2-fluorophenyl]methanol (129 mg).

[0172]

Preparation Example 663

Methyl 3-{[(tert-butoxycarbonyl)amino]methyl}benzoate (4.6 g) was mixed with toluene (50 ml), followed by cooling to 0°C. Sodium bis(2-methoxyethoxy)aluminum hydride (65% toluene solution) (20 g) was added dropwise over 30 minutes, followed by stirring at 0°C for 1 hour. A 1 M aqueous NaOH solution (30 ml) was added dropwise to the reaction mixture, and $CHCl_3$ was then added thereto. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/EtOAc) to obtain tert-butyl [3-(hydroxymethyl)benzyl]carbamate (4.1 g).

[0173]

Preparation Example 671

4,4'-Bipiperidine dihydrochloride (2.95 g) was mixed with MeOH (25 ml), and a mixture of benzyl chloroformate (2.2 g) and toluene (5 ml) was added dropwise thereto over 1 hour while keeping the solution neutral by adding a 6 M aqueous NaOH solution at the same time. The reaction mixture was stirred at room temperature for 30 minutes and then concentrated under reduced pressure. $CHCl_3$, and a saturated aqueous sodium hydrogen carbonate solution were added to the reaction mixture. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography ($CHCl_3$/MeOH) to obtain benzyl 4,4'-bipiperidine-1-carboxylate (1.5 g).

[0174]

Preparation Example 674

tert-Butyl 3-(piperidin-4-yloxy)azetidine-1-carboxylate (2.78 g) was mixed with THF (40 ml), and TEA (3.5 ml) and benzyl chloroformate (2.7 g) were added thereto, followed by stirring at room temperature for 3 hours. EtOAc and water were added to the reaction mixture, and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/EtOAc).

The purified product thus obtained was mixed with EtOH (40 ml), and a 4 M hydrogen chloride/dioxane solution (30 ml) was added thereto, followed by stirring at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and $CHCl_3$ and a 1 M aqueous NaOH solution were then added thereto. The organic layer was dried over Na_2SO_4 and then concentrated under reduced pressure to obtain benzyl 4-(azetidin-3-yloxy)piperidine-1-carboxylate (1.97 g).

[0175]

Preparation Example 677

2-(Hydroxymethyl)pyrrolidine (500 mg) was mixed with dichloromethane (5 ml), and TEA (0.9 ml) and acetyl chloride (407 mg) were added thereto at 0°C, followed by stirring at room temperature overnight. 8 M Potassium hydroxide was added to the reaction mixture, followed by stirring at room temperature for 1 hour. The reaction mixture was extracted by the addition of water and $CHCl_3$/MeOH (4:1), the organic layer was washed with water and saturated brine, and dried over anhydrous Na_2SO_4, and the solvent was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (MeOH/$CHCl_3$) to obtain 1-[2-(hydroxymethyl)pyrrolidin-1-yl]ethanone (442 mg).

[0176]

Preparation Example 680

{2-Fluoro-3-[2-(piperidin-4-yl)pyrimidin-5-yl]phenyl}methanol (80 mg) was mixed with dichloromethane (1.6 ml), and TEA (85 mg) and acetyl chloride (48 mg) were added thereto at 0°C. The reaction mixture was concentrated under reduced pressure, the residue was mixed with MeOH, and a 1 M aqueous NaOH solution (0.8 ml) was added thereto, followed by stirring for 3 hours. 1 M hydrochloric acid was added to the reaction mixture, and $CHCl_3$ water was added to the reaction liquid. The aqueous layer was extracted with $CHCl_3$, and the prepared organic layer was dried over Na_2SO_4 and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography ($CHCl_3$/MeOH) to obtain 1-(4-{5-[2-fluoro-3-(hydroxymethyl)phenyl]pyrimidin-2-yl}piperidin-1-yl)ethanone (90 mg).

[0177]

Preparation Example 686

1-[3-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]-4,4'-bipiperidine (125 mg) and TEA (0.15 ml) were mixed with DCE (3 ml), and acetyl chloride (39 mg) was added thereto, followed by stirring at room temperature for 1 hour. A saturated aqueous sodium hydrogen carbonate solution and $CHCl_3$ were added to the reaction mixture, and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was mixed with THF (3 ml), and a 1 M TBAF/THF solution (0.6 ml) was added thereto, followed by stirring at room temperature for 1 hour. To the reaction mixture were added an aqueous ammonium chloride solution and EtOAc, the organic layer was dried over Na_2SO_4, and the solvent was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/EtOAc) to obtain 1-{1'-[2-fluoro-3-(hydroxymethyl)phenyl]-4,4'-bipiperidin-1-yl}ethanone (84 mg).

[0178]

Preparation Example 707

[3-(2-Chloropyrimidin-5-yl)-2-fluorophenyl]methanol (600 mg) was mixed with DMF (12 ml), and piperazine (2.2 g) was added thereto, followed by stirring at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and water was added to the residue, followed by stirring at 0°C for 1 hour. The produced solid was collected by filtration, washed with water, and then dried at 50°C under reduced pressure to obtain {2-fluoro-3-[2-(piperazin-1-yl)pyrimidin-5-yl]phenyl}methanol (697 mg).

[0179]

Preparation Example 709

5-{4-[3-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]piperazin-1-yl}pyrimidin-2-yl trifluoromethanesulfonate (200 mg) was mixed with THF (4 ml), and 2-methoxyethanamine (864 mg) was added thereto, followed by stirring at 60°C overnight. Water and EtOAc were added to the reaction mixture, and the organic layer was

concentrated under reduced pressure. The obtained residue was mixed with THF (5 ml), and a 1 M TBAF/THF solution (1.6 ml) was added thereto, followed by stirring at room temperature overnight. Water and EtOAc were added to the reaction mixture, and the organic layer was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (EtOAc/hexane) to obtain [2-fluoro-3-(4-{2-[(2-methoxyethyl)amino]pyrimidin-5-yl}piperazin-1-yl)phenyl]methanol (105 mg).

[0180]

Preparation Example 712

tert-Butyl 3-(pyridin-4-yloxy)azetidine-1-carboxylate (494 mg) was mixed with DCE (5 ml), and TFA (2 ml) was added thereto, followed by stirring at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure, and the obtained residue was purified by basic silica gel column chromatography ($CHCl_3$/MeOH) to obtain 4-(azetidin-3-yloxy)pyridine (268 mg).

[0181]

Preparation Example 749

Using 2-(3-methoxyazetidin-1-yl)pyrazine (451 mg) as a starting material and N-chlorosuccinimide as a halogenating agent under the same reaction conditions as in Preparation Example 614, 2-chloro-5-(3-methoxyazetidin-1-yl)pyrazine (303 mg) was prepared.

[0182]

Preparation Example 752

1-[3-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]piperazine (400 mg) was suspended in toluene (8 ml), and 3-chloropyridazine hydrochloride (242 mg), $Pd_2(dba)_3$(56 mg), dicyclohexyl(2', 6'-dimethoxybiphenyl-2-yl)phosphine (51 mg), and sodium tert-butoxide (308 mg) were added thereto, followed by stirring at 100°C overnight. The reaction mixture was cooled to room temperature, and filtered by the addition of $CHCl_3$ and Celite, and the filtrate was concentrated. The obtained residue was purified by silica gel column chromatography (EtOAc: hexane=70:30 to 100:0), and then purified by basic silica gel column chromatography (EtOAc/hexane) to obtain 3-{4-[3-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]piperazin-1-yl}pyridazine (325 mg).

[0183]

Preparation Example 754

3-Methoxyazetidine hydrochloride (100 mg) was mixed with THF (3 ml), and chloroacetic acid anhydride (166 mg) and sodium hydrogen carbonate (272 mg) were added thereto, followed by stirring at room temperature overnight. Water and sodium chloride were added to the reaction mixture, followed by stirring for 30 minutes. Then,

after extraction with EtOAc twice, the organic layer was washed with saturated brine and dried over Na_2SO_4, and the organic layer was concentrated under reduced pressure to obtain 2-chloro-1-(3-methoxyazetidin-1-yl)ethanone (130 mg).

[0184]

Preparation Example 758

A mixture of 1-[3-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]piperazine and MeCN was added to 2-chloro-1-(3-methoxyazetidin-1-yl)ethanone (130 mg) and potassium carbonate (219 mg), followed by stirring at 80°C for 3 hours. $CHCl_3$ was added to the reaction mixture, and the insoluble matter was removed by filtration. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (MeOH/$CHCl_3$) to obtain 2-{4-[3-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]piperazin-1-yl}-1-(3-methoxyazetidin-1-yl)ethanone (354 mg).

[0185]

Preparation Example 760

5-[3-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]-2-[4-(vinylsulfonyl)piperazin-1-yl]pyrimidine (360 mg) was mixed with THF (3 ml) and MeOH (4 ml), and a 1 M aqueous NaOH solution (1.46 ml) was added thereto, followed by stirring at room temperature for 3 hours. $CHCl_3$ was added to the reaction mixture, which was washed with water and saturated brine, and dried over Na_2SO_4. Then, the organic layer was concentrated under reduced pressure to obtain 5-[3-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]-2-{4-[(2-methoxyethyl)sulfonyl]piperazin-1-yl}pyrimidine (353 mg).

[0186]

Preparation Example 761

1-Acetylpiperidine-4-carboxylic acid (161 mg) was mixed with dichloromethane (5 ml), and oxalyl chloride (124 mg) and DMF (3 mg) were added thereto, followed by stirring at room temperature for 1 hour. TEA and 3-(2-aminopyrimidin-5-yl)-2-fluorobenzaldehyde (170 mg) were added thereto at 0°C, followed by stirring at room temperature overnight. A mixture of 1-acetylpiperidine-4-carboxylic acid (161 mg), oxalyl chloride (0.084 ml), and DMF in dichloromethane (3 ml), which is mixed in advance and was stirred for 1 hour, was added thereto at 0°C, followed by stirring at room temperature for 3 hours. Furthermore, a mixture of 1-acetylpiperidine-4-carboxylic acid (161 mg), oxalyl chloride (0.084 ml), and DMF in dichloromethane (3 ml), after mixing with the reaction mixture in advance, and then stirring for 1 hour, was added thereto at 0°C, followed by stirring at room temperature overnight. Furthermore, a mixture of 1-acetylpiperidine-4-carboxylic acid (322 mg), oxalyl chloride (0.168 ml), and DMF in dichloromethane (6 ml) which is mixed in advance

and was stirred for 1 hour, was added thereto at 0°C, followed by stirring at room temperature for 3 hours. Furthermore, a mixture of 1-acetylpiperidine-4-carboxylic acid (322 mg), oxalyl chloride (0.168 ml), and DMF in dichloromethane (6 ml) which is mixed in advance and was stirred for 1 hour, was added thereto at 0°C, followed by stirring at room temperature overnight. $CHCl_3$ and water were added to the reaction mixture, and the insoluble matter was removed by filtration. The organic layer was washed with water and saturated brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The obtained residue was mixed with MeOH, and $NaHCO_3$ was added thereto, followed by stirring at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography ($MeOH/CHCl_3$) to obtain 1-acetyl-N-[5-(2-fluoro-3-formylphenyl)pyrimidin-2-yl]piperidine-4-carboxyamide (363 mg).

[0187]

Preparation Example 766

tert-Butyl 4-(2-iodoethyl)piperidine-1-carboxylate (6.75 g) was mixed with dichloromethane (90 ml), and benzyl 4-hydroxypiperidine-1-carboxylate (4.0 g), silver trifluoromethane sulfonate (10.3 g), and 2,6-di-tert-butylpyridine (12 ml) was added thereto, followed by stirring at room temperature overnight. The reaction mixture was filtered using Celite as a filtration adjuvant, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/EtOAc) to obtain tert-butyl 4-[2-({1-[(benzyloxy)carbonyl]piperidin-4-yl}oxy)ethyl]piperidine-1-carboxylate (3.4 g).

[0188]

Preparation Example 767

5-[3-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]-2-(piperidin-4-ylmethoxy)pyrimidine (200 mg) was mixed with THF (4 ml), and ethylisocyanate (91 mg) was added thereto, followed by stirring at room temperature overnight. A 1 M TBAF/THF solution (1 ml) was added to the reaction mixture, followed by further stirring at room temperature for 3 hours. Water and EtOAc were added to the reaction mixture, and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography ($MeOH/ CHCl_3$) to obtain N-ethyl-4-[({5-[2-fluoro-3-(hydroxymethyl)phenyl]pyrimidin-2-yl}oxy)methyl]piperidine-1-carboxyamide (159.3 mg).

[0189]

Preparation Example 772

5-[3-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]-2-(piperazin-1-yl)pyrimidine (500 mg) was mixed with dichloromethane (10 ml), and DIPEA (482 mg) and 2-chloroethanesulfonyl chloride (304 mg) were added thereto at 0°C, followed by stirring at 0°C for 1.5 hours. $CHCl_3$ and water were added to the reaction mixture, and the organic layer was washed with water and saturated brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (EtOAc/hexane) to obtain 5-[3-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]-2-[4-(vinylsulfonyl)piperazin-1-yl]pyrimidine (360 mg).

[0190]

Preparation Example 776

1-[3-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]piperazine (140 mg) was mixed with DCE (4 ml), and ethanesulfonyl chloride (122 mg) and TEA (145 mg) were added thereto, followed by stirring at room temperature for 2 hours. $CHCl_3$ and water were added to the reaction mixture, and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was mixed with THF (4 ml), and a 1 M TBAF/THF solution (0.9 ml) was added thereto, followed by stirring at room temperature for 2 hours. EtOAc and water were added to the reaction mixture, and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (EtOAc/hexane) to obtain {3-[4-(ethylsulfonyl)piperazin-1-yl]-2-fluorophenyl}methanol (123.9 mg).

[0191]

Preparation Example 791

4-Nitrophenyl 4-[({5-[3-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]pyrimidin-2-yl}oxy)methyl]piperidine-1-carboxylate (200 mg) was mixed with NMP (5 ml), and isopropyl amine (0.3 ml) was added thereto, followed by stirring at 70°C for 6 hours. $iPrNH_2$ (0.3 ml) was added to the reaction mixture, followed by stirring at 70°C overnight. $iPrNH_2$ (0.4 ml) was added to the reaction mixture, followed by stirring at 70°C for 3 hours. The reaction mixture was cooled to room temperature and concentrated under reduced pressure, and then a 1 M aqueous NaOH solution and EtOAc were added thereto. The organic layer was concentrated under reduced pressure. The obtained residue was mixed with THF (4 ml), and a 1 M TBAF/THF solution (0.7 ml) was added thereto, followed by stirring at room temperature for 2 hours. EtOAc and water were added to the reaction mixture, and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (EtOAc/hexane/MeOH/$CHCl_3$) to obtain

4-[({5-[2-fluoro-3-(hydroxymethyl)phenyl]pyrimidin-2-yl}oxy)methyl]-N-isopropylpiperidine-1-carboxyamide (107.4 mg).

[0192]

Preparation Example 793

tert-Butyl 3-(pyridin-4-ylmethoxy)azetidine-1-carboxylate (4.8 g) was mixed with acetic acid (25 ml) and EtOAc (25 ml), and 10% platinum/carbon was added thereto under argon atmosphere, followed by stirring at room temperature overnight under hydrogen atmosphere of 1 atm. The reaction mixture was filtered using Celite as a filtration adjuvant, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH) to obtain tert-butyl 3-(piperidin-4-ylmethoxy)azetidine-1-carboxylate (4.8 g).

[0193]

Preparation Example 796

Benzyl 3-oxopiperazine-1-carboxylate (400 mg) and 3-(bromomethyl)pyridine hydrobromide (647 mg) were mixed with DMF (8 ml), and sodium hydride (55% suspended in oil) (194 mg) was added thereto at 0°C, followed by stirring at room temperature for 3 hours. Water and $CHCl_3$ were added to the reaction mixture at 0°C, and the organic layer was washed with water and saturated brine, dried over anhydrous sodium carbonate, and concentrated under reduced pressure. The obtained residue was purified by basic silica gel column chromatography (EtOAc/hexane) to obtain benzyl 3-oxo-4-(pyridin-3-ylmethyl)piperazine-1-carboxylate (345 mg).

[0194]

Preparation Example 801

2-(2-Fluoro-3-{4-[2-(3-methoxyazetidin-1-yl)pyrimidin-5-yl]piperazin-1-yl}benzyl)-1H-isoindole-1,3(2H)-dione (135 mg) was suspended in EtOH (3 ml), and hydrazine hydrate (67 mg) was added thereto, followed by stirring at 80°C overnight. The reaction mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (28% aqueous ammonia/MeOH/$CHCl_3$) to obtain 1-(2-fluoro-3-{4-[2-(3-methoxyazetidin-1-yl)pyrimidin-5-yl]piperazin-1-yl}phenyl)methanamine (100 mg).

[0195]

Preparation Example 803

tert-Butyl 3-hydroxyazetidine-1-carboxylate (1.0 g) and 6-methylpyridin-3-ol (570 mg) were mixed with THF (10 ml), and triphenylphosphine (2.3 g) was added thereto. A 1.9 M DIAD/toluene solution (4.5 ml) was added dropwise thereto, followed by stirring at 55°C overnight. The reaction mixture was concentrated under reduced pressure, and EtOAc and 1 M hydrochloric acid were added thereto. The aqueous layer was adjusted to pH of around 10 by the addition of a 4 M aqueous NaOH solution, followed by extraction

with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography ($CHCl_3$/MeOH). The purified product thus obtained was mixed with DCE (6 ml), and TFA (3 ml) was added thereto, followed by stirring at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure, and then $CHCl_3$ and a 1 M aqueous NaOH solution were added thereto. The organic layer was dried over Na_2SO_4 and then concentrated under reduced pressure to obtain 5-(azetidin-3-yloxy)-2-methylpyridine (858 mg).

[0196]

Preparation Example 805

4-Bromo-2,6-dimethylpyridine (2 g) was mixed with THF (30 ml) and cooled to -78°C under argon atmosphere. A 1.65 M n-butyl lithium/hexane solution (8.5 ml) was added dropwise thereto, followed by stirring at -78°C for 10 minutes, and DMF (1.3 ml) was added thereto. The reaction mixture was warmed to 0°C over 1 hour, followed by stirring at 0°C for 1 hour. Water and EtOAc were added to the reaction mixture, and the organic layer was dried over Na_2SO_4, and the reaction mixture was concentrated under reduced pressure. The obtained residue was mixed with MeOH (30 ml), and $NaBH_4$ (610 mg) was added thereto, followed by stirring at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, and $CHCl_3$ and water were added to the obtained residue. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography ($CHCl_3$/MeOH) to obtain (2,6-dimethylpyridin-4-yl)methanol (1.5 g).

[0197]

Preparation Example 806

(2,6-Dimethylpyridin-4-yl)methanol (457 mg) was mixed with DCE (8 ml), and thionyl chloride (0.6 ml) and DMF (19 mg) were added thereto, followed by stirring at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure to obtain 4-(chloromethyl)-2,6-dimethylpyridine hydrochloride (640 mg).

[0198]

Preparation Example 807

1-(2-tert-Butoxypyridin-4-yl)-4-[3-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]piperazine (3.14 g) was mixed with CH_2Cl_2 (50 ml), and TFA (5.1 ml) was added thereto, followed by stirring at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and the residue was mixed with MeOH (2 ml). A 8 M NH_3/MeOH solution (10 ml) was added thereto at 0°C, followed by stirring at room temperature for 2 hours. The solid in the reaction mixture was collected by filtration, washed with MeOH, and dried at 50°C under reduced pressure to obtain 4-{4-[2-fluoro-3-(hydroxymethyl)phenyl]piperazin-1-yl}pyridin-2(1H)-one (1.76 g).

[0199]

Preparation Example 809

tert-Butyl 4-[1-(diphenylmethyl)azetidin-3-yl]piperidine-1-carboxylate (1.9 g) was mixed with MeOH (50 ml), and 1 M hydrochloric acid (5.1 ml) and 20% palladium carbon hydroxide (600 mg) were added thereto, followed by stirring at room temperature for 4 hours under hydrogen atmosphere of 3 atm. After returning to normal pressure under argon atmosphere, a 1 M aqueous NaOH solution (1 ml) was added thereto. The reaction mixture was filtered using Celite as a filtration adjuvant, and the filtrate was concentrated under reduced pressure. $CHCl_3$ and a 1 M aqueous NaOH solution were added to the obtained residue, and the organic layer was dried over Na_2SO_4 and then concentrated under reduced pressure. The obtained residue was purified by basic silica gel column chromatography ($CHCl_3$/MeOH) to obtain tert-butyl 4-(azetidin-3-yl)piperidine-1-carboxylate (1.1 g).

[0200]

Preparation Example 810

tert-Butyl 4-{1-[3-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]azetidin-3-yl}piperidine-1-carboxylate (2 g) was mixed with CH_2Cl_2 (20 ml), and TFA (5 ml) was added thereto, followed by stirring at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure. The obtained residue was mixed with CH_2Cl_2 (30 ml), and TEA (6 ml) and TBSCl (2.5 g) were added thereto, followed by stirring at 60°C overnight. Water was added to the reaction mixture, and the organic layer was dried over Na_2SO_4 and then concentrated under reduced pressure. The obtained residue was mixed with MeOH (20 ml), and a 1 M aqueous NaOH solution (5 ml), followed by stirring at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, $CHCl_3$ and water were added to the obtained residue, and the organic layer was dried over Na_2SO_4 and then concentrated under reduced pressure. The obtained residue was purified by basic silica gel column chromatography (hexane/EtOAc) to obtain 4-{1-[3-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]azetidin-3-yl}piperidine (1.6 g).

[0201]

Preparation Example 821

tert-Butyl 3-{[6-(hydroxymethyl)pyridin-3-yl]oxy}azetidine-1-carboxylate (198 mg) was mixed with THF (3 ml), and sodium hydride (55% suspended in oil) (50 mg) was added thereto at 0°C, followed by stirring at 0°C for 30 minutes. Methyl iodide (0.4 ml) was added to the reaction mixture, followed by stirring at room temperature for 3 hours. EtOAc and water were added to the reaction mixture, and the organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The obtained residue was purified by

silica gel column chromatography ($CHCl_3$/MeOH). The purified product thus obtained was mixed with DCE (2.8 ml), and TFA (902 mg) was added thereto, followed by stirring at room temperature for 5 hours. $CHCl_3$ and a 1 M aqueous NaOH solution were added to the reaction mixture, and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by basic silica gel column chromatography ($CHCl_3$/MeOH) to obtain 5-(azetidin-3-yloxy)-2-(methoxymethyl)pyridine.

[0202]

Preparation Example 830

(3-{3-[(6-tert-Butoxypyridin-3-yl)oxy]azetidin-1-yl}-2-fluorophenyl)methanol (760 mg) was mixed with dichloromethane (5 ml), and TFA (2 ml) was added thereto, followed by stirring at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure, and a 1 M aqueous NaOH solution and $CHCl_3$ were added thereto. The organic layer was dried over Na_2SO_4 and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography ($CHCl_3$/MeOH) to obtain 5-({1-[2-fluoro-3-(hydroxymethyl)phenyl]azetidin-3-yl}oxy)pyridin-2(1H)-one (428 mg).

[0203]

Preparation Example 834

4-{1-[3-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]azetidin-3-yl}piperidine (120 mg) and triethylamine (145 mg) were mixed with dichloromethane (3 ml), and propanoyl chloride (48 mg) was added thereto, followed by stirring at room temperature for 1 hour. A 1 M aqueous NaOH solution and $CHCl_3$ were added to the reaction mixture, and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was mixed with THF (3 ml), and a 1 M TBAF/THF (0.5 ml) solution was added thereto, followed by stirring at room temperature for 1 hour. A saturated aqueous ammonium chloride solution and EtOAc were added to the reaction mixture, and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography ($CHCl_3$/MeOH) to obtain 1-(4-{1-[2-fluoro-3-(hydroxymethyl)phenyl]azetidin-3-yl}piperidin-1-yl)propan-1-one (101 mg).

[0204]

Preparation Example 836

4-{1-[3-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]azetidin-3-yl}piperidine (120 mg) and methoxy acetic acid (47 mg) was mixed with dichloromethane (3 ml), and WSC hydrochloride (100 mg) and HOBt (70 mg) was added thereto, followed by stirring at room temperature for 3 hours. A 1 M aqueous NaOH solution and $CHCl_3$ were added

to the reaction mixture, and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was mixed with THF (3 ml), and a 1 M TBAF/THF solution (0.66 ml) was added thereto, followed by stirring at room temperature for 1 hour. EtOAc and a saturated aqueous ammonium chloride solution were added to the reaction mixture, and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/EtOAc) to obtain 1-(4-{1-[2-fluoro-3-(hydroxymethyl)phenyl]azetidin-3-yl}piperidin-1-yl)-2-methoxyethanone (106 mg).

[0205]

Preparation Example 840

4-{4-[2-Fluoro-3-(hydroxymethyl)phenyl]piperazin-1-yl}pyridin-2(1H)-one (300 mg) was suspended in DMF (7.5 ml), and potassium carbonate (273 mg), 2-bromoethylmethyl ether (275 mg), and tetrabutylammonium iodide (37 mg) were added thereto, followed by stirring at 60°C overnight. Water and $CHCl_3$ were added to the reaction mixture, and the organic layer was washed with saturated brine and then dried over Na_2SO_4. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (MeOH/$CHCl_3$) to obtain (2-fluoro-3-{4-[2-(2-methoxyethoxy)pyridin-4-yl]piperazin-1-yl}phenyl)methanol (104 mg).

[0206]

Preparation Example 841

Benzyl 3-hydroxyazetidine-1-carboxylate (2.3 g) and 6-tert-butoxypyridin-3-ol (1.5 g) were mixed with THF (25 ml), and triphenylphosphine (4 g) was added thereto. A 1.9 M DIAD/toluene solution (8 ml) was added dropwise thereto, followed by stirring at 55°C overnight. The reaction mixture was concentrated under reduced pressure. The obtained residue was mixed with ethanol (25 ml), and 10% palladium carbon (800 mg) were added thereto, followed by stirring at room temperature for 5 hours under hydrogen atmosphere. The reaction mixture was filtered using Celite as a filtration adjuvant, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography ($CHCl_3$/MeOH) to obtain 5-(azetidin-3-yloxy)-2-tert-butoxypyridine (595 mg).

[0207]

Preparation Example 842

5-({1-[2-Fluoro-3-(hydroxymethyl)phenyl]azetidin-3-yl}oxy)pyridin-2(1H)-one (160 mg) was mixed with DMF (3 ml), and methyl iodide (114 mg) and potassium carbonate (200 mg) were added thereto, followed by stirring at 60°C for 2 hours. The reaction mixture was concentrated under reduced pressure, and to the residue were added $CHCl_3$

and water. The organic layer was dried over Na_2SO_4 and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography ($CHCl_3$/MeOH) to obtain 5-({1-[2-fluoro-3-(hydroxymethyl)phenyl]azetidin-3-yl}oxy)-1-methylpyridin-2(1H)-one (106 mg).

[0208]

Preparation Example 845

4-({1-[3-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]azetidin-3-yl}oxy)piperidine (250 mg) and dioxane (7 ml) were mixed, and methyl 5-bromopyridine-2-carboxylate (170 mg), palladium acetate (II)(15 mg), dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (60 mg), and tripotassium phosphate (400 mg) were added thereto, followed by stirring 100°C for 48 hours. The reaction mixture was cooled to room temperature, and filtered by the addition of $CHCl_3$ and Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc). The purified product thus obtained was mixed with THF (5 ml), and a 1.0 M TBAF/THF solution (0.63 ml) was added thereto, followed by stirring at room temperature for 1 hour. A saturated aqueous ammonium chloride solution and $CHCl_3$ were added to the reaction mixture, and the organic layer was dried over Na_2SO_4 and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography ($CHCl_3$/MeOH) to obtain methyl 5-[4-({1-[2-fluoro-3-(hydroxymethyl)phenyl]azetidin-3-yl}oxy)piperidin-1-yl]pyridine-2-carboxylate (263 mg).

[0209]

Preparation Example 847

tert-Butyl 4-{1-[3-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]azetidin-3-yl}piperidine-1-carboxylate (2.9 g) and dichloromethane (29 ml) were mixed, and TFA (7.3 ml) was added thereto, followed by stirring at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure, and $CHCl_3$ and a saturated aqueous sodium hydrogen carbonate solution were added thereto. The aqueous layer was concentrated under reduced pressure, and $CHCl_3$ was added to the residue, followed by stirring and filtrating. The filtrate was dried over Na_2SO_4 and then concentrated under reduced pressure. The obtained residue was purified by basic silica gel column chromatography ($CHCl_3$/MeOH) to obtain {2-fluoro-3-[3-(piperidin-4-yl)azetidin-1-yl]phenyl}methanol (1.6 g).

[0210]

Preparation Example 853

5-{4-[2-Fluoro-3-(hydroxymethyl)phenyl]piperazin-1-yl}pyridin-2(1H)-one (352 mg) and DMF (10 ml) were mixed, and potassium carbonate (240 mg) and methyl iodide (200 mg) were added thereto, followed by stirring at 60°C overnight. Methyl iodide (49 mg) and potassium carbonate (48.1 mg) were added thereto, followed by stirring at 60°C for 4 hours. The reaction mixture was cooled to room temperature, and water and $CHCl_3$ were added thereto at 0°C. The organic layer was washed with water and saturated brine, and then dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography ($CHCl_3$/MeOH) to obtain 5-{4-[2-fluoro-3-(hydroxymethyl)phenyl]piperazin-1-yl}-1-methylpyridin-2(1H)-one (256 mg).

[0211]

Preparation Example 855

6-Iodoimidazo[1,2-a]pyridine (400 mg), tert-butyl 3-hydroxyazetidine-1-carboxylate (500 mg), and toluene (2 ml) were mixed, and copper iodide (I) (40 mg), 1,10-phenanthrene (60 mg), and cesium carbonate (1 g) were added thereto, followed by stirring at 100°C overnight. $CHCl_3$ and water were added to the reaction mixture, and the organic layer was dried over Na_2SO_4 and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography ($CHCl_3$/MeOH). The purified product thus obtained was mixed with dichloromethane (5 ml), and TFA (1.5 ml) was added thereto, followed by stirring at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure, and the residue was purified by basic silica gel column chromatography ($CHCl_3$/MeOH) to obtain 6-(azetidin-3-yloxy)imidazo[1,2-a]pyridine (310 mg).

[0212]

Preparation Example 857

tert-Butyl 3-oxoazetidine-1-carboxylate (1 g) and THF (20 ml), which had been cooled to 0°C, were mixed, and a 1.12 M methylmagnesium bromide/THF solution (10 ml) was added thereto, followed by stirring at the same temperature for 1 hour. Water and EtOAc were added to the reaction mixture, the organic layer was dried over Na_2SO_4, and the solvent was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/EtOAc) to obtain tert-butyl 3-hydroxy-3-methylazetidine-1-carboxylate (1.0 g).

[0213]

Preparation Example 859

5-(Chloromethyl)-2-methylpyridine hydrochloride (1.13 g) and DMF (9 ml) were mixed, and triphenylphosphine (1.67 g) and sodium iodide (5 mg) were added thereto, followed by stirring at 90°C for 6 hours. The reaction mixture was cooled to room

temperature, and the precipitated solid was collected by filtration and washed with toluene to obtain [(6-methylpyridin-3-yl)methyl](triphenyl)phosphonium chloride hydrochloride (2.79 g).

[0214]

Preparation Example 860

Under argon atmosphere, (2-bromopyridin-4-yl)methanol (2.53 g), cyclopropylboronic acid (3.6 g), tripotassium phosphate (10 g), tricyclohexylphosphine (750 mg), toluene (60 ml), and water (3 ml) were mixed, and palladium acetate (II) (300 mg) were added thereto, followed by stirring at 100°C for 5 hours. Cyclopropylboronic acid (1.8 g) was added thereto, followed by stirring at 100°C for 2 hours. The reaction mixture was concentrated under reduced pressure, and $CHCl_3$ and water were added thereto. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure.

The obtained residue was purified by silica gel column chromatography (hexane/EtOAc) to obtain (2-cyclopropylpyridin-4-yl)methanol (2.0 g).

[0215]

Preparation Example 893

Under argon atmosphere, [(3-bromo-2-fluorobenzyl)oxy](tert-butyl)dimethylsilane (5.5 g), 3-[(benzyloxy)methyl]azetidine (2.5 g), and toluene (50 ml) were mixed, and (1E,4E)-1,5-diphenylpenta-1,4-dien-3-one palladium (3:2) (900 mg), BINAP (1.8 g), and sodium tert-butoxide (2.5 g) were added thereto, followed by stirring at 90°C for 3 hours. The reaction mixture was cooled to room temperature, and EtOAc were added thereto, followed by filtering using Celite as a filtration adjuvant. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/EtOAc). The purified product thus obtained was mixed with EtOH (40 ml), and 10% palladium carbon (1 g) was added thereto, followed by stirring at room temperature overnight under hydrogen atmosphere of 1 atm and filtering using Celite as a filtration adjuvant. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH) to obtain {1-[3-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]azetidin-3-yl}methanol (4.59 g).

[0216]

Preparation Example 894

Under argon atmosphere, 4-({1-[3-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]azetidin-3-yl}oxy)piperidine (500 mg), 5-bromo-2-tert-butoxypyridine (500 mg), and toluene (10 ml) were mixed, and (1E,4E)-1,5-diphenylpenta-1,4-dien-3-one palladium (3:2) (80 mg), BINAP (160 mg), sodium tert-butoxide (200 mg) were added thereto, followed by stirring at 90°C for 3 hours.

The reaction mixture was cooled to room temperature, and EtOAc was added thereto, followed by filtering using Celite as a filtration adjuvant. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc). The purified product thus obtained was mixed with dichloromethane (5 ml), and TFA (2 ml) was added thereto, followed by stirring at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and to the residue were added MeOH (3 ml) and a 1 M aqueous NaOH solution (2.5 ml), followed by stirring at room temperature for 1 hour. 1 M hydrochloric acid (2.5 ml) was added thereto, and the reaction mixture was concentrated under reduced pressure. To the residue were added $CHCl_3$ and water, and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography ($CHCl_3$/MeOH) to obtain 5-[4-({1-[2-fluoro-3-(hydroxymethyl)phenyl]azetidin-3-yl}oxy)piperidin-1-yl]pyridin-2(1H)-one (473 mg).

[0217]

Preparation Example 922

tert-Butyl 3-{[6-(hydroxymethyl)pyridin-3-yl]oxy}azetidine-1-carboxylate (242 mg) and THF (3 ml) were mixed, and triethylamine (182 mg) and methanesulfonyl chloride (147 mg) were added thereto, followed by stirring at room temperature for 1 hour. In another flask, THF (3 ml) and EtOH (237 mg) were mixed, and NaH was added thereto, followed by stirring at room temperature for 10 minutes. The reaction mixture prepared immediately before was added thereto, followed by stirring at room temperature for 1 hour. Water and EtOAc were added to the reaction mixture, and the organic layer was concentrated under reduced pressure. DCE (4 ml) and TFA (1 ml) were added to the obtained residue, followed by stirring at room temperature for 5 hours, and then concentrating under reduced pressure. $CHCl_3$ and a 1 M aqueous NaOH solution were added to the residue, and the organic layer was dried over Na_2SO_4 and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography ($CHCl_3$/MeOH) to obtain 5-(azetidin-3-yloxy)-2-(ethoxymethyl)pyridine (180 mg).

[0218]

Preparation Example 926

{1-[3-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]azetidin-3-yl}methylmethanesulfonate (150 mg), 6-methylpyridin-3-ol (70 mg), and DMF (2 ml) were mixed, and potassium carbonate (120 mg) were added thereto, followed by stirring at 80°C for 6 hours. The reaction mixture was concentrated under reduced pressure, and $CHCl_3$ and a saturated aqueous sodium hydrogen carbonate solution were then added thereto. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. THF (2

ml) and a 1 M TBAF/THF solution (0.6 ml) were added to the obtained residue, followed by stirring at room temperature for 1 hour. $CHCl_3$ and a saturated aqueous ammonium chloride solution were added to the reaction mixture, and the organic layer was dried over Na_2SO_4 and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/EtOAc) to obtain [2-fluoro-3-(3-{[(6-methylpyridin-3-yl)oxy]methyl}azetidin-1-yl)phenyl]methanol (112 mg).

[0219]

Preparation Example 938

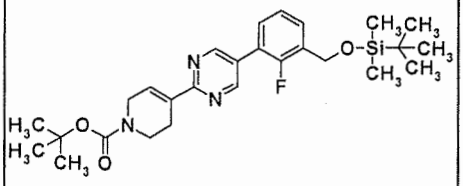
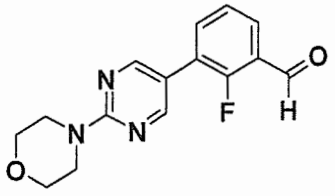
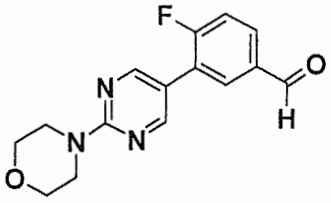
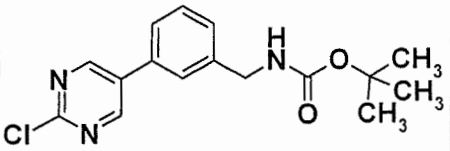
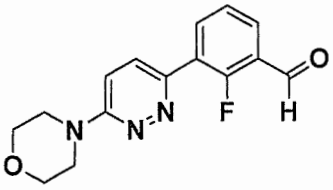
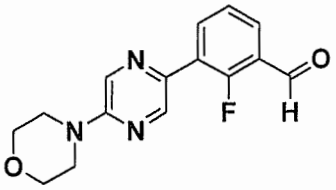
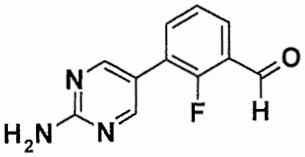
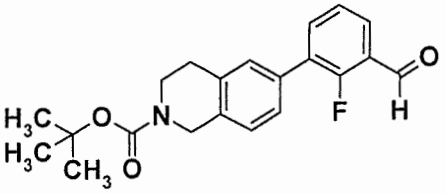
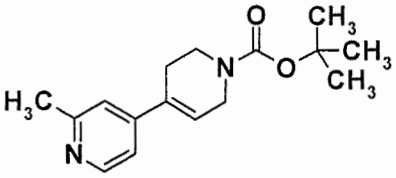
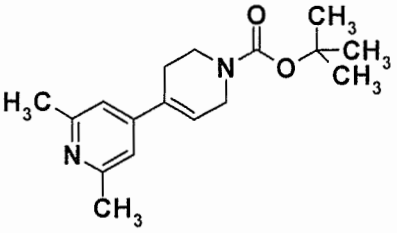
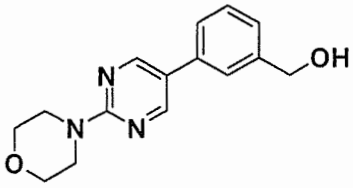
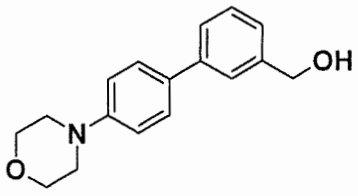
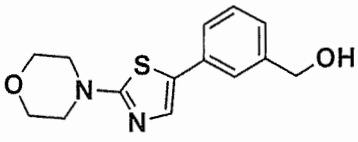
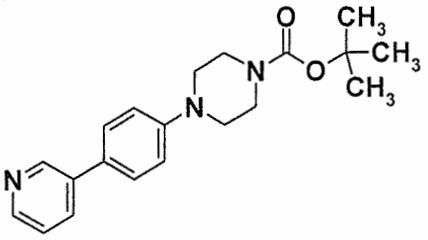
TFA (0.5 ml) was added to a mixture of [3-(3-{[(6-tert-butoxypyridin-3-yl)oxy]methyl}azetidin-1-yl)-2-fluorophenyl]methanol (146 mg) and dichloromethane (1 ml), followed by stirring at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure and the residue was purified by basic silica gel column chromatography ($CHCl_3$/methanol). The purified product thus obtained was mixed with DMF (2 ml), and potassium carbonate (100 mg) and methyl iodide (68 mg) was added thereto, followed by stirring at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure, and $CHCl_3$ and water were added to the residue. The organic layer was dried over Na_2SO_4 and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography ($CHCl_3$/methanol) to obtain 5-({1-[2-fluoro-3-(hydroxymethyl)phenyl]azetidin-3-yl}methoxy)-1-methylpyridin-2(1H)-one (129 mg).

[0220]

The compounds of Preparation Examples shown in the tables below were prepared using the respective corresponding starting materials in the same manner as the methods of Preparation Examples above. The structures, the preparation methods, and the physicochemical data for the compounds of Preparation Examples are shown in the tables below.

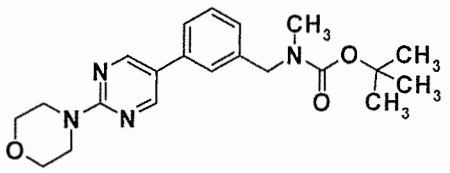
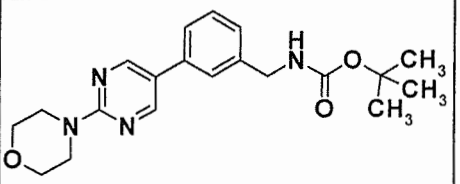
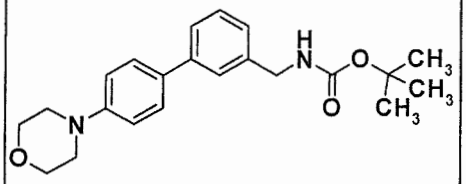
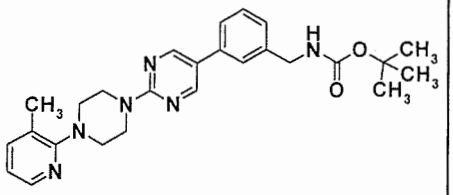
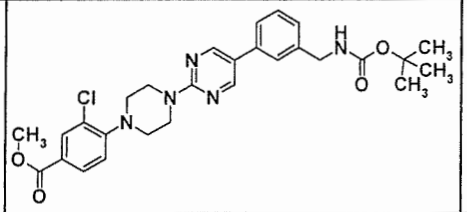
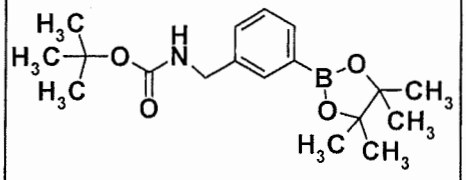
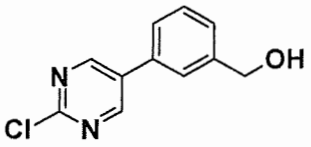
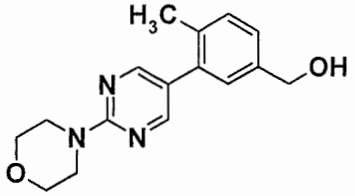
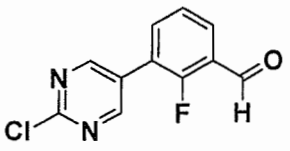
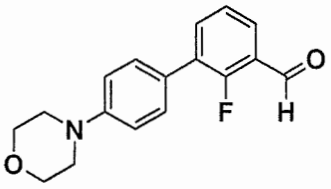
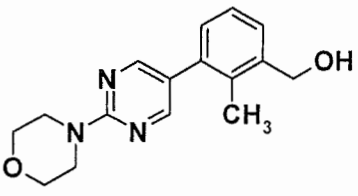
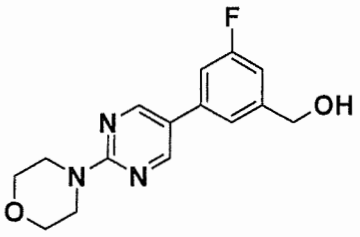
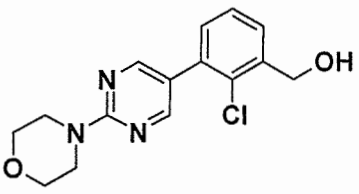
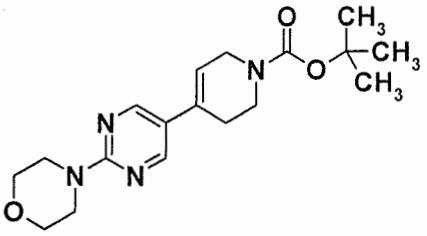
[0221]

[Table 3]

Rf	Syn	Structure	Rf	Syn	Structure
1	R12		2	R12	
3	R12		4	R12	
5	R12		6	R12	
7	R12		8	R12	
9	R12		10	R12	
11	R12		12	R12	
13	R12		14	R12	

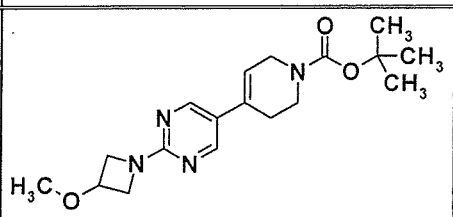
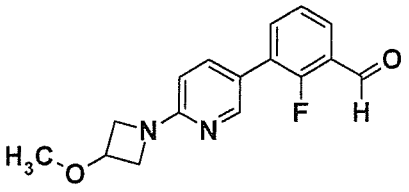
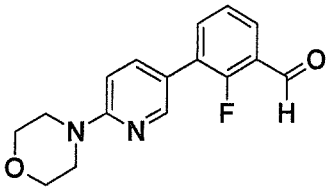
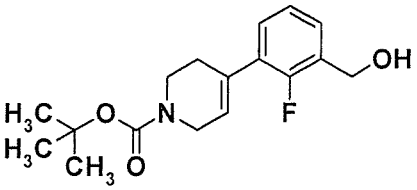
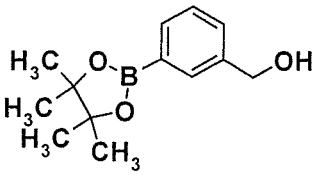
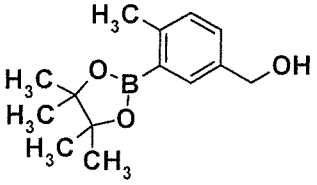
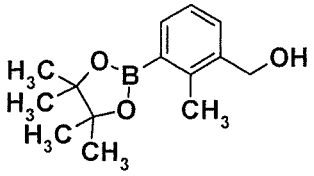
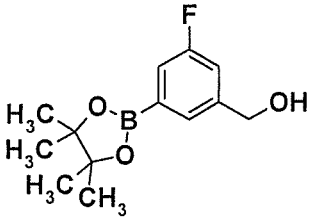
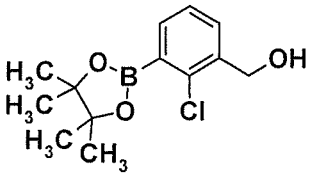
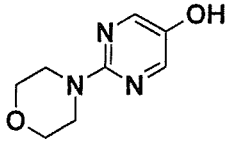
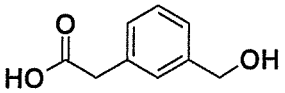
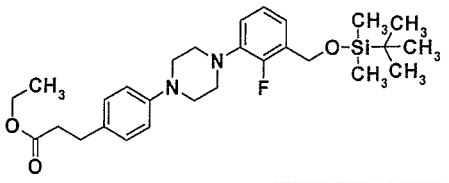
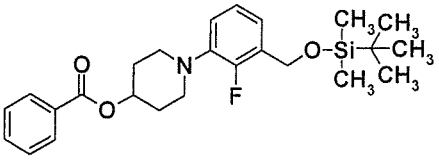
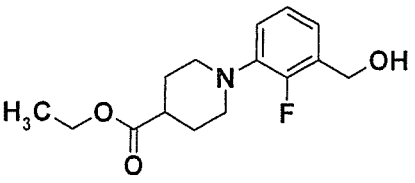
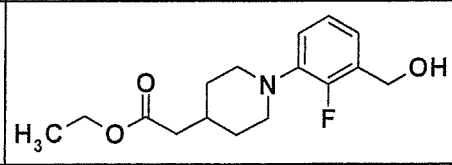
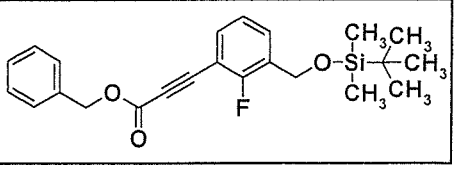
[0222]

[Table 4]

Rf	Syn	Structure	Rf	Syn	Structure
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17	R12		18	R12	
19	R12		20	R12	
21	R12		22	R12	
23	R12		24	R12	
25	R12		26	R12	
27	R12		28	R12	

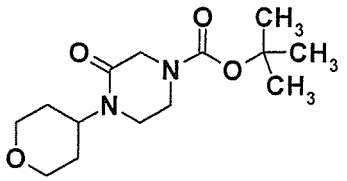
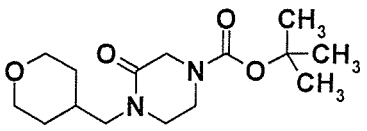
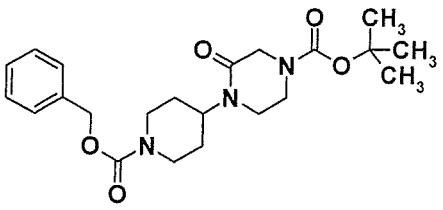
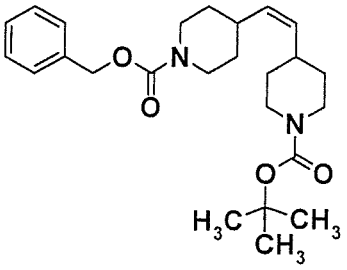
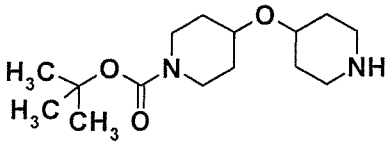
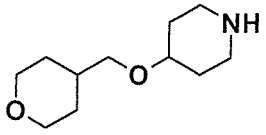
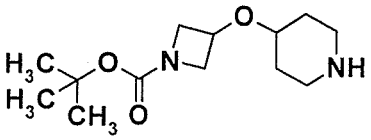
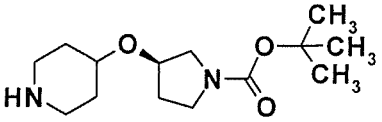
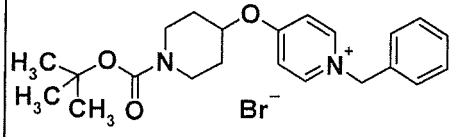
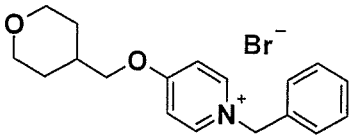
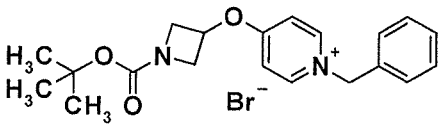
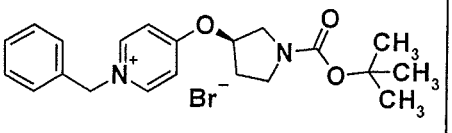
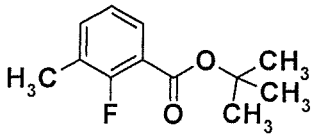
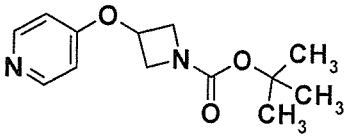
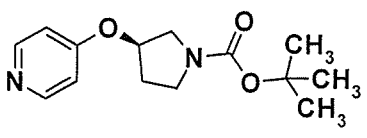
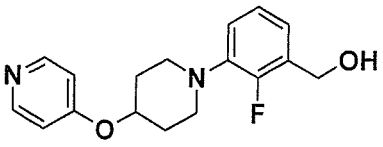
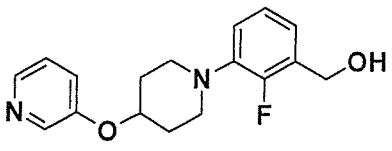
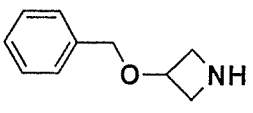
[0223]

[Table 5]

Rf	Syn	Structure	Rf	Syn	Structure
29	R12		30	R12	
31	R12		32	R32	
33	R33		34	R33	
35	R33		36	R33	
37	R33		38	R38	
39	R39		40	R41	
41	R41		42	R42	
43	R42		44	R44	

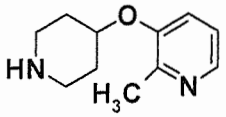
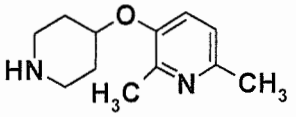
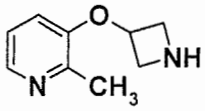
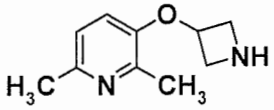
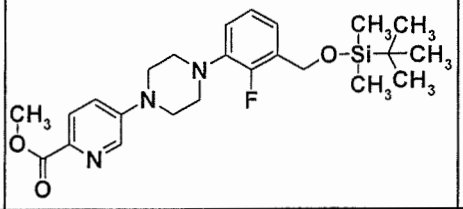
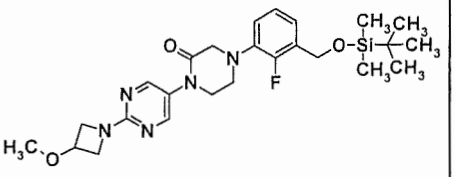
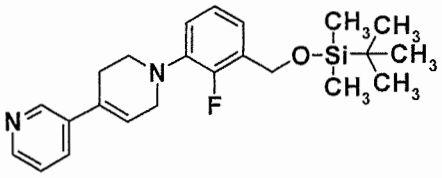
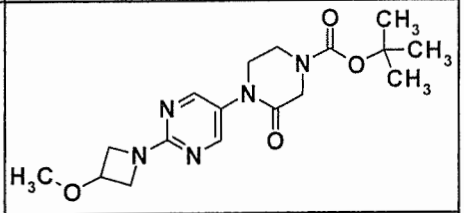
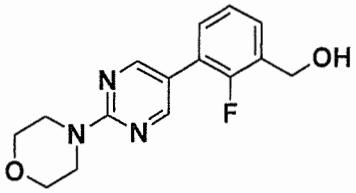
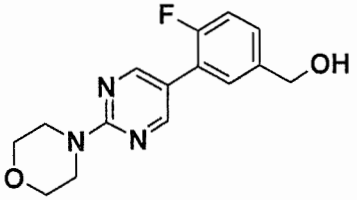
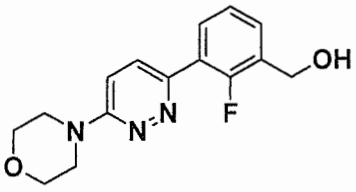
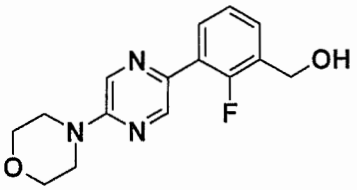
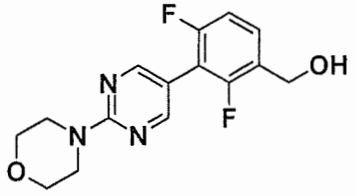
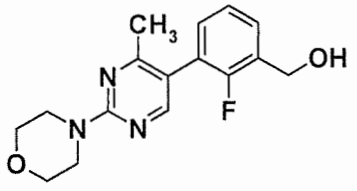
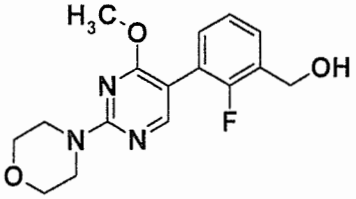
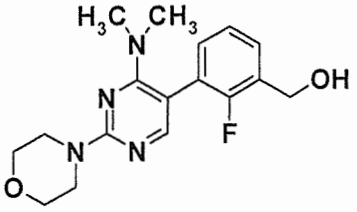
[0224]

[Table 6]

Rf	Syn	Structure	Rf	Syn	Structure
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47	R45		48	R48	
49	R50		50	R50	
51	R50		52	R50	
53	R54		54	R54	
55	R54		56	R54	
57	R57		58	R58	
59	R58		60	R60	
61	R60		62	R62	

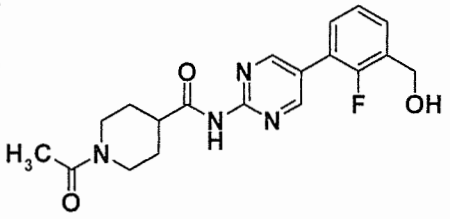
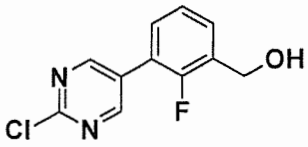
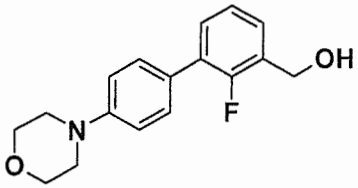
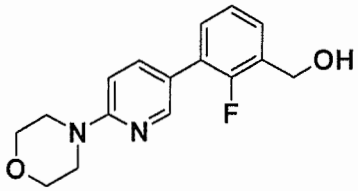
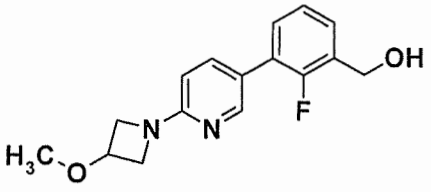
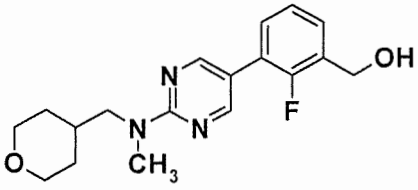
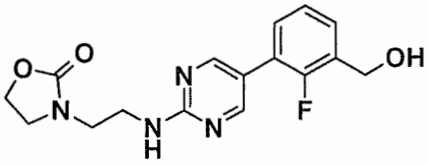
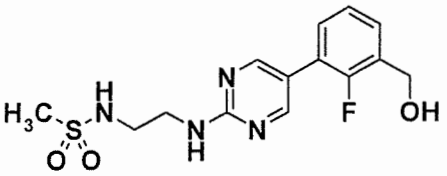
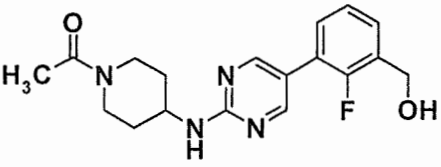
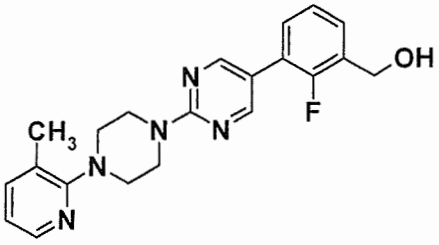
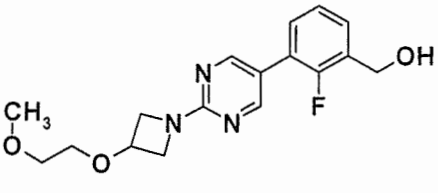
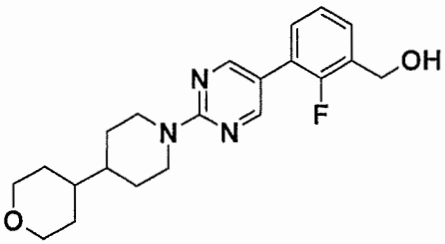
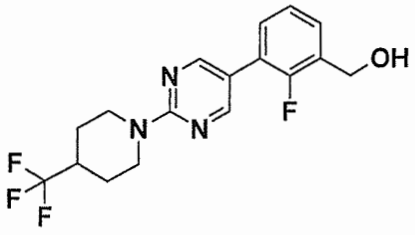
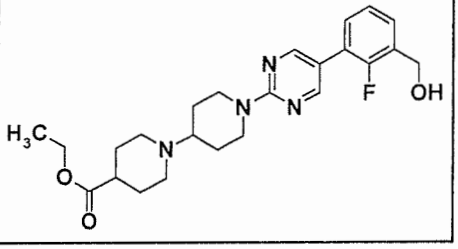
[0225]

[Table 7]

Rf	Syn	Structure	Rf	Syn	Structure
63	R63		64	R63	
65	R63		66	R63	
67	R67		68	R67	
69	R69		70	R70	
71	R81		72	R81	
73	R81		74	R81	
75	R81		76	R81	
77	R81		78	R81	

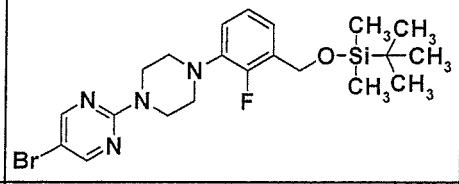
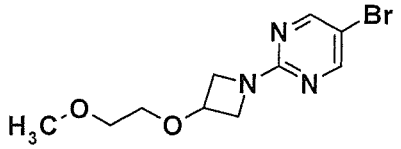
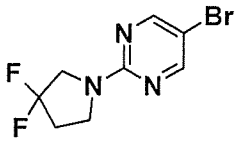
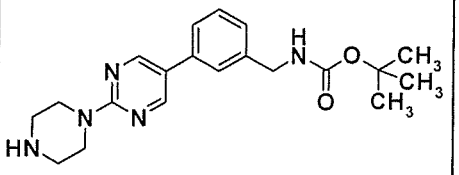
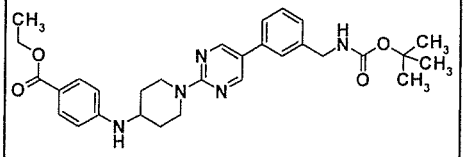
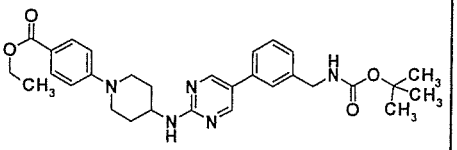
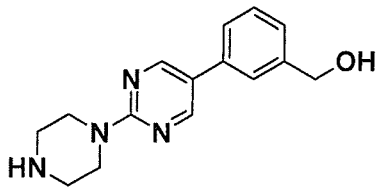
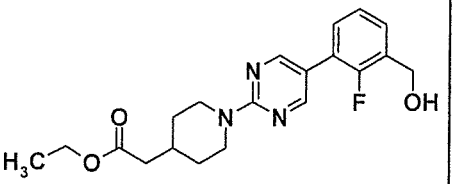
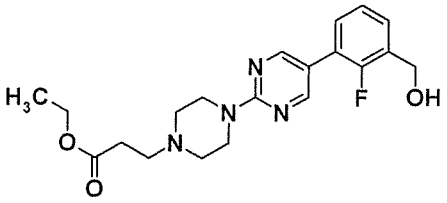
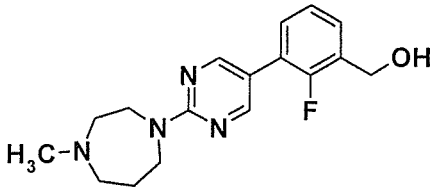
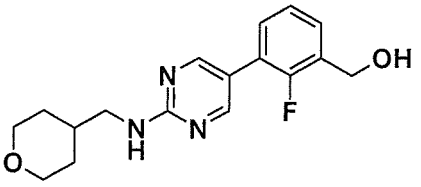
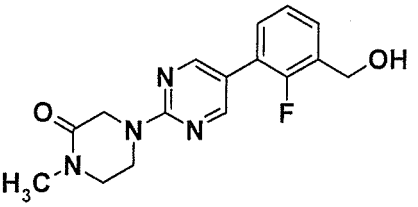
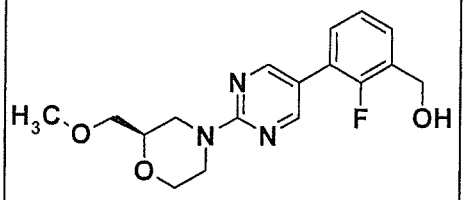
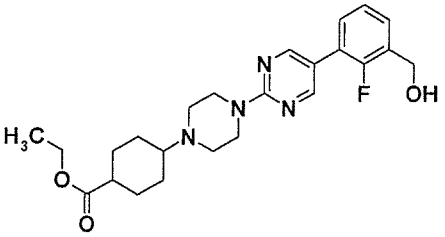
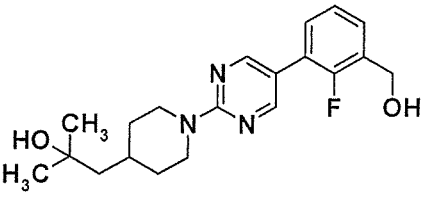
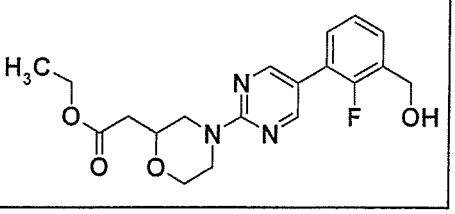
[0226]

[Table 8]

Rf	Syn	Structure	Rf	Syn	Structure
79	R81		80	R81	
81	R81		82	R81	
83	R81		84	R135	
85	R135		86	R135	
87	R135		88	R135	
89	R135		90	R135	
91	R135		92	R135	

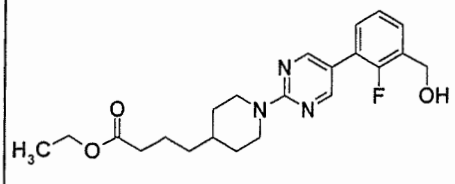
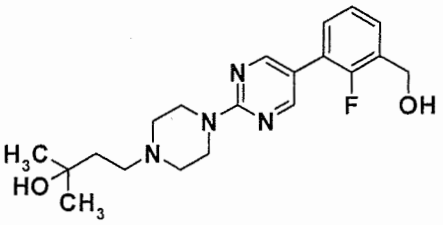
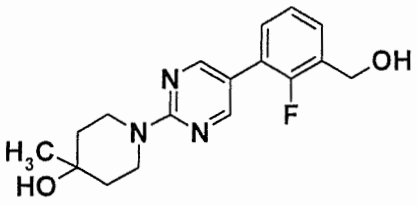
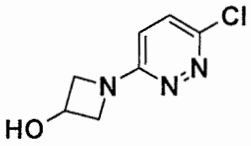
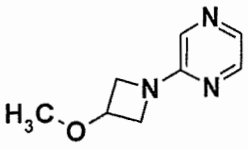
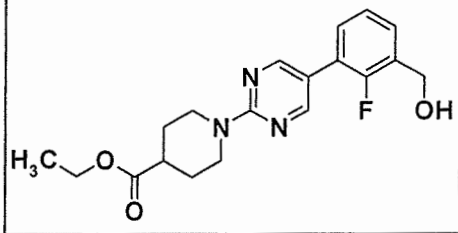
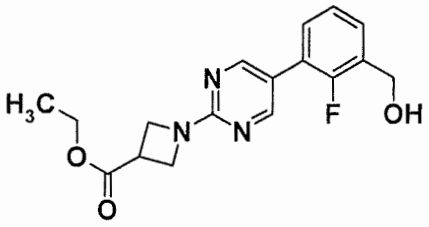
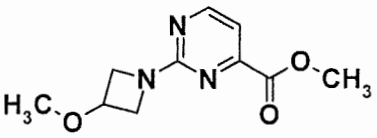
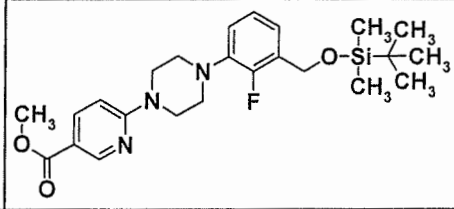
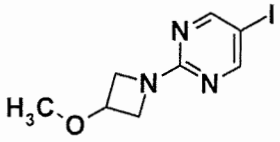
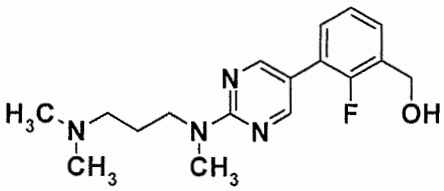
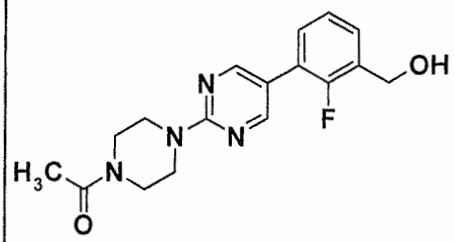
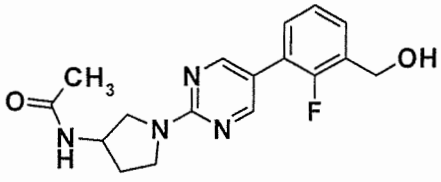
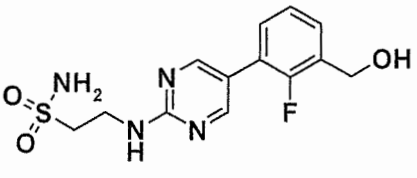
[0227]

[Table 9]

Rf	Syn	Structure	Rf	Syn	Structure
93	R135		94	R135	
95	R135		96	R135	
97	R135		98	R135	
99	R135		100	R135	
101	R135		102	R135	
103	R135		104	R135	
105	R135		106	R135	
107	R135		108	R135	

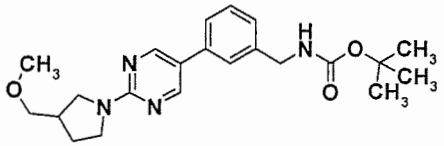
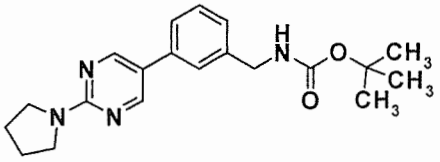
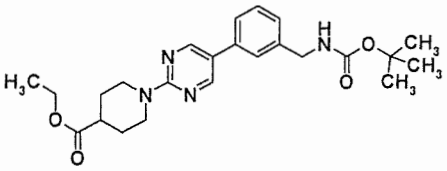
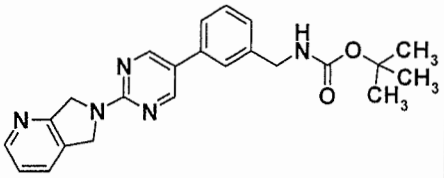
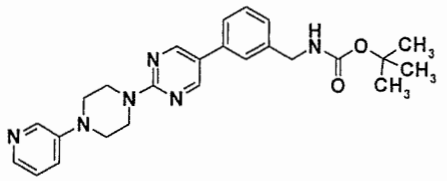
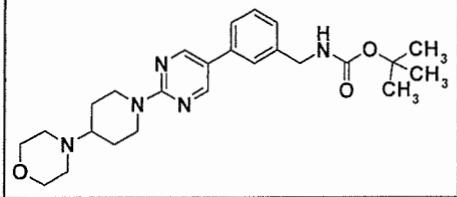
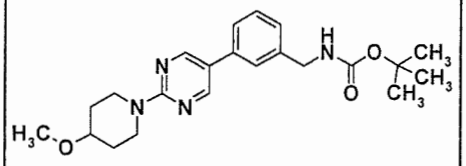
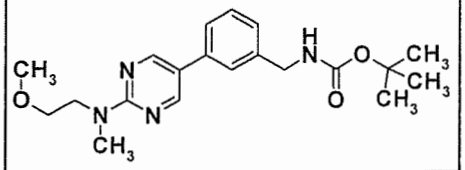
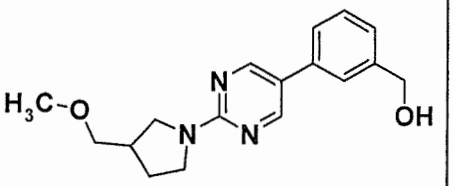
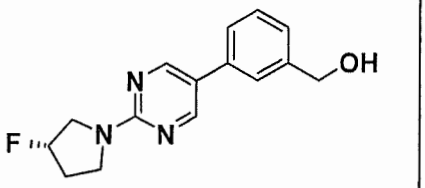
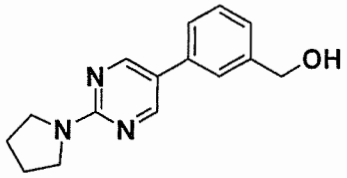
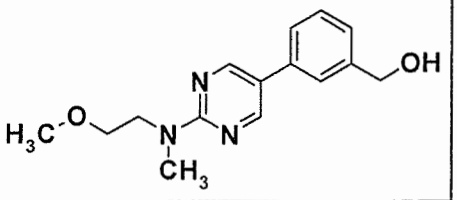
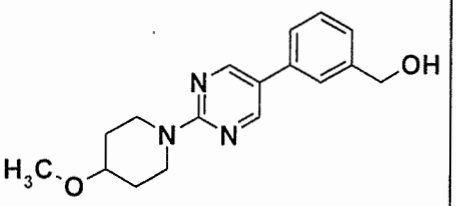
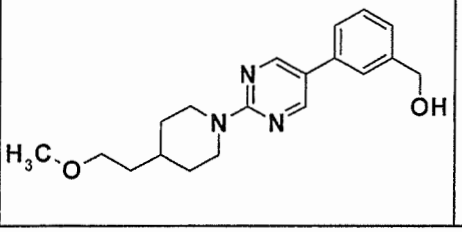
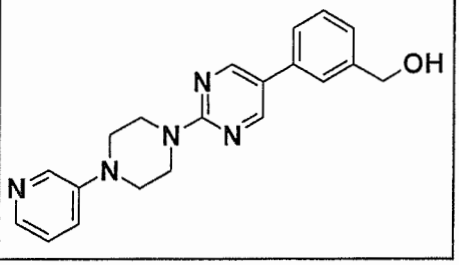
[0228]

[Table 10]

Rf	Syn	Structure	Rf	Syn	Structure
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111	R135		112	R135	
113	R135		114	R135	
115	R135		116	R135	
117	R135		118	R135	
119	R135		120	R135	
121	R135		122	R135	

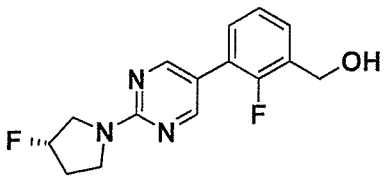
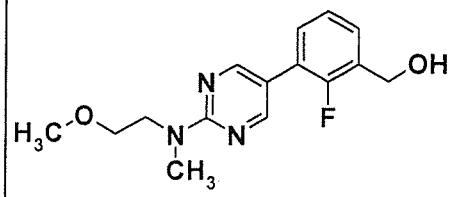
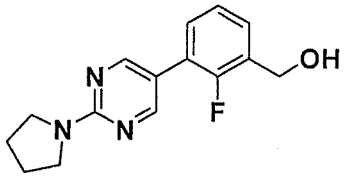
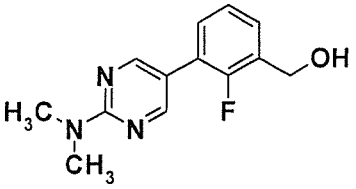
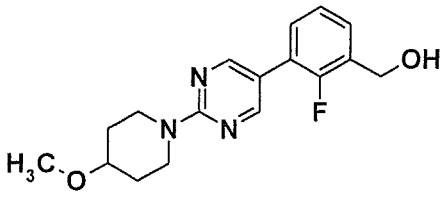
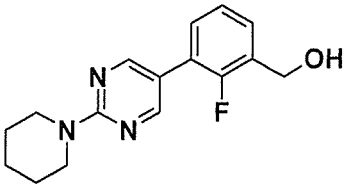
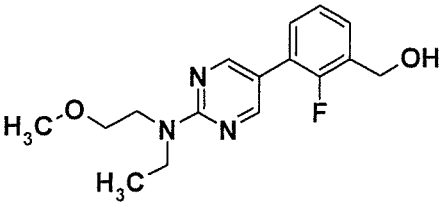
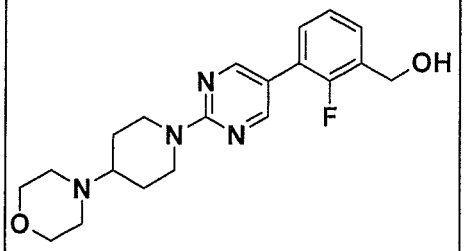
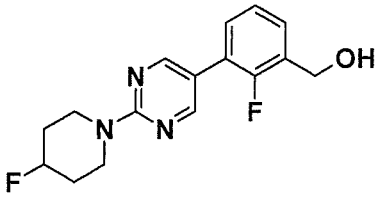
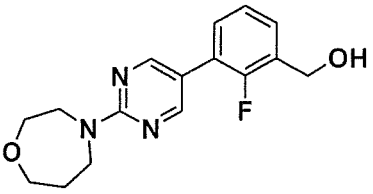
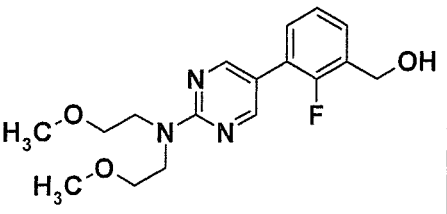
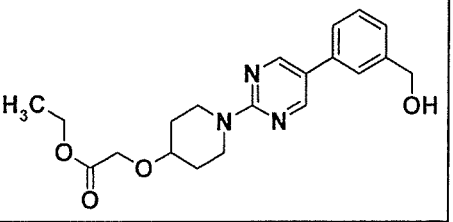
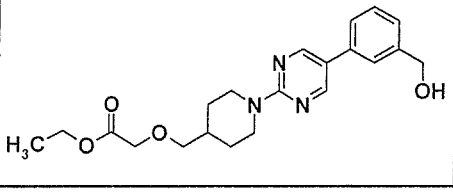
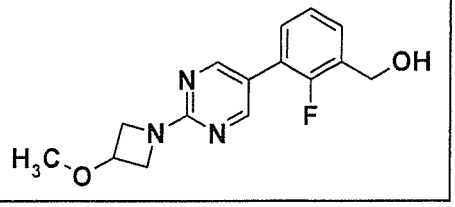
[0229]

[Table 11]

Rf	Syn	Structure	Rf	Syn	Structure
123	R135		124	R135	
125	R135		126	R135	
127	R135		128	R135	
129	R135		130	R135	
131	R135		132	R135	
133	R135		134	R135	
135	R135		136	R135	
137	R135		138	R135	

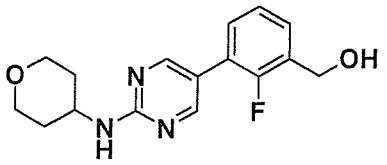
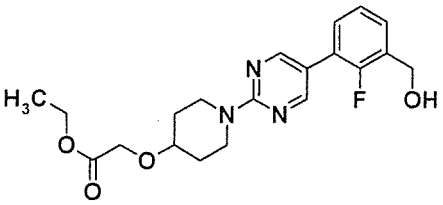
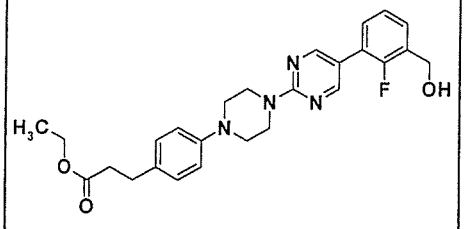
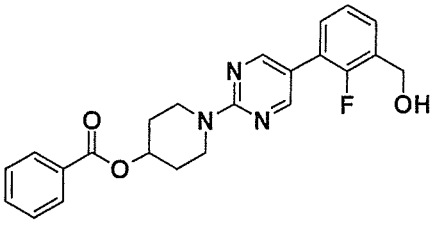
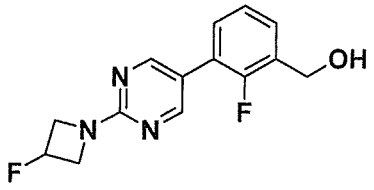
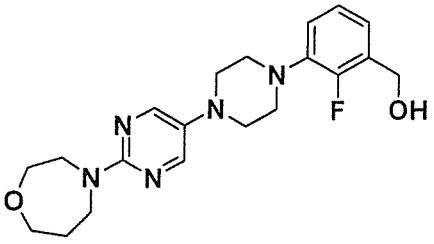
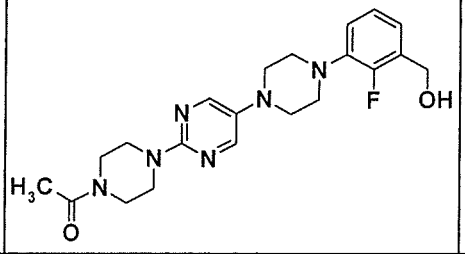
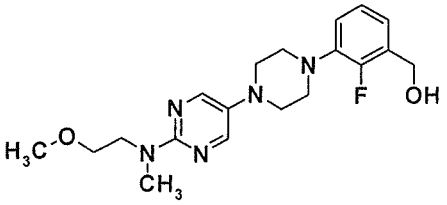
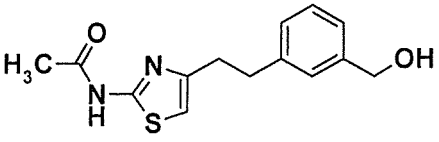
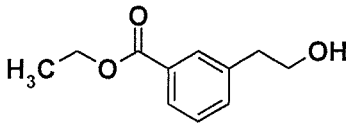
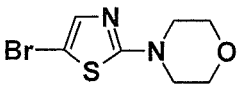
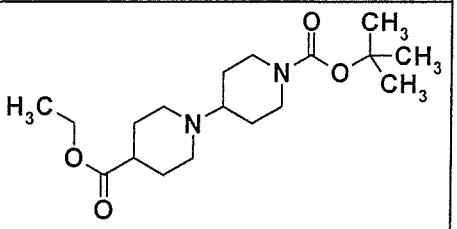
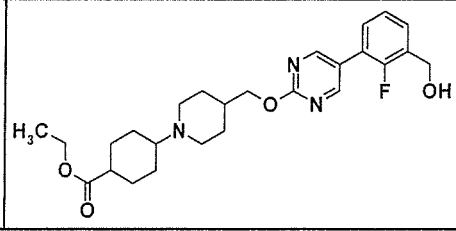
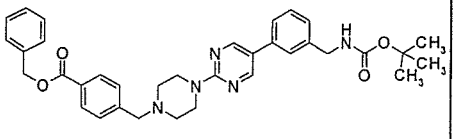
[0230]

[Table 12]

Rf	Syn	Structure	Rf	Syn	Structure
139	R135		140	R135	
141	R135		142	R135	
143	R135		144	R135	
145	R135		146	R135	
147	R135		148	R135	
149	R135		150	R135	
151	R135		152	R135	

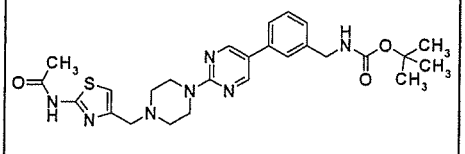
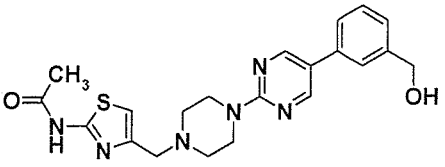
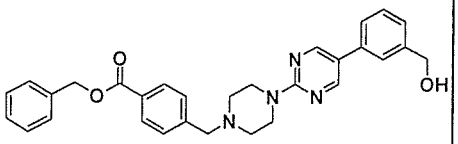
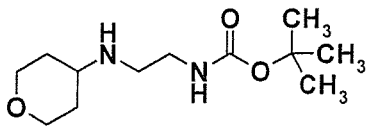
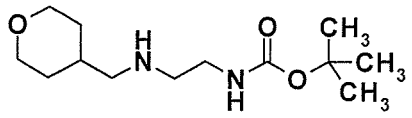
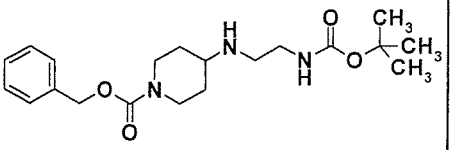
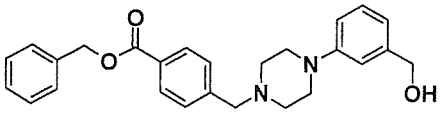
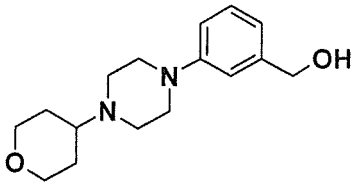
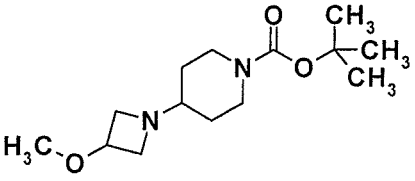
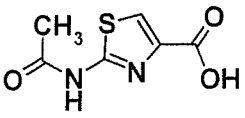
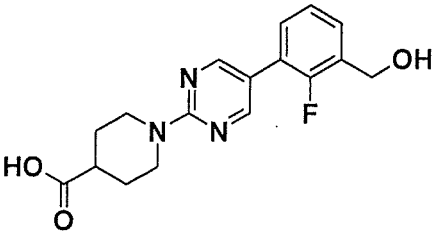
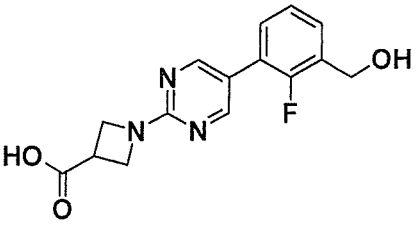
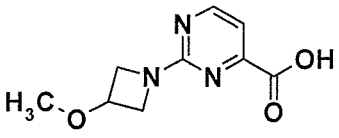
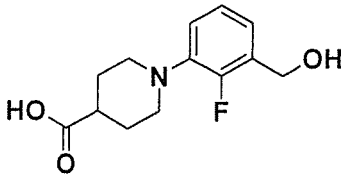
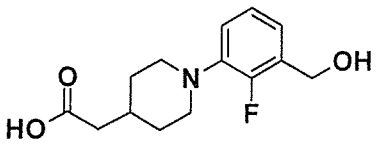
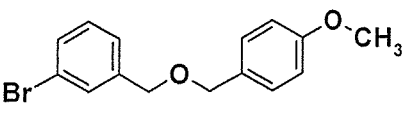
[0231]

[Table 13]

Rf	Syn	Structure	Rf	Syn	Structure
153	R135		154	R135	
155	R135		156	R135	
157	R135		158	R159	
159	R159		160	R159	
161	R162		162	R162	
163	R163		164	R174	
165	R174		166	R174	

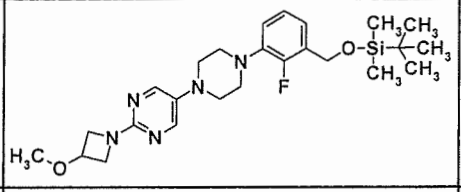
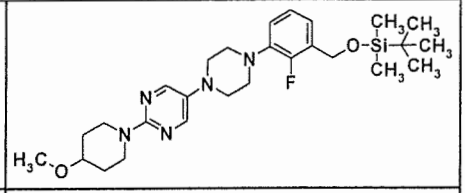
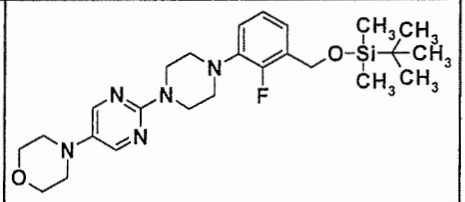
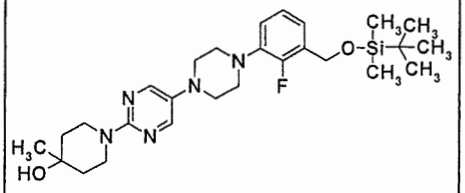
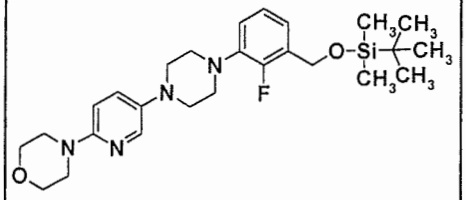
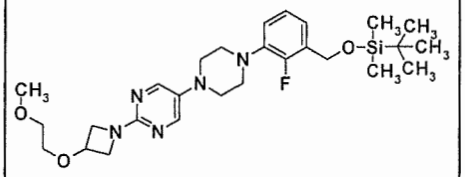
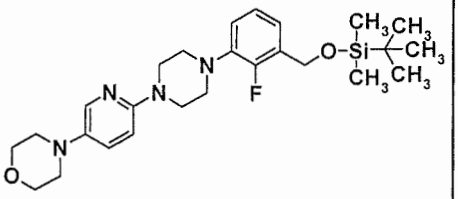
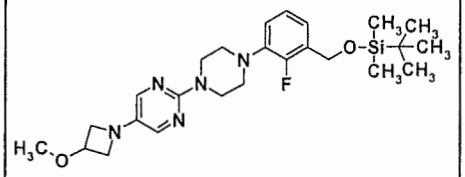
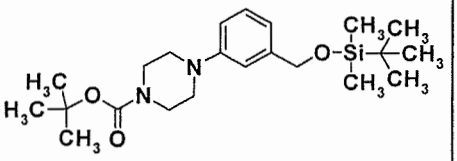
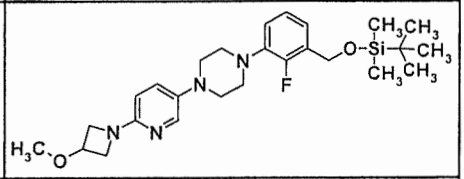
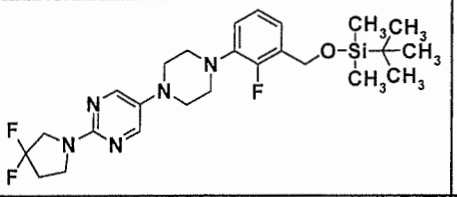
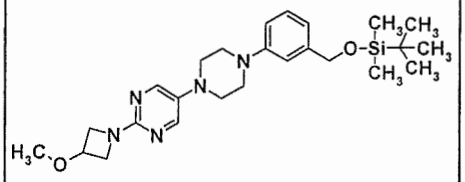
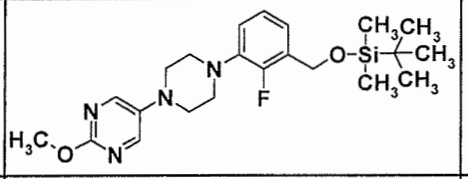
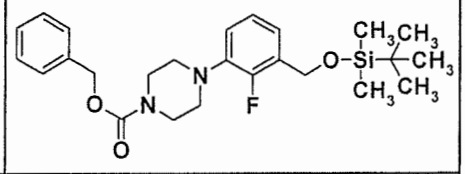
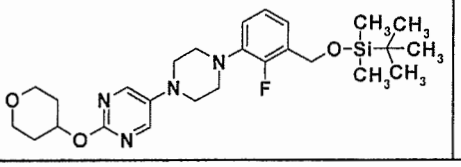
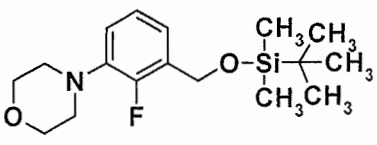
[0232]

[Table 14]

Rf	Syn	Structure	Rf	Syn	Structure
167	R174		168	R174	
169	R174		170	R174	
171	R174		172	R174	
173	R174		174	R174	
175	R174		176	R177	
177	R177		178	R177	
179	R177		180	R177	
181	R177		182	R182	

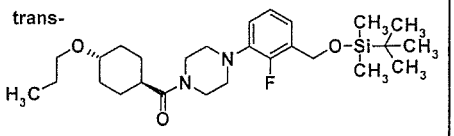
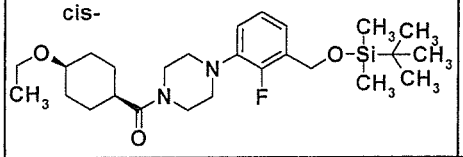
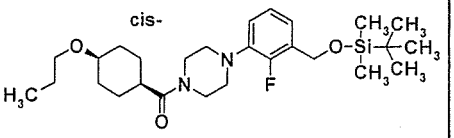
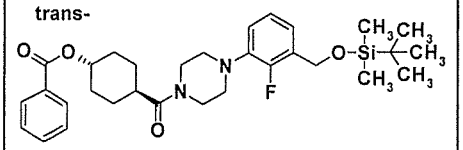
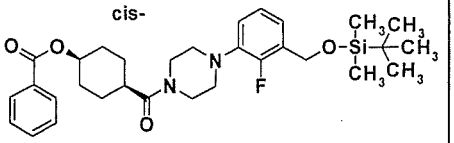
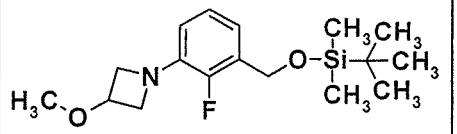
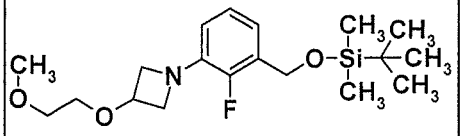
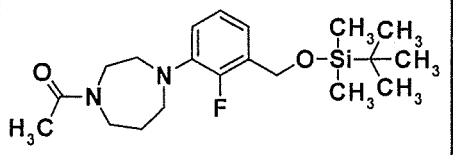
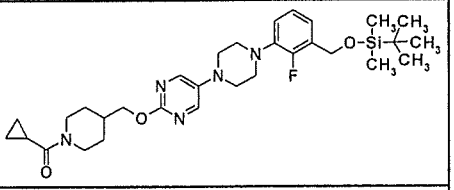
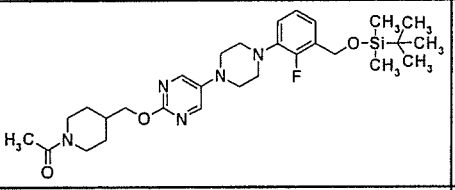
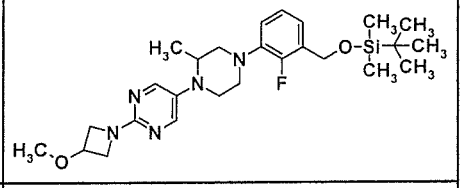
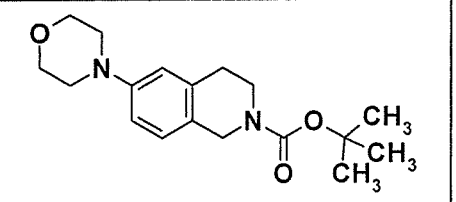
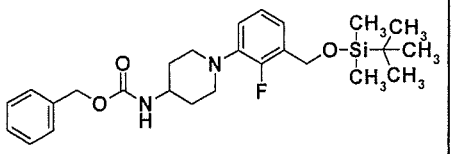
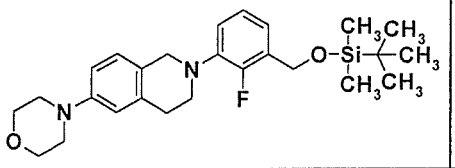
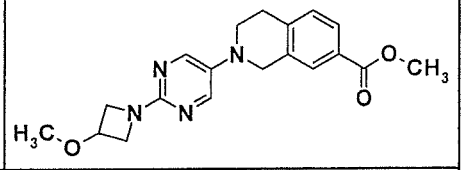
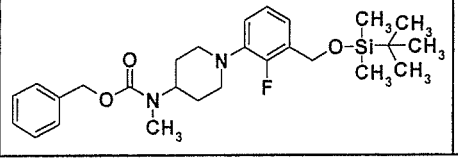
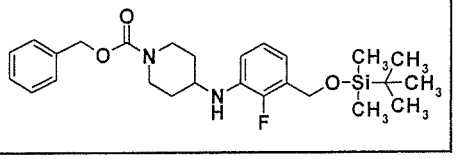
[0233]

[Table 15]

Rf	Syn	Structure	Rf	Syn	Structure
183	R228		184	R228	
185	R228		186	R228	
187	R228		188	R228	
189	R228		190	R228	
191	R228		192	R228	
193	R228		194	R228	
195	R228		196	R228	
197	R228		198	R228	

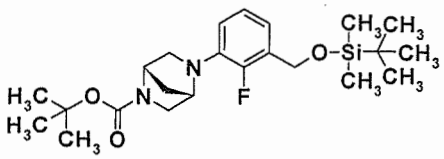
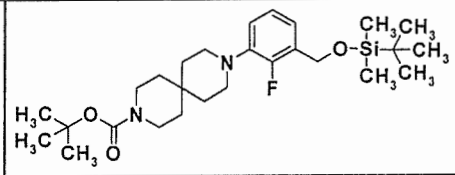
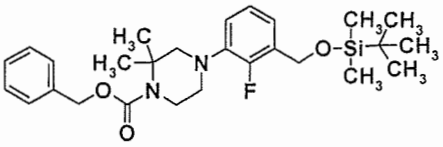
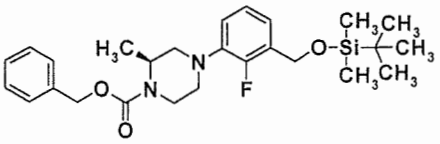
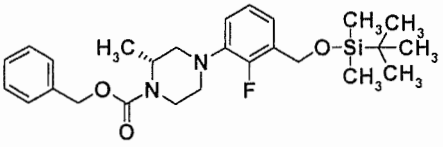
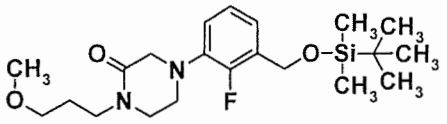
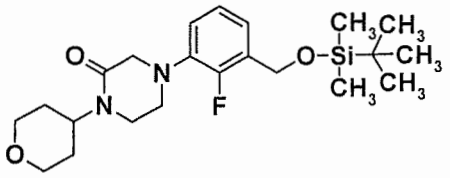
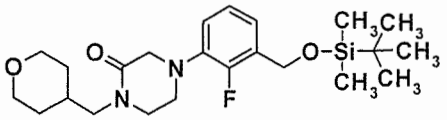
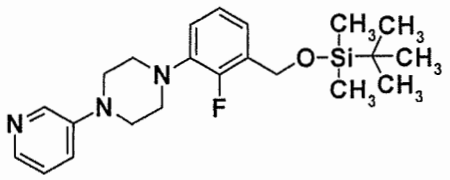
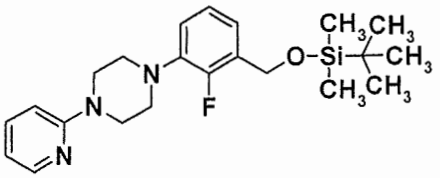
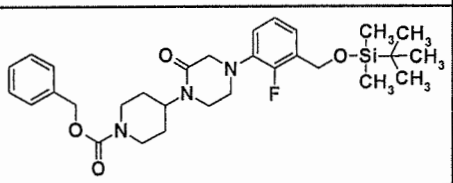
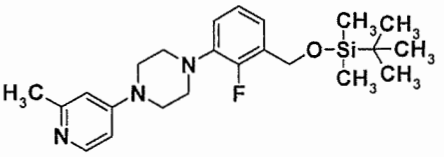
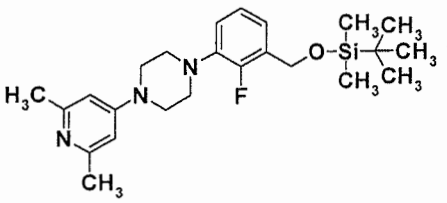
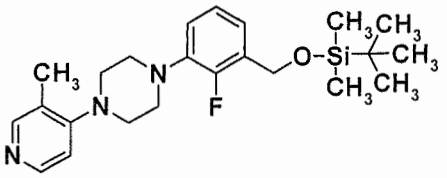
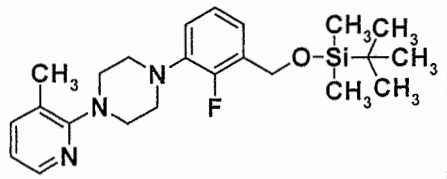
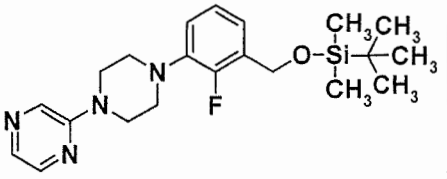
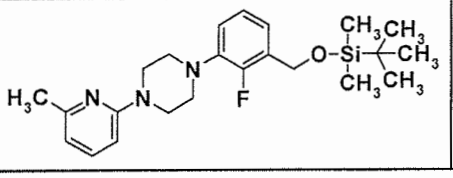
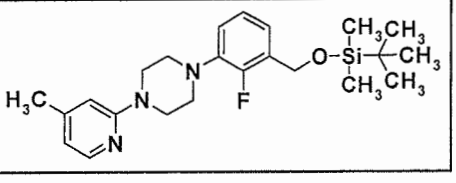
[0234]

[Table 16]

Rf	Syn	Structure	Rf	Syn	Structure
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201	R228		202	R228	
203	R228		204	R228	
205	R228		206	R228	
207	R228		208	R228	
209	R228		210	R228	
211	R228		212	R228	
213	R228		214	R228	
215	R228		216	R228	

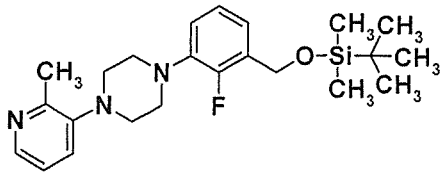
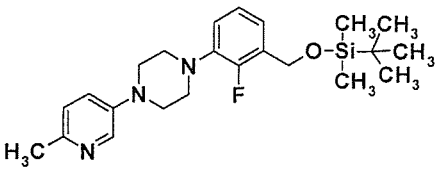
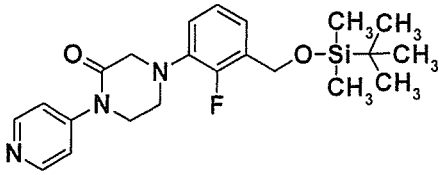
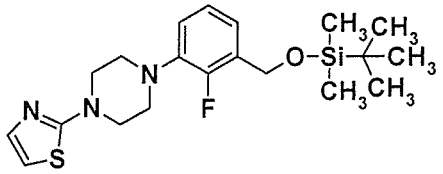
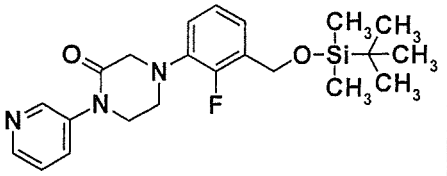
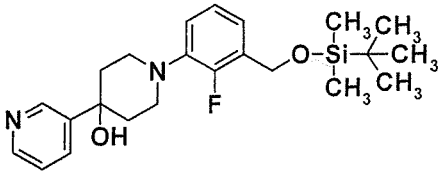
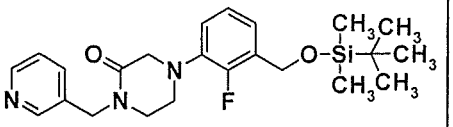
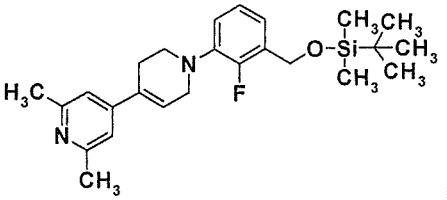
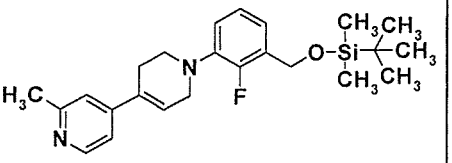
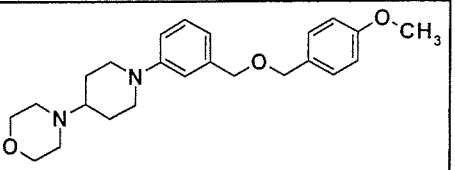
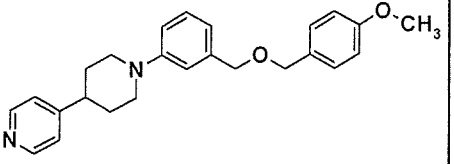
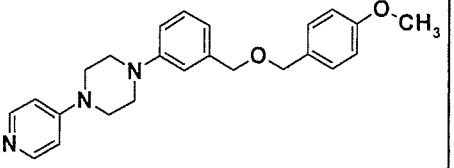
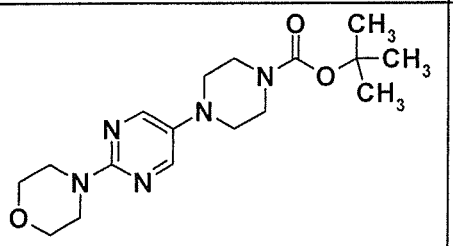
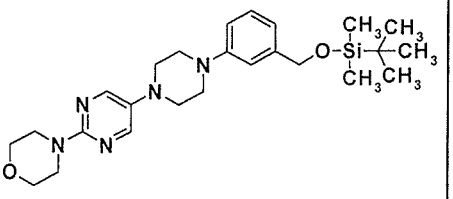
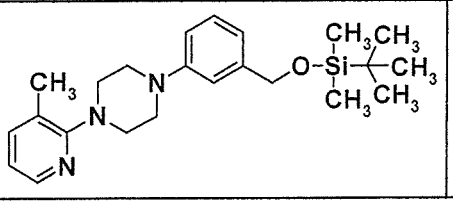
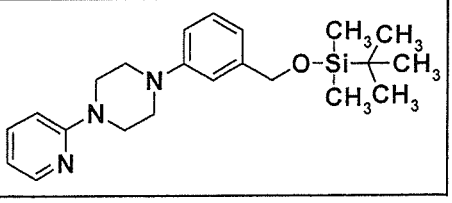
[0235]

[Table 17]

Rf	Syn	Structure	Rf	Syn	Structure
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219	R228		220	R228	
221	R228		222	R228	
223	R228		224	R228	
225	R228		226	R228	
227	R228		228	R228	
229	R228		230	R228	
231	R228		232	R228	
233	R228		234	R228	

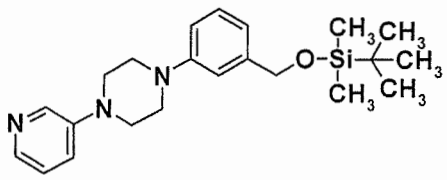
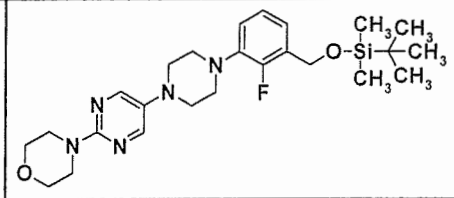
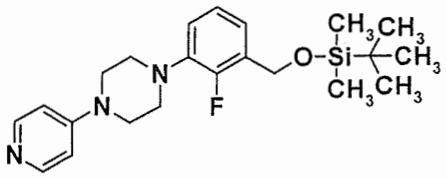
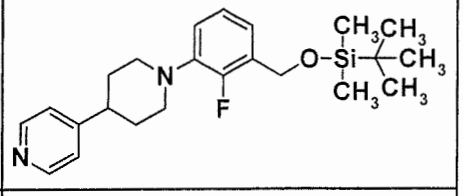
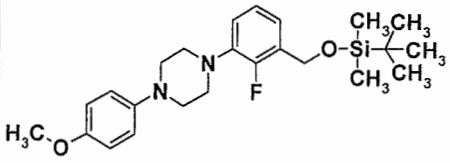
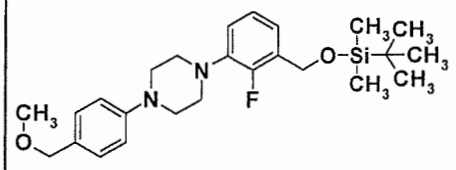
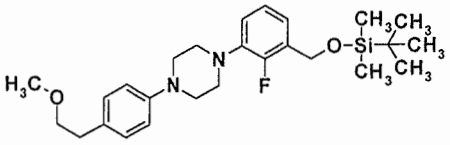
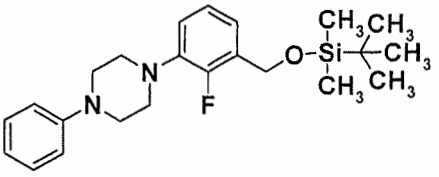
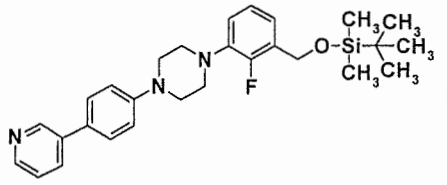
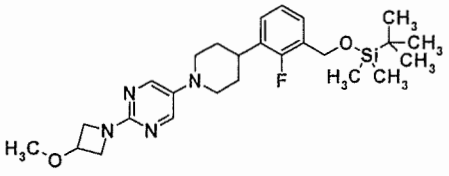
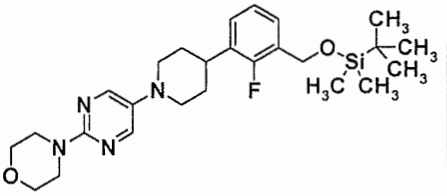
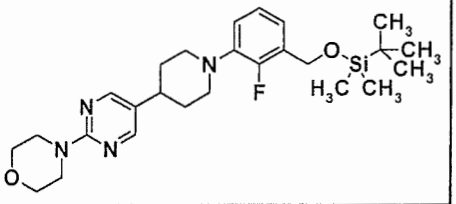
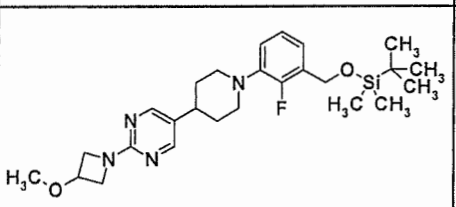
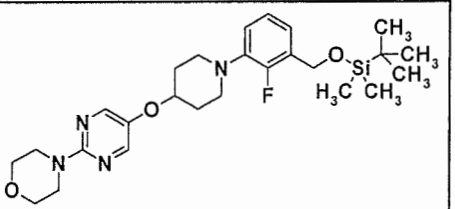
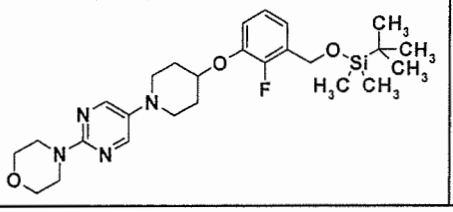
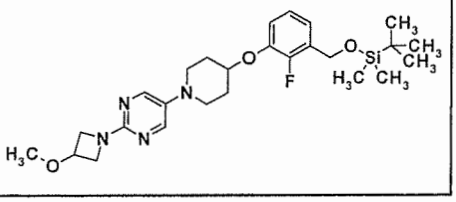
[0236]

[Table 18]

Rf	Syn	Structure	Rf	Syn	Structure
235	R228		236	R228	
237	R228		238	R228	
239	R228		240	R228	
241	R228		242	R228	
243	R228		244	R228	
245	R228		246	R228	
247	R228		248	R228	
249	R228		250	R228	

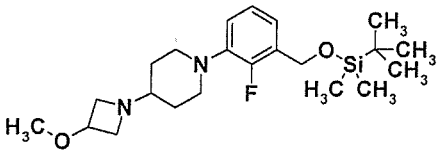
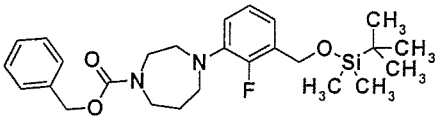
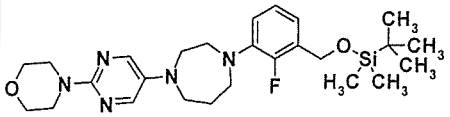
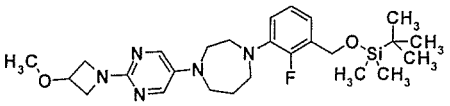
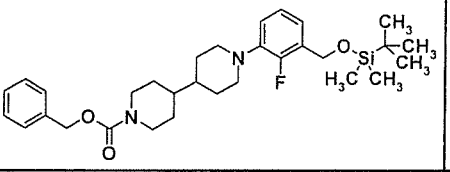
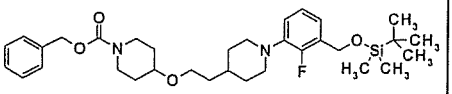
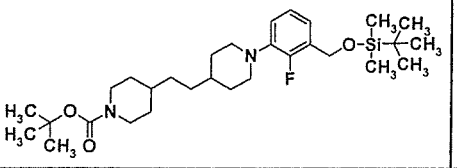
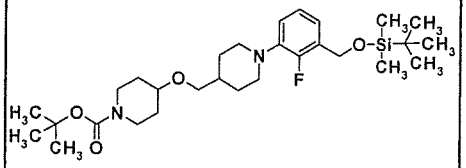
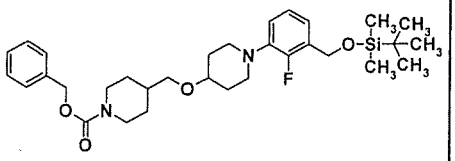
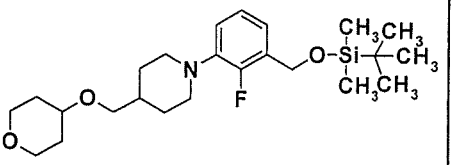
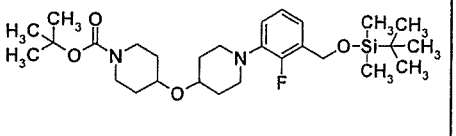
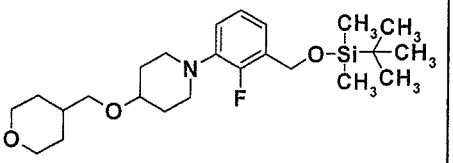
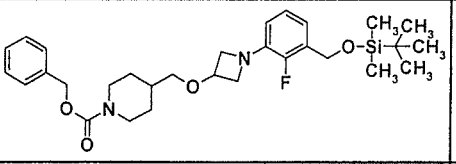
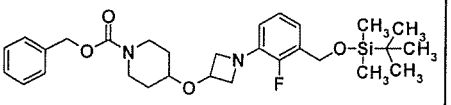
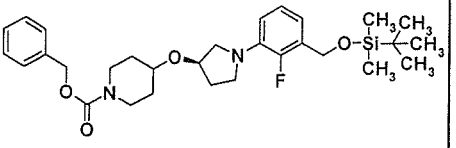
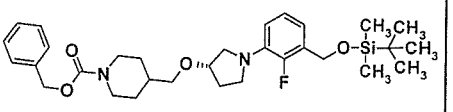
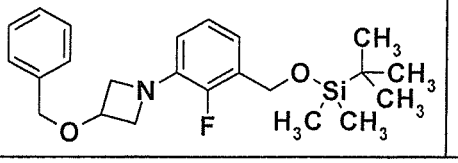
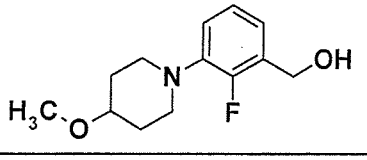
[0237]

[Table 19]

Rf	Syn	Structure	Rf	Syn	Structure
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253	R228		254	R228	
255	R228		256	R228	
257	R228		258	R228	
259	R228		260	R228	
261	R228		262	R228	
263	R228		264	R228	
265	R228		266	R228	

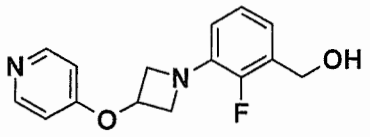
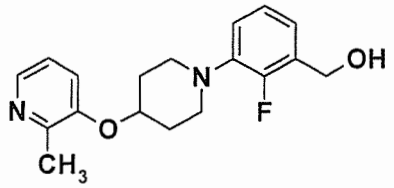
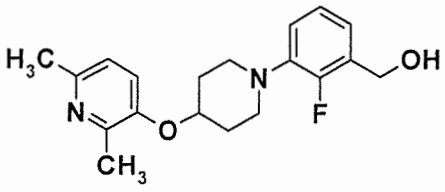
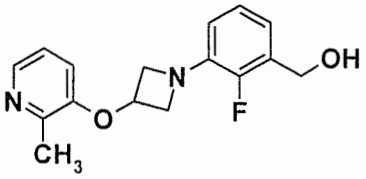
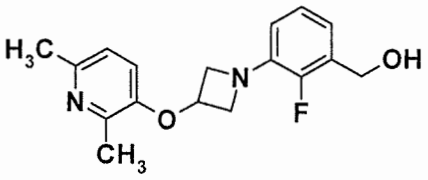
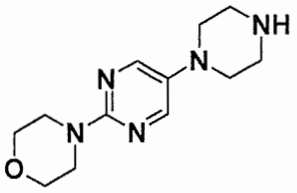
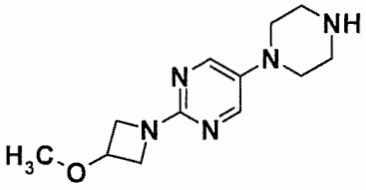
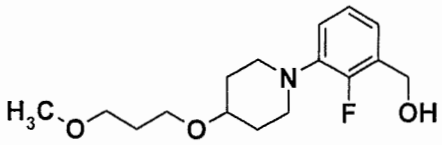
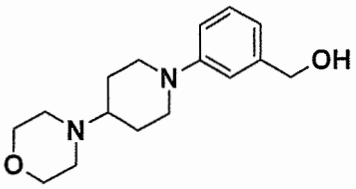
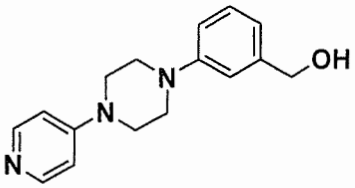
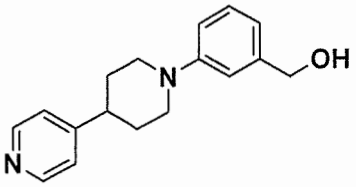
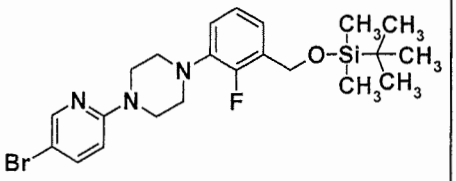
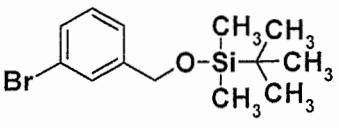
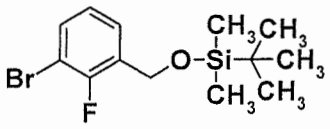
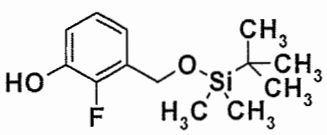
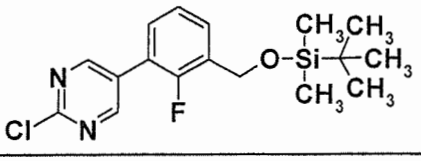
[0238]

[Table 20]

Rf	Syn	Structure	Rf	Syn	Structure
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269	R228		270	R228	
271	R228		272	R228	
273	R228		274	R228	
275	R228		276	R228	
277	R228		278	R228	
279	R228		280	R228	
281	R228		282	R228	
283	R228		284	R285	

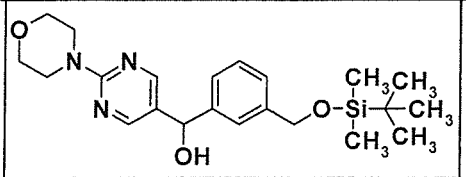
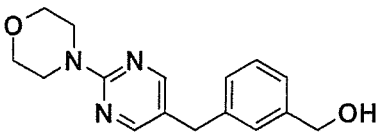
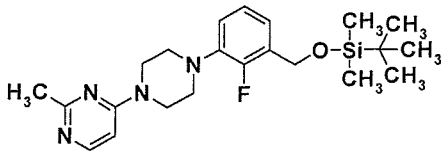
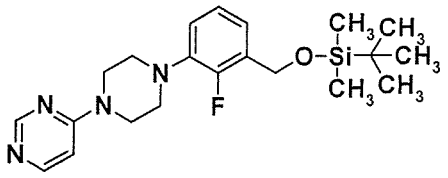
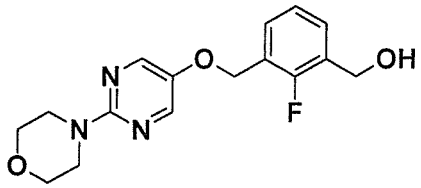
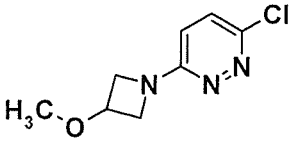
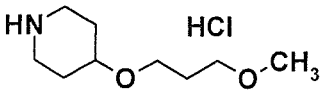
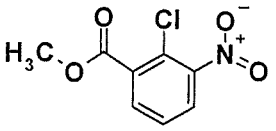
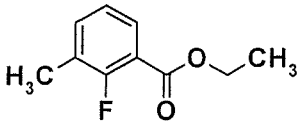
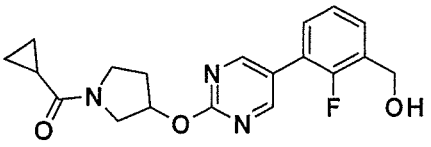
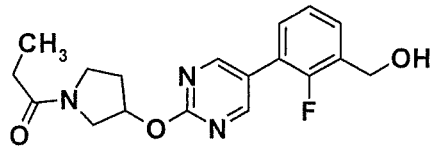
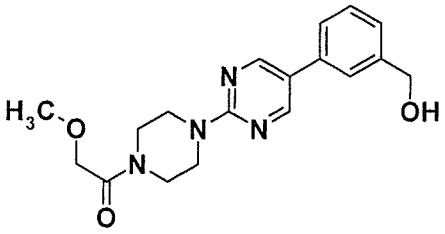
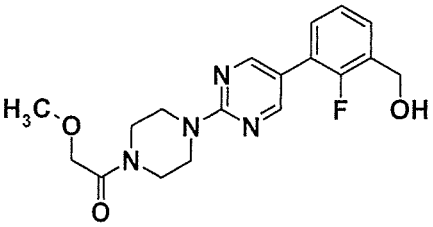
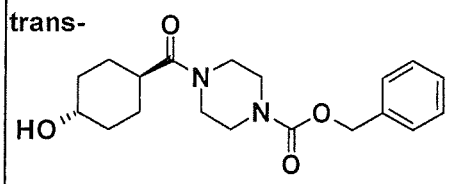
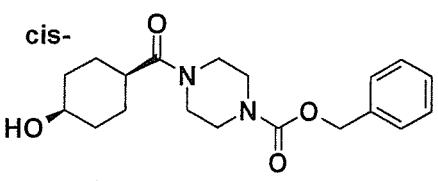
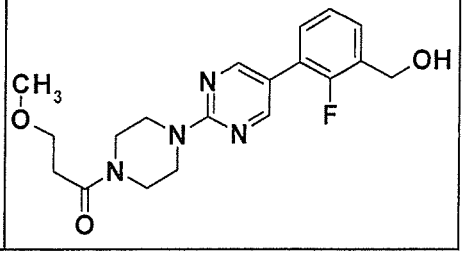
[0239]

[Table 21]

Rf	Syn	Structure	Rf	Syn	Structure
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287	R285		288	R285	
289	R285		290	R290	
291	R290		292	R285	
293	R294		294	R294	
295	R294		296	R297	
297	R297		298	R297	
299	R297		300	R297	

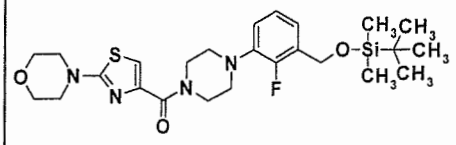
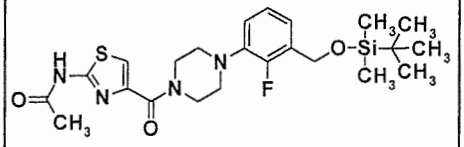
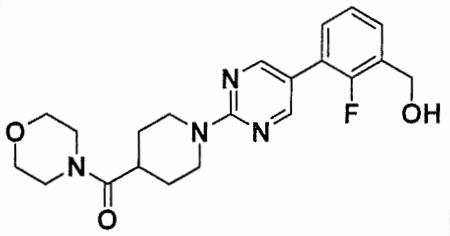
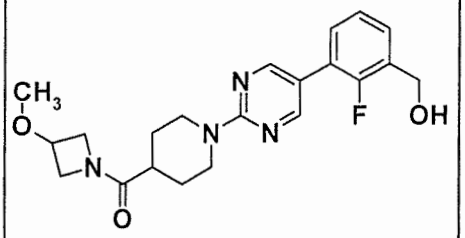
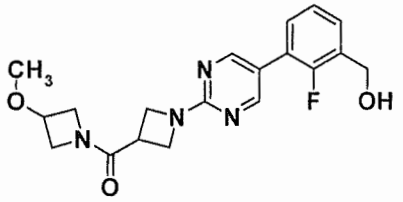
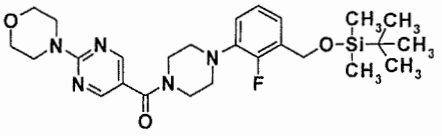
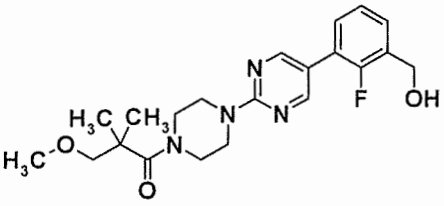
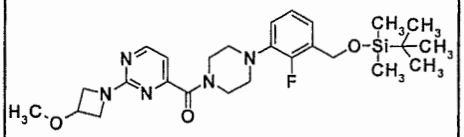
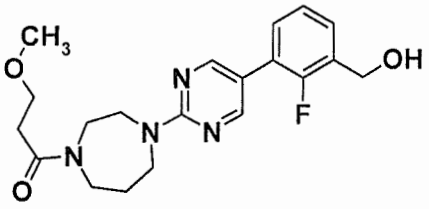
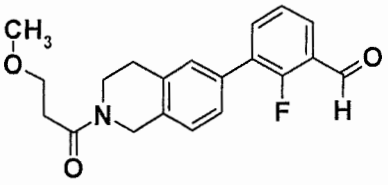
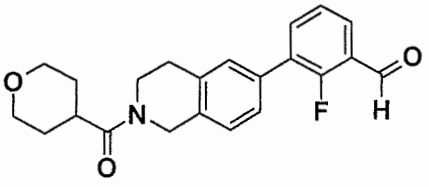
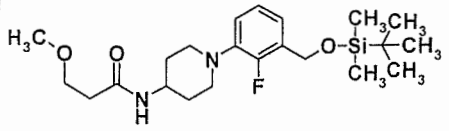
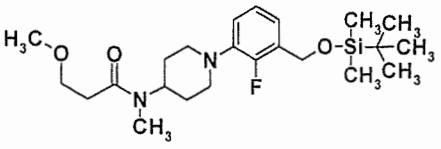
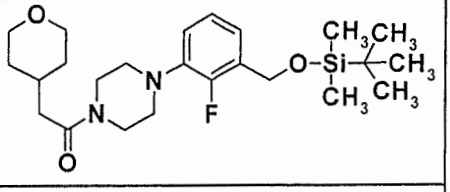
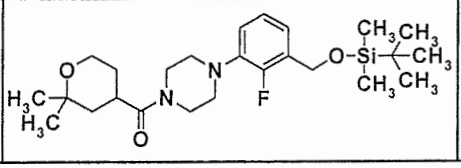
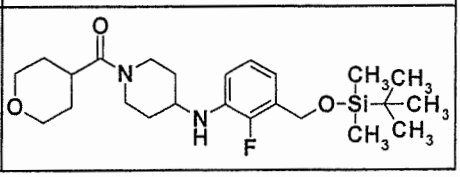
[0240]

[Table 22]

Rf	Syn	Structure	Rf	Syn	Structure
301	R301		302	R302	
303	R304		304	R304	
305	R305		306	R306	
307	R307		308	R309	
309	R309		310	R336	
311	R336		312	R336	
313	R336		314	R336	
315	R336		316	R336	

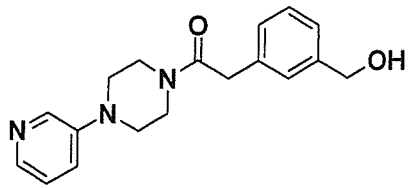
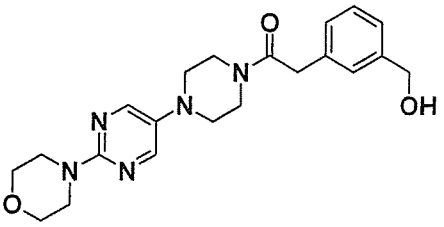
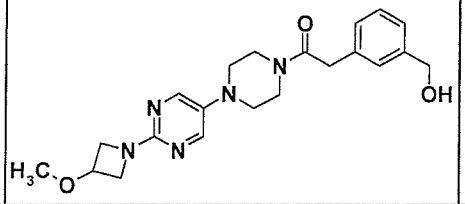
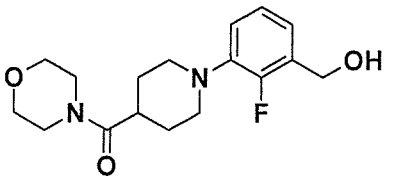
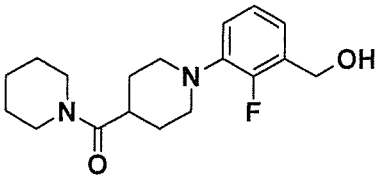
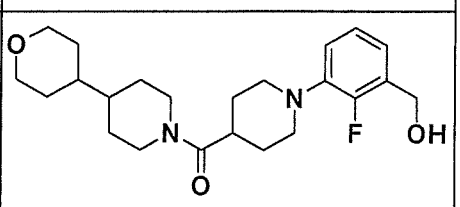
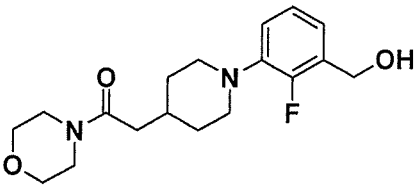
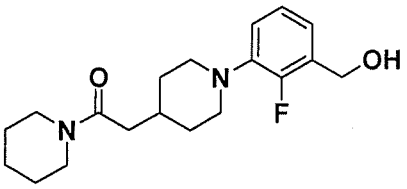
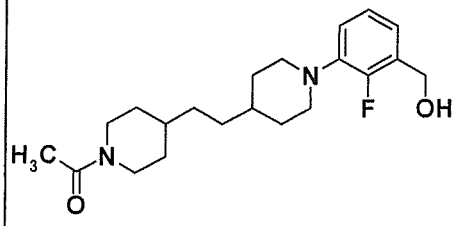
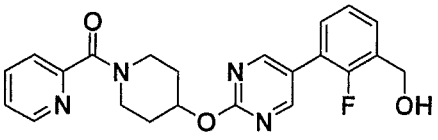
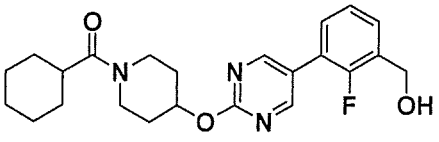
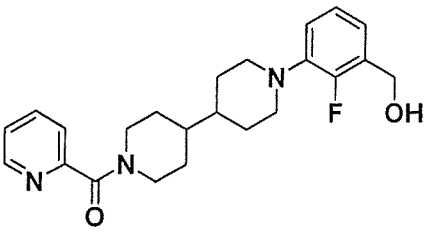
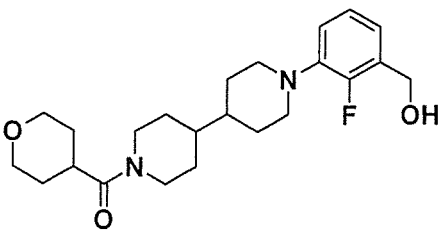
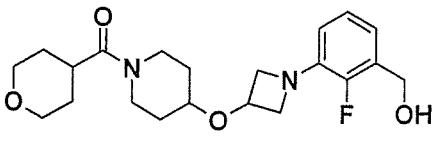
[0241]

[Table 23]

Rf	Syn	Structure	Rf	Syn	Structure
317	R336		318	R336	
319	R336		320	R336	
321	R336		322	R336	
323	R336		324	R336	
325	R336		326	R336	
327	R336		328	R336	
329	R336		330	R336	
331	R336		332	R336	

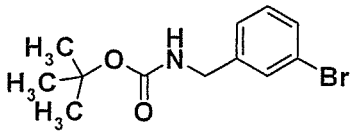
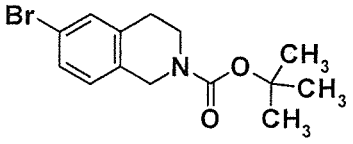
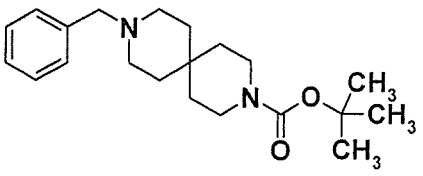
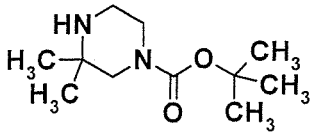
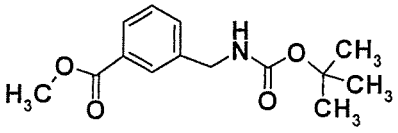
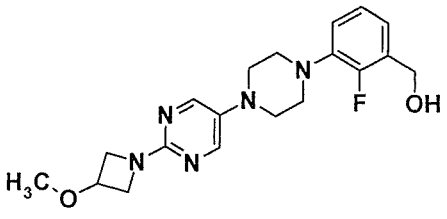
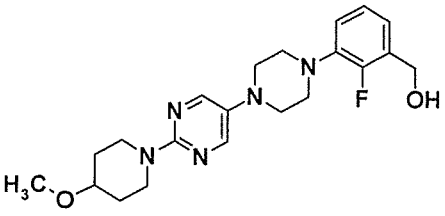
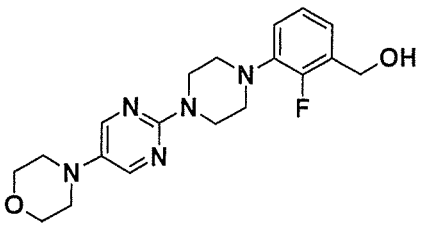
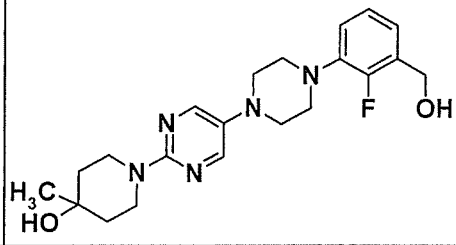
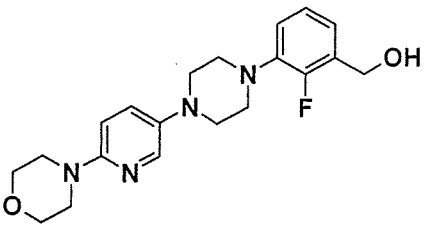
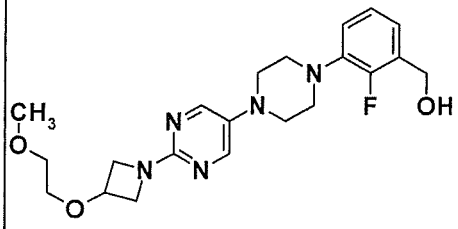
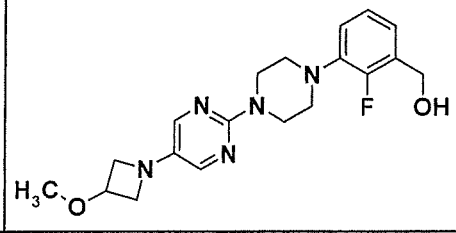
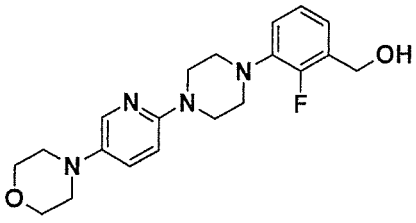
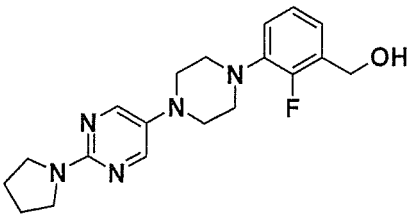
[0242]

[Table 24]

Rf	Syn	Structure	Rf	Syn	Structure
333	R336		334	R336	
335	R336		336	R336	
337	R336		338	R336	
339	R336		340	R336	
341	R341		342	R343	
343	R343		344	R343	
345	R343		346	R343	

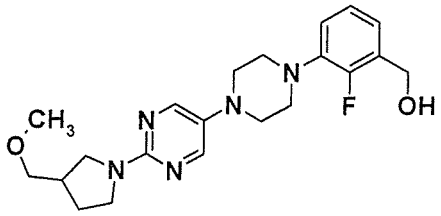
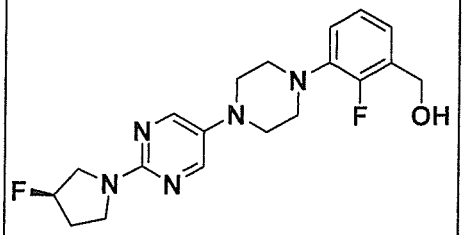
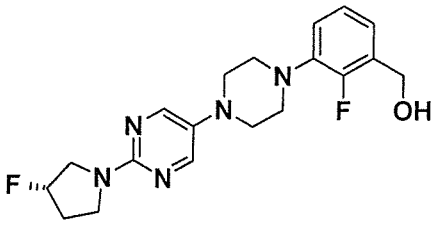
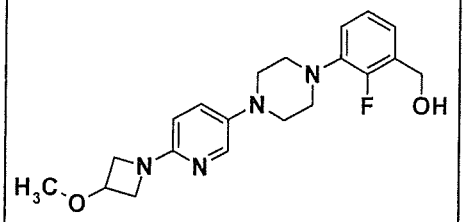
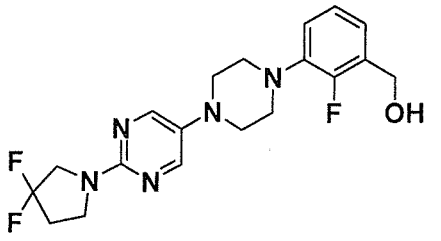
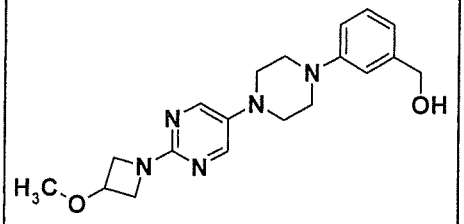
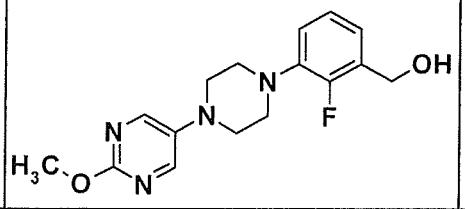
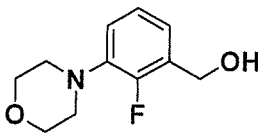
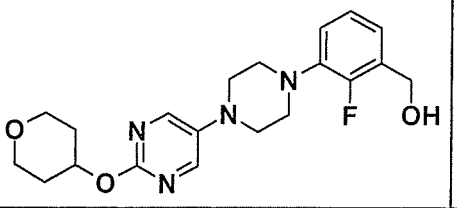
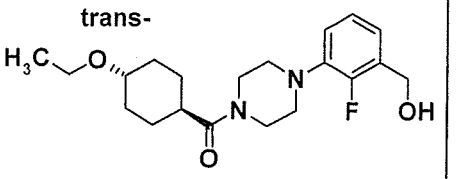
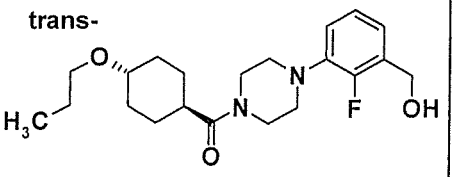
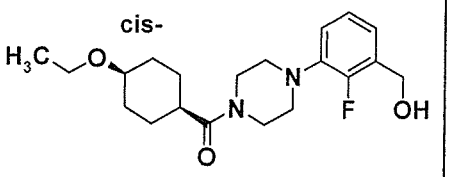
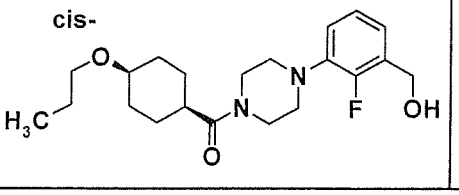
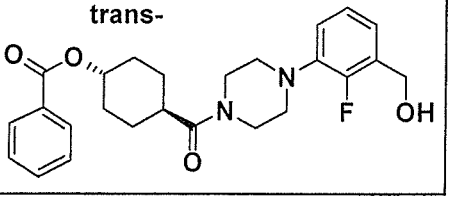
[0243]

[Table 25]

Rf	Syn	Structure	Rf	Syn	Structure
347	R347		348	R347	
349	R347		350	R347	
351	R347		352	R376	
353	R376		354	R376	
355	R376		356	R376	
357	R376		358	R376	
359	R376		360	R376	

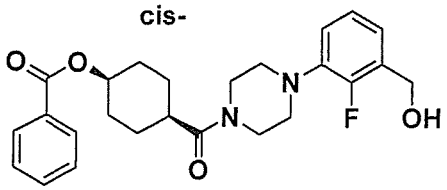
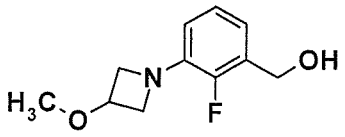
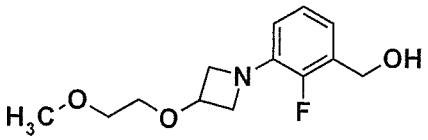
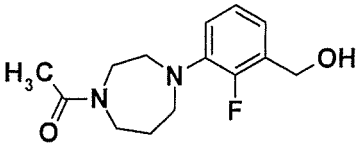
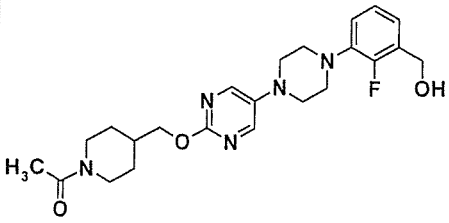
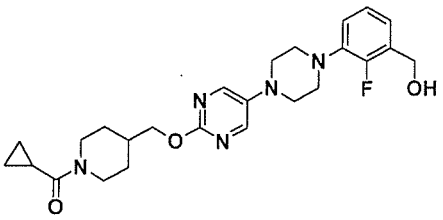
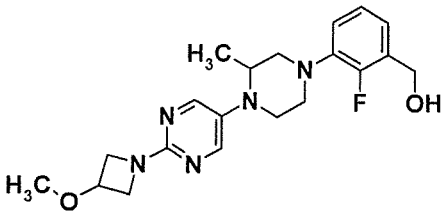
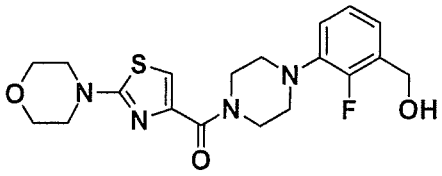
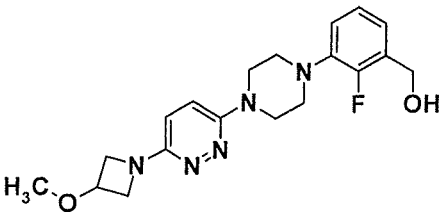
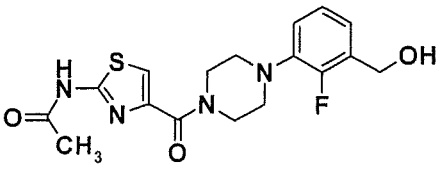
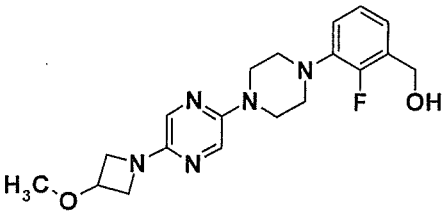
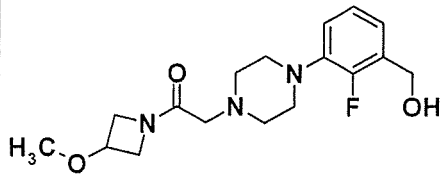
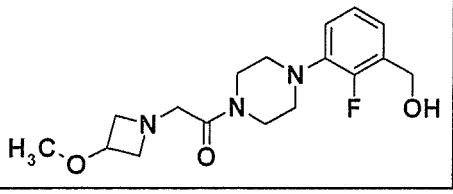
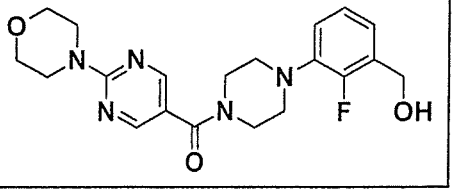
[0244]

[Table 26]

Rf	Syn	Structure	Rf	Syn	Structure
361	R376		362	R376	
363	R376		364	R376	
365	R376		366	R376	
367	R376		368	R376	
369	R376		370	R376	
371	R376		372	R376	
373	R376		374	R376	

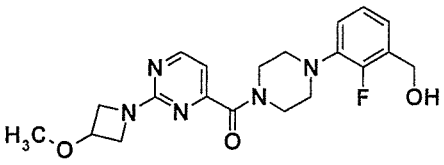
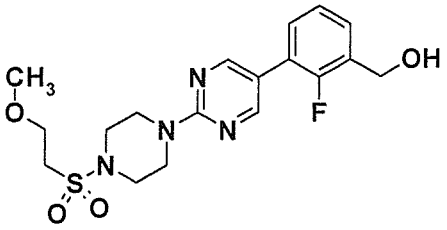
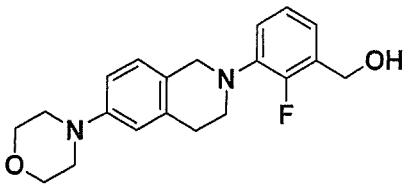
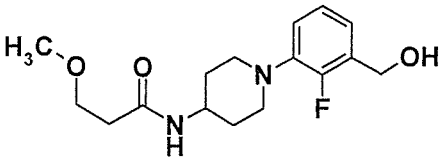
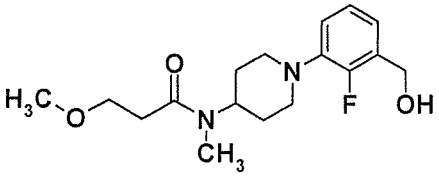
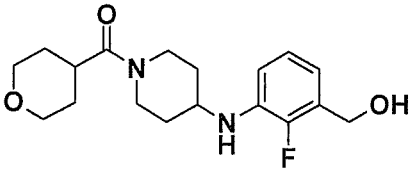
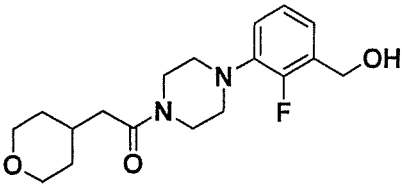
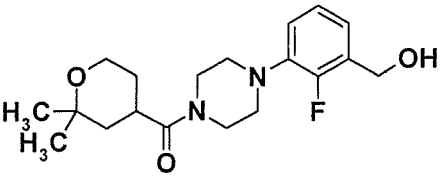
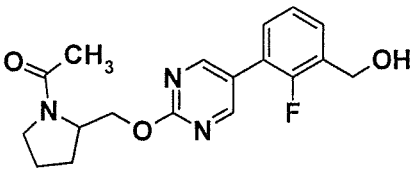
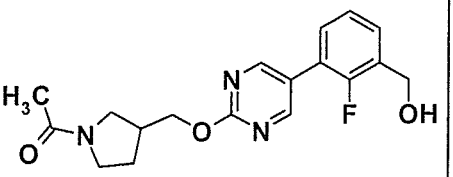
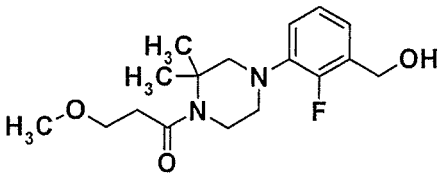
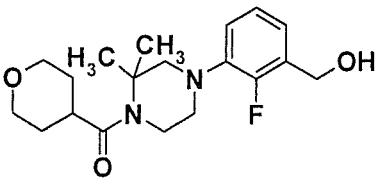
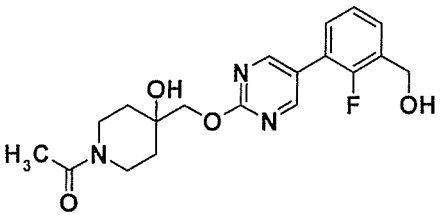
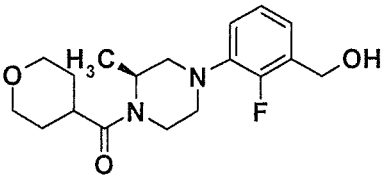
[0245]

[Table 27]

Rf	Syn	Structure	Rf	Syn	Structure
375	R376		376	R376	
377	R376		378	R376	
379	R376		380	R376	
381	R376		382	R376	
383	R376		384	R376	
385	R376		386	R376	
387	R376		388	R376	

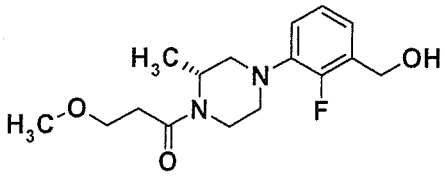
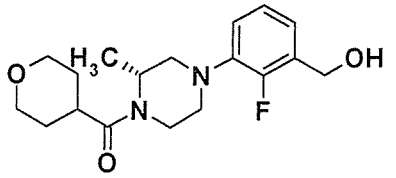
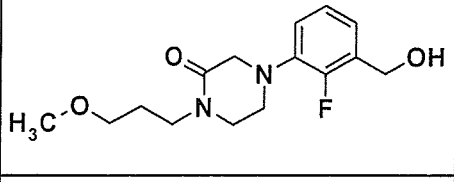
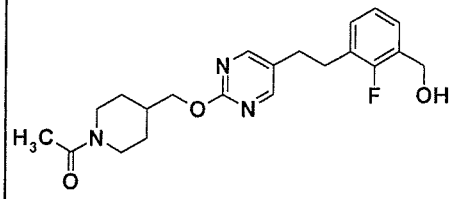
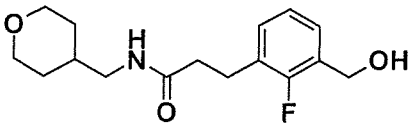
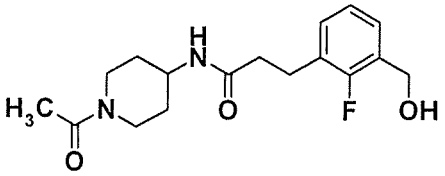
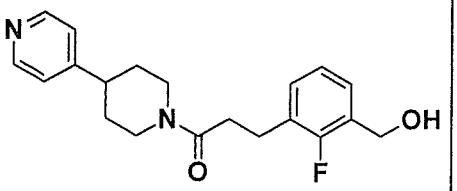
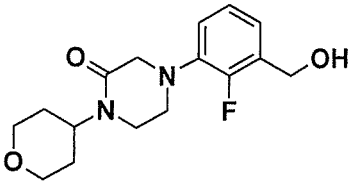
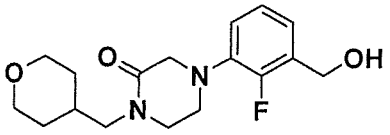
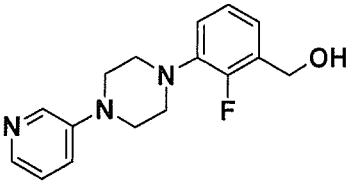
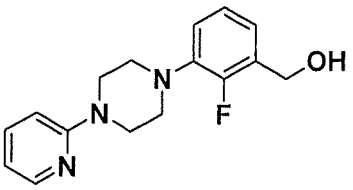
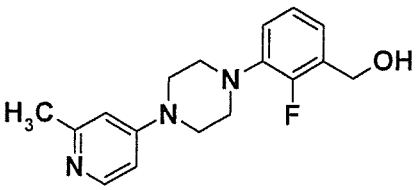
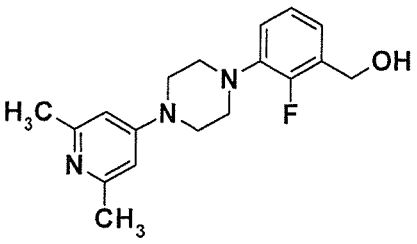
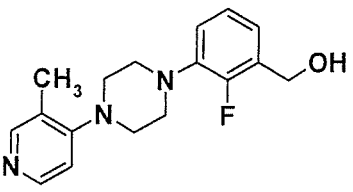
[0246]

[Table 28]

Rf	Syn	Structure	Rf	Syn	Structure
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391	R376		392	R376	
393	R376		394	R376	
395	R376		396	R376	
397	R376		398	R376	
399	R376		400	R376	
401	R376		402	R376	

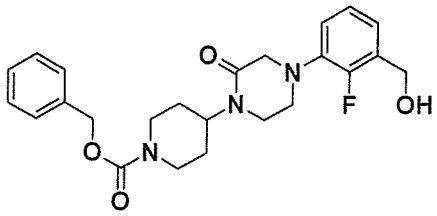
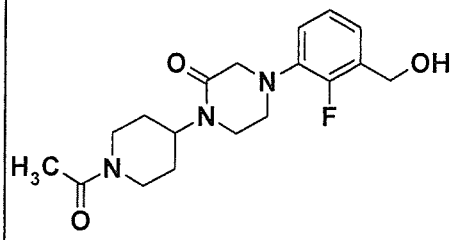
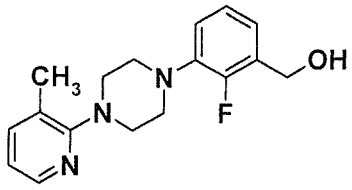
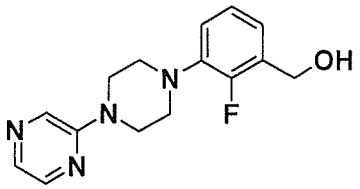
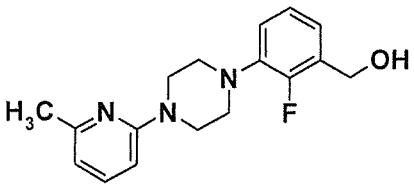
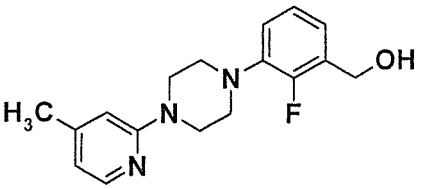
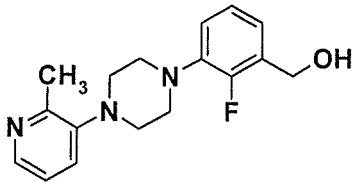
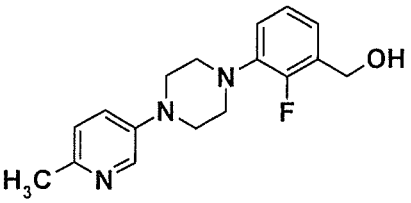
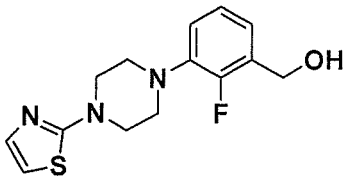
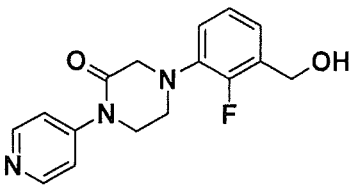
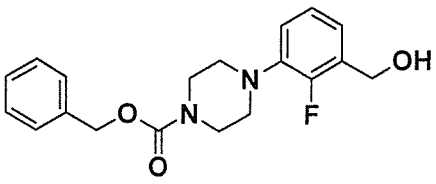
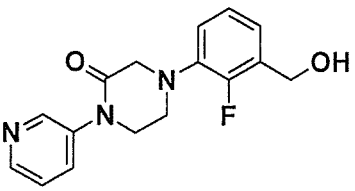
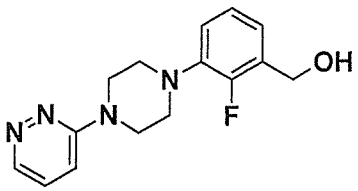
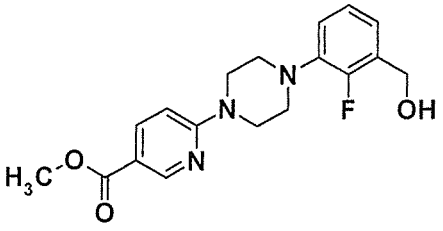
[0247]

[Table 29]

Rf	Syn	Structure	Rf	Syn	Structure
403	R376		404	R376	
405	R376		406	R376	
407	R376		408	R376	
409	R376		410	R376	
411	R376		412	R376	
413	R376		414	R376	
415	R376		416	R376	

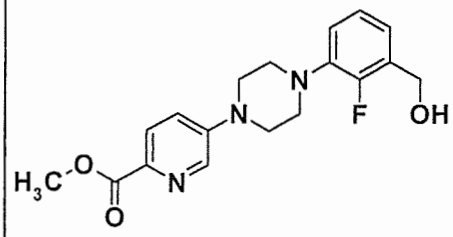
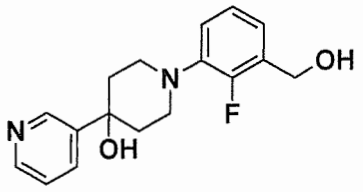
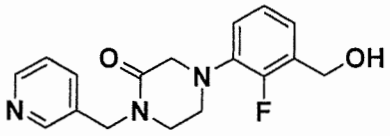
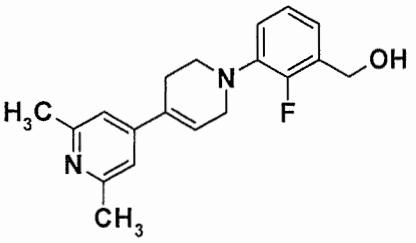
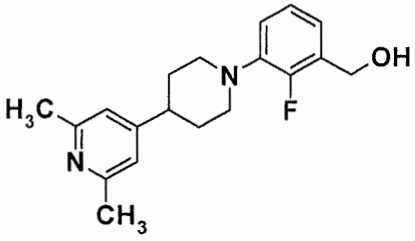
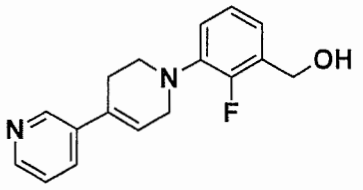
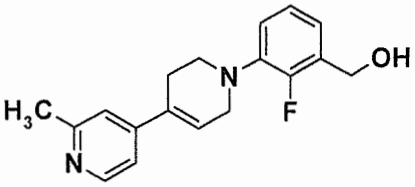
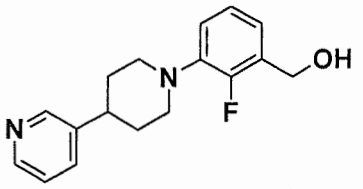
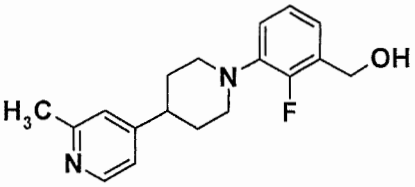
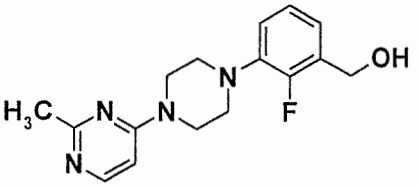
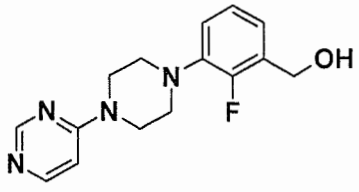
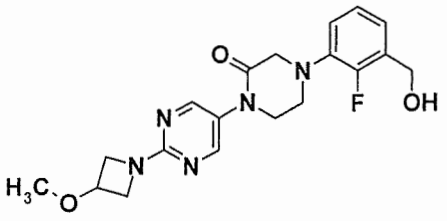
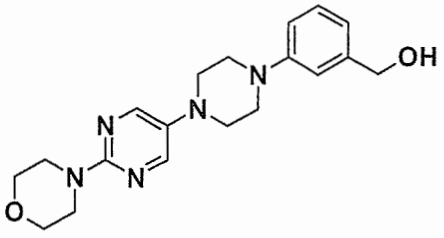
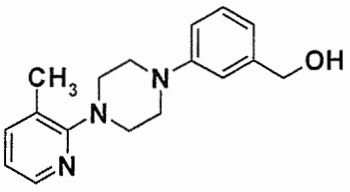
[0248]

[Table 30]

Rf	Syn	Structure	Rf	Syn	Structure
417	R376		418	R376	
419	R376		420	R376	
421	R376		422	R376	
423	R376		424	R376	
425	R376		426	R376	
427	R376		428	R376	
429	R376		430	R376	

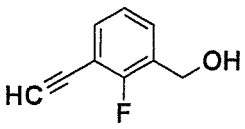
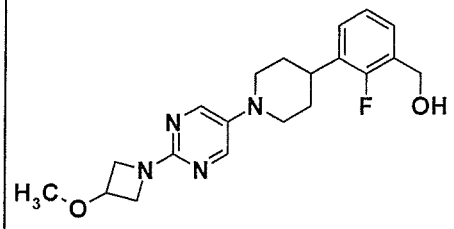
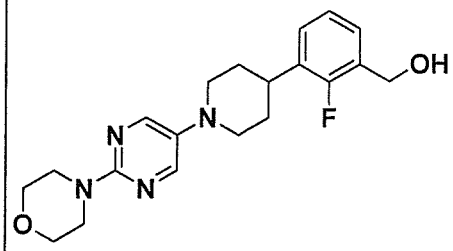
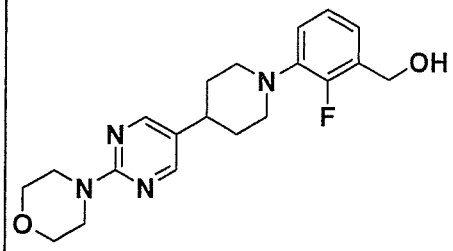
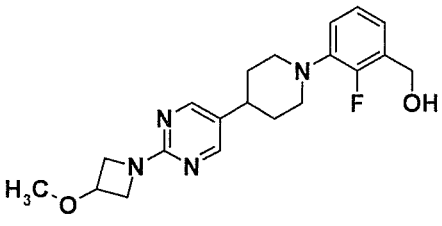
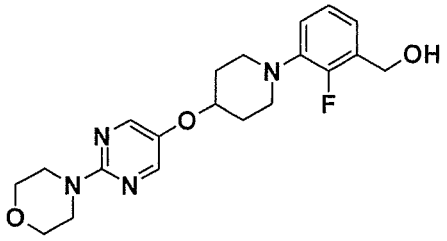
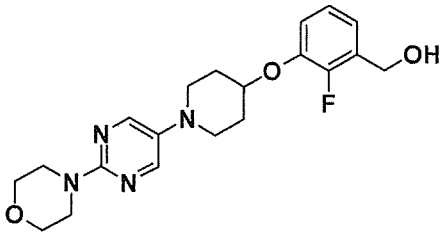
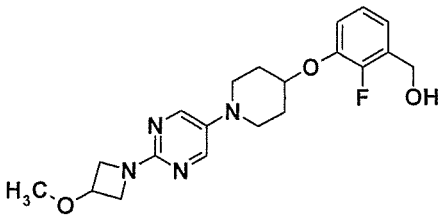
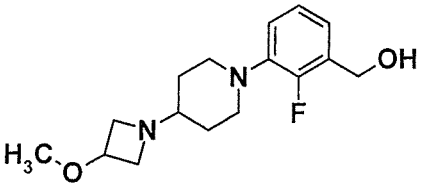
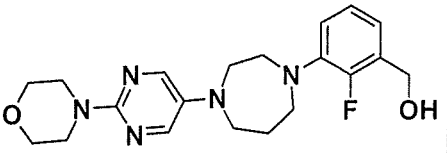
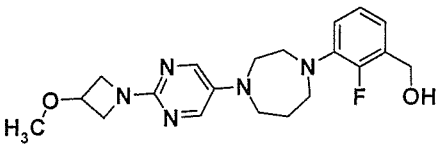
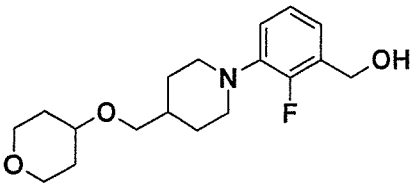
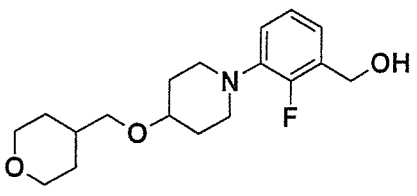
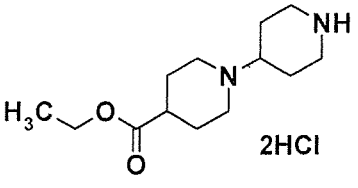
[0249]

[Table 31]

Rf	Syn	Structure	Rf	Syn	Structure
431	R376		432	R376	
433	R376		434	R376	
435	R376		436	R376	
437	R376		438	R376	
439	R376		440	R376	
441	R376		442	R376	
443	R376		444	R376	

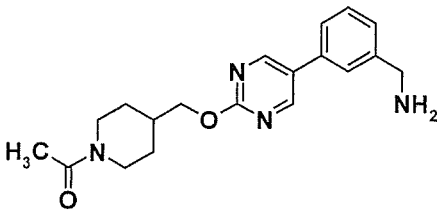
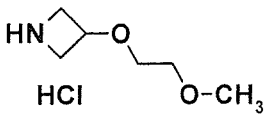
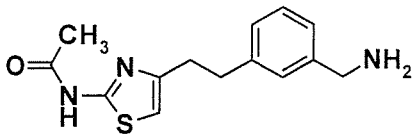
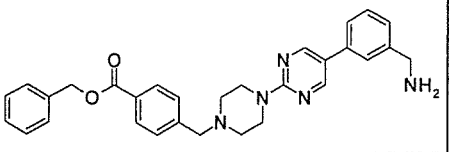
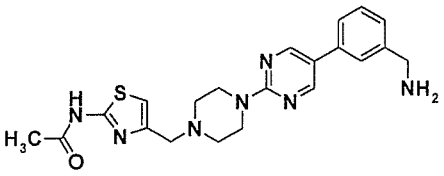
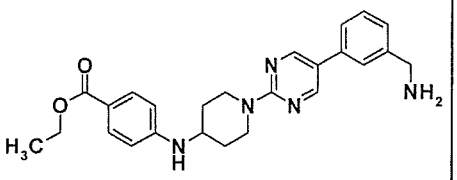
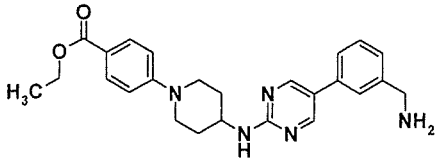
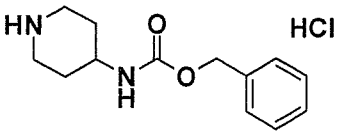
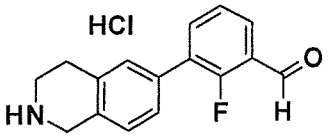
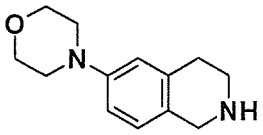
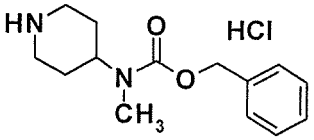
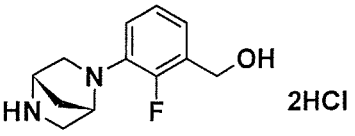
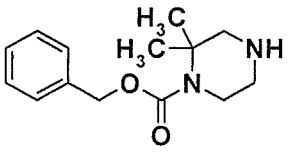
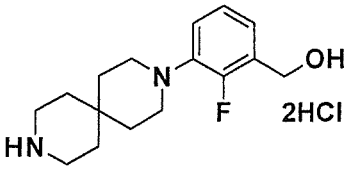
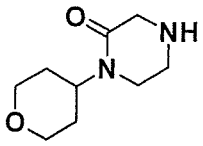
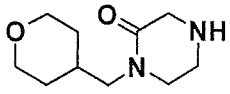
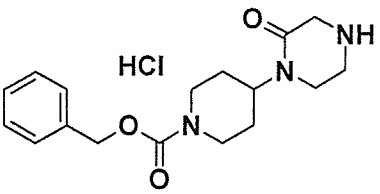
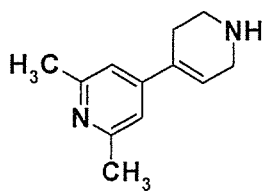
[0250]

[Table 32]

Rf	Syn	Structure	Rf	Syn	Structure
445	R376		446	R376	
447	R376		448	R376	
449	R376		450	R376	
451	R376		452	R376	
453	R376		454	R376	
455	R376		456	R376	
457	R376		458	R478	

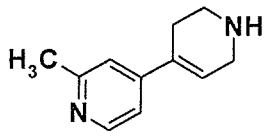
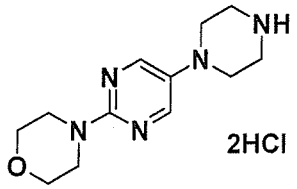
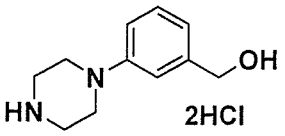
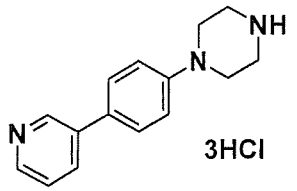
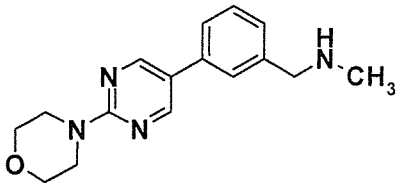
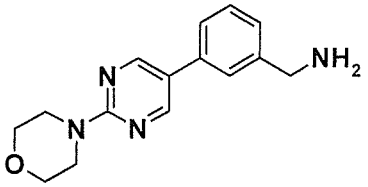
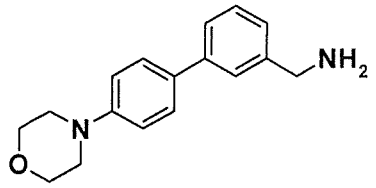
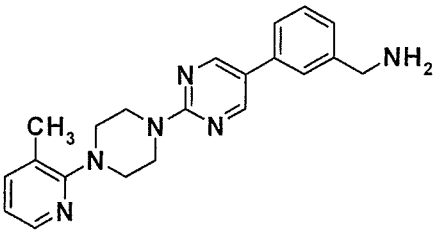
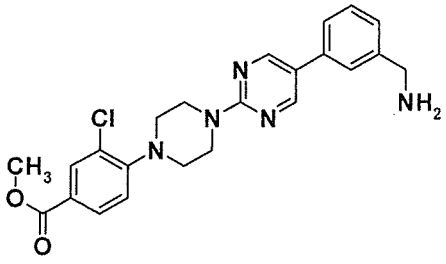
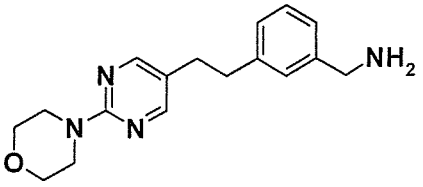
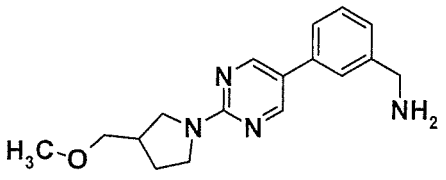
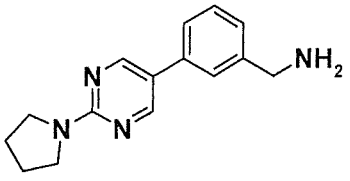
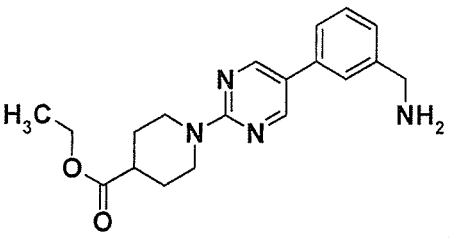
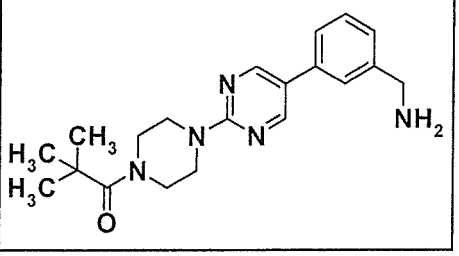
[0251]

[Table 33]

Rf	Syn	Structure	Rf	Syn	Structure
459	R478		460	R478	
461	R478		462	R478	
463	R478		464	R478	
465	R478		466	R478	
467	R478		468	R478	
469	R478		470	R478	
471	R478		472	R478	
473	R478		474	R478	
475	R478		476	R478	

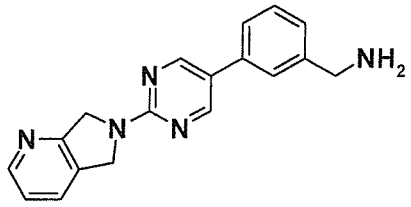
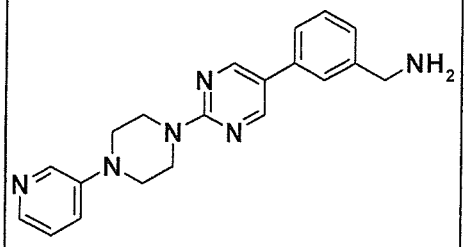
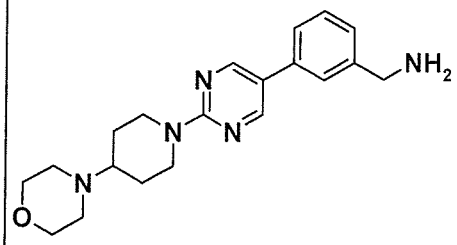
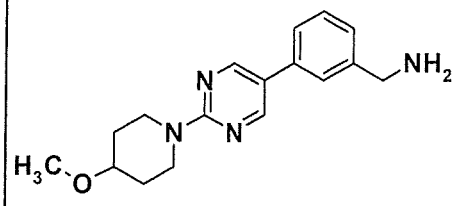
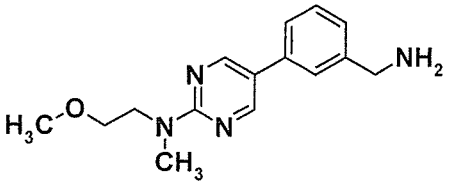
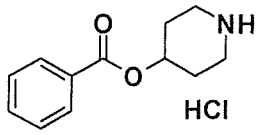
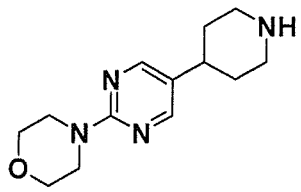
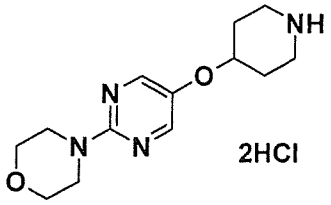
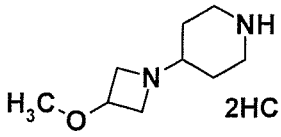
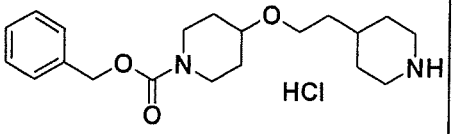
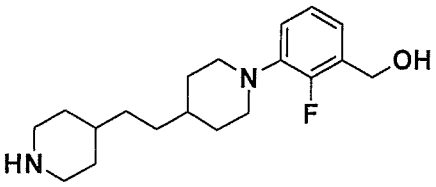
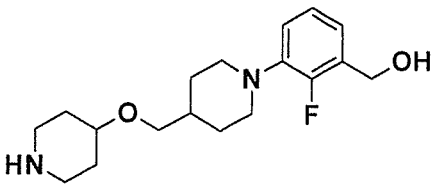
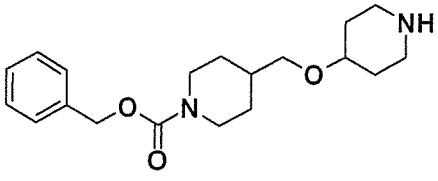
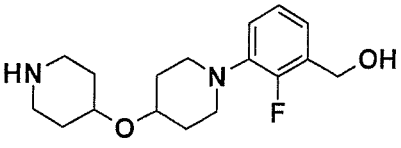
[0252]

[Table 34]

Rf	Syn	Structure	Rf	Syn	Structure
477	R478		478	R478	
479	R478		480	R478	
481	R478		482	R478	
483	R478		484	R478	
485	R478		486	R478	
487	R478		488	R478	
489	R478		490	R478	

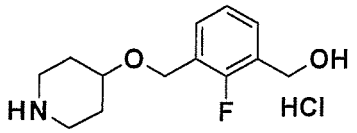
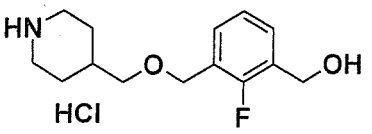
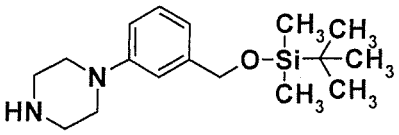
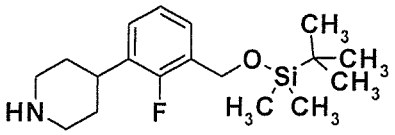
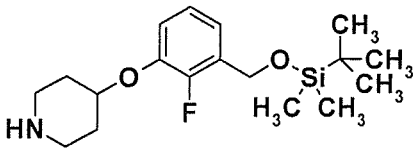
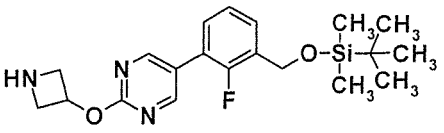
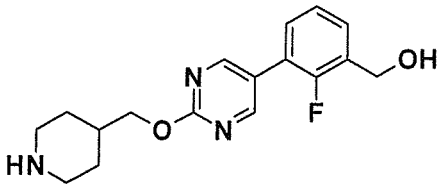
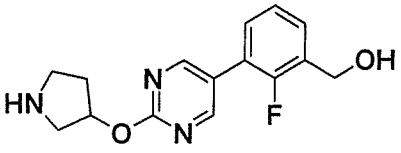
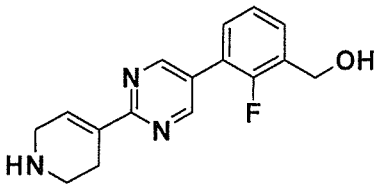
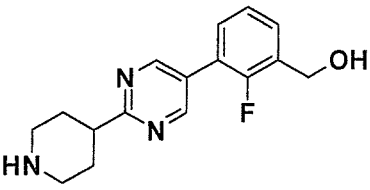
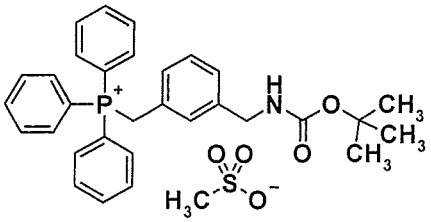
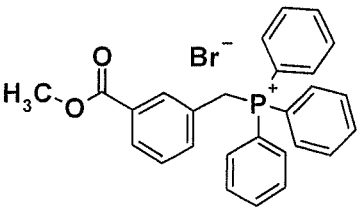
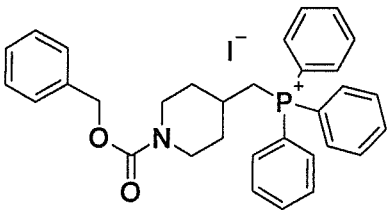
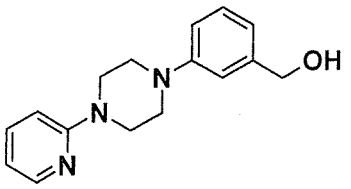
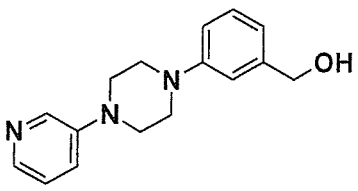
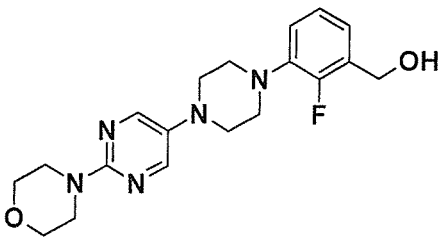
[0253]

[Table 35]

Rf	Syn	Structure	Rf	Syn	Structure
491	R478		492	R478	
493	R478		494	R478	
495	R478		496	R478	
497	R478		498	R478	
499	R478		500	R478	
501	R478		502	R478	
503	R478		504	R478	

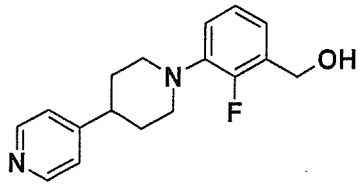
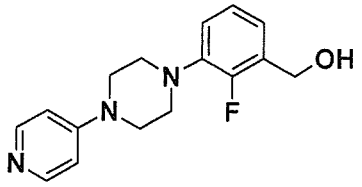
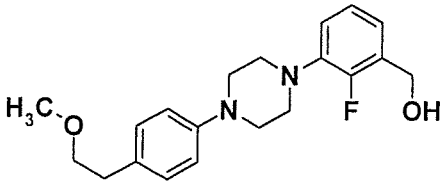
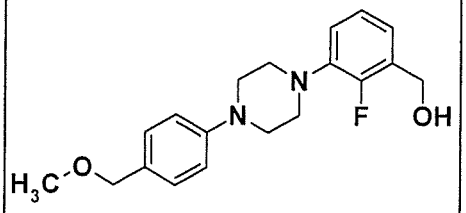
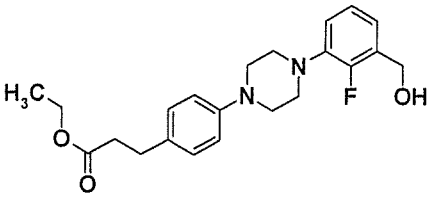
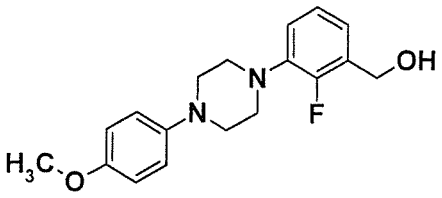
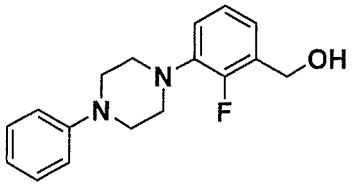
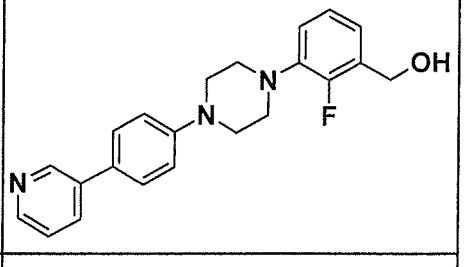
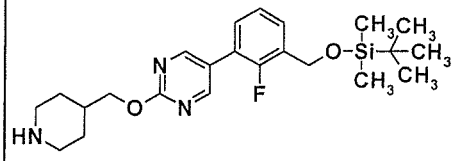
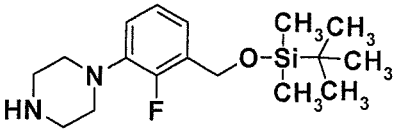
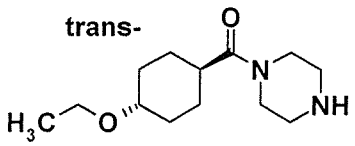
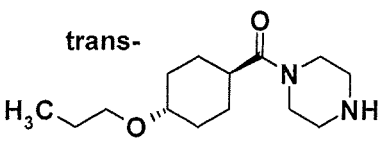
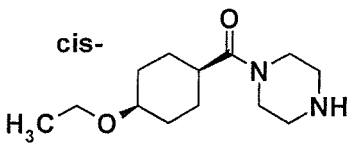
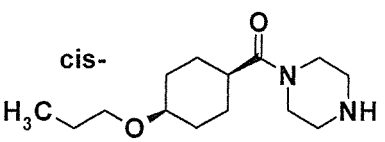
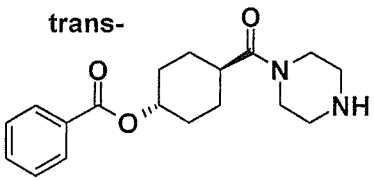
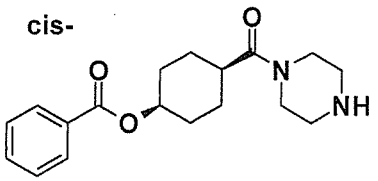
[0254]

[Table 36]

Rf	Syn	Structure	Rf	Syn	Structure
505	R478		506	R478	
507	R508		508	R508	
509	R508		510	R508	
511	R514		512	R514	
513	R514		514	R514	
515	R516		516	R516	
517	R516		518	R518	
519	R518		520	R518	

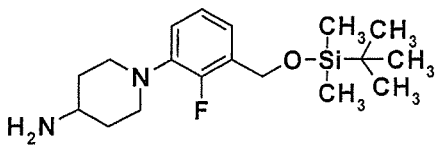
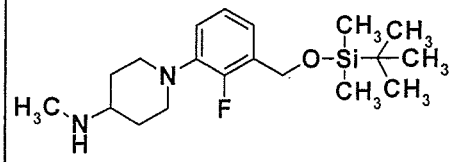
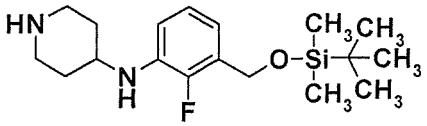
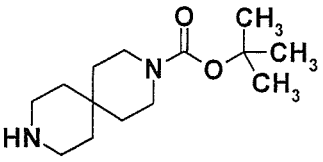
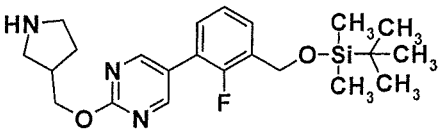
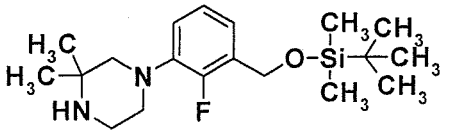
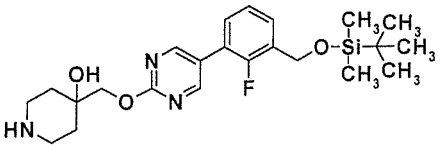
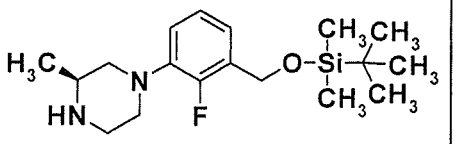
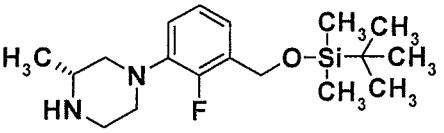
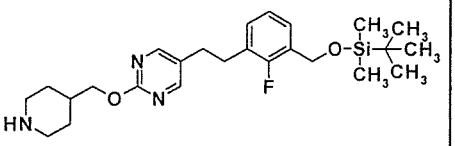
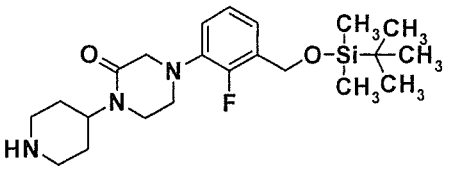
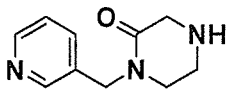
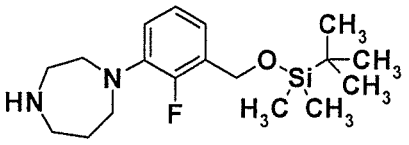
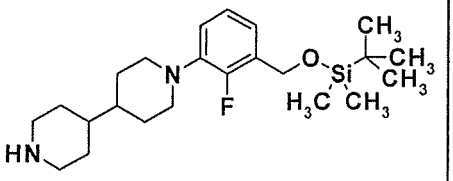
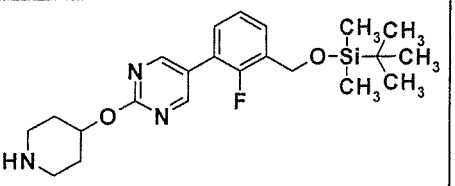
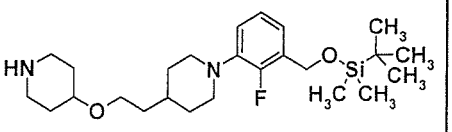
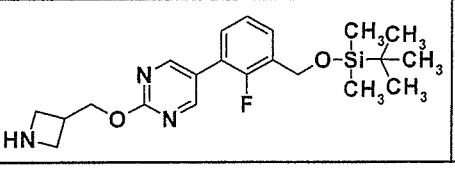
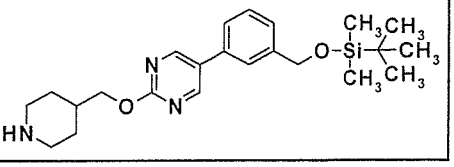
[0255]

[Table 37]

Rf	Syn	Structure	Rf	Syn	Structure
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523	R518		524	R518	
525	R518		526	R518	
527	R518		528	R518	
529	R548		530	R548	
531	R548		532	R548	
533	R548		534	R548	
535	R548		536	R548	

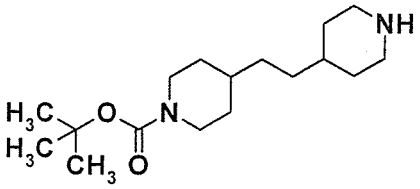
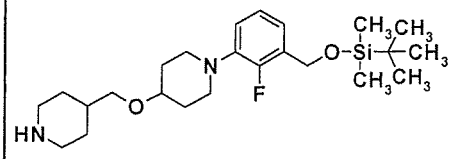
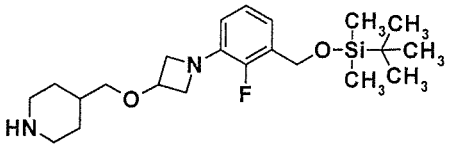
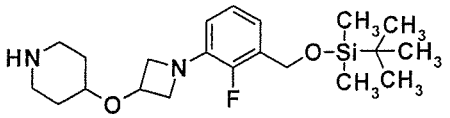
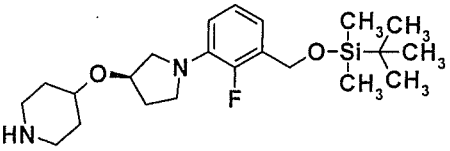
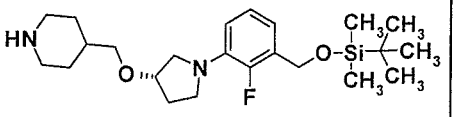
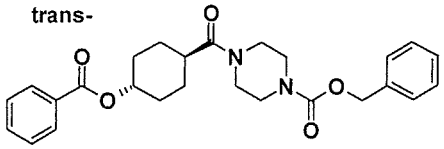
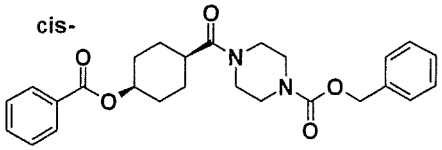
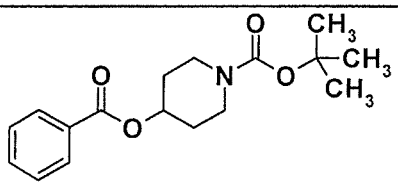
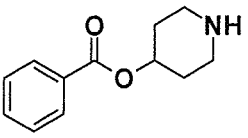
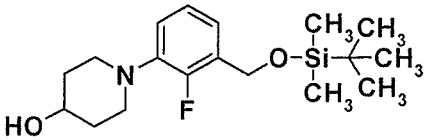
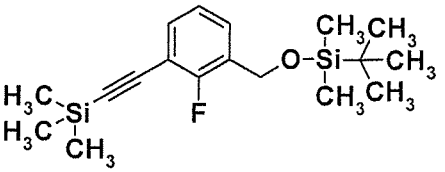
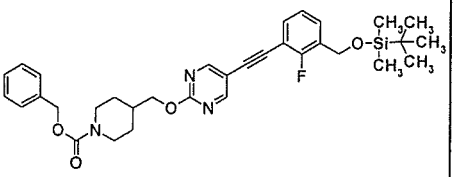
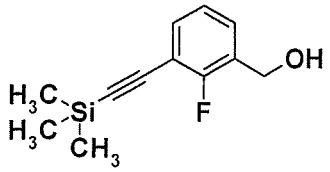
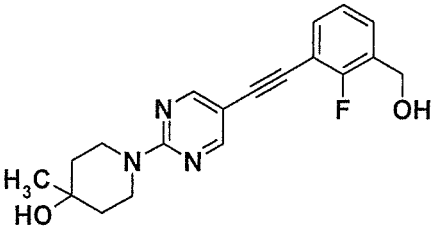
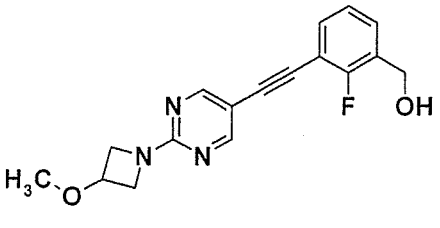
[0256]

[Table 38]

Rf	Syn	Structure	Rf	Syn	Structure
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539	R548		540	R548	
541	R548		542	R548	
543	R548		544	R548	
545	R548		546	R548	
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551	R548		552	R548	
553	R548		554	R548	

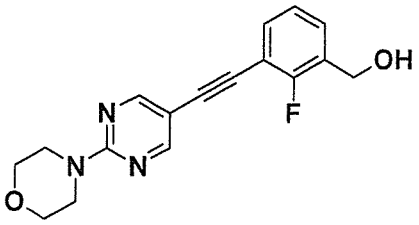
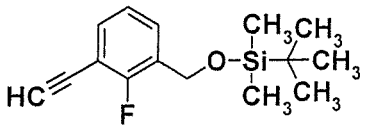
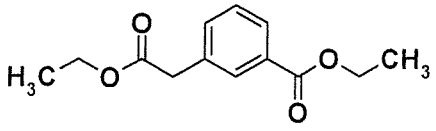
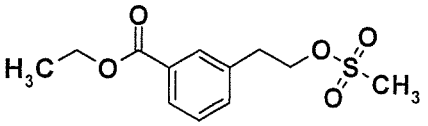
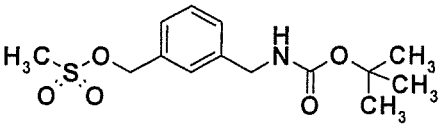
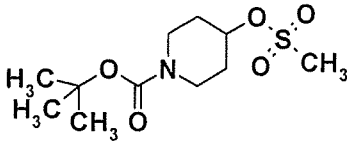
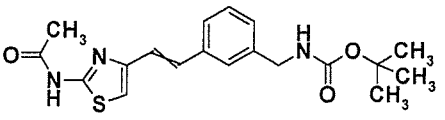
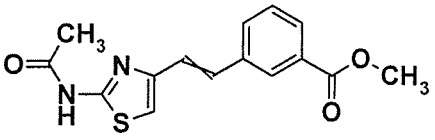
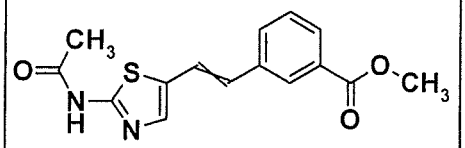
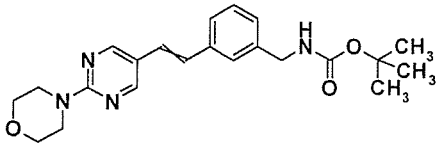
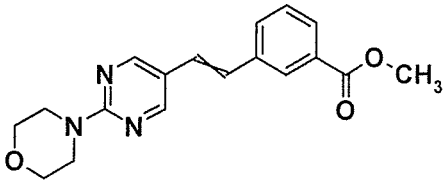
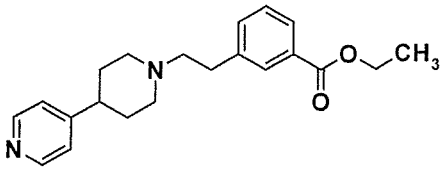
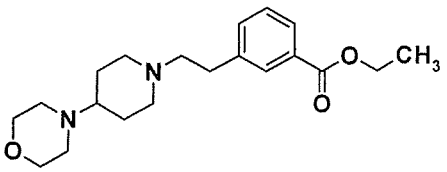
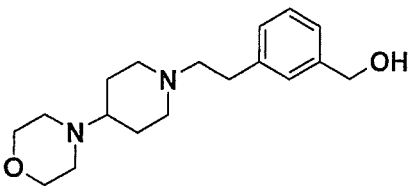
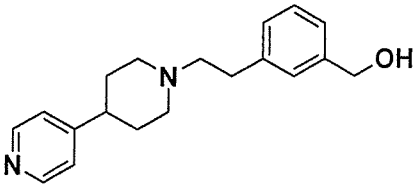
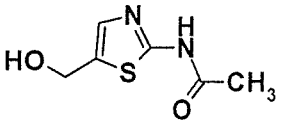
[0257]

[Table 39]

Rf	Syn	Structure	Rf	Syn	Structure
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557	R548		558	R548	
559	R548		560	R548	
561	R563		562	R563	
563	R563		564	R564	
565	R177		566	R568	
567	R568		568	R568	
569	R568		570	R568	

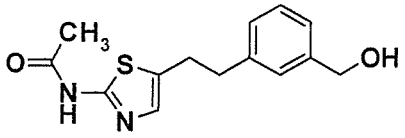
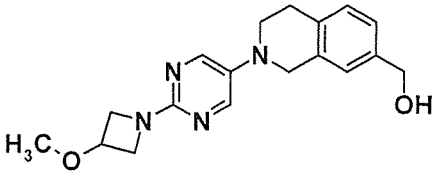
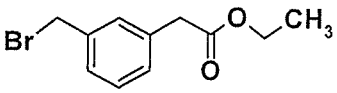
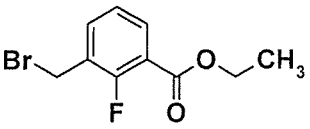
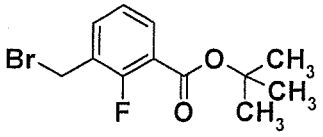
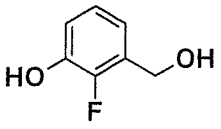
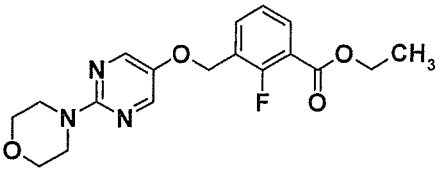
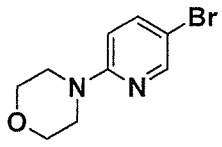
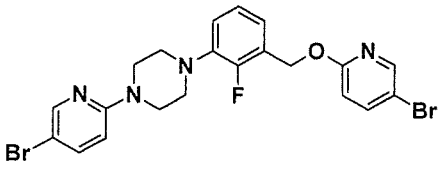
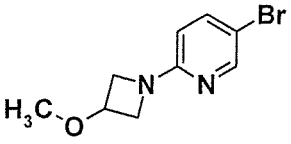
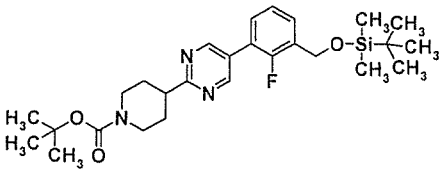
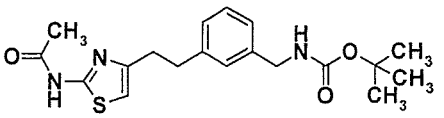
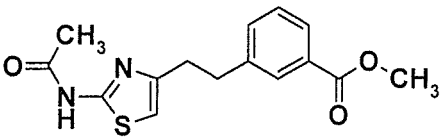
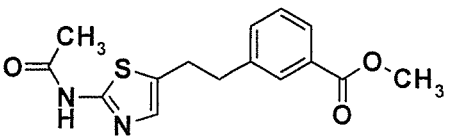
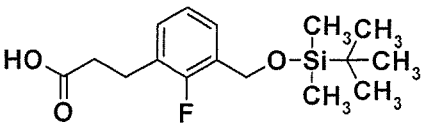
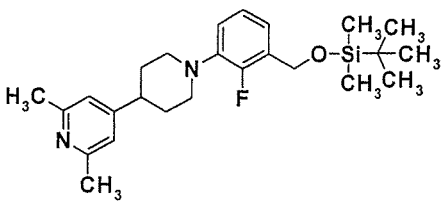
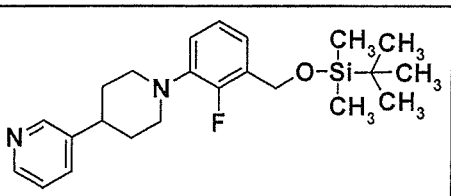
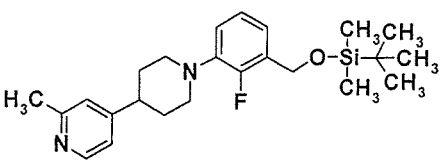
[0258]

[Table 40]

Rf	Syn	Structure	Rf	Syn	Structure
571	R568		572	R572	
573	R573		574	R574	
575	R574		576	R574	
577	R581		578	R581	
579	R581		580	R581	
581	R581		582	R582	
583	R582		584	R584	
585	R584		586	R584	

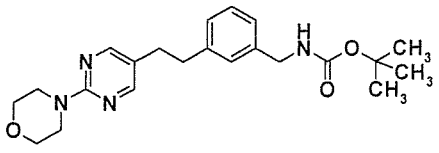
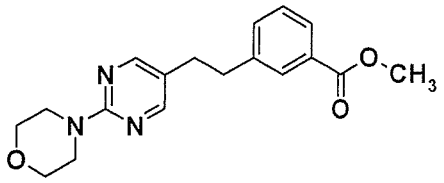
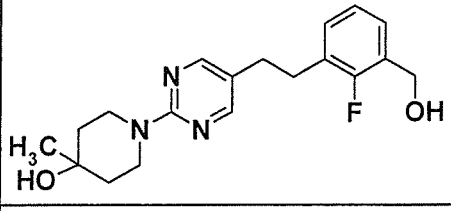
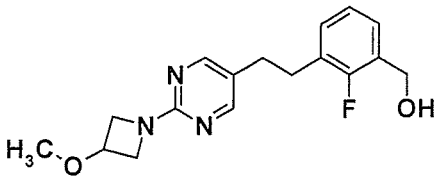
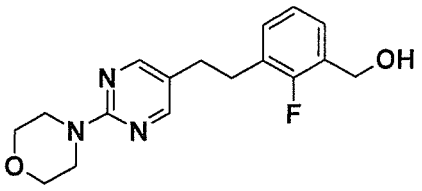
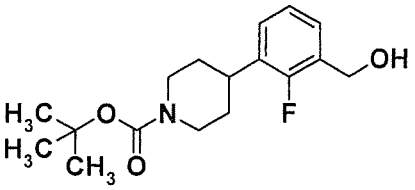
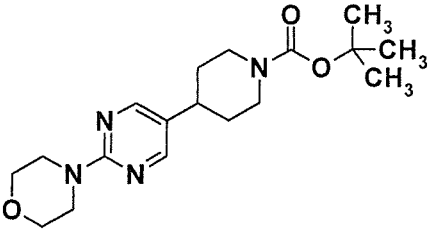
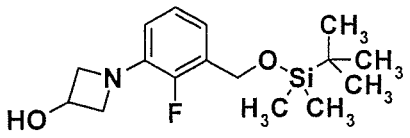
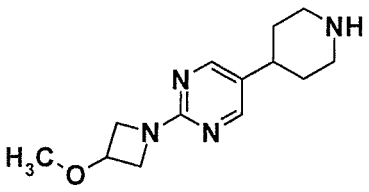
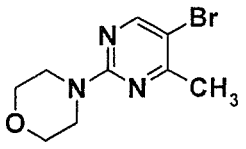
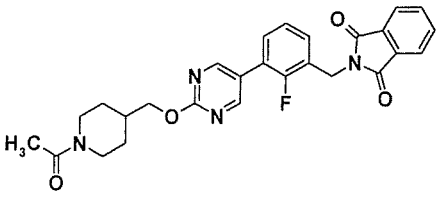
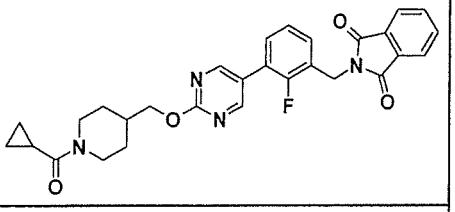
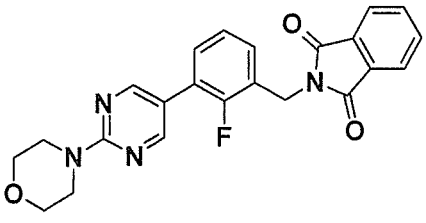
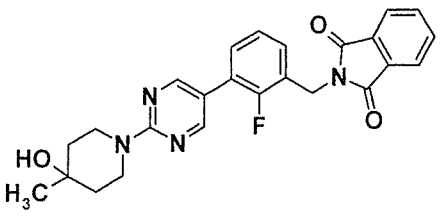
[0259]

[Table 41]

Rf	Syn	Structure	Rf	Syn	Structure
587	R584		588	R584	
589	R589		590	R589	
591	R589		592	R592	
593	R593		594	R594	
595	R596		596	R596	
597	R603		598	R603	
599	R603		600	R603	
601	R603		602	R603	
603	R603		604	R603	

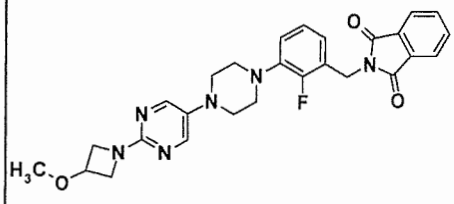
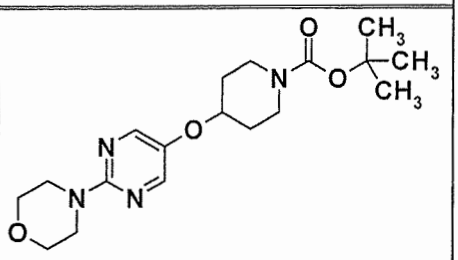
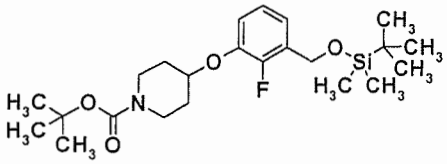
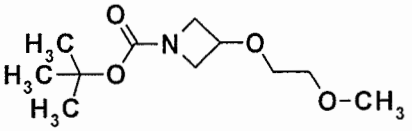
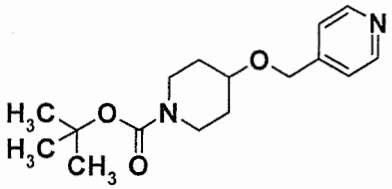
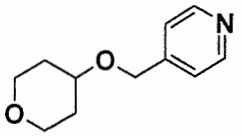
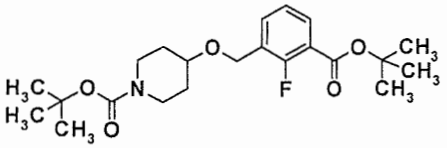
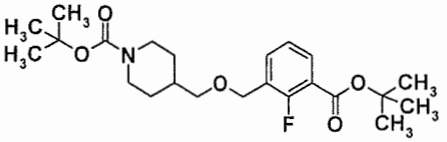
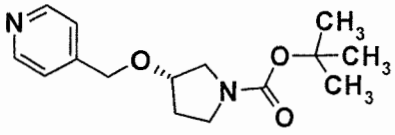
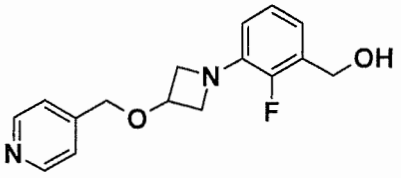
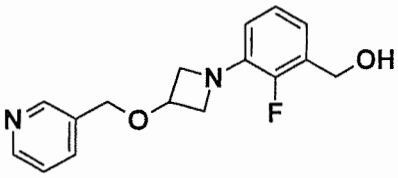
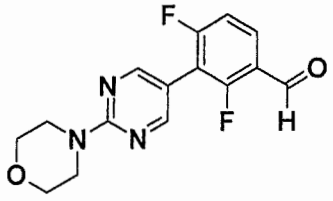
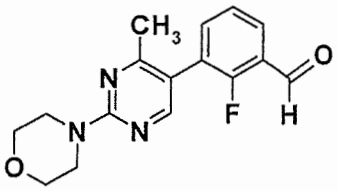
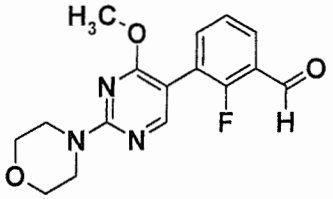
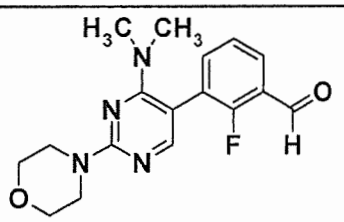
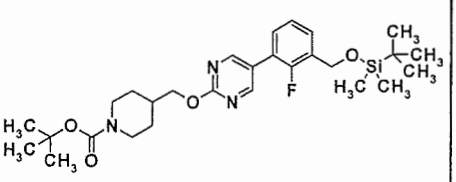
[0260]

[Table 42]

Rf	Syn	Structure	Rf	Syn	Structure
605	R603		606	R603	
607	R603		608	R603	
609	R603		610	R603	
611	R603		612	R603	
613	R613		614	R614	
615	R617		616	R617	
617	R617		618	R617	

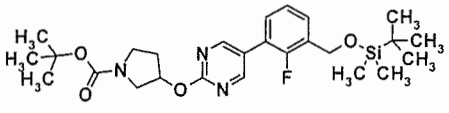
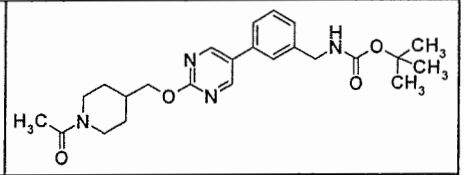
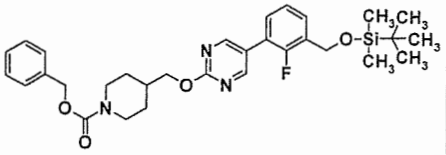
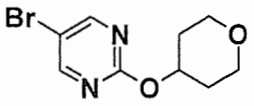
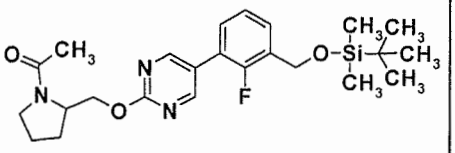
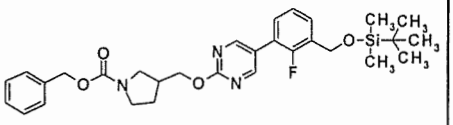
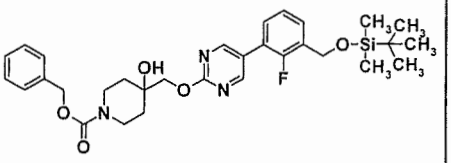
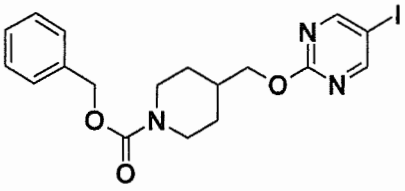
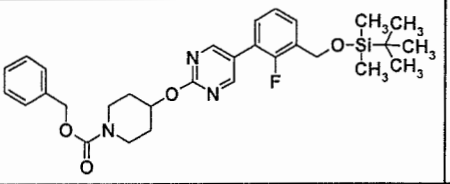
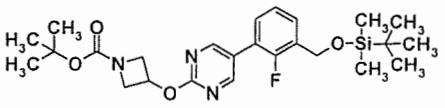
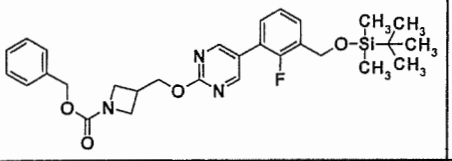
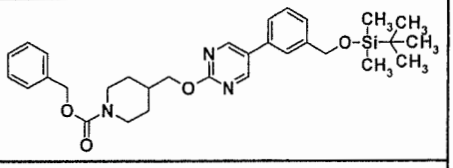
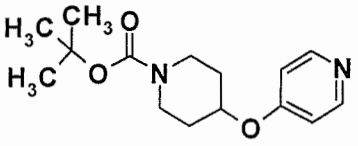
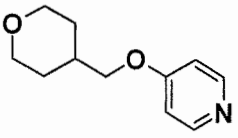
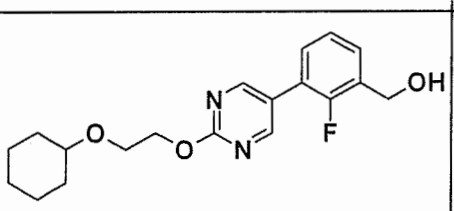
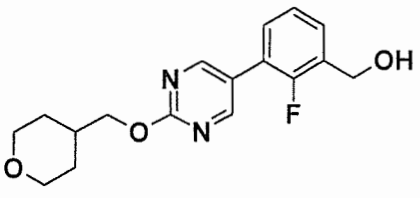
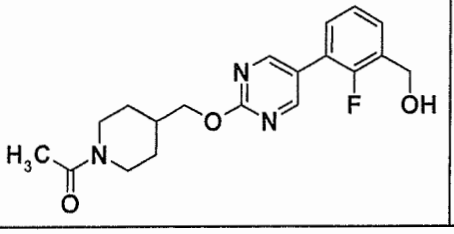
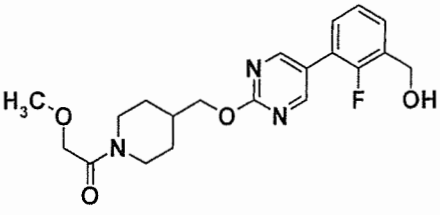
[0261]

[Table 43]

Rf	Syn	Structure	Rf	Syn	Structure
619	R617		620	R617	
621	R306		622	R306	
623	R306		624	R306	
625	R306		626	R306	
627	R306		628	R306	
629	R306		630	R631	
631	R631		632	R631	
633	R631		634	R638	

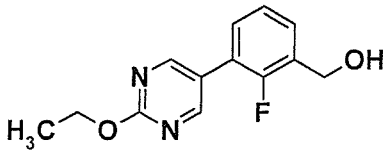
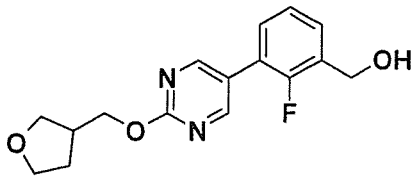
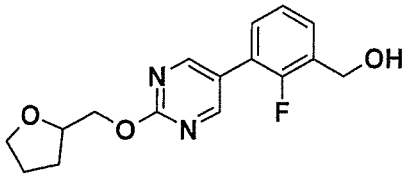
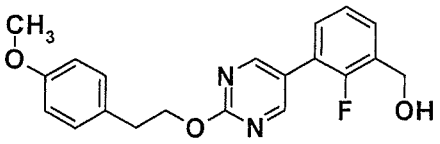
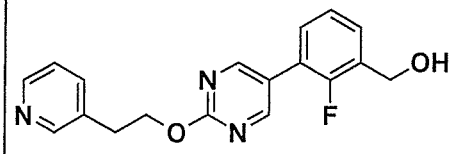
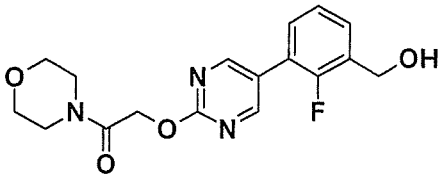
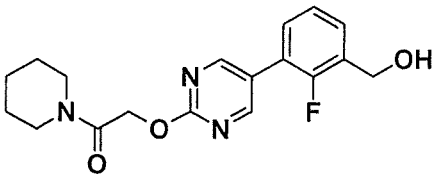
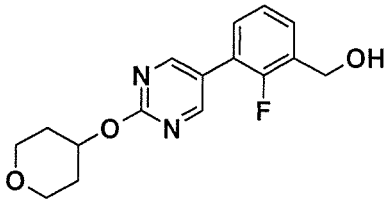
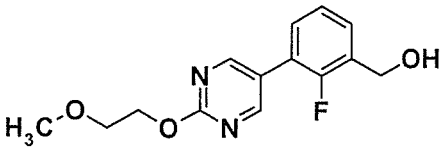
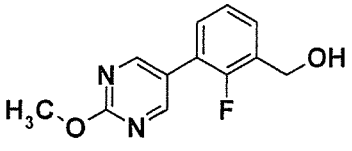
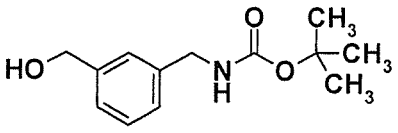
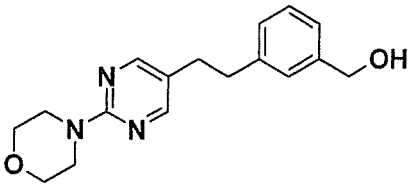
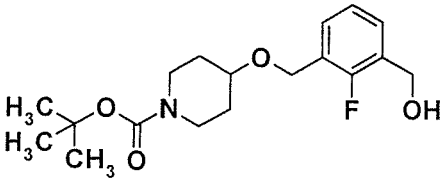
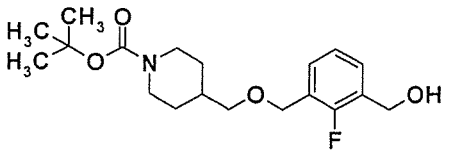
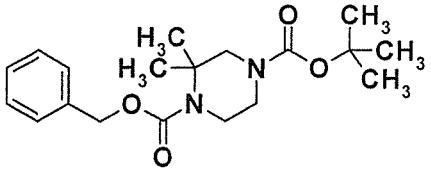
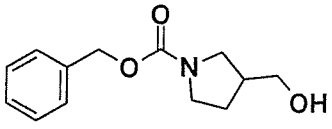
[0262]

[Table 44]

Rf	Syn	Structure	Rf	Syn	Structure
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637	R638		638	R638	
639	R638		640	R638	
641	R638		642	R638	
643	R638		644	R638	
645	R638		646	R638	
647	R638		648	R638	
649	R651		650	R651	
651	R651		652	R651	

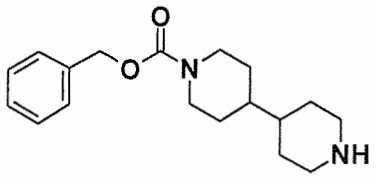
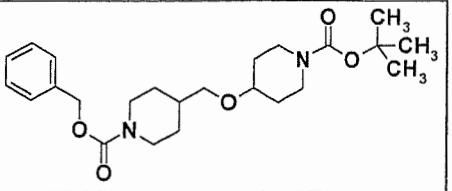
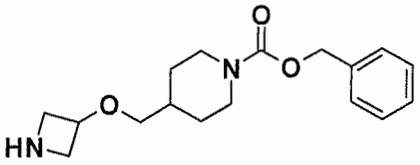
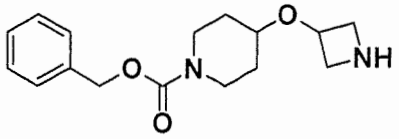
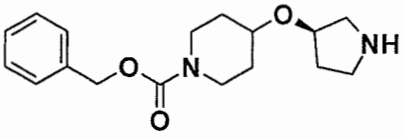
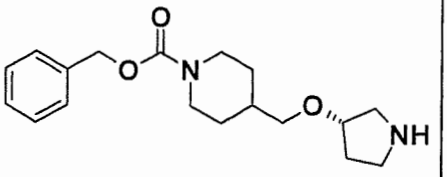
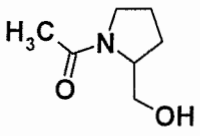
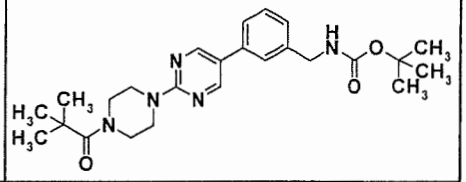
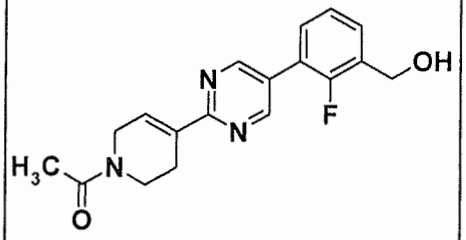
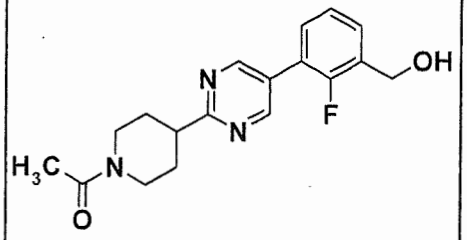
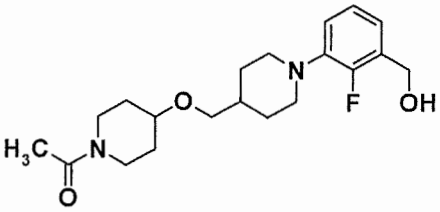
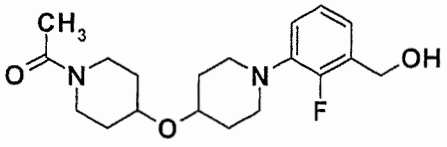
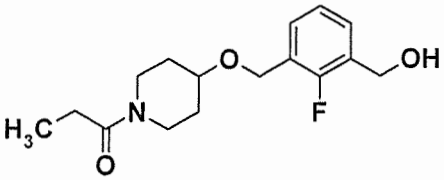
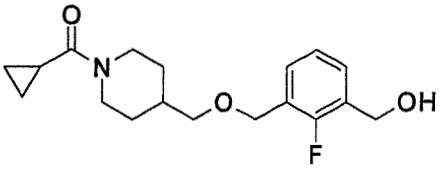
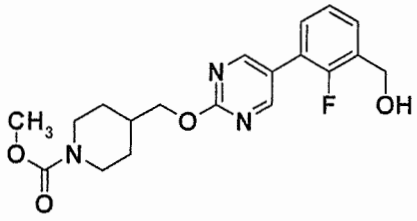
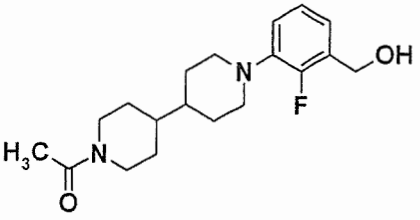
[0263]

[Table 45]

Rf	Syn	Structure	Rf	Syn	Structure
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655	R651		656	R651	
657	R651		658	R651	
659	R651		660	R651	
661	R651		662	R653	
663	R663		664	R663	
665	R663		666	R663	
669	R671		670	R671	

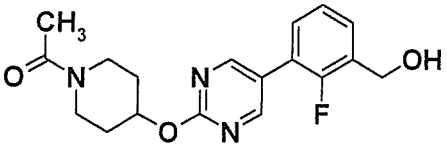
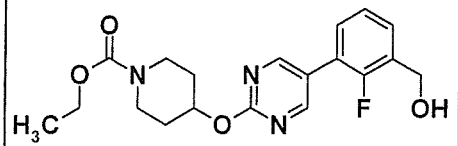
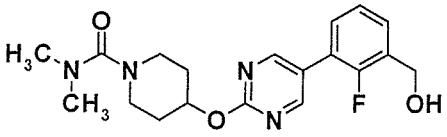
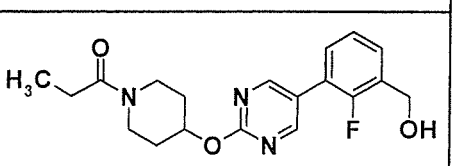
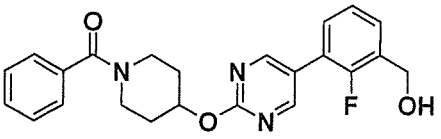
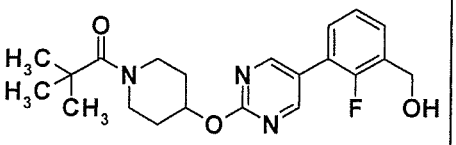
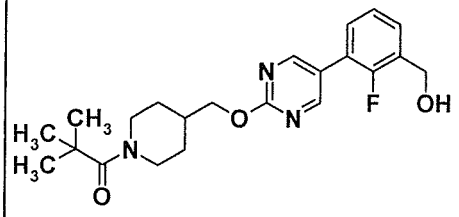
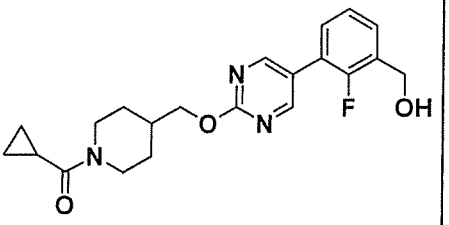
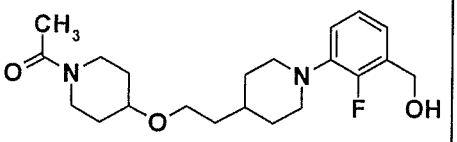
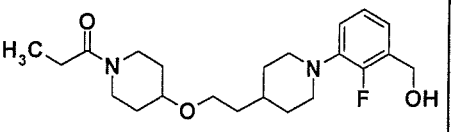
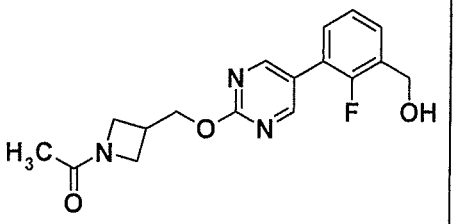
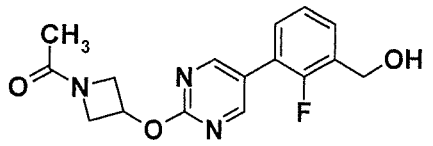
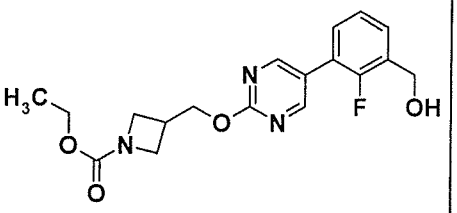
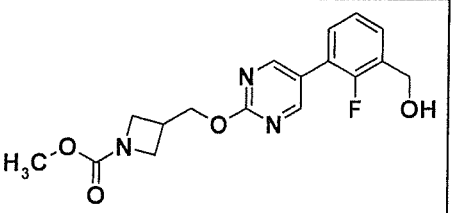
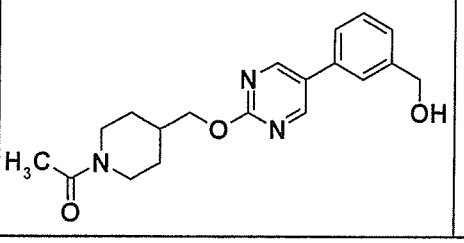
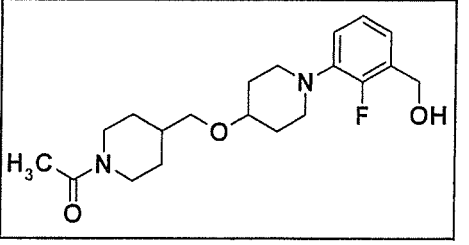
[0264]

[Table 46]

Rf	Syn	Structure	Rf	Syn	Structure
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673	R674		674	R674	
675	R674		676	R674	
677	R677		678	R677	
679	R680		680	R680	
681	R680		682	R680	
683	R680		684	R680	
685	R686		686	R686	

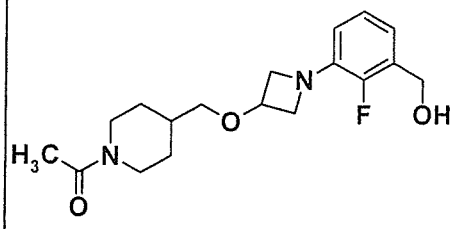
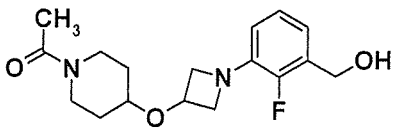
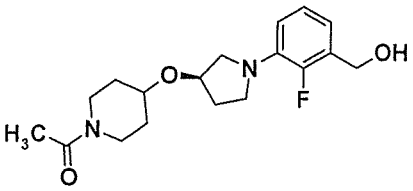
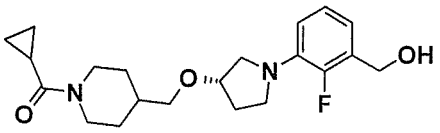
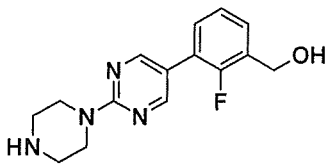
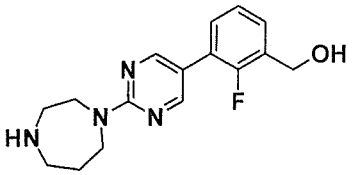
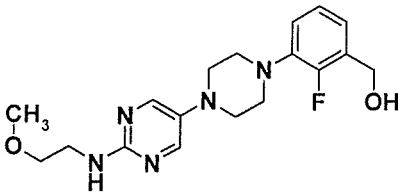
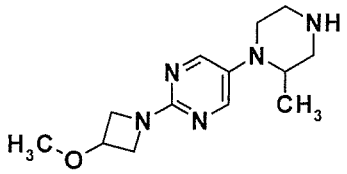
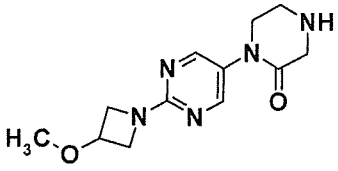
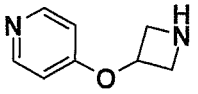
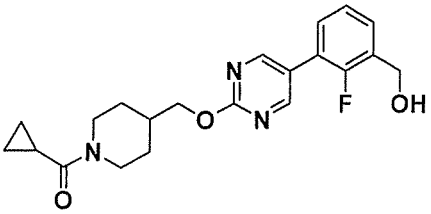
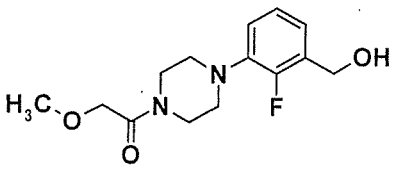
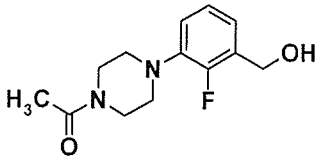
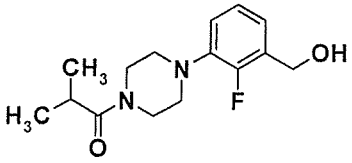
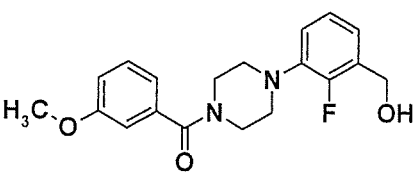
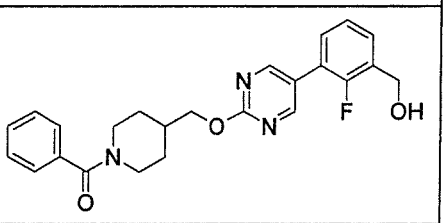
[0265]

[Table 47]

Rf	Syn	Structure	Rf	Syn	Structure
687	R686		688	R686	
689	R686		690	R686	
691	R686		692	R686	
693	R686		694	R686	
695	R686		696	R686	
697	R686		698	R686	
699	R686		700	R686	
701	R686		702	R686	

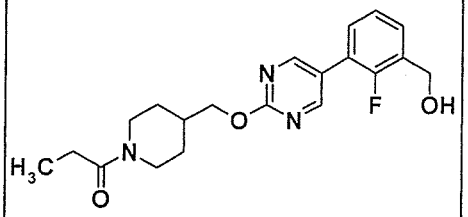
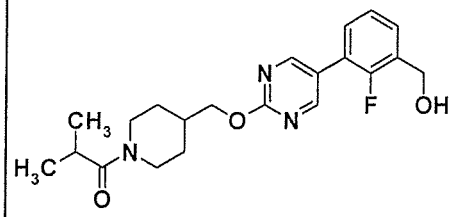
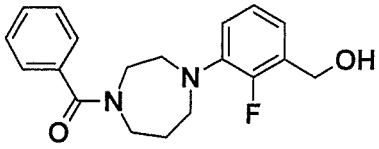
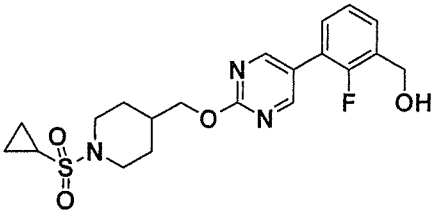
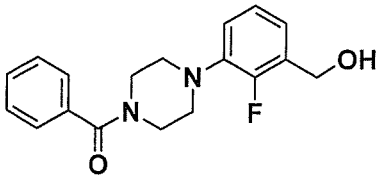
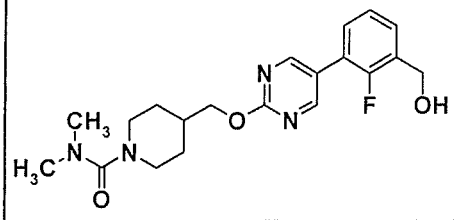
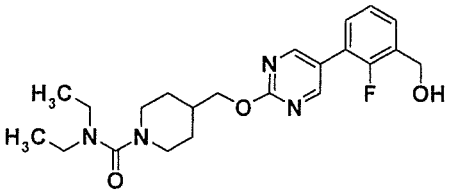
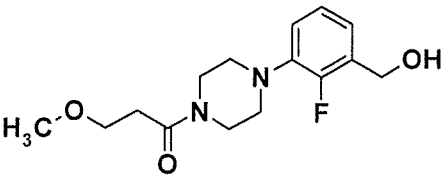
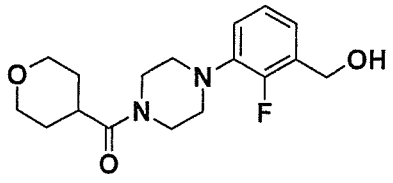
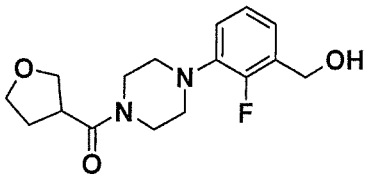
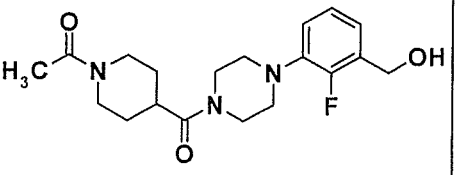
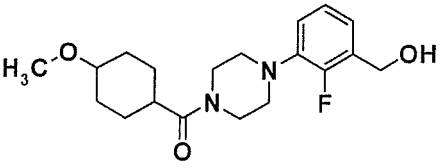
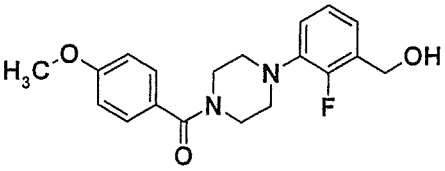
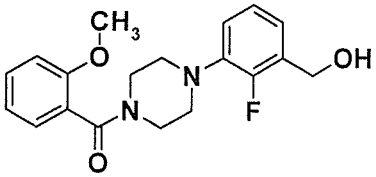
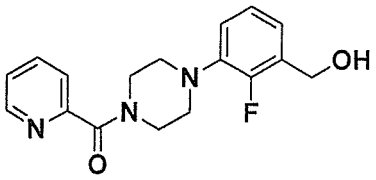
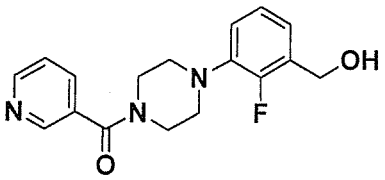
[0266]

[Table 48]

Rf	Syn	Structure	Rf	Syn	Structure
703	R686		704	R686	
705	R686		706	R686	
707	R707		708	R707	
709	R709		710	R712	
711	R712		712	R712	
713	R686		714	R686	
715	R686		716	R686	
717	R686		718	R686	

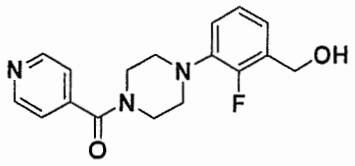
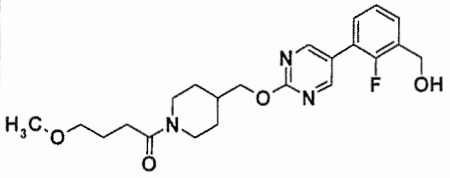
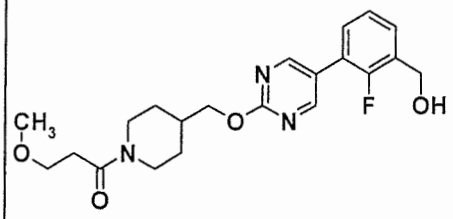
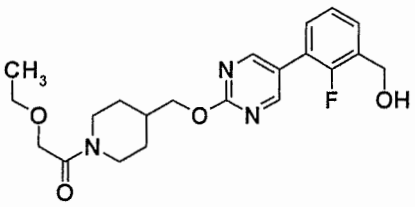
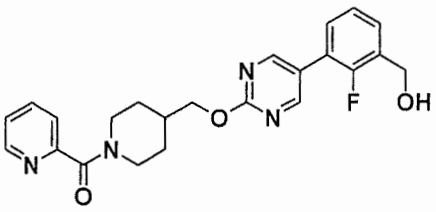
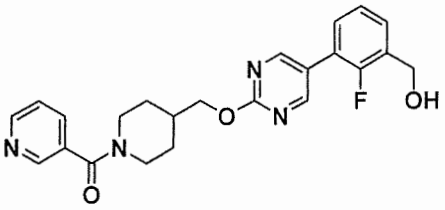
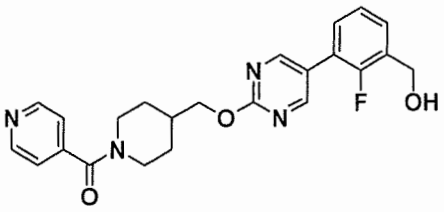
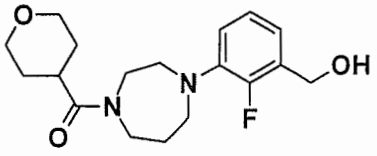
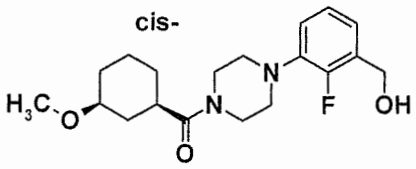
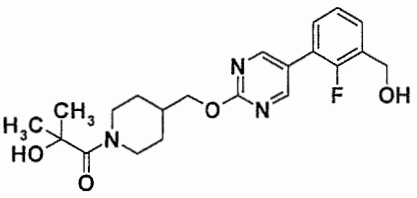
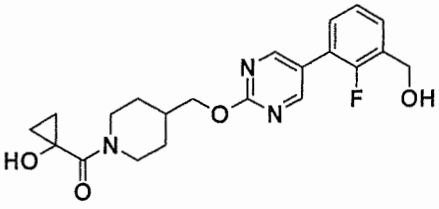
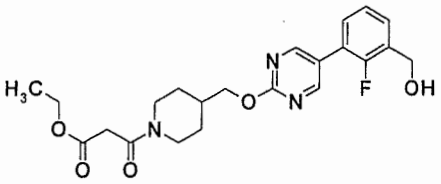
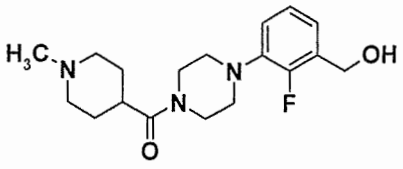
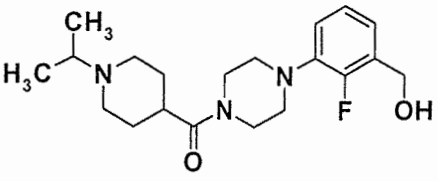
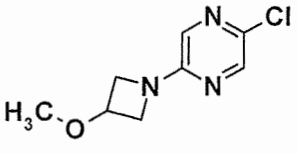
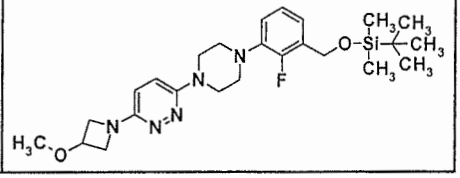
[0267]

[Table 49]

Rf	Syn	Structure	Rf	Syn	Structure
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721	R686		722	R686	
723	R686		724	R686	
725	R686		726	R343	
727	R343		728	R343	
729	R343		730	R343	
731	R343		732	R343	
733	R343		734	R343	

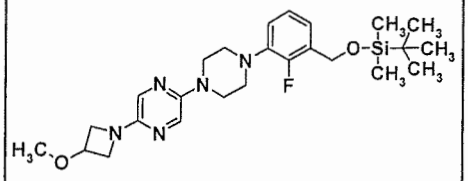
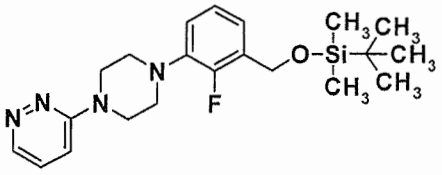
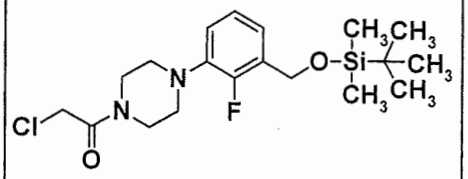
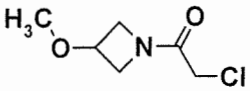
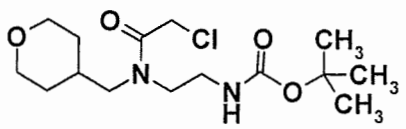
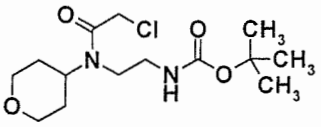
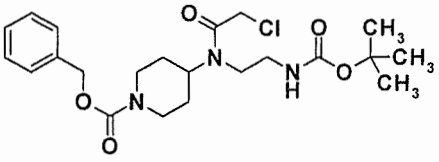
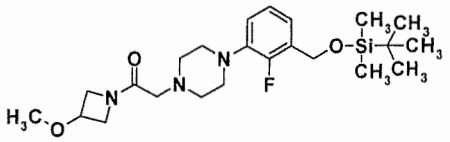
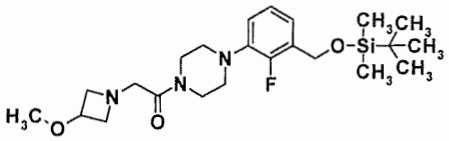
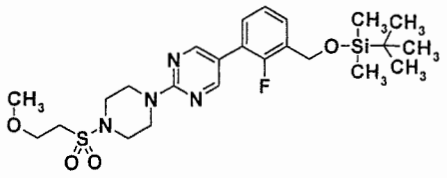
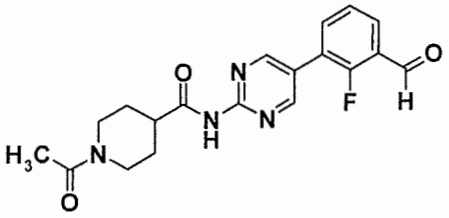
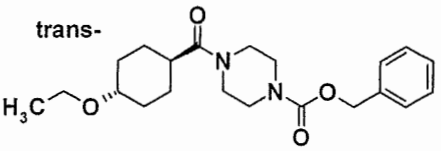
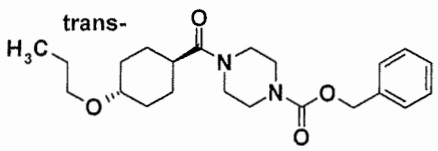
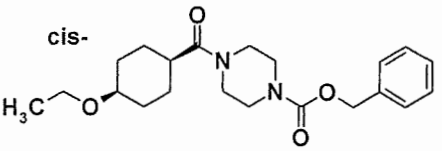
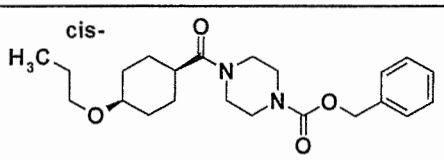
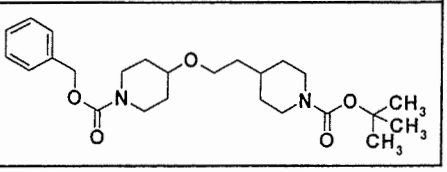
[0268]

[Table 50]

Rf	Syn	Structure	Rf	Syn	Structure
735	R343		736	R343	
737	R343		738	R343	
739	R343		740	R343	
741	R343		742	R343	
743	R343		744	R343	
745	R343		746	R343	
747	R343		748	R343	
749	R749		750	R752	

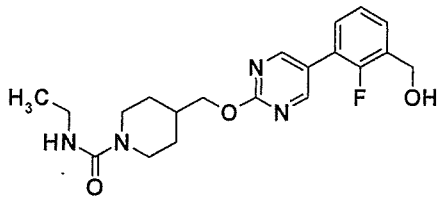
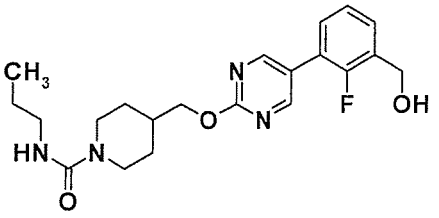
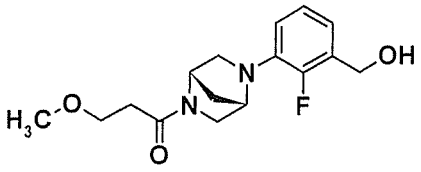
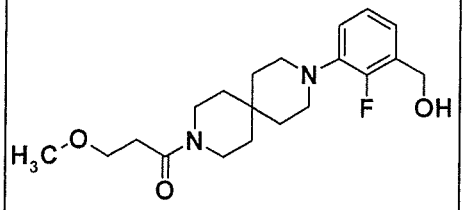
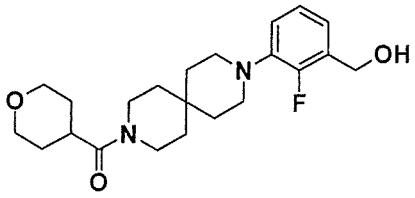
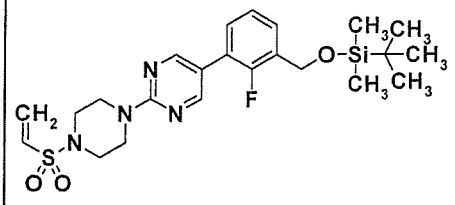
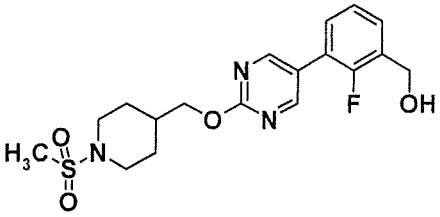
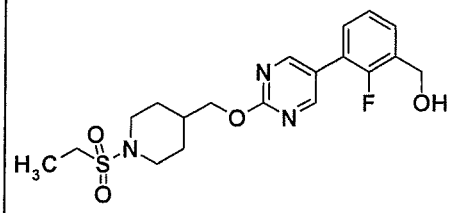
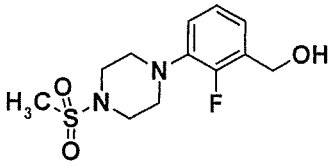
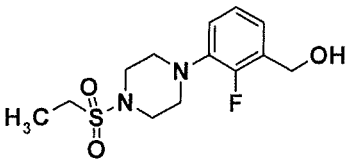
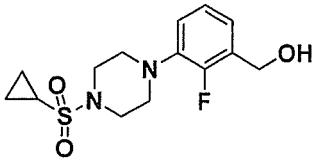
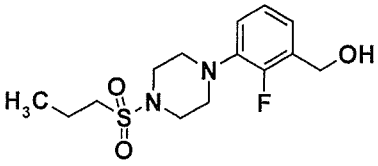
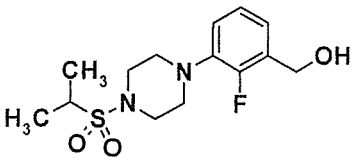
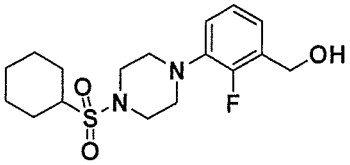
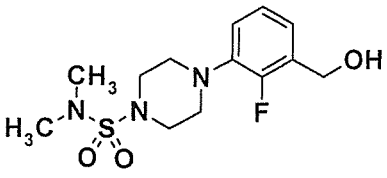
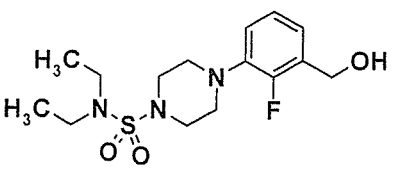
[0269]

[Table 51]

Rf	Syn	Structure	Rf	Syn	Structure
751	R752		752	R752	
753	R754		754	R754	
755	R754		756	R754	
757	R754		758	R758	
759	R758		760	R760	
761	R761		762	R766	
763	R766		764	R766	
765	R766		766	R766	

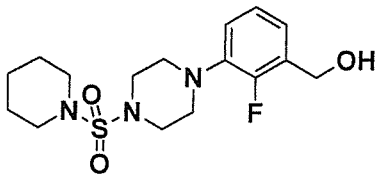
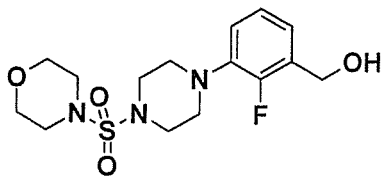
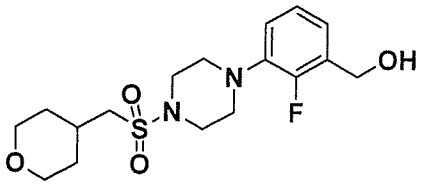
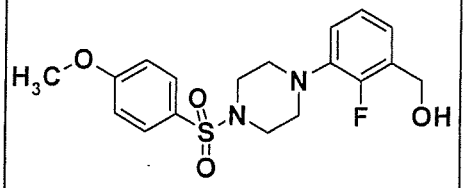
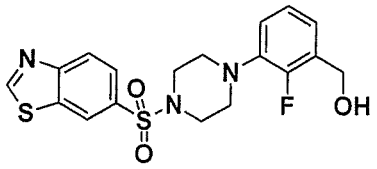
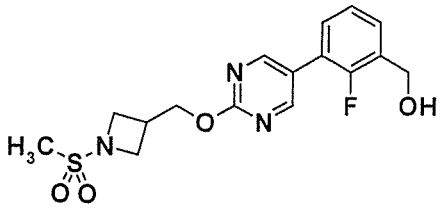
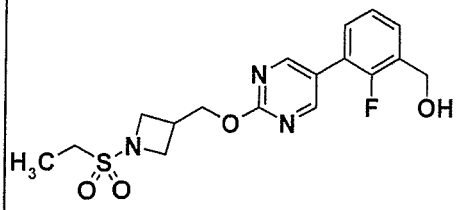
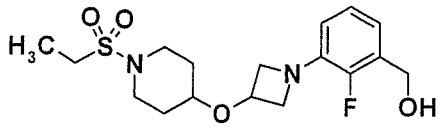
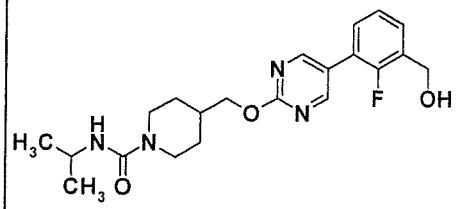
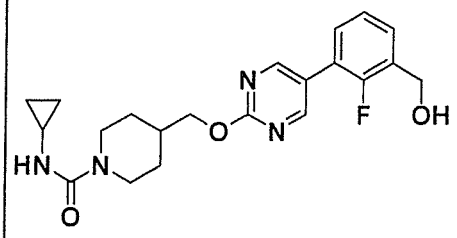
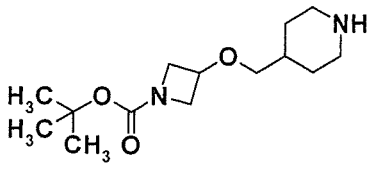
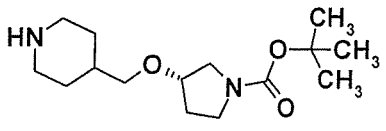
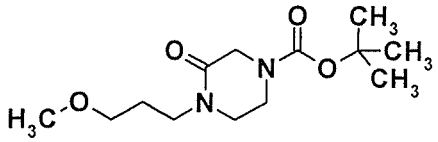
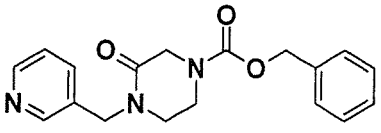
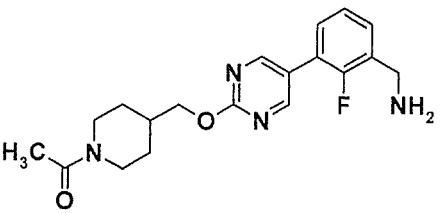
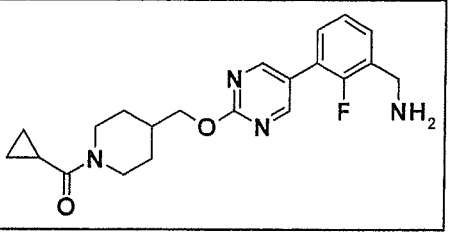
[0270]

[Table 52]

Rf	Syn	Structure	Rf	Syn	Structure
767	R767		768	R767	
769	R341		770	R341	
771	R341		772	R772	
773	R776		774	R776	
775	R776		776	R776	
777	R776		778	R776	
779	R776		780	R776	
781	R776		782	R776	

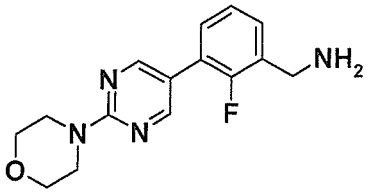
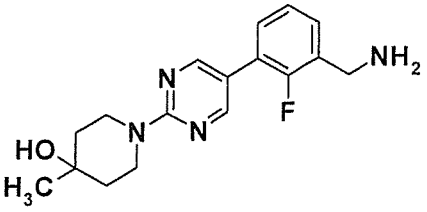
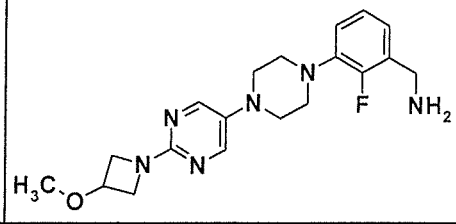
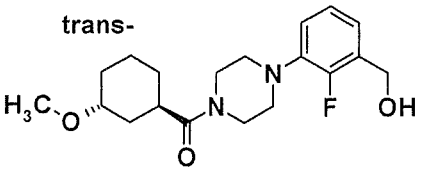
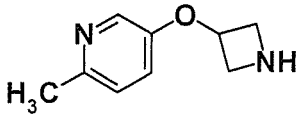
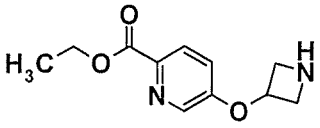
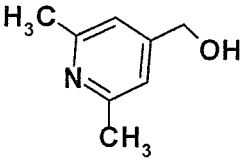
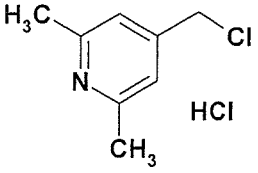
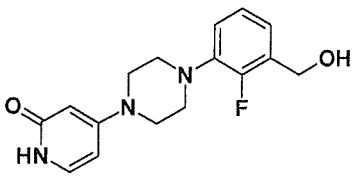
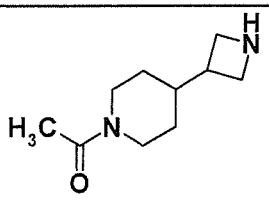
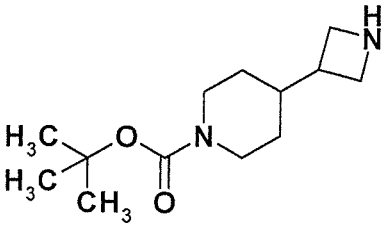
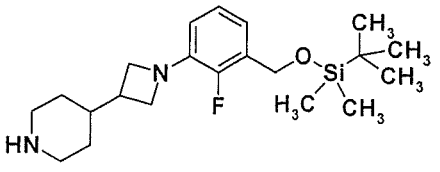
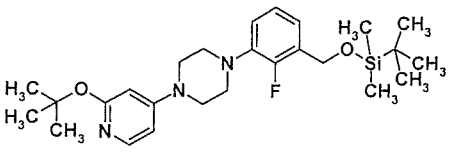
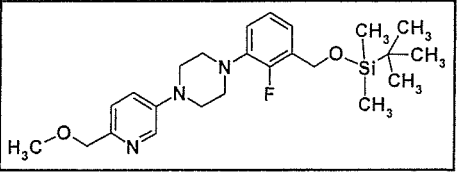
[0271]

[Table 53]

Rf	Syn	Structure	Rf	Syn	Structure
783	R776		784	R776	
785	R776		786	R776	
787	R776		788	R776	
789	R776		790	R776	
791	R791		792	R791	
793	R793		794	R793	
795	R796		796	R796	
797	R801		798	R801	

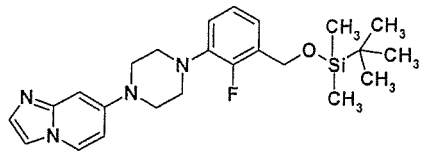
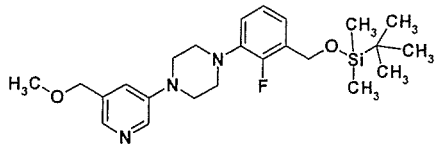
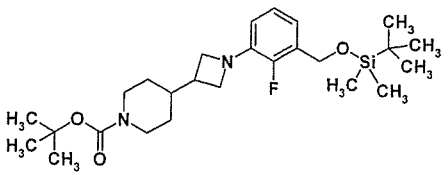
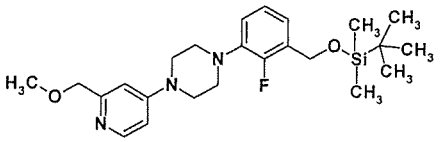
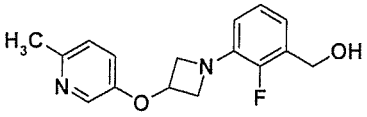
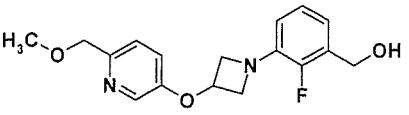
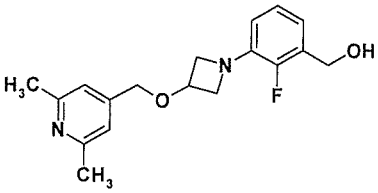
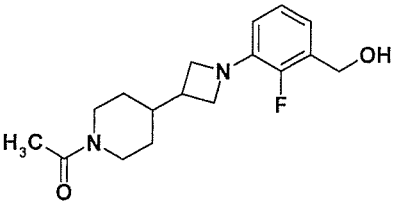
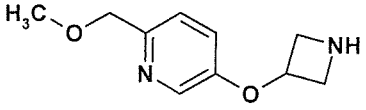
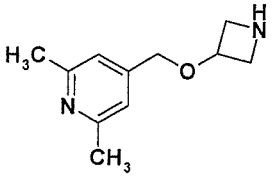
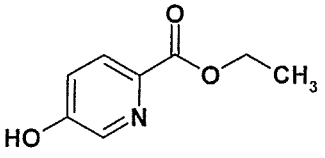
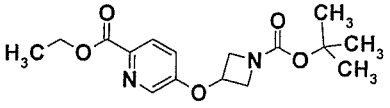
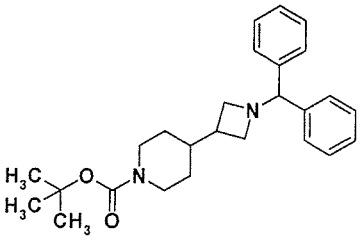
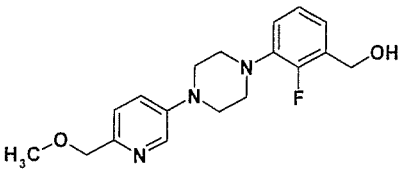
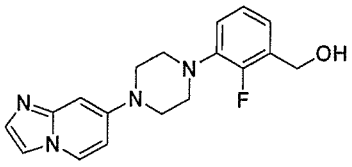
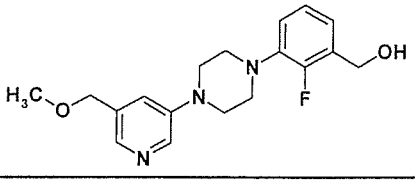
[0272]

[Table 54]

Rf	Syn	Structure	Rf	Syn	Structure
799	R801		800	R801	
801	R801		802	R343	
803	R803		804	R803	
805	R805		806	R806	
807	R807		808	R809	
809	R809		810	R810	
811	R228		812	R228	

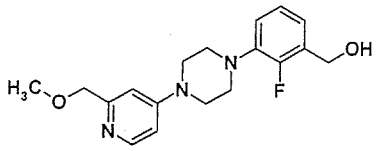
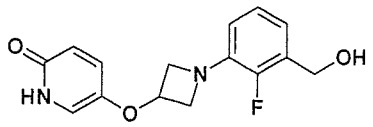
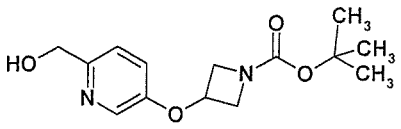
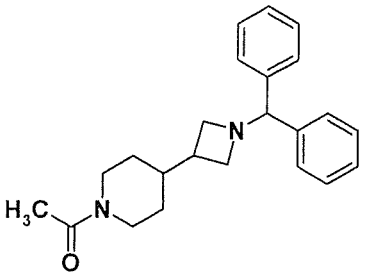
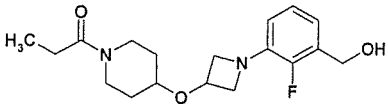
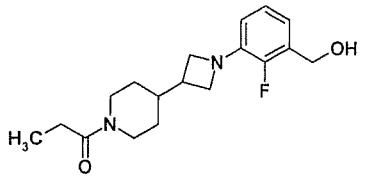
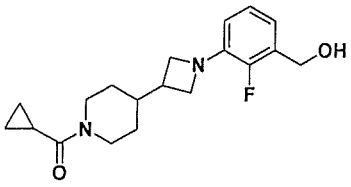
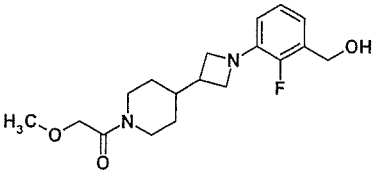
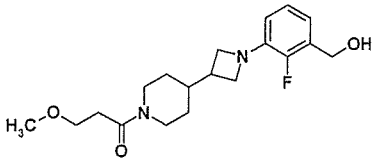
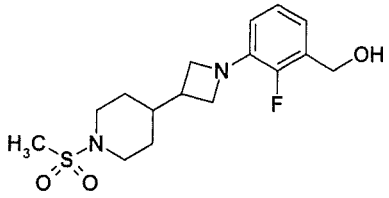
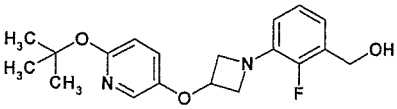
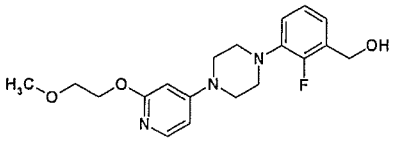
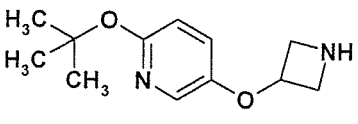
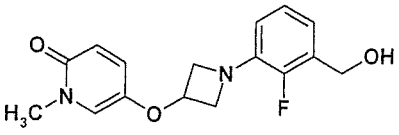
[0273]

[Table 55]

Rf	Syn	Structure	Rf	Syn	Structure
813	R228		814	R228	
815	R228		816	R228	
817	R285		818	R285	
819	R285		820	R285	
821	R821		822	R821	
823	R309		824	R347	
825	R347		826	R376	
827	R376		828	R376	

[0274]

[Table 56]

Rf	Syn	Structure	Rf	Syn	Structure
829	R376		830	R830	
831	R663		832	R677	
833	R686		834	R834	
835	R834		836	R836	
837	R836		838	R776	
839	R285		840	R840	
841	R841		842	R842	

[0275]

[Table 57]

Rf	Data
1	ESI+: 500
2	ESI+: 288
3	ESI+: 288
4	ESI+: 320
5	ESI+: 288
6	ESI+: 288
7	ESI+: 218
8	ESI+: 356
9	ESI+: 275
10	ESI+: 289
11	ESI+: 272
12	ESI+: 270
13	ESI+: 277
14	ESI+: 340
15	ESI+: 385
16	ESI+: 371
17	ESI+: 369
18	ESI+: 461
19	ESI+: 538, 540
20	ESI+: 334
21	ESI+: 221
22	ESI+: 286
23	ESI+: 237
24	ESI+: 286
25	ESI+: 286
26	APCI/ESI+: 290
27	APCI/ESI+: 306
28	APCI/ESI+: 347
29	APCI/ESI+: 347
30	APCI/ESI+: 287
31	APCI/ESI+: 287
32	ESI+: 308
33	EI: 234

[0276]

[Table 58]

Rf	Data
34	EI: 248
35	EI: 248
36	EI: 252
37	EI: 268
38	APCI/ESI+: 182
39	EI: 166
40	ESI+: 501
41	ESI+: 444
42	APCI/ESI+: 282
43	APCI/ESI+: 296
44	ESI+: 399
45	ESI+: 285
46	ESI+: 299
47	ESI+: 418
48	ESI+: 429
49	ESI+: 285
50	ESI+: 200
51	ESI+: 257
52	ESI+: 271
53	ESI+: 369 [M]+
54	ESI+: 284 [M]+
55	ESI+: 341 [M]+
56	ESI+: 355 [M]+
57	ESI+: 211
58	ESI+: 251
59	ESI+: 265
60	ESI+: 303
61	ESI+: 303
62	ESI+: 164
63	ESI+: 193
64	ESI+: 207
65	ESI+: 165
66	ESI+: 179

[0277]

[Table 59]

Rf	Data
67	ESI+: 460
68	ESI+: 502
69	ESI+: 399
70	ESI+: 364
71	ESI+: 290
72	ESI+: 290
73	ESI+: 290
74	ESI+: 290
75	ESI+: 308
76	ESI+: 304
77	ESI+: 320
78	ESI+: 333
79	ESI+: 373
80	ESI+: 239
81	ESI+: 288
82	APCI/ESI+: 289
83	APCI/ESI+: 289
84	ESI+: 332.15
85	ESI+: 333.09
86	ESI+: 341
87	ESI+: 345
88	ESI+: 380
89	ESI+: 334
90	ESI+: 372
91	ESI+: 356
92	ESI+: 443
93	APCI/ESI+: 481, 483
94	APCI/ESI+: 288, 290
95	APCI/ESI+: 264, 266
96	ESI+: 370
97	ESI+: 532
98	ESI+: 532
99	ESI+: 271

[0278]

[Table 60]

Rf	Data
100	ESI+: 374
101	ESI+: 389
102	ESI+: 317
103	ESI+: 318
104	ESI+: 317
105	ESI+: 334
106	ESI+: 443
107	ESI+: 360
108	ESI+: 376
109	ESI+: 402
110	ESI+: 375
111	ESI+: 318
112	ESI+: 186
113	ESI+: 166
114	ESI+: 360
115	ESI+: 332
116	ESI+: 224
117	ESI+: 460
118	ESI+: 292
119	ESI+: 319
120	ESI+: 331
121	ESI+: 331
122	ESI+: 327
123	ESI+: 399
124	ESI+: 355
125	ESI+: 441
126	ESI+: 404
127	ESI+: 447
128	ESI+: 454
129	ESI+: 399
130	ESI+: 373
131	ESI+: 300
132	ESI+: 274

[0279]

[Table 61]

Rf	Data
133	ESI+: 256
134	ESI+: 274
135	ESI+: 300
136	ESI+: 314
137	ESI+: 328
138	ESI+: 348
139	ESI+: 292
140	ESI+: 292
141	ESI+: 274
142	APCI/ESI+: 248
143	APCI/ESI+: 318
144	APCI/ESI+: 288
145	ESI+: 306
146	APCI/ESI+: 373
147	APCI/ESI+: 306
148	APCI/ESI+: 304
149	APCI/ESI+: 336
150	ESI+: 372
151	ESI+: 386
152	ESI+: 290
153	APCI/ESI+: 304
154	APCI/ESI+: 390
155	APCI/ESI+: 465
156	APCI/ESI+: 408
157	APCI/ESI+: 278
158	ESI+: 388
159	ESI+: 415
160	ESI+: 376
161	ESI+: 277
162	EI: 194
163	ESI+: 249
164	ESI+: 341
165	ESI+: 472

[0280]

[Table 62]

Rf	Data
166	ESI+: 594
167	ESI+: 524
168	ESI+: 425
169	ESI+: 495
170	ESI+: 245
171	ESI+: 259
172	ESI+: 378
173	ESI+: 417
174	ESI+: 277
175	ESI+: 271
176	ESI+: 187
177	ESI+: 332
178	ESI+: 304
179	ESI+: 210
180	APCI/ESI+: 254
181	APCI/ESI+: 268
182	ESI+: 306
183	APCI/ESI+: 488
184	APCI/ESI+: 516
185	APCI/ESI+: 488
186	APCI/ESI+: 516
187	APCI/ESI+: 487
188	APCI/ESI+: 532
189	APCI/ESI+: 487
190	APCI/ESI+: 488
191	APCI/ESI+: 407
192	ESI+: 487
193	APCI/ESI+: 508
194	ESI+: 470
195	APCI/ESI+: 433
196	APCI/ESI+: 459
197	APCI/ESI+: 503
198	APCI/ESI+: 326

[0281]

[Table 63]

Rf	Data
199	APCI/ESI+: 479
200	APCI/ESI+: 493
201	APCI/ESI+: 479
202	APCI/ESI+: 493
203	APCI/ESI+: 555
204	APCI/ESI+: 555
205	APCI/ESI+: 326
206	APCI/ESI+: 370
207	APCI/ESI+: 381
208	APCI/ESI+: 584
209	APCI/ESI+: 558
210	ESI+: 502
211	ESI+: 319
212	ESI+: 473
213	ESI+: 457
214	ESI+: 355
215	ESI+: 487
216	ESI+: 473
217	ESI+: 437
218	ESI+: 493
219	ESI+: 487
220	ESI+: 473
221	ESI+: 473
222	ESI+: 411
223	ESI+: 423
224	ESI+: 437
225	ESI+: 402
226	ESI+: 402
227	ESI+: 556
228	ESI+: 416
229	ESI+: 430
230	ESI+: 416
231	ESI+: 416

[0282]

[Table 64]

Rf	Data
232	ESI+: 403
233	ESI+: 416
234	ESI+: 416
235	ESI+: 416
236	ESI+: 416
237	ESI+: 416
238	ESI+: 408
239	ESI+: 416
240	ESI+: 417
241	ESI+: 430
242	ESI+: 427
243	ESI+: 413
244	ESI+: 397
245	ESI+: 389
246	ESI+: 390
247	ESI+: 350
248	ESI+: 470
249	ESI+: 398
250	ESI+: 384
251	ESI+: 384
252	ESI+: 488
253	ESI+: 402
254	ESI+: 401
255	ESI+: 431
256	ESI+: 445
257	ESI+: 459
258	ESI+: 401
259	ESI+: 478
260	APCI/ESI+: 487
261	APCI/ESI+: 487
262	APCI/ESI+: 487
263	APCI/ESI+: 487
264	APCI/ESI+: 503

[0283]

[Table 65]

Rf	Data
265	ESI+: 503
266	APCI/ESI+: 503
267	APCI/ESI+: 409
268	APCI/ESI+: 473
269	APCI/ESI+: 502
270	APCI/ESI+: 502
271	APCI/ESI+: 541
272	ESI+: 585
273	ESI+: 535
274	ESI+: 537
275	ESI+: 571
276	ESI+: 438
277	ESI+: 523
278	ESI+: 438
279	ESI+: 543
280	ESI+: 529
281	ESI+: 543
282	ESI+: 557
283	ESI+: 402
284	APCI/ESI+: 240
285	ESI+: 275
286	ESI+: 317
287	ESI+: 331
288	ESI+: 289
289	ESI+: 303
290	ESI+: 250
291	ESI+: 250
292	ESI+: 298
293	ESI+: 277
294	ESI+: 270
295	ESI+: 269
296	APCI/ESI+: 480, 482
297	EI: 300, 302

[0284]

[Table 66]

Rf	Data
298	ESI+: 319 321
299	ESI+: 257
300	APCI/ESI+: 353
301	ESI+: 416
302	ESI+: 286
303	ESI+: 417
304	ESI+: 403
305	APCI/ESI+: 320
306	ESI+: 200
307	APCI/ESI+: 174
308	EI: 215
309	EI: 182
310	ESI+: 358
311	ESI+: 346
312	ESI+: 343
313	APCI/ESI+: 361
314	APCI/ESI+: 347
315	APCI/ESI+: 347
316	ESI+: 375
317	
318	ESI+: 493
319	ESI+: 401
320	ESI+: 401
321	ESI+: 373
322	ESI+: 516
323	ESI+: 403
324	ESI+: 516
325	ESI+: 389
326	ESI+: 342
327	ESI+: 368
328	ESI+: 425
329	ESI+: 439
330	ESI+: 451

[0285]

[Table 67]

Rf	Data
331	ESI+: 465
332	ESI+: 451
333	APCI/ESI+: 312
334	ESI+: 398
335	ESI+: 398
336	APCI/ESI+: 323
337	APCI/ESI+: 321
338	APCI/ESI+: 405
339	APCI/ESI+: 337
340	APCI/ESI+: 335
341	ESI+: 363
342	APCI/ESI+: 409
343	APCI/ESI+: 414
344	APCI/ESI+: 398
345	APCI/ESI+: 405
346	ESI+: 393
347	FAB+: 286,288
348	ESI+: 312,314
349	ESI+: 345
350	ESI+: 215
351	FAB+: 266
352	APCI/ESI+: 374
353	APCI/ESI+: 402
354	APCI/ESI+: 374
355	APCI/ESI+: 402
356	APCI/ESI+: 373
357	APCI/ESI+: 418
358	APCI/ESI+: 374
359	APCI/ESI+: 373
360	ESI+: 358
361	ESI+: 402
362	APCI/ESI+: 376
363	APCI/ESI+: 376

[0286]

[Table 68]

Rf	Data
364	APCI/ESI+: 373
365	APCI/ESI+: 394
366	APCI/ESI+: 356
367	APCI/ESI+: 319
368	APCI/ESI+: 212
369	APCI/ESI+: 389
370	APCI/ESI+: 365
371	APCI/ESI+: 379
372	APCI/ESI+: 365
373	APCI/ESI+: 379
374	APCI/ESI+: 441
375	APCI/ESI+: 441
376	APCI/ESI+: 211
377	APCI/ESI+: 256
378	APCI/ESI+: 267
379	APCI/ESI+: 444
380	APCI/ESI+: 470
381	ESI+: 388
382	ESI+: 407
383	ESI+: 374
384	ESI+: 379
385	ESI+: 374
386	ESI+: 338
387	ESI+: 338
388	ESI+: 402
389	ESI+: 402
390	ESI+: 411
391	ESI+: 343
392	ESI+: 311
393	ESI+: 325
394	ESI+: 337
395	ESI+: 337
396	ESI+: 351

[0287]

[Table 69]

Rf	Data
397	ESI+: 346
398	ESI+: 346
399	ESI+: 325
400	ESI+: 351
401	ESI+: 376
402	ESI+: 337
403	ESI+: 311
404	ESI+: 337
405	ESI+: 297
406	ESI+: 388
407	ESI+: 296
408	ESI+: 323
409	ESI+: 343
410	ESI+: 309
411	ESI+: 323
412	ESI+: 288
413	ESI+: 288
414	ESI+: 302
415	ESI+: 316
416	ESI+: 302
417	ESI+: 442
418	ESI+: 350
419	ESI+: 302
420	ESI+: 289
421	ESI+: 302
422	ESI+: 302
423	ESI+: 302
424	ESI+: 302
425	ESI+: 294
426	ESI+: 302
427	ESI+: 345
428	ESI+: 302
429	ESI+: 289

[0288]

[Table 70]

Rf	Data
430	ESI+: 346
431	ESI+: 346
432	ESI+: 303
433	ESI+: 316
434	ESI+: 313
435	ESI+: 315
436	ESI+: 285
437	ESI+: 299
438	ESI+: 287
439	ESI+: 301
440	ESI+: 303
441	ESI+: 289
442	ESI+: 388
443	ESI+: 356
444	ESI+: 284
445	EI: 150
446	APCI/ESI+: 373
447	APCI/ESI+: 373
448	APCI/ESI+: 373
449	APCI/ESI+: 373
450	APCI/ESI+: 389
451	APCI/ESI+: 389
452	APCI/ESI+: 389
453	APCI/ESI+: 295
454	APCI/ESI+: 388
455	APCI/ESI+: 388
456	ESI+: 324
457	ESI+: 324
458	ESI+: 242
459	ESI+: 341
460	ESI+: 132
461	ESI+: 276
462	ESI+: 494

[0289]

[Table 71]

Rf	Data
463	ESI+: 424
464	ESI+: 432
465	ESI+: 432
466	ESI+: 235
467	ESI+: 256
468	ESI+: 219
469	ESI+: 249
470	ESI+: 223
471	ESI+: 249
472	ESI+: 279
473	ESI+: 185
474	ESI+: 199
475	ESI+: 318
476	ESI+: 189
477	ESI+: 175
478	ESI+: 250
479	ESI+: 193
480	ESI+: 240
481	ESI+: 285
482	ESI+: 271
483	ESI+: 269
484	ESI+: 361
485	ESI+: 438, 440
486	ESI+: 299
487	ESI+: 299
488	ESI+: 255
489	ESI+: 341
490	ESI+: 354
491	ESI+: 304
492	ESI+: 347
493	ESI+: 354
494	ESI+: 299
495	ESI+: 273

[0290]

[Table 72]

Rf	Data
496	ESI+: 206
497	APCI/ESI+: 249
498	APCI/ESI+: 265
499	ESI+: 171
500	ESI+: 347
501	ESI+: 321
502	ESI+: 323
503	ESI+: 333
504	ESI+: 309
505	ESI+: 240
506	ESI+: 254
507	APCI/ESI+: 307
508	APCI/ESI+: 324
509	ESI+: 340
510	APCI/ESI+: 390
511	ESI+: 318
512	ESI+: 290
513	ESI+: 286
514	ESI+: 288
515	ESI+: 482 [M]+
516	ESI+: 411 [M]+
517	ESI+: 494 [M]+
518	ESI+: 270
519	ESI+: 270
520	ESI+: 374
521	ESI+: 287
522	ESI+: 288
523	ESI+: 345
524	ESI+: 331
525	ESI+: 387
526	ESI+: 317
527	ESI+: 287
528	ESI+: 364

[0291]

[Table 73]

Rf	Data
529	ESI+: 432
530	APCI/ESI+: 325
531	APCI/ESI+: 241
532	APCI/ESI+: 255
533	APCI/ESI+: 241
534	APCI/ESI+: 255
535	APCI/ESI+: 317
536	APCI/ESI+: 317
537	ESI+: 339
538	ESI+: 353
539	ESI+: 339
540	ESI+: 255
541	ESI+: 418
542	ESI+: 353
543	ESI+: 448
544	ESI+: 339
545	ESI+: 339
546	ESI+: 460
547	ESI+: 422
548	ESI+: 192
549	APCI/ESI+: 339
550	APCI/ESI+: 407
551	APCI/ESI+: 418
552	APCI/ESI+: 451
553	APCI/ESI+: 404
554	ESI+: 414
555	ESI+: 297
556	ESI+: 437
557	ESI+: 409
558	ESI+: 395
559	ESI+: 409
560	ESI+: 423
561	APCI/ESI+: 451

[0292]

[Table 74]

Rf	Data
562	APCI/ESI+: 451
563	ESI+: 306
564	ESI+: 206
565	ESI+: 340
566	ESI+: 337
567	ESI+: 590
568	EI: 222
569	ESI+: 342
570	APCI/ESI+: 314
571	APCI/ESI+: 314
572	ESI+: 265
573	EI: 236 +
574	FAB+: 273
575	ESI+: 316
576	FAB+: 280
577	ESI+: 374
578	ESI+: 303
579	ESI+: 303
580	ESI+: 397
581	ESI+: 326
582	ESI+: 339
583	ESI+: 347
584	ESI+: 305
585	ESI+: 297
586	ESI+: 173
587	ESI+: 277
588	ESI+: 327
589	EI: 256, 258
590	ESI+: 261, 263
591	ESI+: 289, 291
592	EI: 142
593	APCI/ESI+: 362
594	APCI/ESI+: 243, 245

[0293]

[Table 75]

Rf	Data
595	APCI/ESI+: 521, 523, 524
596	APCI/ESI+: 243, 245
597	ESI+: 502
598	ESI+: 376
599	ESI+: 305
600	ESI+: 305
601	ESI+: 313
602	ESI+: 429
603	ESI+: 401
604	ESI+: 415
605	ESI+: 399
606	ESI+: 328
607	APCI/ESI+: 346
608	APCI/ESI+: 318
609	APCI/ESI+: 318
610	APCI/ESI+: 310
611	APCI/ESI+: 349
612	ESI+: 312
613	APCI/ESI+: 249
614	ESI+: 258, 260
615	ESI+: 489
616	ESI+: 515
617	ESI+: 419
618	ESI+: 447
619	ESI+: 503
620	APCI/ESI+: 365
621	ESI+: 440
622	FAB+: 232
623	ESI+: 293
624	ESI+: 194
625	ESI+: 410
626	ESI+: 424
627	ESI+: 279

[0294]

[Table 76]

Rf	Data
628	ESI+: 289
629	ESI+: 289
630	ESI+: 306
631	ESI+: 302
632	ESI+: 318
633	ESI+: 331
634	ESI+: 532
635	ESI+: 504
636	ESI+: 441
637	ESI+: 566
638	APCI/ESI+: 259
639	ESI+: 460
640	ESI+: 552
641	ESI+: 582
642	ESI+: 454
643	APCI/ESI+: 552
644	ESI+: 490
645	APCI/ESI+: 538
646	ESI+: 548
647	ESI+: 279
648	ESI+: 194
649	ESI+: 347
650	APCI/ESI+: 319
651	APCI/ESI+: 360
652	APCI/ESI+: 390
653	APCI/ESI+: 249
654	APCI/ESI+: 305
655	APCI/ESI+: 305
656	APCI/ESI+: 355
657	APCI/ESI+: 326
658	APCI/ESI+: 348
659	APCI/ESI+: 346
660	APCI/ESI+: 305

[0295]

[Table 77]

Rf	Data
661	APCI/ESI+: 279
662	APCI/ESI+: 235
663	ESI+: 238
664	ESI+: 300
665	ESI+: 340
666	ESI+: 354
669	ESI+: 349
670	ESI+: 236
671	APCI/ESI+: 303
672	ESI+: 433
673	ESI+: 305
674	ESI+: 291
675	ESI+: 305
676	ESI+: 319
677	ESI+: 144
678	ESI+: 454
679	ESI+: 328
680	ESI+: 330
681	ESI+: 365
682	ESI+: 351
683	ESI+: 296
684	ESI+: 322
685	APCI/ESI+: 376
686	APCI/ESI+: 335
687	ESI+: 346
688	APCI/ESI+: 376
689	APCI/ESI+: 375
690	APCI/ESI+: 360
691	APCI/ESI+: 408
692	APCI/ESI+: 388
693	APCI/ESI+: 402
694	APCI/ESI+: 386
695	APCI/ESI+: 379

[0296]

[Table 78]

Rf	Data
696	APCI/ESI+: 393
697	ESI+: 332
698	ESI+: 318
699	ESI+: 362
700	ESI+: 348
701	ESI+: 342
702	ESI+: 365
703	ESI+: 337
704	ESI+: 323
705	ESI+: 337
706	ESI+: 377
707	ESI+: 289
708	ESI+: 303
709	APCI/ESI+: 362
710	ESI+: 264
711	ESI+: 264
712	ESI+: 151
713	ESI+: 386
714	APCI/ESI+: 283
715	APCI/ESI+: 253
716	APCI/ESI+: 281
717	APCI/ESI+: 345
718	APCI/ESI+: 422
719	APCI/ESI+: 374
720	APCI/ESI+: 388
721	APCI/ESI+: 329
722	APCI/ESI+: 422
723	APCI/ESI+: 315
724	ESI+: 389
725	ESI+: 417
726	APCI/ESI+: 297
727	APCI/ESI+: 323
728	APCI/ESI+: 309

[0297]

[Table 79]

Rf	Data
729	APCI/ESI+: 364
730	APCI/ESI+: 351
731	APCI/ESI+: 345
732	APCI/ESI+: 345
733	APCI/ESI+: 316
734	APCI/ESI+: 316
735	APCI/ESI+: 316
736	APCI/ESI+: 418
737	APCI/ESI+: 404
738	APCI/ESI+: 404
739	APCI/ESI+: 423
740	APCI/ESI+: 423
741	APCI/ESI+: 423
742	APCI/ESI+: 337
743	APCI/ESI+: 351
744	APCI/ESI+: 404
745	APCI/ESI+: 402
746	APCI/ESI+: 432
747	APCI/ESI+: 336
748	APCI/ESI+: 364
749	ESI+: 200
750	ESI+: 488
751	ESI+: 488
752	ESI+: 403
753	ESI+: 401
754	ESI+: 164
755	ESI+: 335
756	ESI+: 321
757	ESI+: 454
758	ESI+: 452
759	ESI+: 452
760	
761	ESI+: 371

[0298]

[Table 80]

Rf	Data
762	APCI/ESI+: 375
763	APCI/ESI+: 389
764	APCI/ESI+: 375
765	APCI/ESI+: 389
766	ESI+: 447
767	APCI/ESI+: 389
768	APCI/ESI+: 403
769	ESI+: 309
770	ESI+: 365
771	ESI+: 391
772	ESI+: 493
773	APCI/ESI+: 396
774	APCI/ESI+: 410
775	APCI/ESI+: 289
776	APCI/ESI+: 303
777	APCI/ESI+: 315
778	APCI/ESI+: 317
779	APCI/ESI+: 317
780	APCI/ESI+: 357
781	APCI/ESI+: 318
782	APCI/ESI+: 346
783	APCI/ESI+: 358
784	APCI/ESI+: 360
785	ESI+: 373
786	ESI+: 381
787	ESI+: 408
788	ESI+: 368
789	ESI+: 382
790	ESI+: 373
791	APCI/ESI+: 403
792	APCI/ESI+: 401
793	ESI+: 271
794	ESI+: 285

[0299]

[Table 81]

Rf	Data
795	ESI+: 273
796	ESI+: 326
797	ESI+: 359
798	ESI+: 385
799	ESI+: 289
800	ESI+: 317
801	ESI+: 373
802	APCI/ESI+: 351
803	ESI+: 165
804	ESI+: 223
805	ESI+: 138
806	ESI+: 156
807	ESI+: 304
808	ESI+: 183
809	ESI+: 241
810	ESI+: 379
811	ESI+: 474
812	ESI+: 446
813	ESI+: 441
814	ESI+: 446
815	NMR-$CDCl_3$: 0.10(6H, s), 0.93(9H, s), 1.04-1.12(2H, m), 1.60-1.70(3H, m), 2.38-2.49(1H, m), 2.63-2.73(2H, m), 3.60-3.66(2H, m), 4.00-4.19(4H, m), 4.75(2H, s), 6.37(1H, t, J = 7Hz), 6.82-6.87(1H, t), 6.96(1H, t, J = 7Hz).
816	ESI+: 446
817	ESI+: 289
818	ESI+: 319
819	ESI+: 317
820	ESI+: 307
821	ESI+: 195
822	ESI+: 193
823	ESI+: 168
824	ESI+: 323
825	ESI+: 407
826	ESI+: 332

[0300]

[Table 82]

Rf	Data
827	ESI+: 327
828	ESI+: 332
829	ESI+: 332
830	ESI+: 291
831	ESI+: 281
832	ESI+: 349
833	ESI+: 337
834	ESI+: 321
835	ESI+: 333
836	ESI+: 337
837	ESI+: 351
838	ESI+: 343
839	ESI+: 347
840	ESI+: 362
841	ESI+: 223
842	ESI+: 305

[0301]

Example 1

CDI (106 mg) was added to a mixture of 1-(3-{2-[2-(morpholin-4-yl)pyrimidin-5-yl]ethyl}phenyl)methaneamine (97 mg) and DMF (2 ml) at 0°C, followed by stirring at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, and EtOAc and a saturated aqueous sodium hydrogen carbonate solution were then added thereto. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to obtain a reaction mixture. Guanidine hydrochloride (40 mg) and potassium tert-butoxide (45 mg) were suspended in DMF (2 ml), and a solution of the reaction mixture obtained immediately before in DMF (1 ml) was added thereto, followed by stirring at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure, water was then added thereto, and the insoluble matter was collected by filtration. The solid thus obtained was purified by silica gel column chromatography ($CHCl_3$/MeOH), and L-tartaric acid (34 mg) was added to a mixture of the purified product (87 mg) in a mixed solvent (3 ml) of MeCN and water at 9:1, followed by stirring at room temperature for 1 hour. The insoluble matter was collected by filtration to obtain

1-carbamimidoyl-3-(3-{2-[2-(morpholin-4-yl)pyrimidin-5-yl]ethyl}benzyl)urea L-tartrate (173 mg).

[0302]

Example 2

CDI (248 mg) was added to a mixture of {3-[4-(2,6-dimethylpyridin-4-yl)piperazin-1-yl]-2-fluorophenyl}methanol (241 mg) and DMF (7 ml), followed by stirring at room temperature for 2 hours. Guanidine carbonate (344 mg) was added to this mixture at room temperature, followed by stirring at room temperature overnight. The organic layer was evaporated under reduced pressure, water was added to the residue, and the generated solid was collected by filtration.

The obtained solid was purified by basic silica gel column chromatography ($CHCl_3$/MeOH). L-tartaric acid (99.3 mg) was added to a mixture of the purified product thus obtained (265 mg) and EtOH (10 ml), followed by stirring at room temperature for 3 hours. The solid was collected by filtration, washed with EtOH, and then dried under reduced pressure at 50°C to obtain 3-[4-(2,6-dimethylpyridin-4-yl)piperazin-1-yl]-2-fluorobenzyl carbamimidoylcarbamate (181 mg).

[0303]

Example 3

1-[2-Fluoro-3-(hydroxymethyl)phenyl]-4-(pyridin-3-yl)piperidin-4-ol (187 mg), DMF (5.5 ml), and CDI (201 mg) were mixed, followed by stirring at room temperature for 2 hours. Guanidine carbonate (279 mg) was added to the reaction mixture, followed by stirring at room temperature overnight. Water was added to the reaction mixture, followed by ice-cooling and stirring for 30 minutes, and the generated solid was collected by filtration, washed with water, and then dried at 50°C under reduced pressure. The obtained solid was purified by silica gel column chromatography ($CHCl_3$/MeOH) to obtain 2-fluoro-3-[4-hydroxy-4-(pyridin-3-yl)piperidin-1-yl]benzyl carbamimidoylcarbamate (160 mg).

[0304]

Example 23

CDI (110 mg) was added to a mixture of 1-{4-[({5-[2-fluoro-3-(hydroxymethyl)phenyl]pyrimidin-2-yl}oxy)methyl]piperidin-1-yl}propan-1-one (124 mg) and DMF (3 ml), followed by stirring at room temperature for 3 hours. Guanidine carbonate (220 mg) was added to the reaction mixture, followed by stirring at room temperature overnight. The organic layer was evaporated under reduced pressure, water was added to the residue, and the generated solid was collected by filtration.

The obtained solid was purified by silica gel column chromatography ($CHCl_3$/MeOH). A 4 M hydrogen chloride/dioxane solution (0.1 ml) was added to a mixture of the purified product thus obtained (135.1 mg) and EtOH (2 ml), followed by stirring at room temperature for 1 hour and concentrating under reduced pressure. The obtained solid was washed with ether and then collected by filtration to obtain 2-fluoro-3-{2-[(1-propionylpiperidin-4-yl)methoxy]pyrimidin-5-yl}benzyl carbamimidoylcarbamate dihydrochloride (140 mg) as a colorless solid.

[0305]

Example 112

CDI (225 mg) was added to a mixture of 1-(4-{5-[3-(hydroxymethyl)phenyl]pyrimidin-2-yl}piperazin-1-yl)-2-methoxyethanone (216 mg) and DMF (6 ml), followed by stirring at room temperature for 2 hours. Then, guanidine carbonate (220 mg) was added to the mixture, followed by stirring at room temperature for 2 hours. Water was added to the reaction mixture, followed by extraction with $CHCl_3$. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. A mixture obtained by dissolving L-tartaric acid (59 mg) in a mixed solvent (1 ml) of MeCN and water at 9:1 was added to a mixture of the obtained residue (166.9 mg) in a mixed solvent (4 ml) of MeCN and water at 9:1, followed by stirring at room temperature. The precipitated solid was collected by filtration to obtain 3-{2-[4-(methoxy acetyl)piperazin-1-yl]pyrimidin-5-yl}benzyl carbamimidoylcarbamate L-tartrate (177 mg) as a colorless solid.

[0306]

Example 316

A 4 M hydrogen chloride/EtOH solution (1.5 ml) was added to a mixture of 2-fluoro-3-{4-[2-(3-methoxyazetidin-1-yl)pyrimidin-5-yl]piperazin-1-yl}benzyl carbamimidoylcarbamate (285 mg) and EtOH (5 ml), followed by stirring at room temperature. The precipitated yellow solid was collected by filtration and washed with EtOH. The obtained solid was dried at 40°C under reduced pressure to obtain 2-fluoro-3-{4-[2-(3-methoxyazetidin-1-yl)pyrimidin-5-yl]piperazin-1-yl}benzyl carbamimidoylcarbamate trihydrochloride (330 mg).

[0307]

Example 317

Ethyl({1-[5-(3-{[(carbamimidoylcarbamoyl)oxy]methyl}phenyl)pyrimidin-2-yl]piperidin-4-yl}oxy)acetate (45 mg) was mixed with ethanol, and L-tartaric acid (15 mg) was added thereto, followed by stirring at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, and then diethyl ether was added thereto. The precipitated solid was collected by filtration to obtain ethyl

({1-[5-(3-{[(carbamimidoylcarbamoyl)oxy]methyl}phenyl)pyrimidin-2-yl]piperidin-4-yl}oxy)acetate L-tartrate (28 mg).

[0308]

Example 318

A 1 M aqueous NaOH solution was added to a mixture of methyl 4-{4-[5-(3-{[(carbamimidoylcarbamoyl)amino]methyl}phenyl)pyrimidin-2-yl]piperazin-1-yl}-3-chlorobenzoate (208 mg), THF (2 ml), and EtOH (2 ml), followed by stirring at room temperature for 2 hours. The reaction mixture was neutralized with 1 M hydrochloric acid, and the precipitated solid was collected by filtration. A 4 M hydrogen chloride/dioxane solution (1 ml) was added to a mixture of the obtained solid and dioxane (3 ml), followed by stirring at room temperature overnight. The insoluble matter was collected by filtration to obtain 4-{4-[5-(3-{[(carbamimidoylcarbamoyl)amino]methyl}phenyl)pyrimidin-2-yl]piperazin-1-yl}-3-chlorobenzoic acid dihydrochloride (112 mg).

[0309]

Example 319

Sodium hydride (50% suspended in mineral oil, 45 mg) was added to a mixture of {3-[2-(morpholin-4-yl)pyrimidin-5-yl]phenyl}methanol (230 mg) and DMF (6 ml) under ice-cooling. After stirring at the same temperature for 30 minutes, CDI (275 mg) was added thereto. The reaction mixture was stirred at room temperature for 2 hours, and guanidine carbonate (460 mg) and DBU(388 mg) were then added thereto, followed by stirring at room temperature overnight. The solvent was evaporated under reduced pressure, water was added to the obtained residue, and the generated insoluble matter was collected by filtration. The obtained solid was purified by basic silica gel column chromatography ($CHCl_3$/MeOH). L-tartaric acid (23 mg) was added to a mixture of the purified product thus obtained (54 mg), MeCN, and water, followed by stirring at room temperature for 30 minutes. The generated insoluble matter was collected by filtration, and washed with MeCN to obtain 3-[2-(morpholin-4-yl)pyrimidin-5-yl]benzyl carbamimidoylcarbamate L-tartrate (66 mg).

[0310]

Example 328

A 1 M aqueous NaOH solution (1.14 ml) was added to a mixture of 5-[4-(3-{[(carbamimidoylcarbamoyl)oxy]methyl}-2-fluorophenyl)piperazin-1-yl]pyridine-2-carboxylate methyl ester (326 mg), THF (9 ml), and MeOH (3 ml), followed by stirring at room temperature overnight. 1 M hydrochloric acid (1.14 ml) was added to the reaction mixture, followed by stirring at room temperature for 1 hour. The generated solid was collected by filtration, washed with water, and then dried at 50°C under reduced pressure to obtain

5-[4-(3-{[(carbamimidoylcarbamoyl)oxy]methyl}-2-fluorophenyl)piperazin-1-yl]pyridine-2-carboxylic acid (293 mg).

[0311]

Example 344

A 1 M aqueous NaOH solution was added to a mixture of ethyl 4-{1-[5-(3-{[(carbamimidoylcarbamoyl)oxy]methyl}-2-fluorophenyl)pyrimidin-2-yl]piperidin-4-yl}butanoate (256 mg), THF (3.3 ml), and EtOH (3.3 ml), followed by stirring at room temperature overnight. The insoluble matter was removed by filtration, the solvent was evaporated under reduced pressure, and to the residue were then added water and 1 M hydrochloric acid (1.052 ml) at 0°C, followed by stirring at 0°C for 30 minutes. The solid was collected by filtration, washed with water, and then dried at 50°C under reduced pressure. To the reaction mixture was added MeCN (8 ml), and a mixture of L-tartaric acid (76.6 mg), MeCN (4 ml), and water (0.2 ml) was added thereto, followed by stirring at room temperature overnight. The solid was collected by filtration, washed with MeCN, and then dried at 50°C under reduced pressure to obtain 4-{1-[5-(3-{[(carbamimidoylcarbamoyl)oxy]methyl}-2-fluorophenyl)pyrimidin-2-yl]piperidin-4-yl}butanoic acid L-tartrate (276 mg).

[0312]

Example 345

To a mixture of 1-[5-(3-{[(carbamimidoylcarbamoyl)oxy]methyl}-2-fluorophenyl)pyrimidin-2-yl]piperidin-4-yl benzoic acid (252 mg) and MeOH was added a 1 M aqueous NaOH solution (1 ml), followed by stirring at room temperature for 3 hours. To the reaction mixture was added a 1 M aqueous HCl solution (1 ml), and then the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH) as it was.

To the purified product thus obtained was added EtOH, and 4 M hydrogen chloride/dioxane (1 ml) was added thereto, followed by stirring at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, and then diethyl ether were added thereto. The precipitated solid was collected by filtration to obtain 2-fluoro-3-[2-(4-hydroxypiperidin-1-yl)pyrimidin-5-yl]benzyl carbamimidoylcarbamate dihydrochloride (110 mg).

[0313]

Example 347

To a mixture of 1-(3-{2-[3-(methoxymethyl)pyrrolidin-1-yl]pyrimidin-5-yl}phenyl)methanamine (158 mg) and DMF (3 ml) was added CDI (110 mg), followed by stirring at room temperature for 1 hour.

The reaction mixture was concentrated under reduced pressure, EtOAc and a saturated aqueous sodium hydrogen carbonate solution were then added thereto, and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to obtain a reaction mixture. Guanidine hydrochloride and sodium hydride were suspended in DMF (2 ml), and a solution of the reaction mixture obtained immediately before in DMF (1 ml) was added thereto, followed by stirring at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, water was added thereto, and the insoluble matter was collected by filtration. The obtained solid was purified by silica gel column chromatography ($CHCl_3$/MeOH). To the purified product thus obtained (73 mg) was added a mixed solvent (3.3 ml) of MeCN and water at 9:1, and further, L-tartaric acid (29 mg) was added thereto, followed by stirring at room temperature for 1 hour. The insoluble matter was collected by filtration to obtain 1-carbamimidoyl-3-(3-{2-[3-(methoxymethyl)pyrrolidin-1-yl]pyrimidin-5-yl}benzyl)urea L-tartrate (65 mg).

[0314]

Example 397

Methyl 4-(4-{5-[3-(aminomethyl)phenyl]pyrimidin-2-yl}piperazin-1-yl)-3-chlorobenzoate (207 mg) was mixed with DMF (5 ml), and CDI (154 mg) was added thereto at 0°C, followed by stirring at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure, and EtOAc and a saturated aqueous sodium hydrogen carbonate solution were then added thereto. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was mixed with DMF (5 ml), and guanidine hydrochloride (50 mg) and DBU(204 mg) were added thereto, followed by stirring at 70°C for 5 hours. The reaction mixture was concentrated under reduced pressure, water was then added thereto, and the insoluble matter was collected by filtration. The obtained solid was purified by basic silica gel column chromatography ($CHCl_3$/MeOH) to obtain methyl 4-{4-[5-(3-{[(carbamimidoylcarbamoyl)amino]methyl}phenyl)pyrimidin-2-yl]piperazin-1-yl}-3-chlorobenzoate (208 mg).

[0315]

Example 398

Ethyl 1-{5-[3-(aminomethyl)phenyl]pyrimidin-2-yl}piperidine-4-carboxylate (303 mg) was mixed with DMF (5 ml), and CDI (188 mg) was added thereto, followed by stirring at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, and EtOAc and a saturated aqueous sodium hydrogen carbonate solution were then added thereto. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Guanidine hydrochloride (170 mg) and sodium hydride (55%

suspended in oil) (77 mg) were suspended in DMF (2 ml), and a solution of the reaction mixture obtained immediately before in DMF (1 ml) was added thereto, followed by stirring at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, water was then added thereto, and the insoluble matter was collected by filtration. The obtained solid was purified by silica gel column chromatography ($CHCl_3$/MeOH) to obtain ethyl 1-[5-(3-{[(carbamimidoylcarbamoyl)amino]methyl}phenyl)pyrimidin-2-yl]piperidine-4-carboxylate (74 mg).

[0316]

Example 546

tert-Butyl [3-(2-chloropyrimidin-5-yl)benzyl]carbamate (16 mg) and 1-methyl-2-pyrrolidinone (0.2 ml) were mixed, and ethyl 4-aminopiperidine-1-carboxylate (8 mg) and sodium carbonate (20 mg) were added thereto, followed by stirring at 90°C overnight. The reaction mixture was cooled to room temperature and then filtered, and the filtrate was purified by preparative liquid chromatography (MeOH/0.1% aqueous formic acid solution). To the purified product thus obtained were added MeOH (0.5 ml) and a 4 M hydrogen chloride/EtOAc solution (0.5 ml), followed by shaking for 2 hours. The reaction mixture was concentrated, and to the obtained residue were added DMF (0.2 ml) and CDI (4 mg), followed by stirring at room temperature for 2 hours. To the reaction mixture was added guanidine carbonate (9 mg), followed by stirring at 90°C overnight. The reaction mixture was cooled to room temperature, and the insoluble matter was then filtered. The filtrate was purified by preparative liquid chromatography (MeOH/0.1% aqueous formic acid solution) to obtain ethyl 4-{[5-(3-{[(carbamimidoylcarbamoyl)amino]methyl}phenyl)pyrimidin-2-yl]amino}piperidine-1-carboxylate (1.9 mg).

[0317]

Example 567

4-{1-[3-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-2-fluorophenyl]azetidin-3-yl}piperidine (70 mg) and TEA (73 mg) were mixed with dichloromethane (2 ml), and acetyl chloride (22 mg) was added thereto, followed by stirring at room temperature for 1 hour. To the reaction mixture were added $CHCl_3$ and a 1 M aqueous NaOH solution, the organic layer was dried over Na_2SO_4, and the organic layer was concentrated under reduced pressure. The obtained residue was mixed with THF (2 ml), and a 1 M TBAF/THF solution (0.3 ml) was added thereto, followed by stirring at room temperature for 1 hour. To the reaction mixture were added $CHCl_3$ and a saturated aqueous ammonium chloride solution, and the organic layer was dried over Na_2SO_4. The reaction mixture was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography ($CHCl_3$/MeOH). The purified product thus obtained was mixed with

DMF, and CDI (65 mg) was added thereto, followed by stirring at room temperature for 3 hours. To the reaction mixture was added guanidine carbonate (140 mg), followed by stirring at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, water was added thereto, and the insoluble matter was collected by filtration. The obtained solid was purified by basic silica gel column chromatography ($CHCl_3$/MeOH). The purified product thus obtained was mixed with EtOH (1 ml), and L-tartaric acid (16 mg) was added thereto, followed by stirring at room temperature for 1 hour. The precipitated solid was collected by filtration to obtain 3-[3-(1-acetylpiperidin-4-yl)azetidin-1-yl]-2-fluorobenzyl carbamimidoylcarbamate L-tartrate (49 mg).

[0318]

Example 568

3-[4-(6-tert-Butoxypyridin-3-yl)piperazin-1-yl]-2-fluorobenzyl carbamimidoylcarbamate (132 mg) was dissolved in dichloromethane (3.4 ml), and TFA (508 mg) was added thereto, followed by stirring at room temperature for 4 hours. The reaction mixture was concentrated under reduced pressure, the residue was mixed with $CHCl_3$/MeOH, and basic silica gel was added thereto, followed by concentrating under reduced pressure. The residue was purified by basic silica gel column chromatography ($CHCl_3$/MeOH). The purified product thus obtained was mixed with EtOH (5 ml), and L-tartaric acid (41.0 mg) were added thereto, followed by stirring at 80°C for 1 hour, and then stirring at room temperature for 1 hour. The solid was collected by filtration, washed with EtOH, and then dried at 50°C under reduced pressure to obtain 2-fluoro-3-[4-(6-oxo-1,6-dihydropyridin-3-yl)piperazin-1-yl]benzylcarbamimidoylcarbamate L-tartrate (125 mg).

[0319]

Example 588

Methyl 5-{4-[({1-[2-fluoro-3-(hydroxymethyl)phenyl]azetidin-3-yl}oxy)methyl]piperidin-1-yl}pyridine-2-carboxylate (69 mg), DMF (2 ml), and CDI (60 mg) were mixed, followed by stirring at room temperature for 3 hours. To the reaction mixture was added guanidine carbonate (120 mg), followed by stirring at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, and water and $CHCl_3$ were added thereto. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography ($CHCl_3$/MeOH).

The purified product thus obtained was mixed with methanol (1 ml) and THF (2 ml), and a 1 M aqueous NaOH solution (0.2 ml) was added thereto, followed by stirring at room temperature overnight. To the reaction mixture was added 1 M hydrochloric acid (0.2

ml), followed by concentrating under reduced pressure. To the residue was added methanol, the insoluble matter was separated by filtration, and the filtrate was concentrated under reduced pressure. To the residue was added methanol, the insoluble matter was separated by filtration, and the filtrate was concentrated under reduced pressure. To the residue were added a small amount of methanol and then diethyl ether. The precipitated solid was collected by filtration to obtain 5-[4-({[1-(3-{[(carbamimidoylcarbamoyl)oxy]methyl}-2-fluorophenyl)azetidin-3-yl]oxy}methyl)piperidin-1-yl]pyridine-2-carboxylic acid (23 mg).

[0320]

Example 615

To a mixture of (3-{3-[(6-tert-butoxypyridin-3-yl)oxy]azetidin-1-yl}-2-fluorophenyl)methanol (120 mg) and DMF (2 ml) was added CDI (130 mg), followed by stirring at room temperature for 3 hours. To the reaction mixture was added guanidine carbonate (260 mg), followed by stirring at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, water and $CHCl_3$ were added thereto, and the organic layer was dried over anhydrous sodium sulfate. After concentrating under reduced pressure, the obtained residue was purified by silica gel column chromatography ($CHCl_3$/MeOH). The purified product thus obtained was mixed with dichloromethane (2 ml), and TFA (0.5 ml) was added thereto, followed by stirring at room temperature overnight. The reaction solution was concentrated under reduced pressure, and a saturated aqueous sodium hydrogen carbonate solution and $CHCl_3$ were then added thereto. The organic layer was dried over Na_2SO_4 and then concentrated under reduced pressure. The obtained residue was mixed with a mixed solution of MeCN and H_2O at 95:5, and L-tartaric acid (41 mg) was added thereto, followed by stirring at room temperature for 1 hour. The solid was collected by filtration to obtain 2-fluoro-3-{3-[(6-oxo-1,6-dihydropyridin-3-yl)oxy]azetidin-1-yl}benzyl carbamimidoylcarbamate L-tartrate (118 mg).

[0321]

Example 619

2-Fluoro-3-[2-(morpholin-4-yl)pyrimidin-5-yl]benzyl carbamimidoylcarbamate hydrochloride (54 mg), $CHCl_3$ (8 ml), and MeOH (3 ml) were mixed, and a saturated aqueous sodium hydrogen carbonate solution was added thereto, followed by stirring for 10 minutes. The organic layer was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The solid residue was washed with EtOAc and filtered to obtain a colorless solid.

The obtained solid was mixed with a mixed solvent of EtOH (0.54 ml) and water (0.54 ml), and a 1 M aqueous phosphoric acid solution, followed by stirring for 1 hour. The solid was collected by filtration, and washed with a mixture (1:1) of EtOH and water.

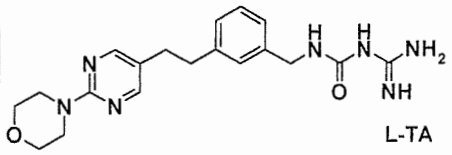
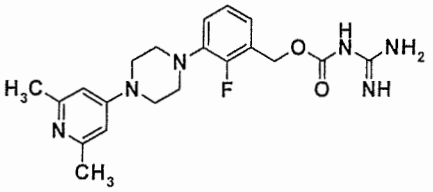
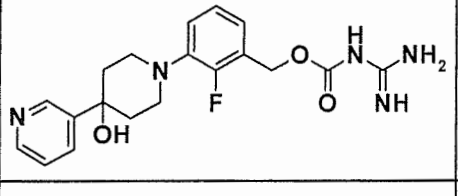
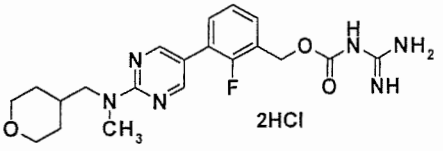
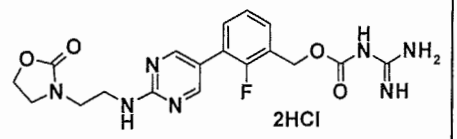
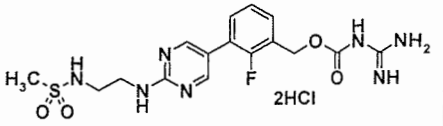
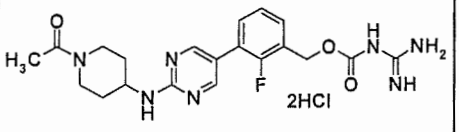
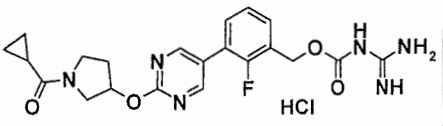
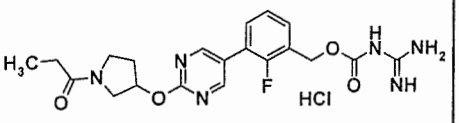
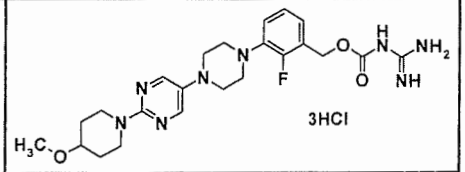
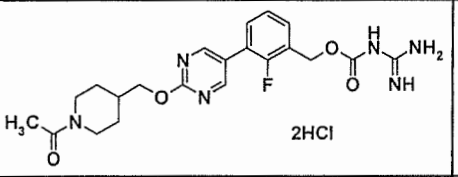
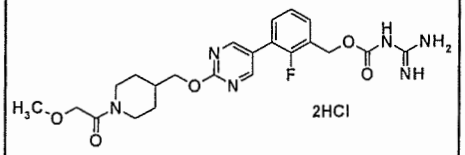
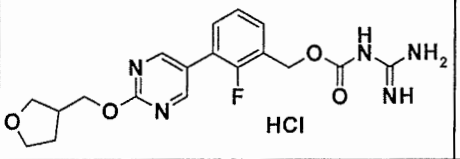
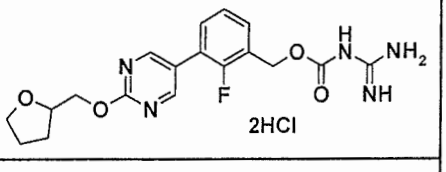
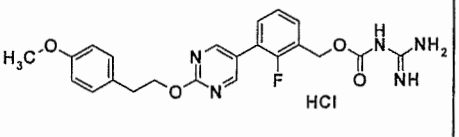
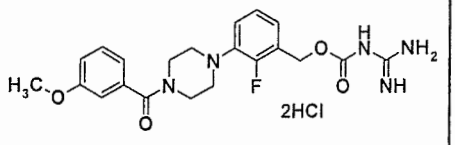
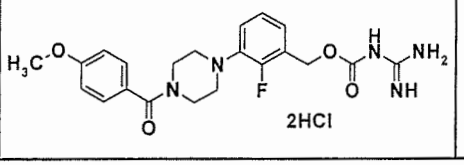
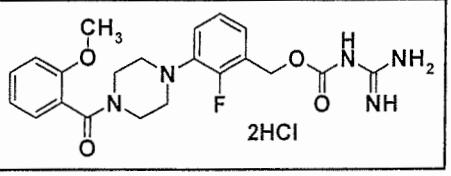
The obtained solid was dried at 50°C under reduced pressure to obtain 2-fluoro-3-[2-(morpholin-4-yl)pyrimidin-5-yl]benzyl carbamimidoylcarbamate phosphate (45 mg) as a colorless solid.

[0322]

The compounds of Examples shown in the tables below were prepared using the respective corresponding starting materials in the same manner as the methods of Examples above. The structures, the preparation methods, and the physicochemical data for the compounds of Examples are shown in the tables below.

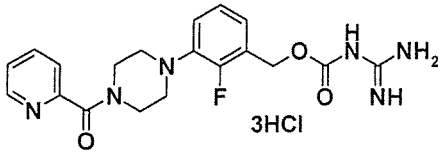
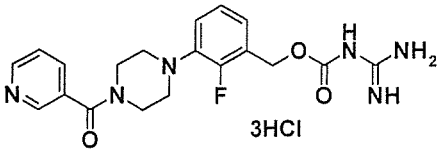
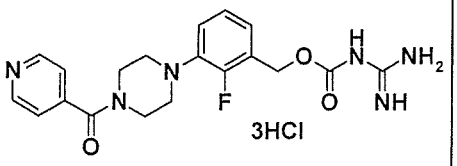
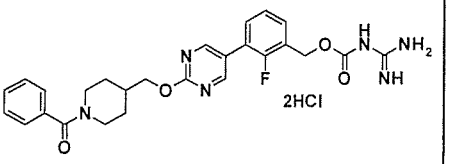
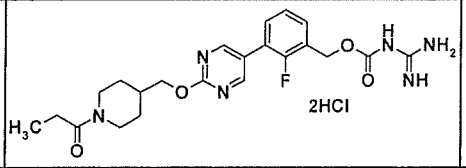
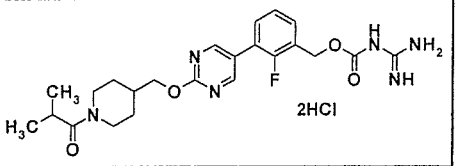
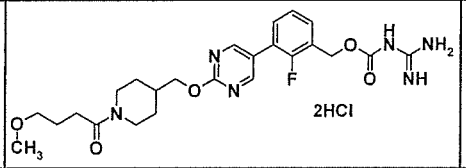
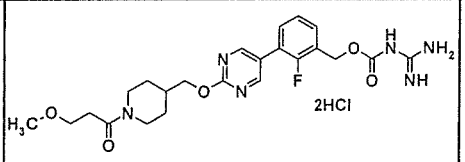
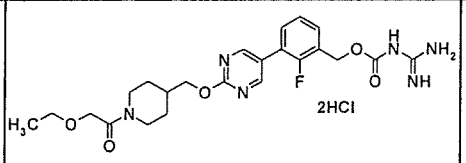
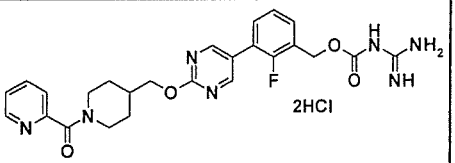
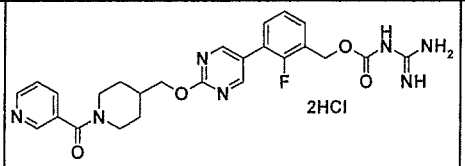
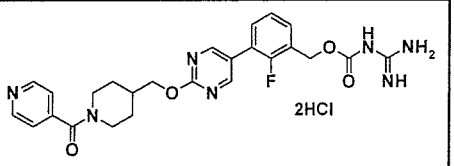
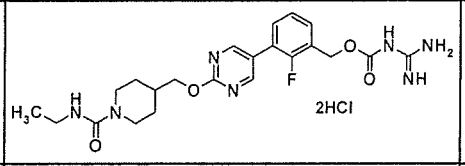
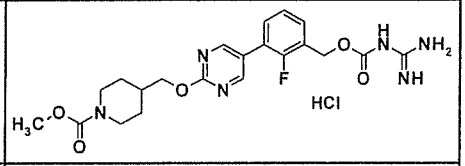
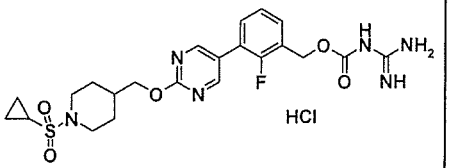
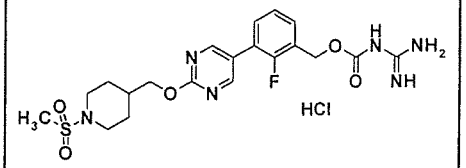
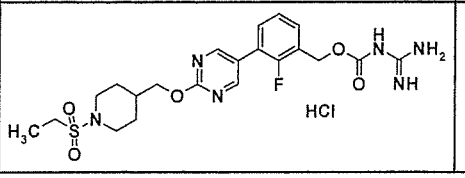
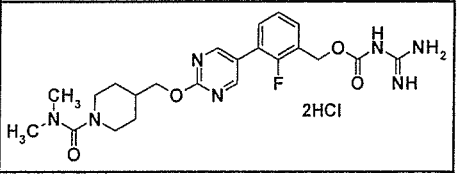
[0323]

[Table 83]

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9	23	 HCl	10	23	 3HCl
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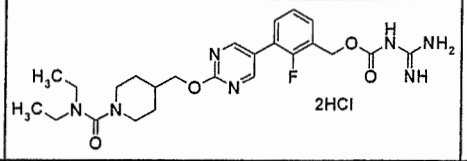
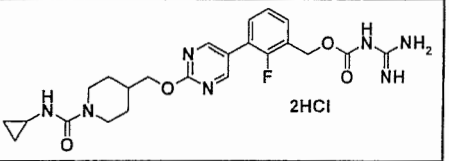
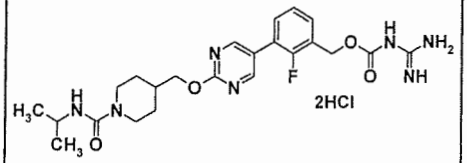
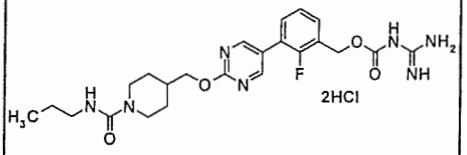
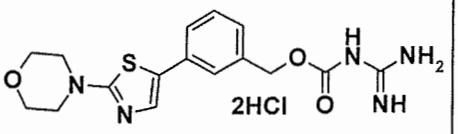
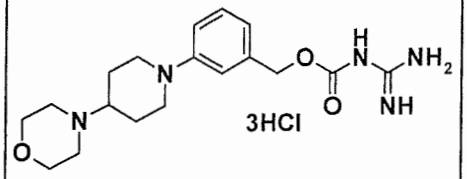
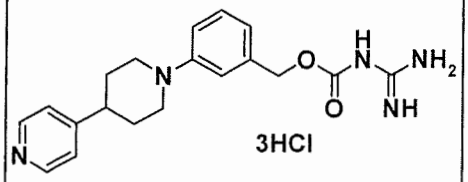
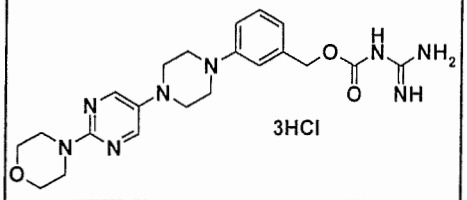
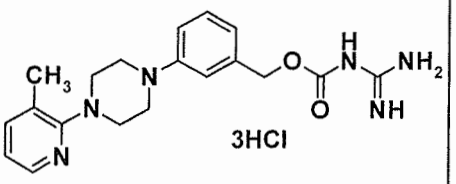
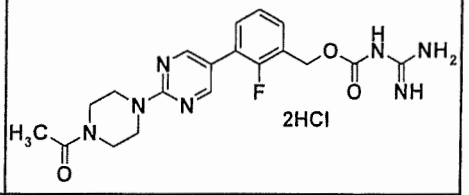
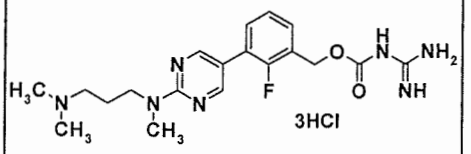
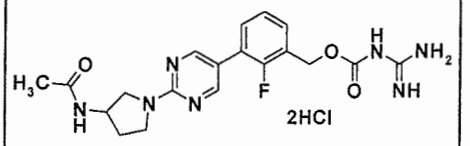
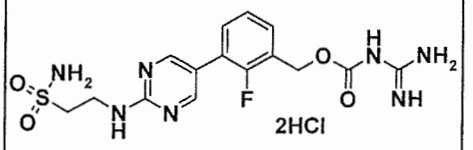
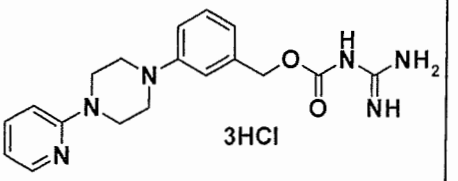
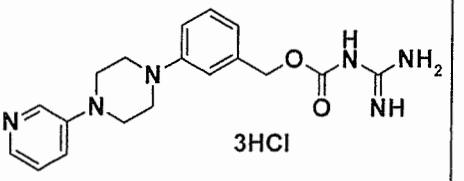
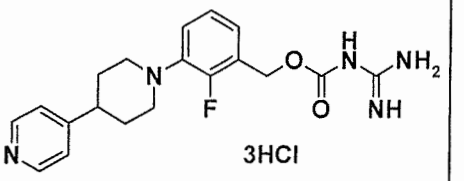
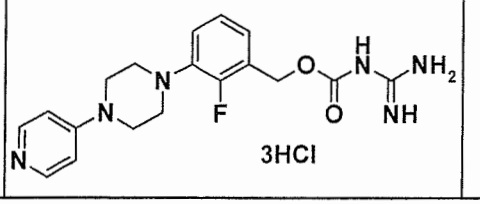
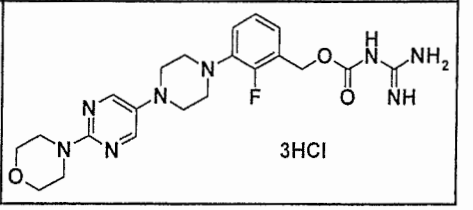
[0324]

[Table 84]

Ex	Syn	Structure	Ex	Syn	Structure
19	23	 3HCl	20	23	 3HCl
21	23	 3HCl	22	23	 2HCl
23	23	 2HCl	24	23	 2HCl
25	23	 2HCl	26	23	 2HCl
27	23	 2HCl	28	23	 2HCl
29	23	 2HCl	30	23	 2HCl
31	23	 2HCl	32	23	 HCl
33	23	 HCl	34	23	 HCl
35	23	 HCl	36	23	 2HCl

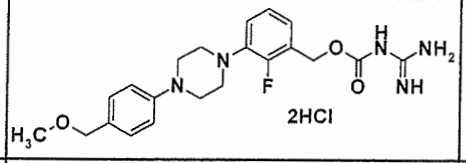
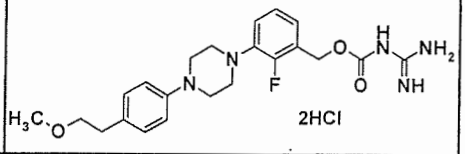
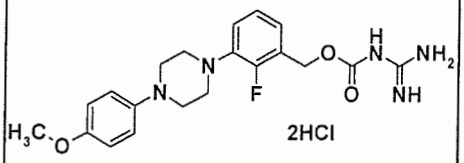
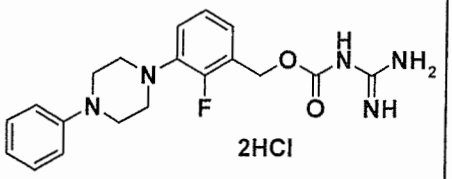
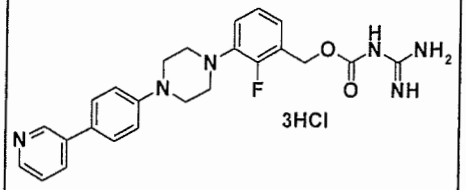
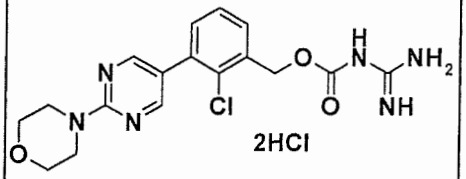
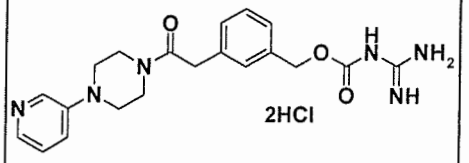
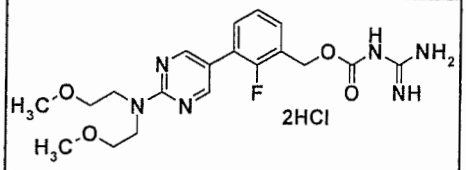
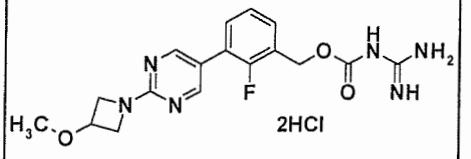
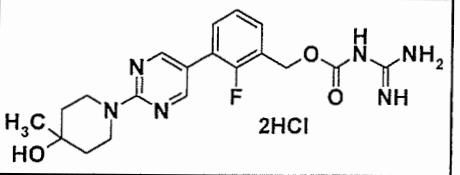
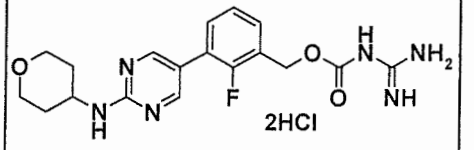
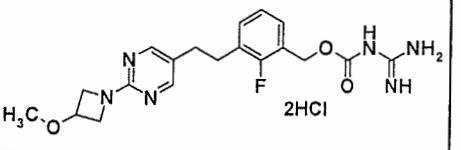
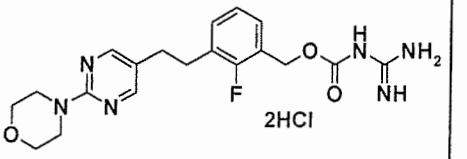
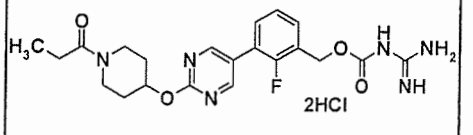
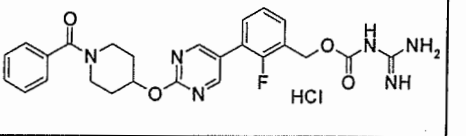
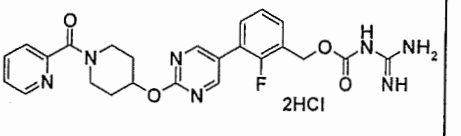
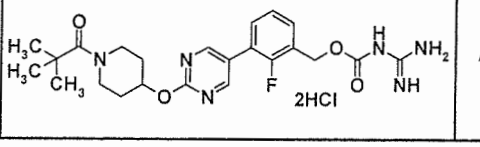
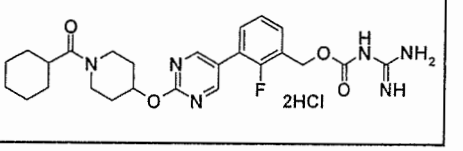
[0325]

[Table 85]

Ex	Syn	Structure	Ex	Syn	Structure
37	23		38	23	
39	23		40	23	
41	23		42	23	
43	23		44	23	
45	23		46	23	
47	23		48	23	
49	23		50	23	
51	23		52	23	
53	23		54	23	

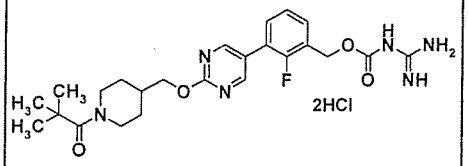
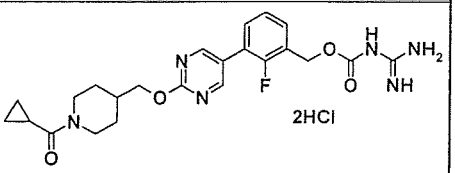
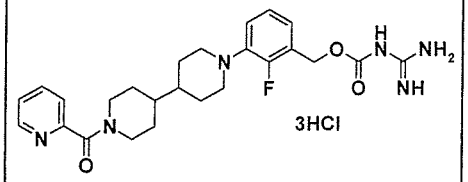
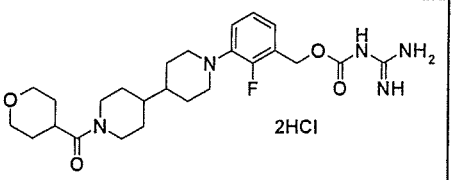
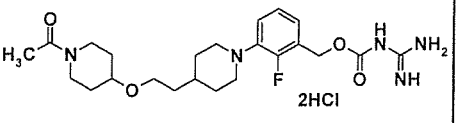
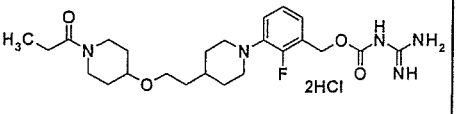
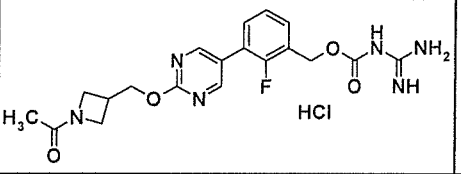
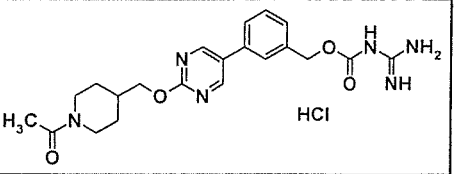
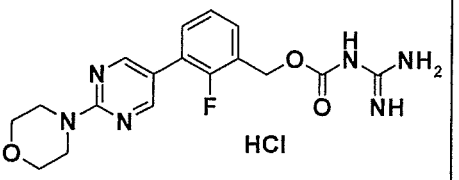
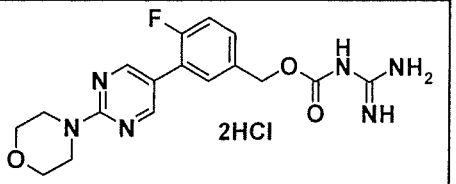
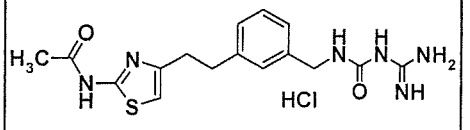
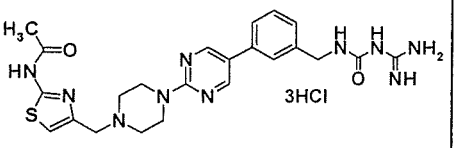
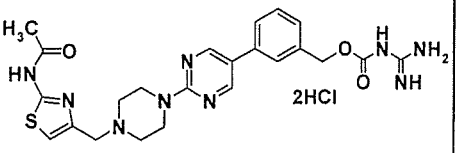
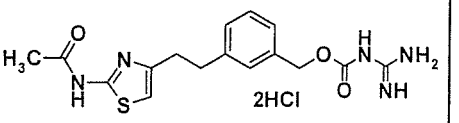
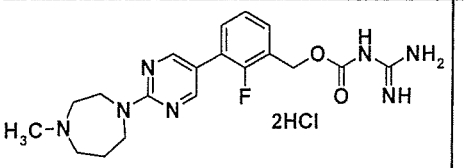
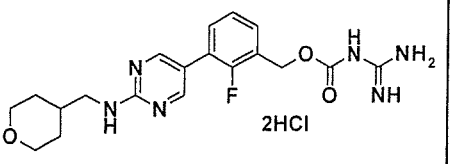
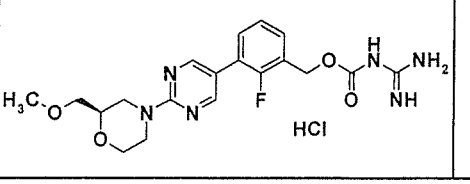
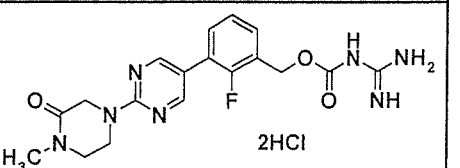
[0326]

[Table 86]

Ex	Syn	Structure	Ex	Syn	Structure
55	23		56	23	
57	23		58	23	
59	23		60	23	
61	23		62	23	
63	23		64	23	
65	23		66	23	
67	23		68	23	
69	23		70	23	
71	23		72	23	

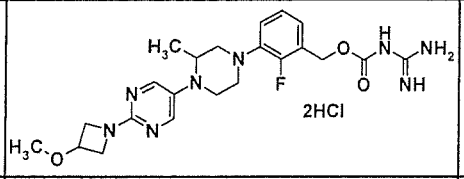
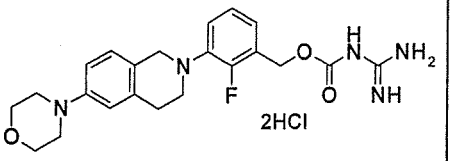
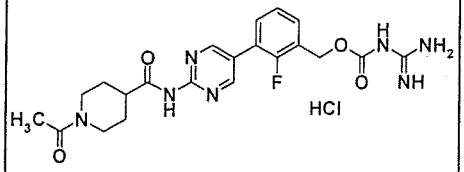
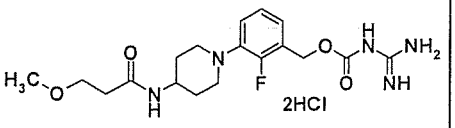
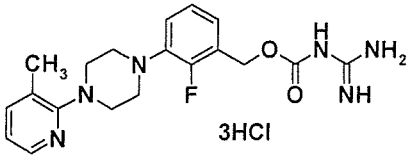
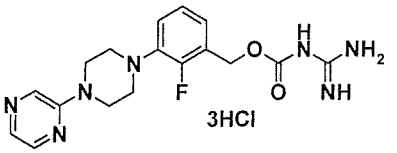
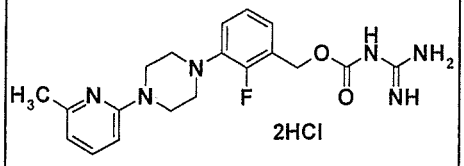
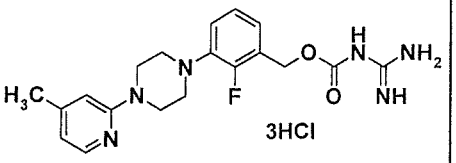
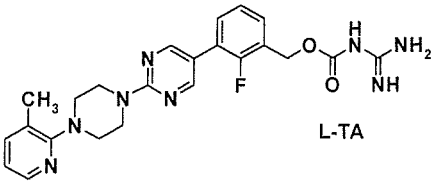
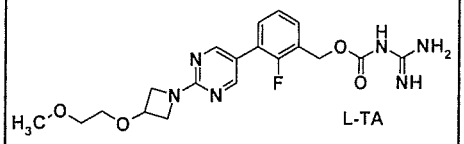
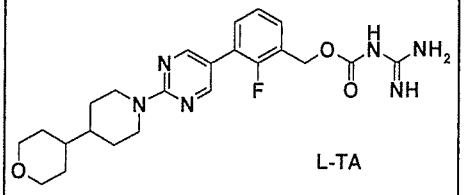
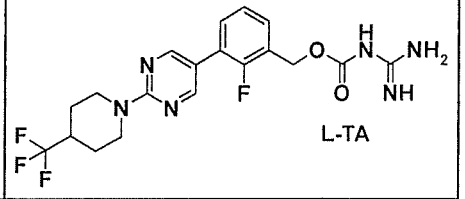
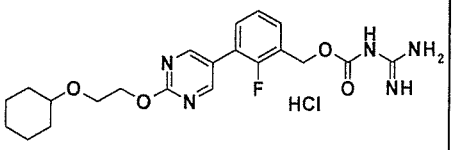
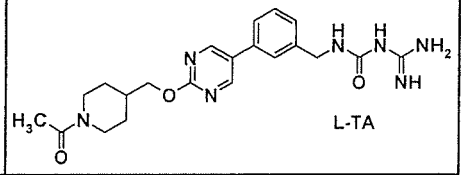
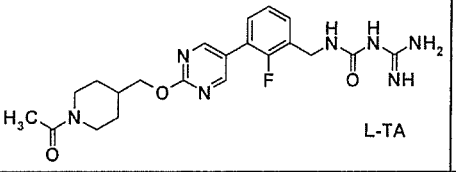
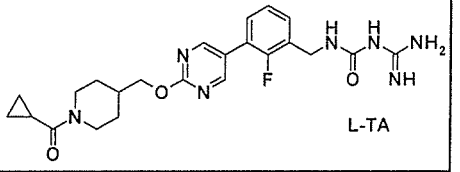
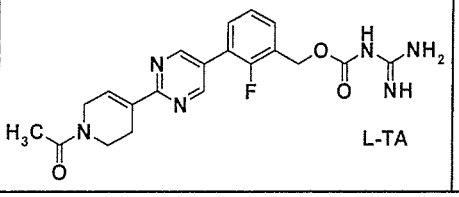
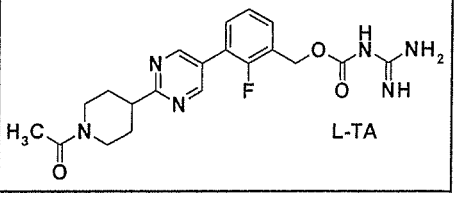
[0327]

[Table 87]

Ex	Syn	Structure	Ex	Syn	Structure
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75	23		76	23	
77	23		78	23	
79	23		80	23	
81	23		82	23	
83	23		84	23	
85	23		86	23	
87	23		88	23	
89	23		90	23	

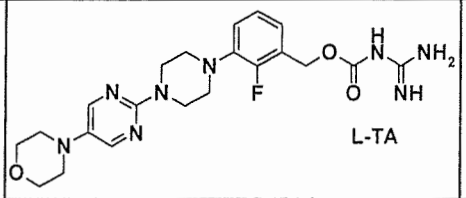
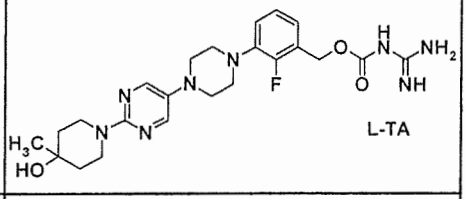
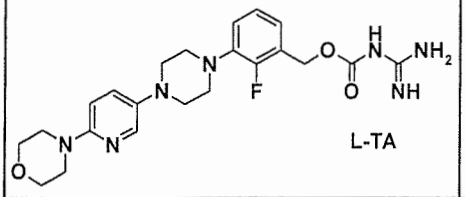
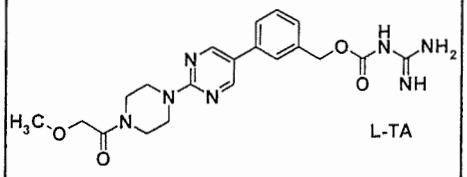
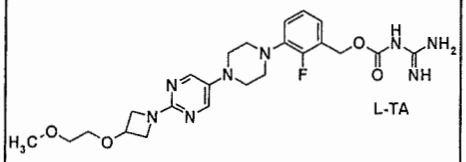
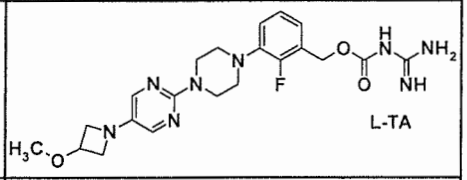
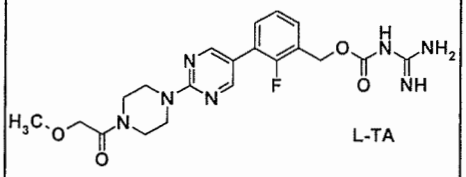
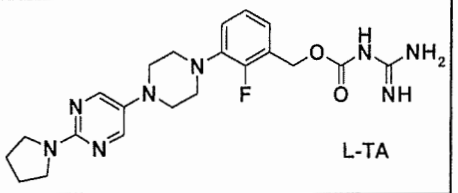
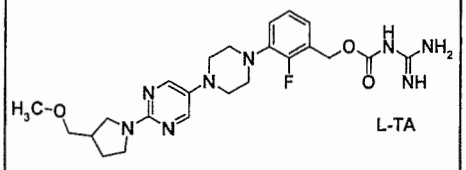
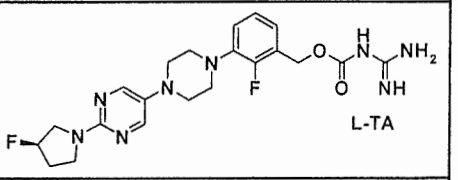
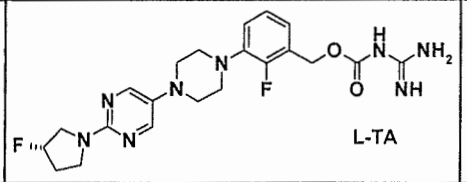
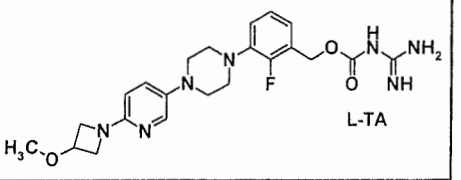
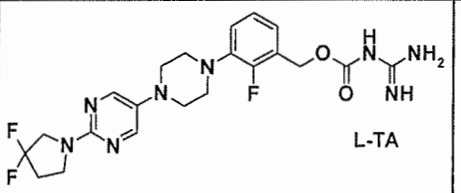
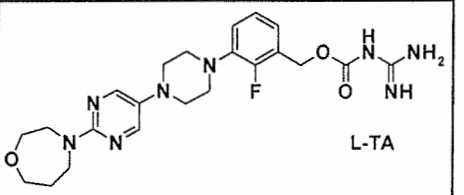
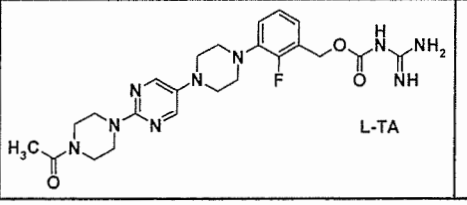
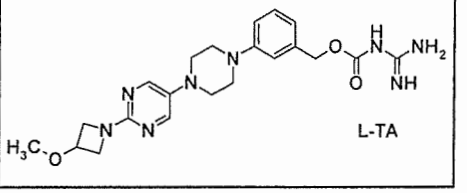
[0328]

[Table 88]

Ex	Syn	Structure	Ex	Syn	Structure
91	23	 2HCl	92	23	 2HCl
93	23	 HCl	94	23	 2HCl
95	23	 3HCl	96	23	 3HCl
97	23	 2HCl	98	23	 3HCl
99	112	 L-TA	100	112	 L-TA
101	112	 L-TA	102	112	 L-TA
103	23	 HCl	104	112	 L-TA
105	112	 L-TA	106	112	 L-TA
107	112	 L-TA	108	112	 L-TA

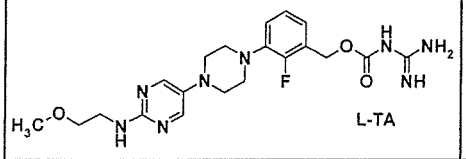
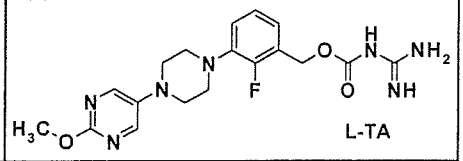
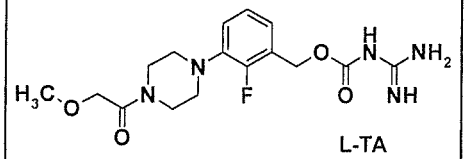
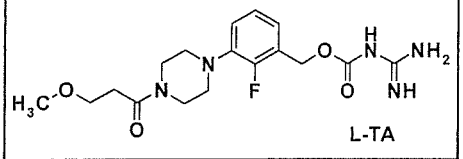
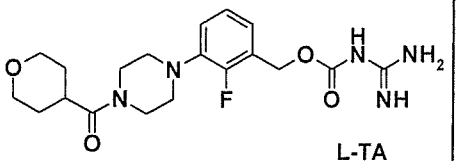
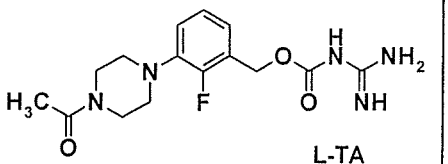
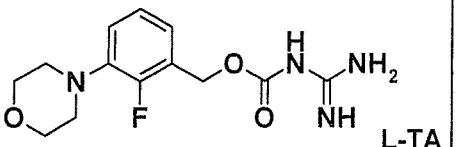
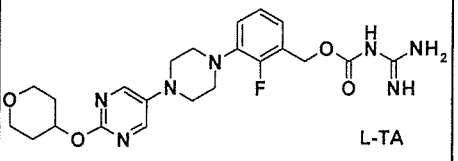
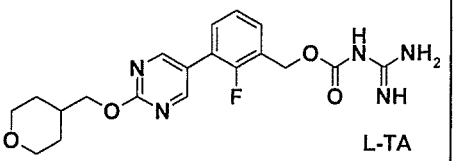
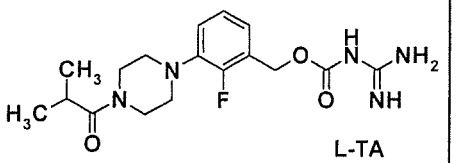
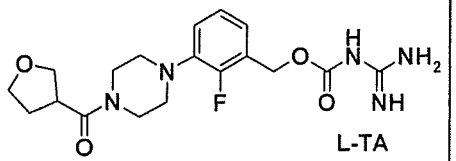
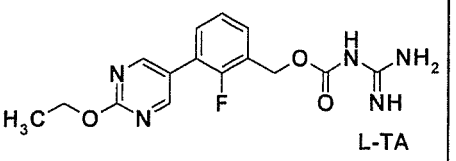
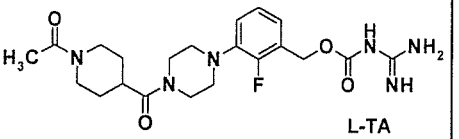
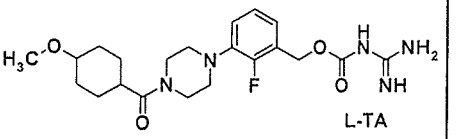
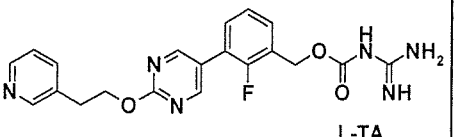
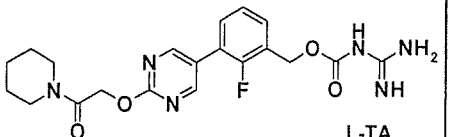
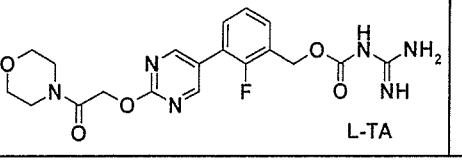
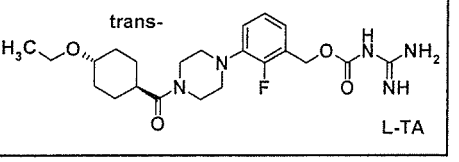
[0329]

[Table 89]

Ex	Syn	Structure	Ex	Syn	Structure
109	112	 L-TA	110	112	 L-TA
111	112	 L-TA	112	112	 L-TA
113	112	 L-TA	114	112	 L-TA
115	112	 L-TA	116	112	 L-TA
117	112	 L-TA	118	112	 L-TA
119	112	 L-TA	120	112	 L-TA
121	112	 L-TA	122	112	 L-TA
123	112	 L-TA	124	112	 L-TA

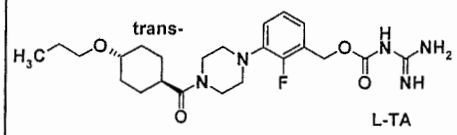
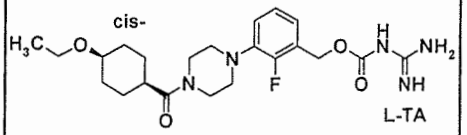
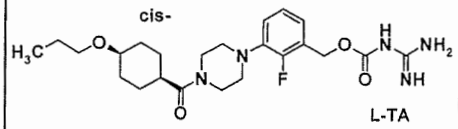
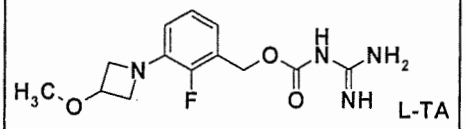
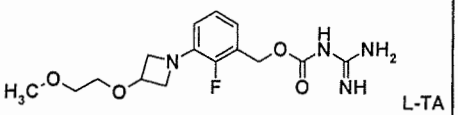
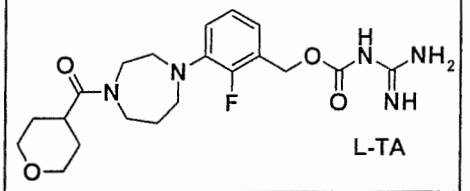
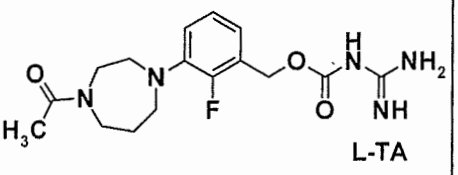
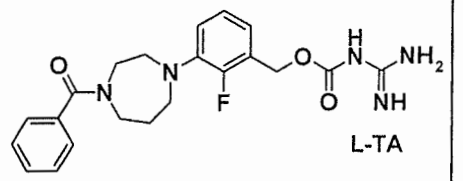
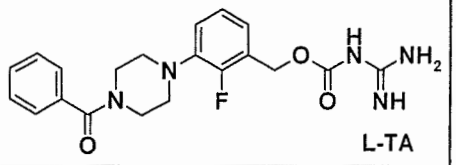
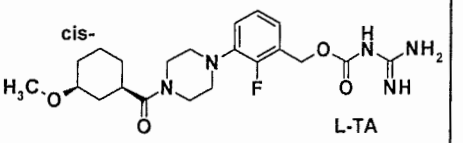
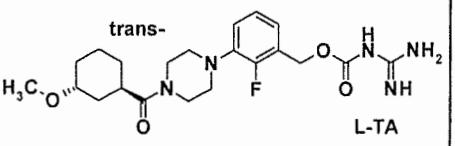
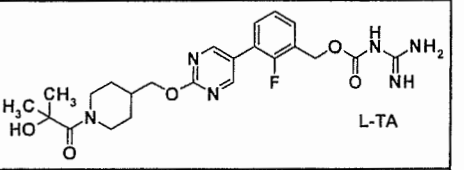
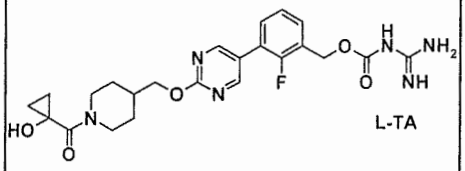
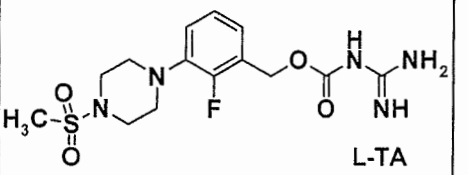
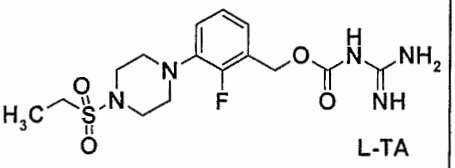
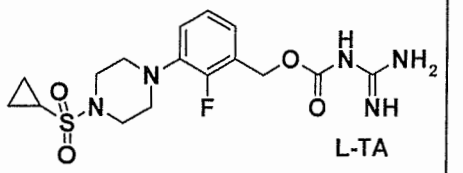
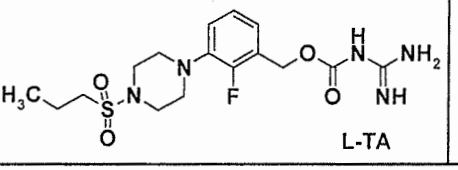
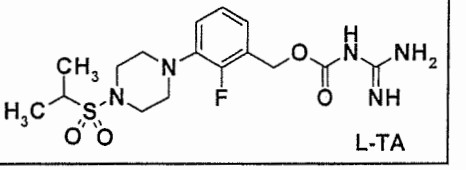
[0330]

[Table 90]

Ex	Syn	Structure	Ex	Syn	Structure
125	112	 L-TA	126	112	 L-TA
127	112	 L-TA	128	112	 L-TA
129	112	 L-TA	130	112	 L-TA
131	112	 L-TA	132	112	 L-TA
133	112	 L-TA	134	112	 L-TA
135	112	 L-TA	136	112	 L-TA
137	112	 L-TA	138	112	 L-TA
139	112	 L-TA	140	112	 L-TA
141	112	 L-TA	142	112	trans-  L-TA

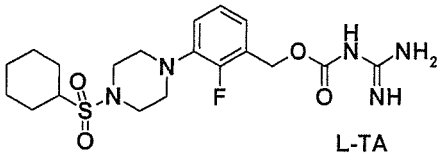
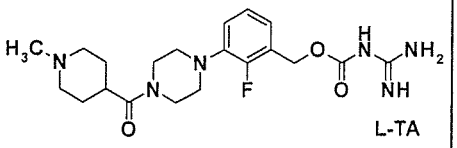
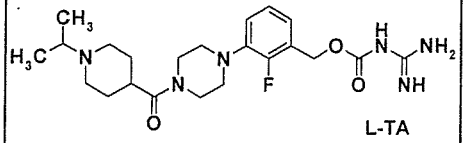
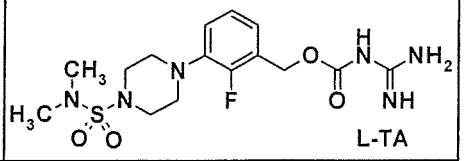
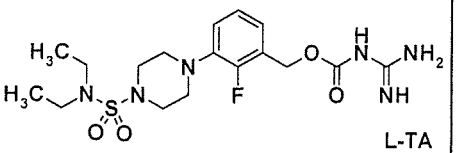
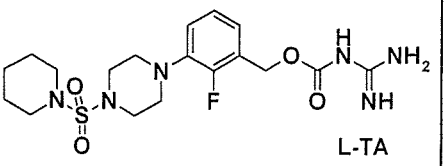
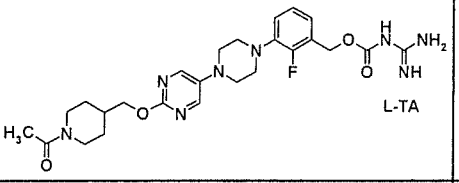
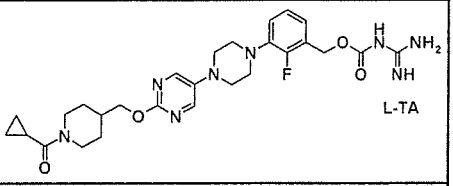
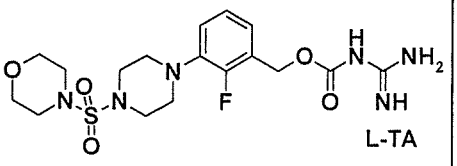
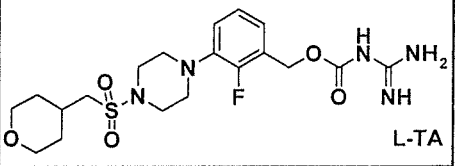
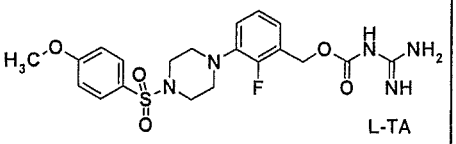
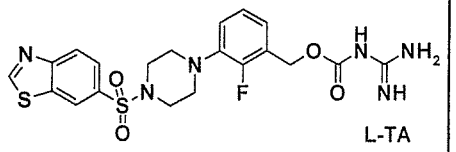
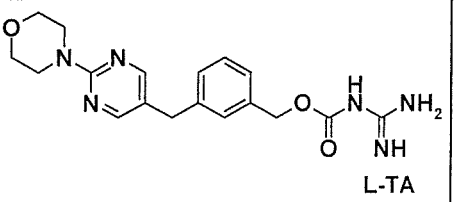
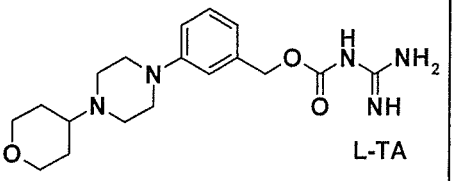
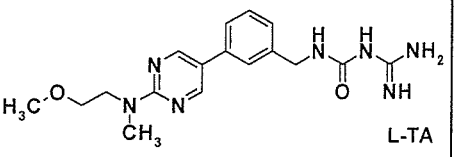
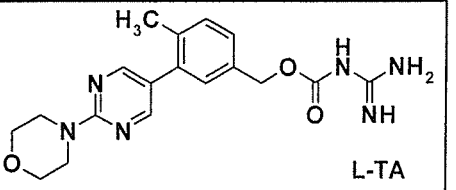
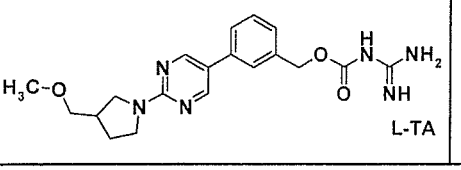
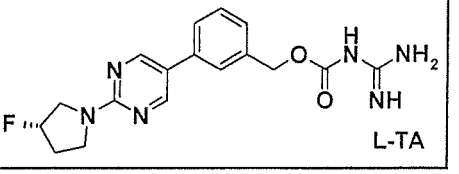
[0331]

[Table 91]

Ex	Syn	Structure	Ex	Syn	Structure
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145	112		146	112	
147	112		148	112	
149	112		150	112	
151	112		152	112	
153	112		154	112	
155	112		156	112	
157	112		158	112	
159	112		160	112	

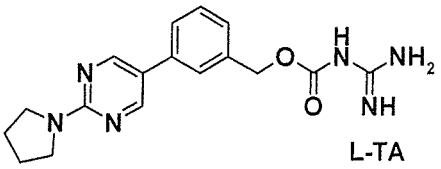
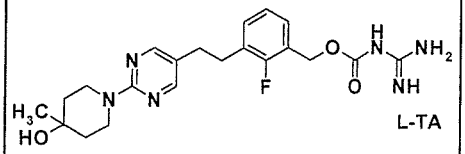
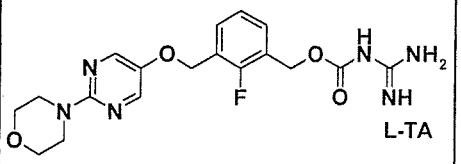
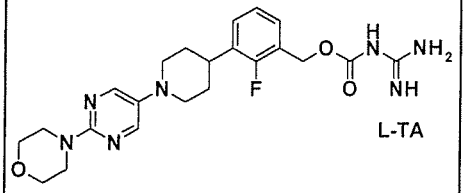
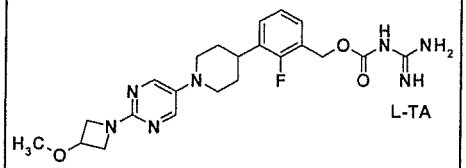
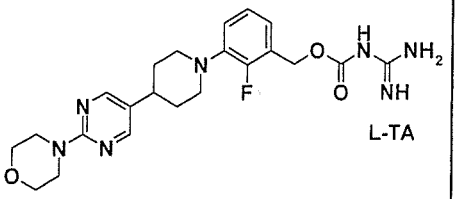
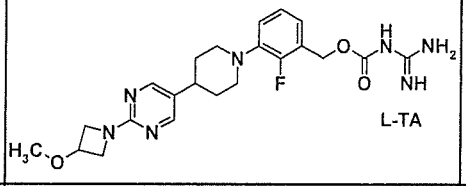
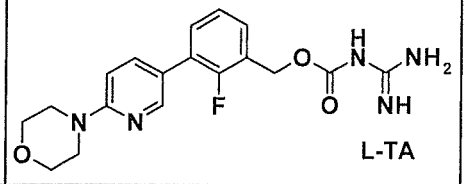
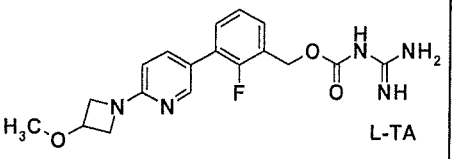
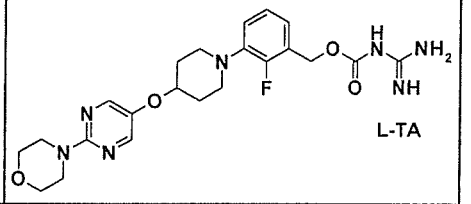
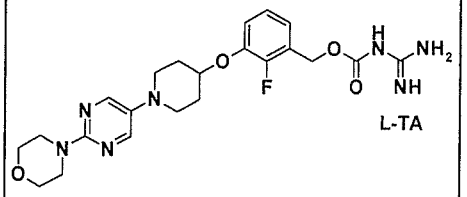
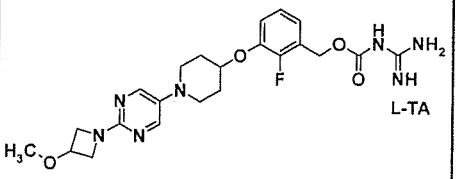
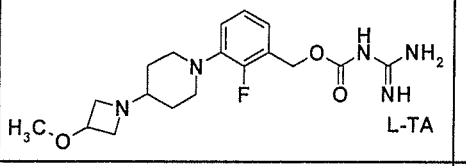
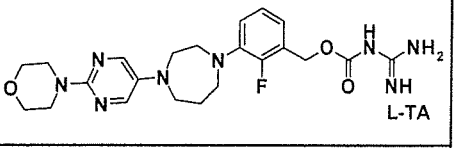
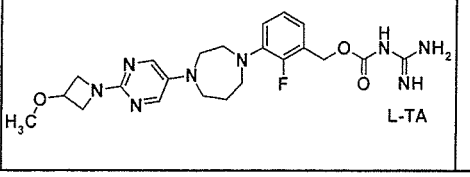
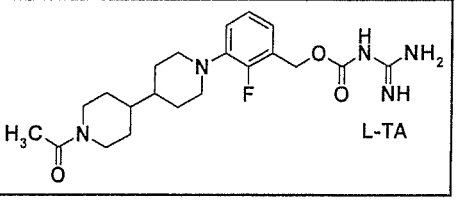
[0332]

[Table 92]

Ex	Syn	Structure	Ex	Syn	Structure
161	112	 L-TA	162	112	 L-TA
163	112	 L-TA	164	112	 L-TA
165	112	 L-TA	166	112	 L-TA
167	112	 L-TA	168	112	 L-TA
169	112	 L-TA	170	112	 L-TA
171	112	 L-TA	172	112	 L-TA
173	112	 L-TA	174	112	 L-TA
175	112	 L-TA	176	112	 L-TA
177	112	 L-TA	178	112	 L-TA

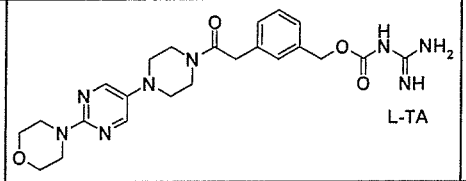
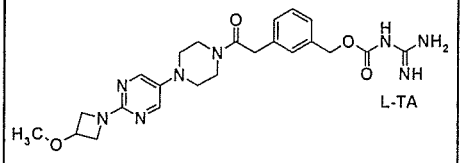
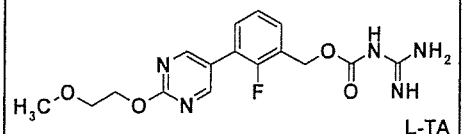
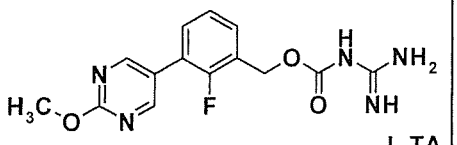
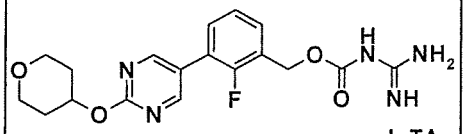
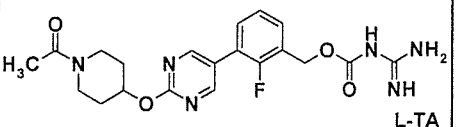
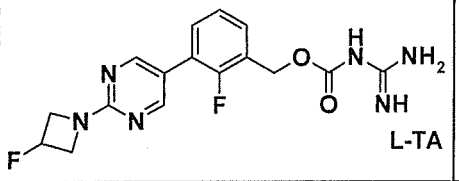
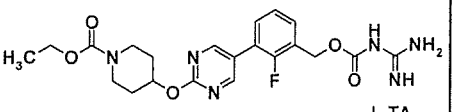
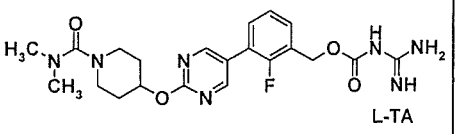
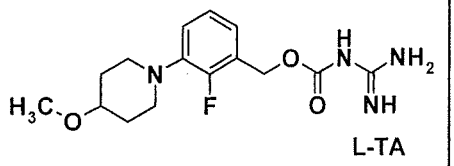
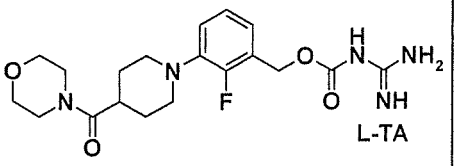
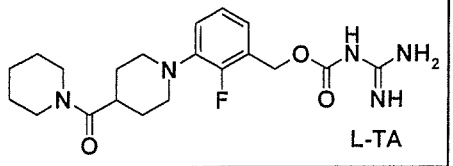
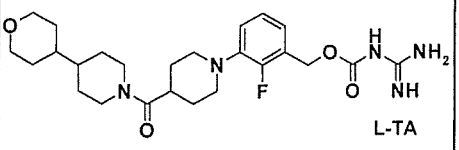
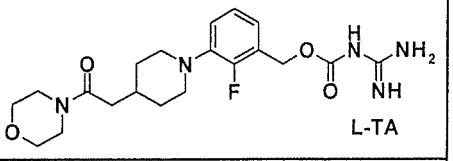
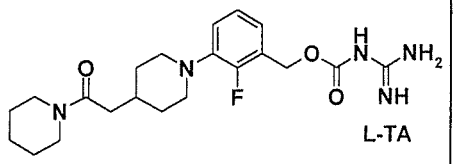
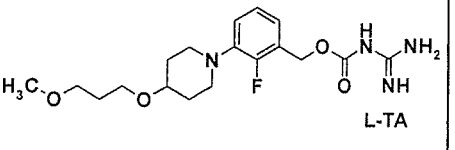
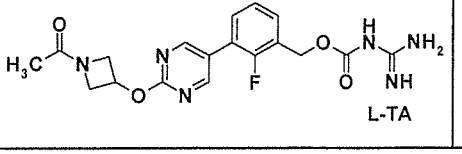
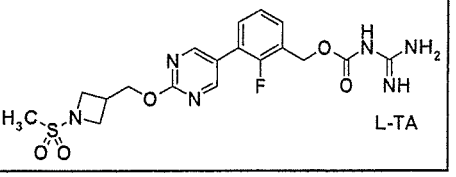
[0333]

[Table 93]

Ex	Syn	Structure	Ex	Syn	Structure
179	112	 L-TA	180	112	 L-TA
181	112	 L-TA	182	112	 L-TA
183	112	 L-TA	184	112	 L-TA
185	112	 L-TA	186	112	 L-TA
187	112	 L-TA	188	112	 L-TA
189	112	 L-TA	190	112	 L-TA
191	112	 L-TA	192	112	 L-TA
193	112	 L-TA	194	112	 L-TA

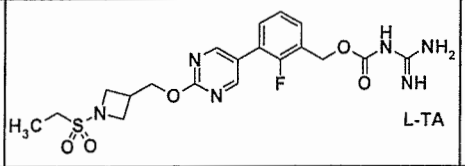
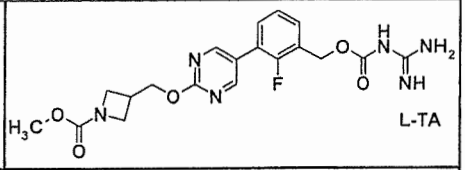
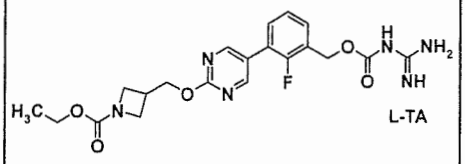
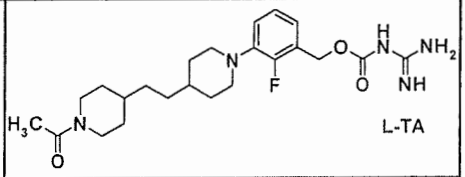
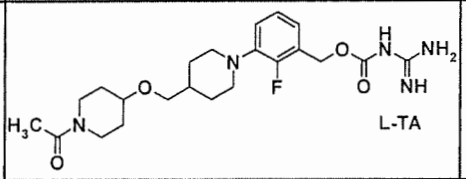
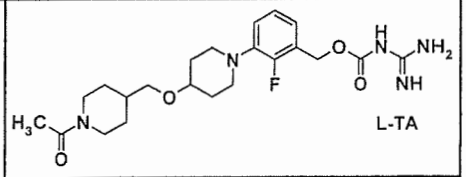
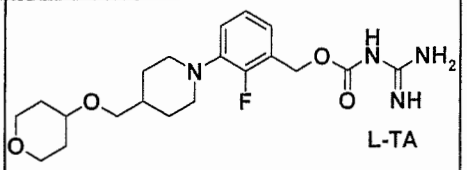
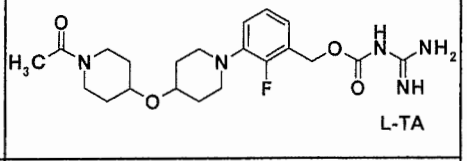
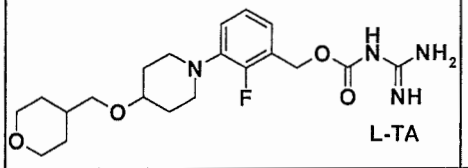
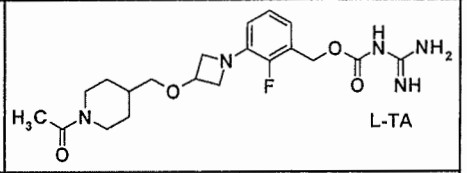
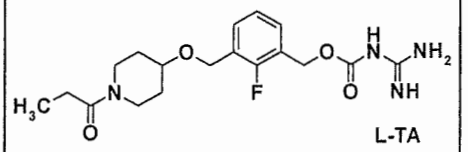
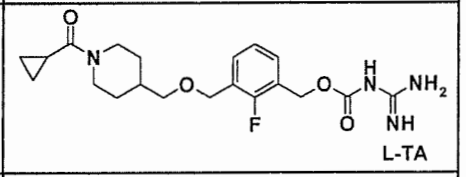
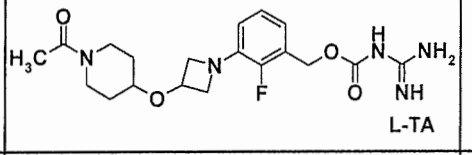
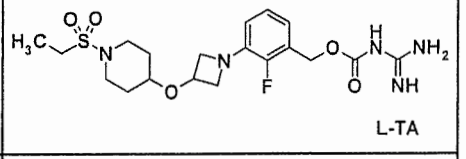
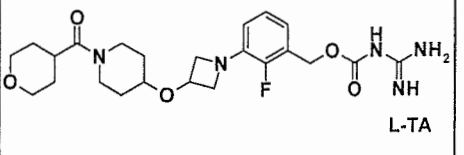
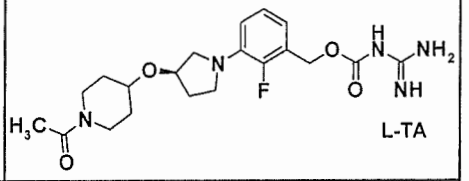
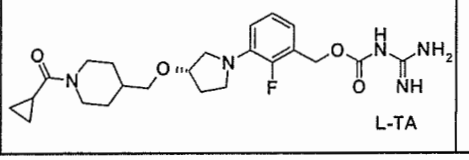
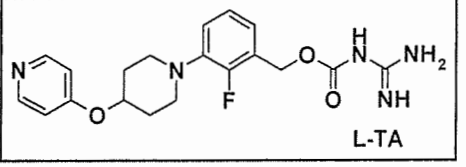
[0334]

[Table 94]

Ex	Syn	Structure	Ex	Syn	Structure
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197	112		198	112	
199	112		200	112	
201	112		202	112	
203	112		204	112	
205	112		206	112	
207	112		208	112	
209	112		210	112	
211	112		212	112	

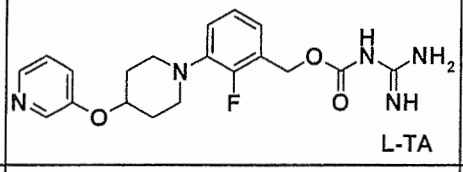
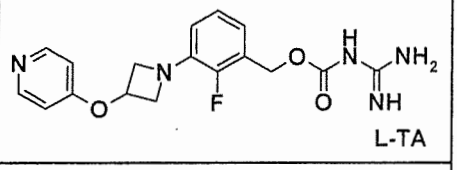
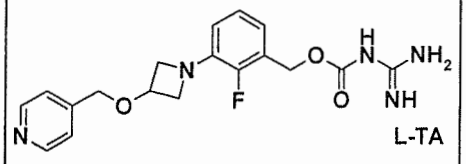
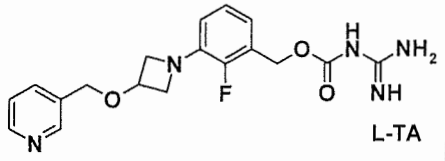
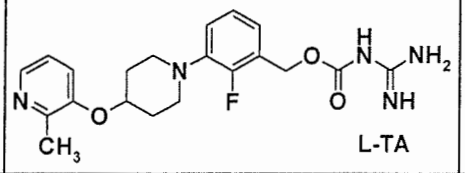
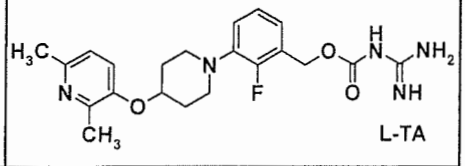
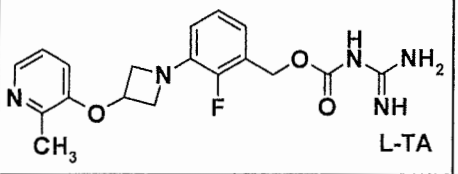
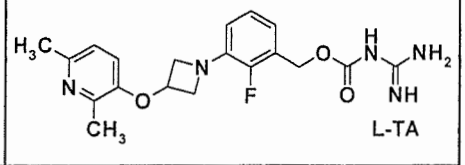
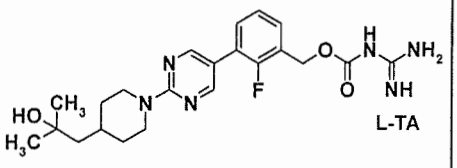
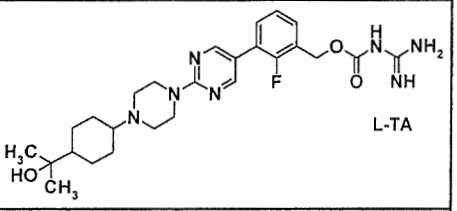
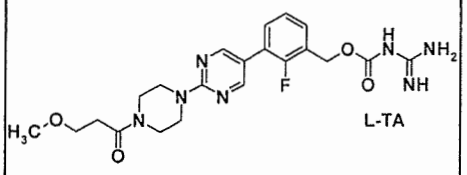
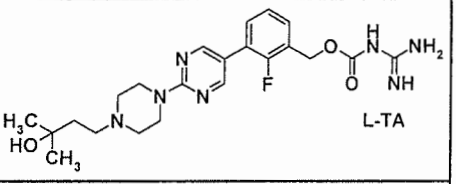
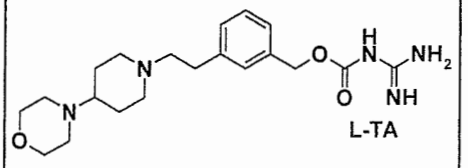
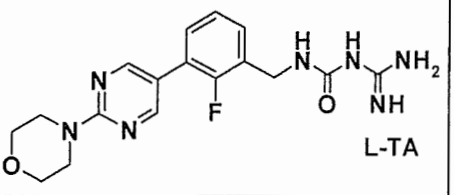
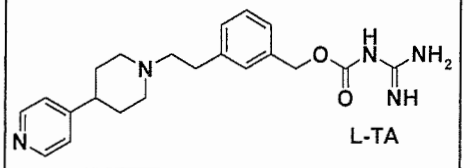
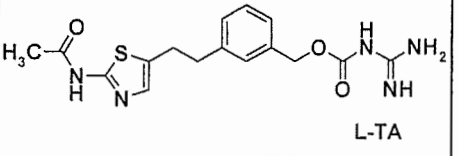
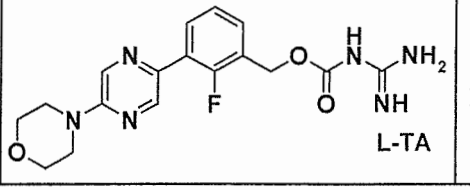
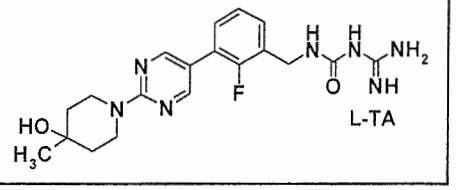
[0335]

[Table 95]

Ex	Syn	Structure	Ex	Syn	Structure
213	112	 L-TA	214	112	 L-TA
215	112	 L-TA	216	112	 L-TA
217	112	 L-TA	218	112	 L-TA
219	112	 L-TA	220	112	 L-TA
221	112	 L-TA	222	112	 L-TA
223	112	 L-TA	224	112	 L-TA
225	112	 L-TA	226	112	 L-TA
227	112	 L-TA	228	112	 L-TA
229	112	 L-TA	230	112	 L-TA

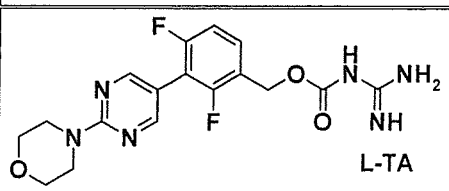
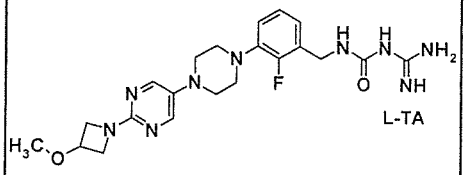
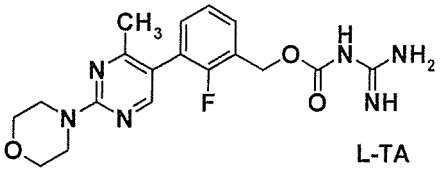
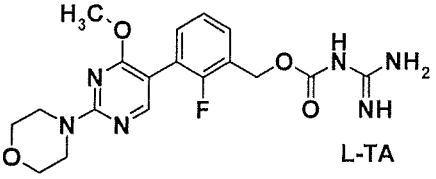
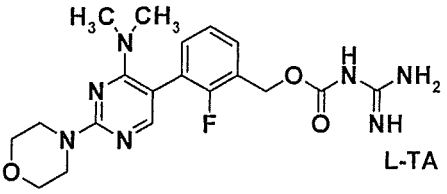
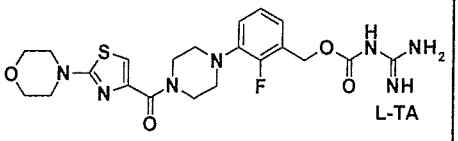
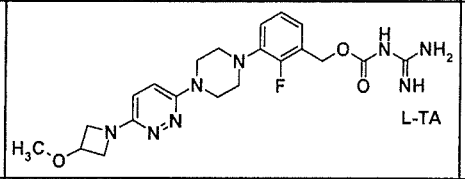
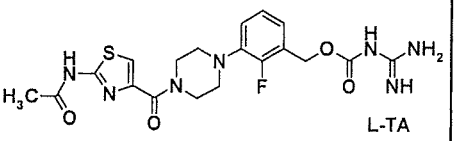
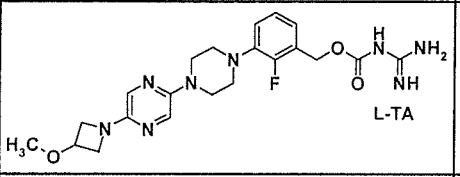
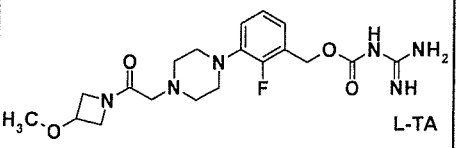
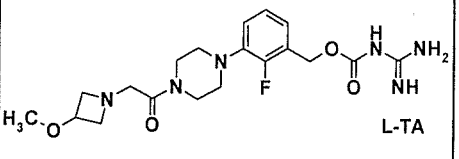
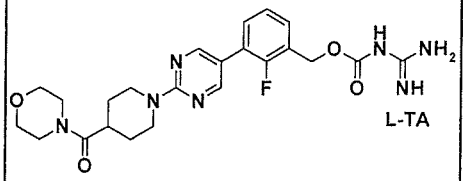
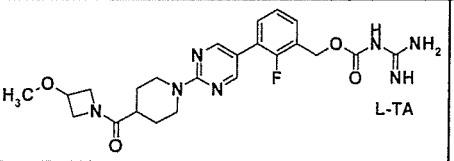
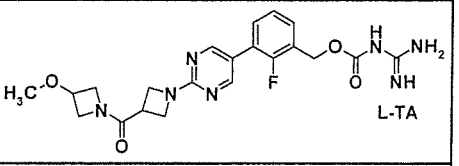
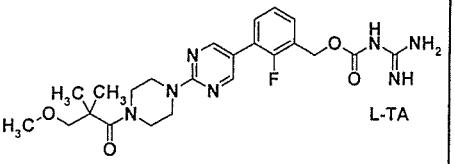
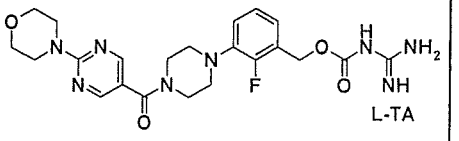
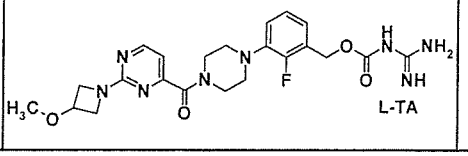
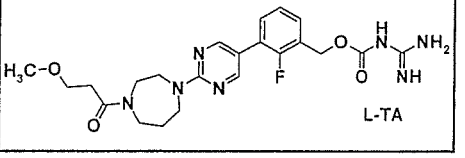
[0336]

[Table 96]

Ex	Syn	Structure	Ex	Syn	Structure
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233	112		234	112	
235	112		236	112	
237	112		238	112	
239	112		240	112	
241	112		242	112	
243	112		244	112	
245	112		246	112	
247	112		248	112	

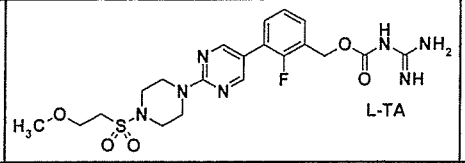
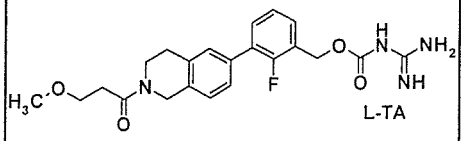
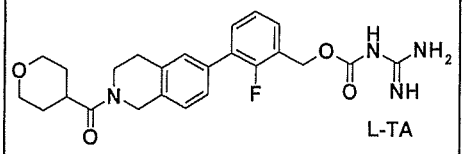
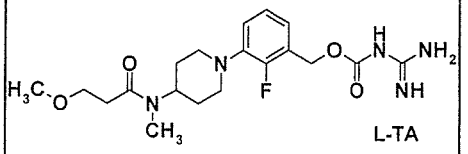
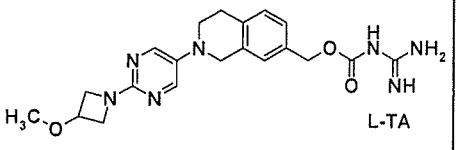
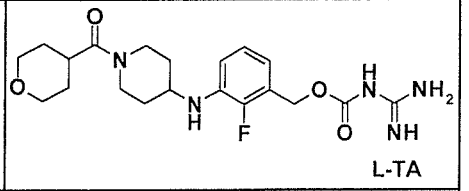
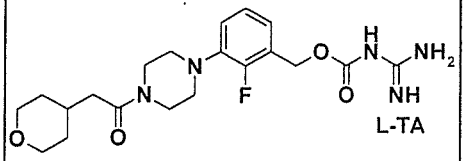
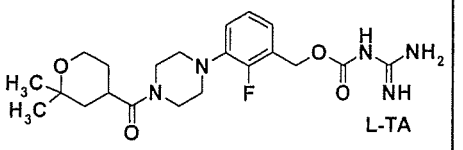
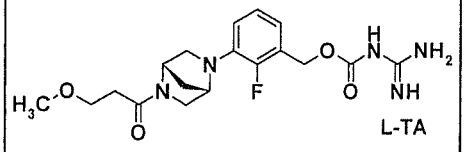
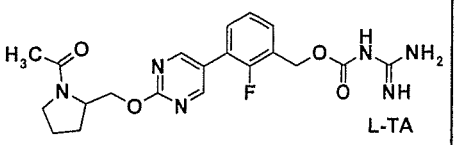
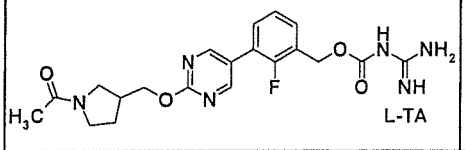
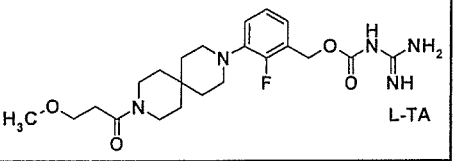
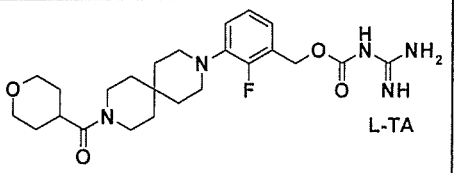
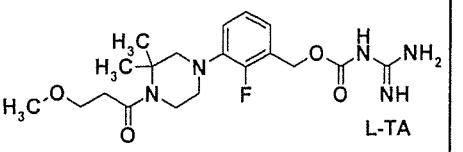
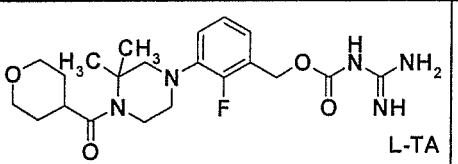
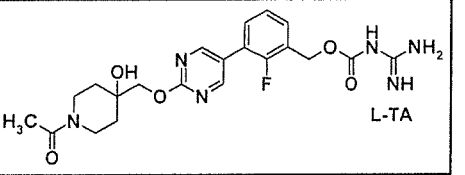
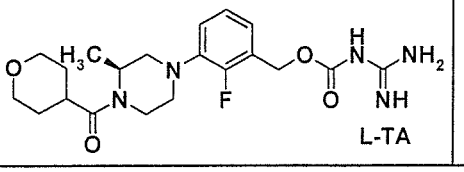
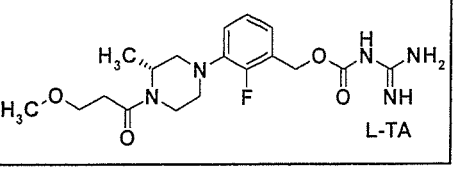
[0337]

[Table 97]

Ex	Syn	Structure	Ex	Syn	Structure
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251	112		252	112	
253	112		254	112	
255	112		256	112	
257	112		258	112	
259	112		260	112	
261	112		262	112	
263	112		264	112	
265	112		266	112	

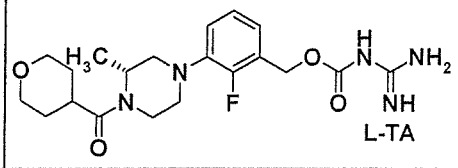
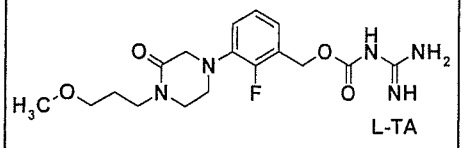
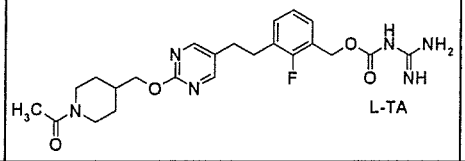
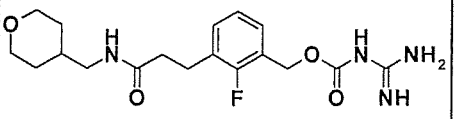
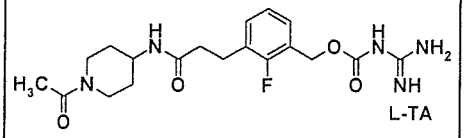
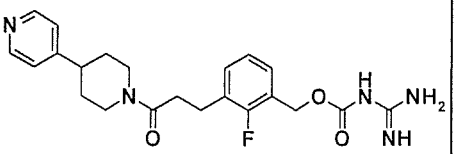
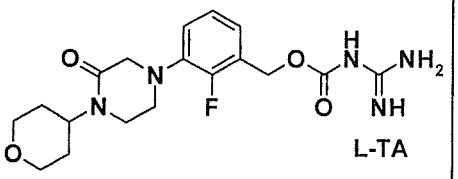
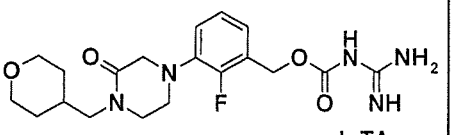
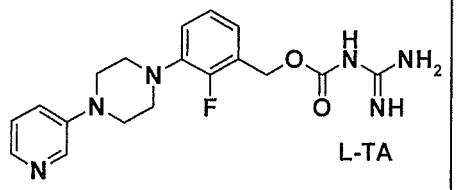
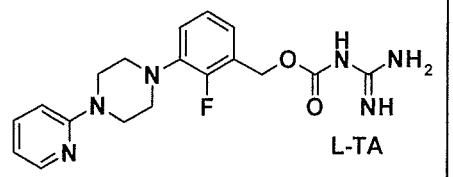
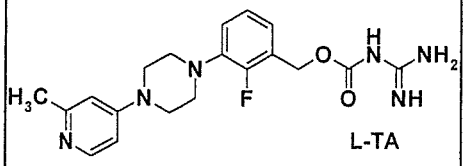
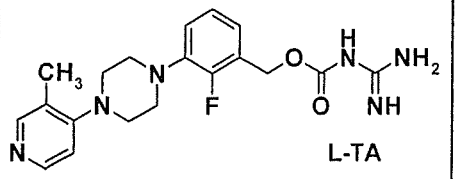
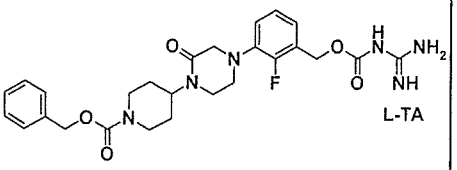
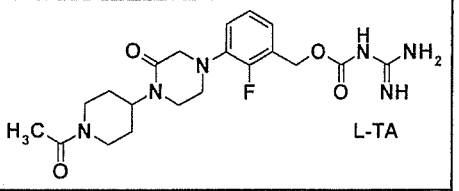
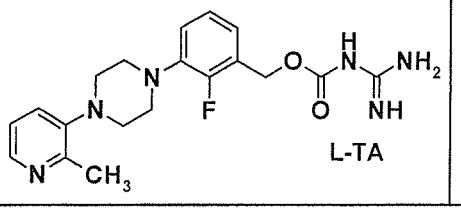
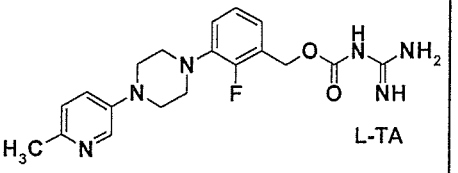
[0338]

[Table 98]

Ex	Syn	Structure	Ex	Syn	Structure
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269	112		270	112	
271	112		272	112	
273	112		274	112	
275	112		276	112	
277	112		278	112	
279	112		280	112	
281	112		282	112	
283	112		284	112	

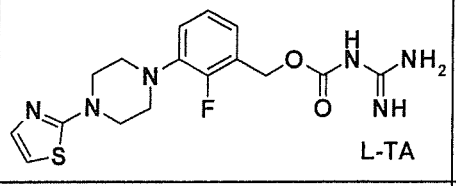
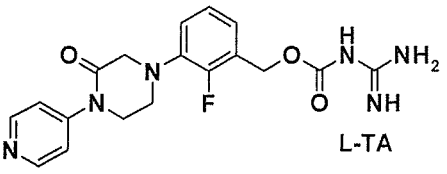
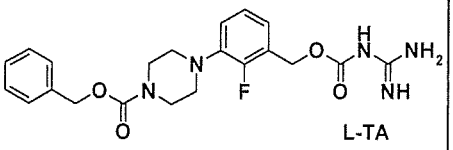
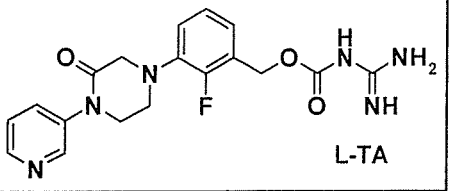
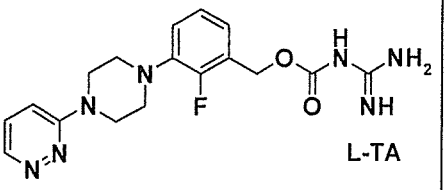
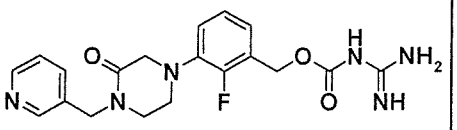
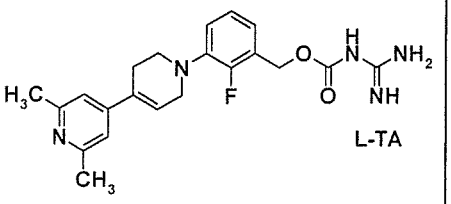
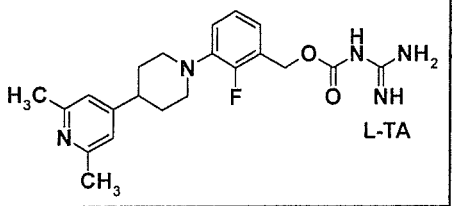
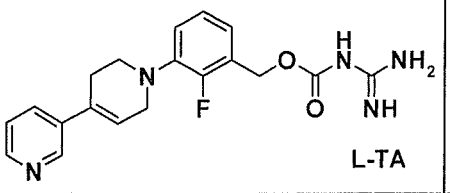
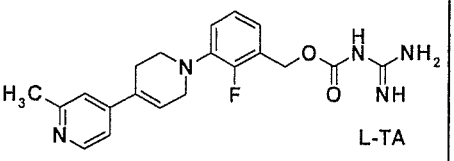
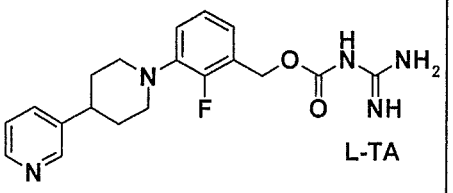
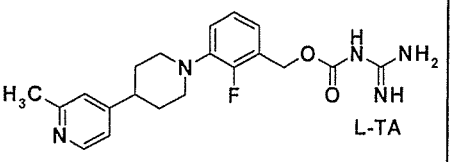
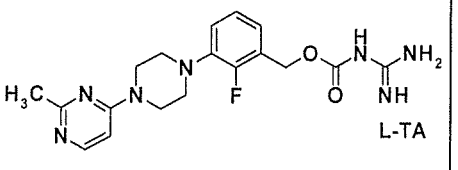
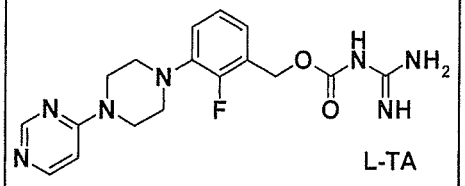
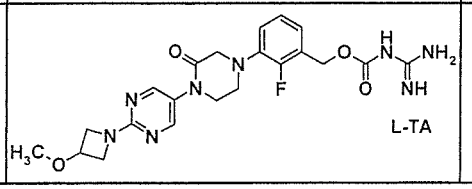
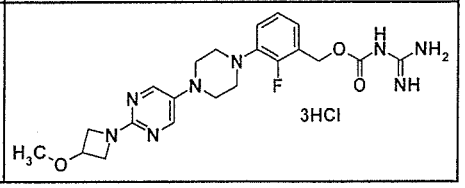
[0339]

[Table 99]

Ex	Syn	Structure	Ex	Syn	Structure
285	112	 L-TA	286	112	 L-TA
287	112	 L-TA	288	112	 L-TA
289	112	 L-TA	290	112	 L-TA
291	112	 L-TA	292	112	 L-TA
293	112	 L-TA	294	112	 L-TA
295	112	 L-TA	296	112	 L-TA
297	112	 L-TA	298	112	 L-TA
299	112	 L-TA	300	112	 L-TA

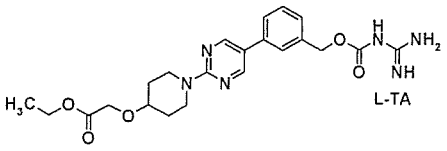
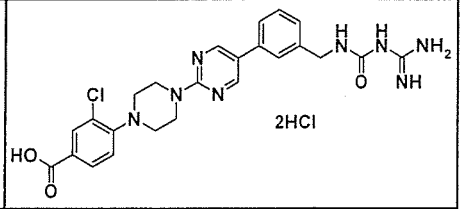
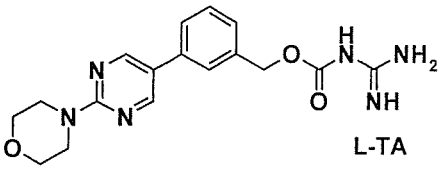
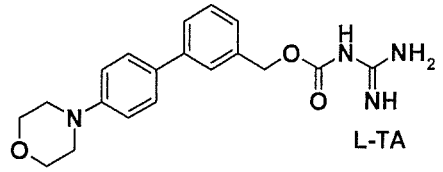
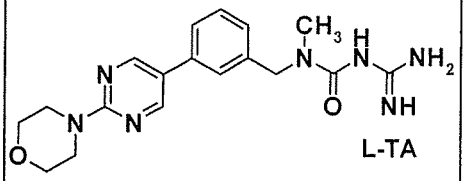
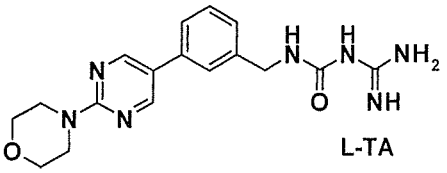
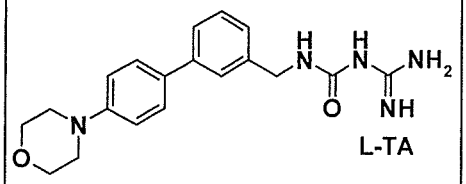
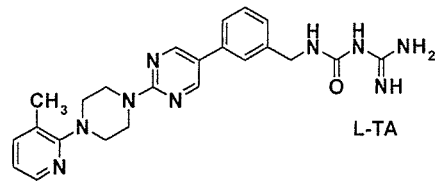
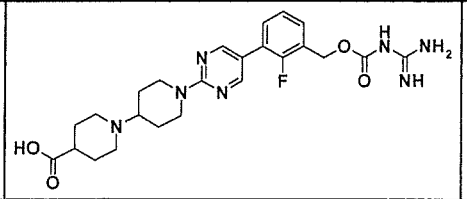
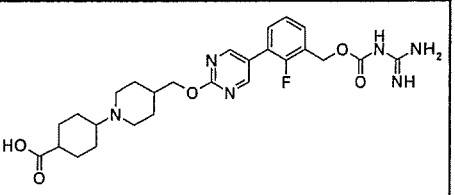
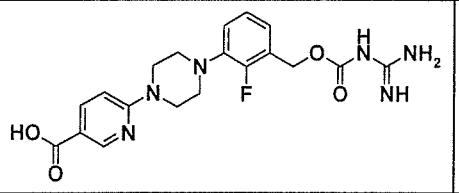
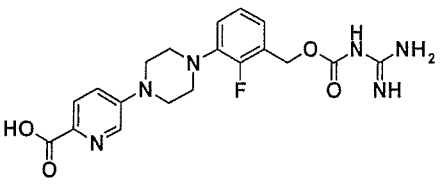
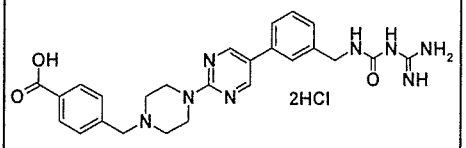
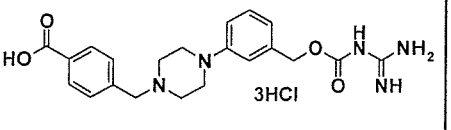
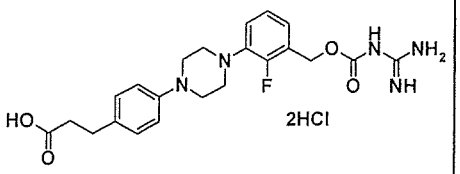
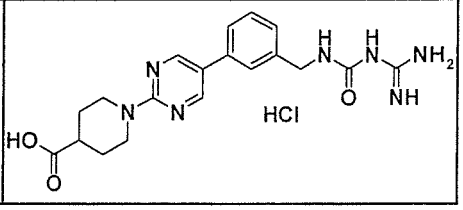
[0340]

[Table 100]

Ex	Syn	Structure	Ex	Syn	Structure
301	112	 L-TA	302	112	 L-TA
303	112	 L-TA	304	112	 L-TA
305	112	 L-TA	306	112	 L-TA
307	112	 L-TA	308	112	 L-TA
309	112	 L-TA	310	112	 L-TA
311	112	 L-TA	312	112	 L-TA
313	112	 L-TA	314	112	 L-TA
315	112	 L-TA	316	316	 3HCl

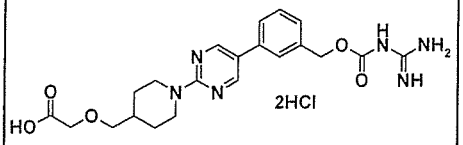
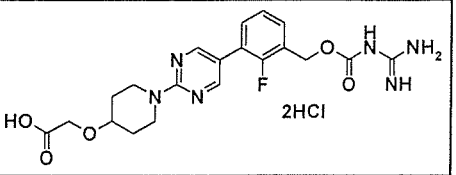
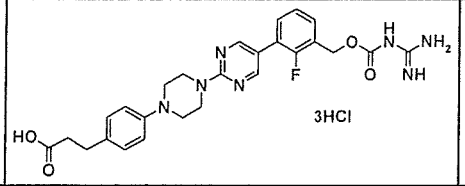
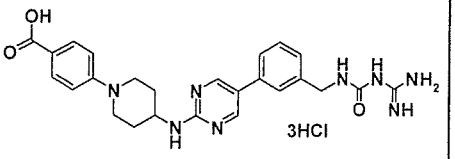
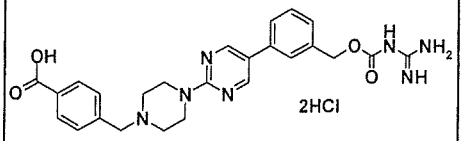
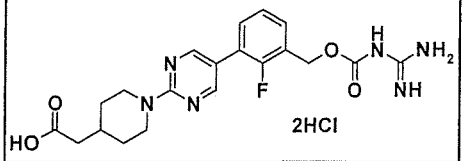
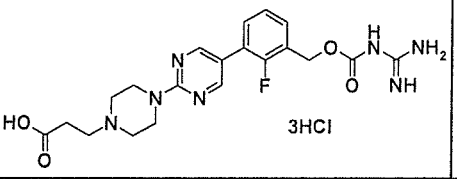
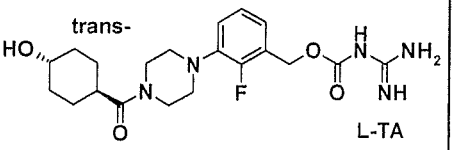
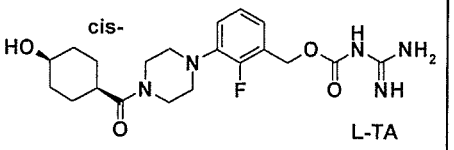
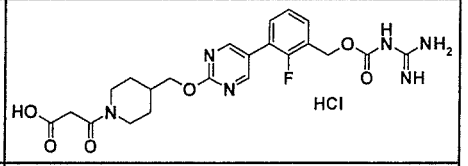
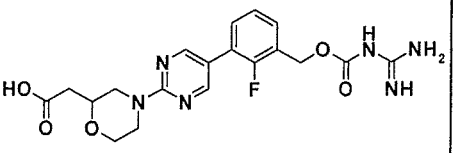
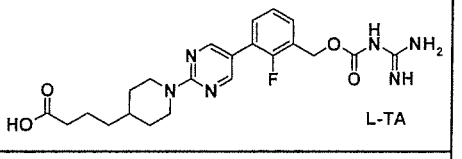
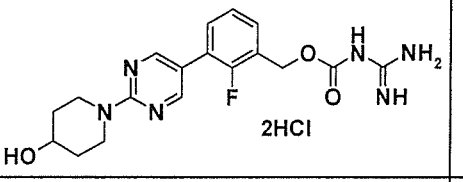
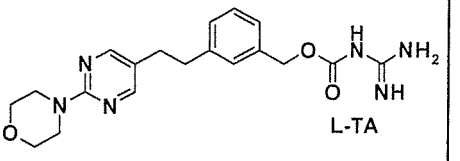
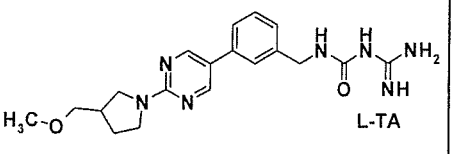
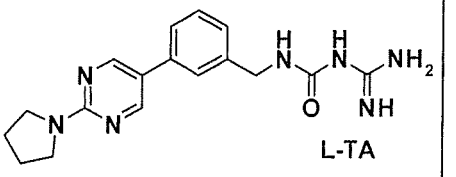
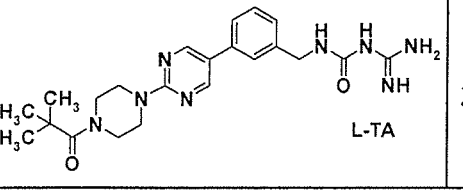
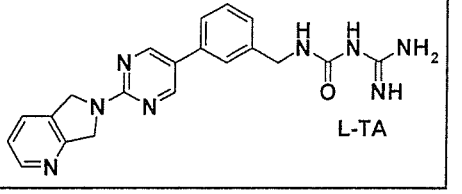
[0341]

[Table 101]

Ex	Syn	Structure	Ex	Syn	Structure
317	317	 L-TA	318	318	 2HCl
319	319	 L-TA	320	319	 L-TA
321	319	 L-TA	322	319	 L-TA
323	319	 L-TA	324	319	 L-TA
325	328		326	328	
327	328		328	328	
329	318	 2HCl	330	318	 3HCl
331	318	 2HCl	332	318	 HCl

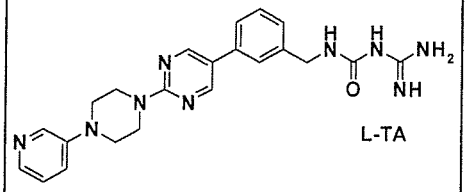
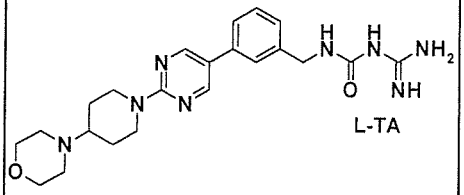
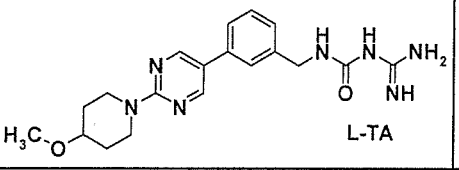
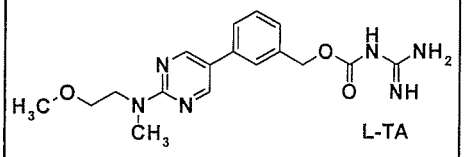
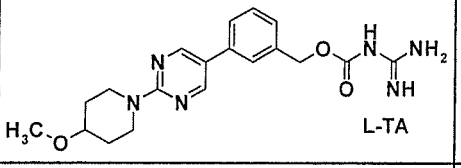
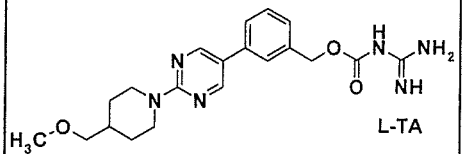
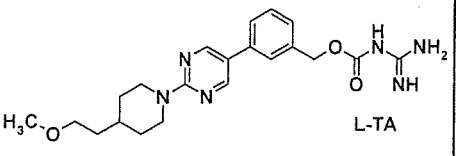
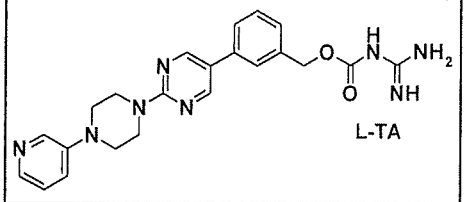
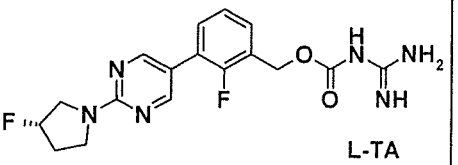
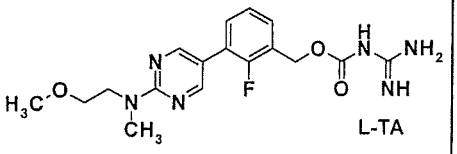
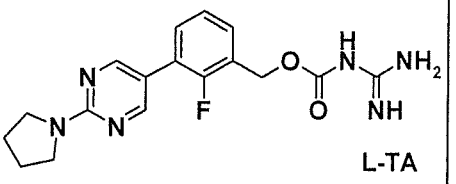
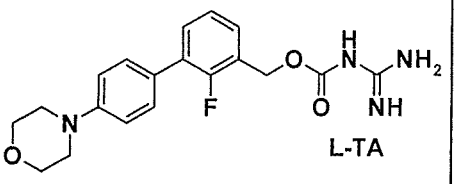
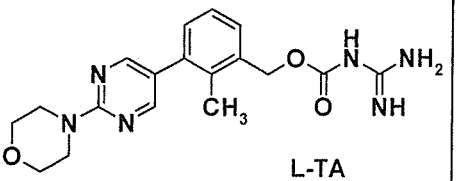
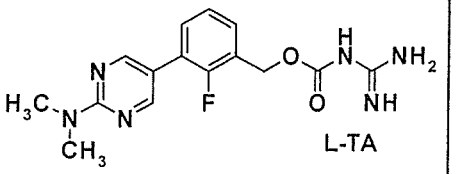
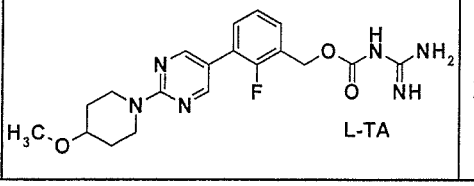
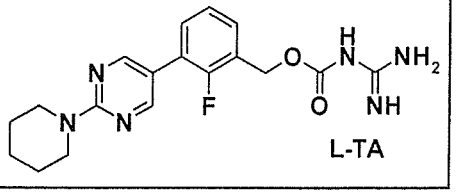
[0342]

[Table 102]

Ex	Syn	Structure	Ex	Syn	Structure
333	318	 2HCl	334	318	 2HCl
335	318	 3HCl	336	318	 3HCl
337	318	 2HCl	338	318	 2HCl
339	318	 3HCl	340	344	 trans- L-TA
341	344	 cis- L-TA	342	318	 HCl
343	344		344	344	 L-TA
345	345	 2HCl	346	347	 L-TA
347	347	 L-TA	348	347	 L-TA
349	347	 L-TA	350	347	 L-TA

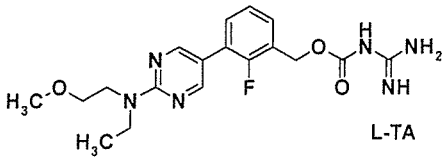
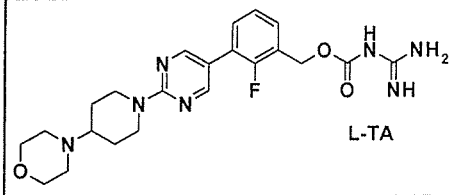
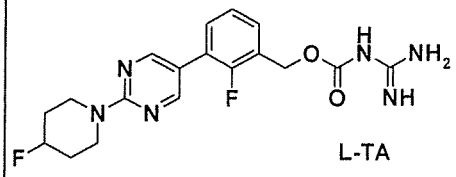
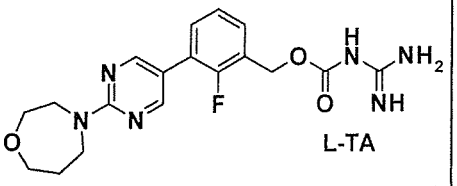
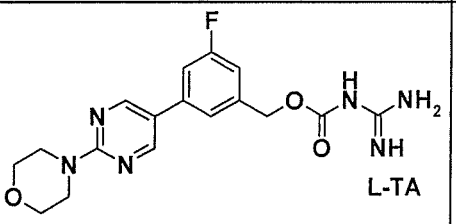
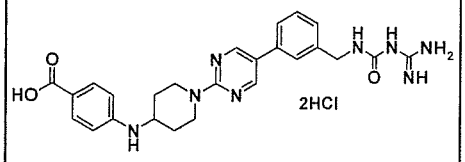
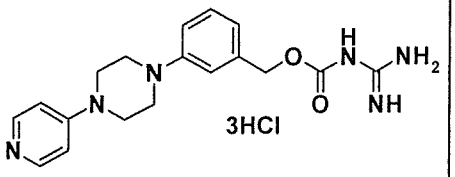
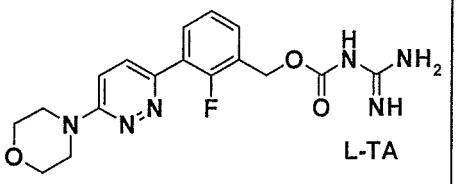
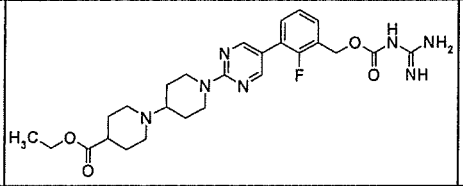
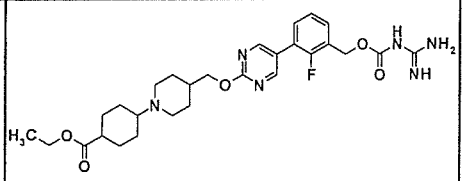
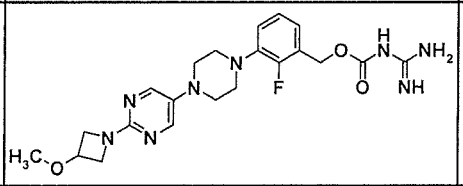
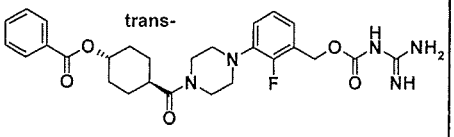
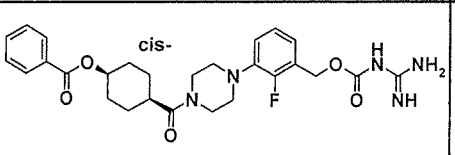
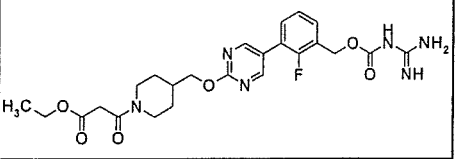
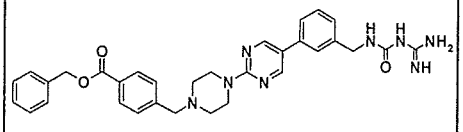
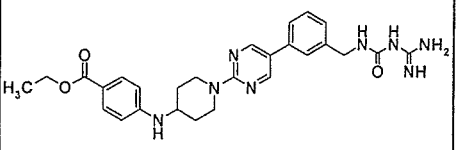
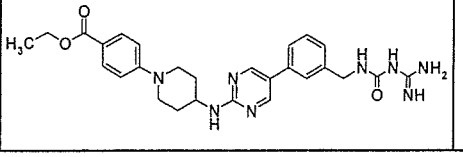
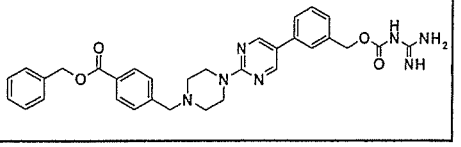
[0343]

[Table 103]

Ex	Syn	Structure	Ex	Syn	Structure
351	347	 L-TA	352	347	 L-TA
353	347	 L-TA	354	347	 L-TA
355	347	 L-TA	356	347	 L-TA
357	347	 L-TA	358	347	 L-TA
359	347	 L-TA	360	347	 L-TA
361	347	 L-TA	362	347	 L-TA
363	347	 L-TA	364	347	 L-TA
365	347	 L-TA	366	347	 L-TA

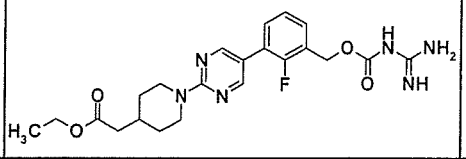
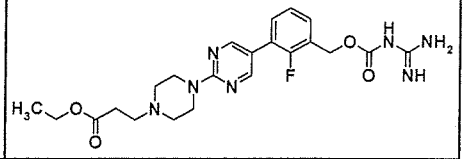
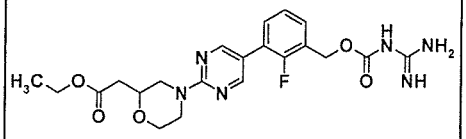
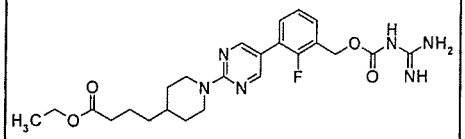
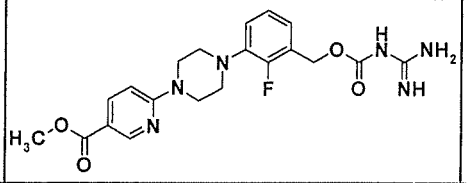
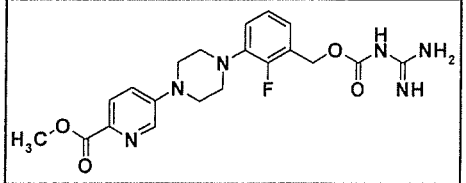
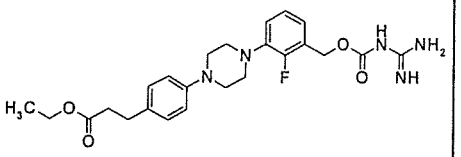
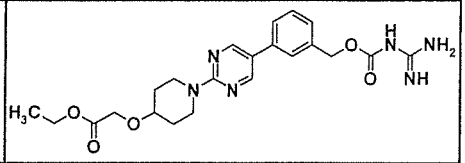
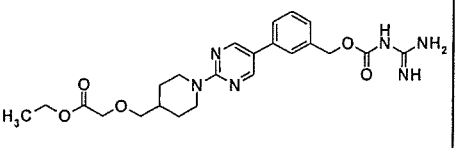
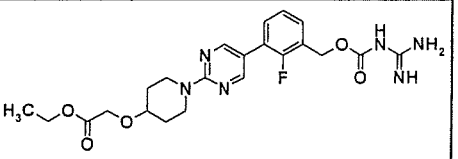
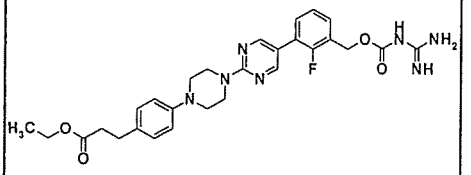
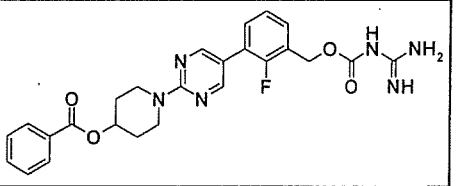
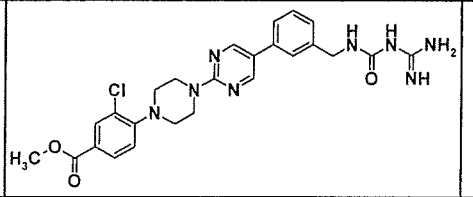
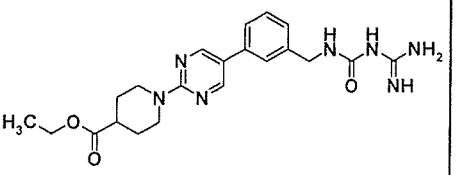
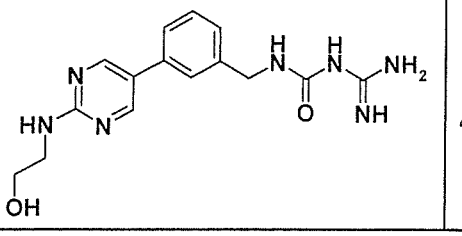
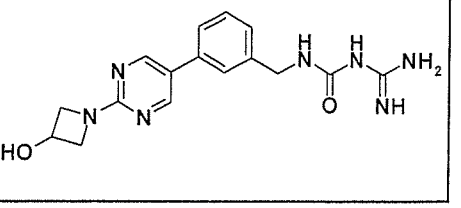
[0344]

[Table 104]

Ex	Syn	Structure	Ex	Syn	Structure
367	347	 L-TA	368	347	 L-TA
369	347	 L-TA	370	347	 L-TA
371	347	 L-TA	372	318	 2HCl
373	23	 3HCl	374	112	 L-TA
375	3		376	3	
377	3		378	3	 trans-
379	3	 cis-	380	3	
381	3		382	3	
383	3		384	3	

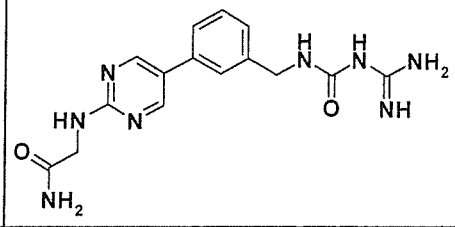
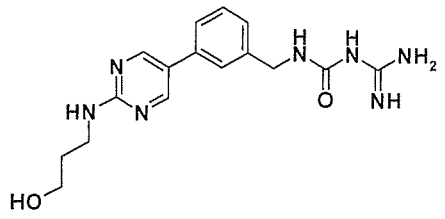
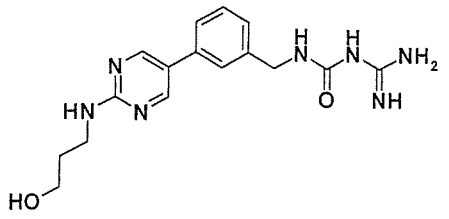
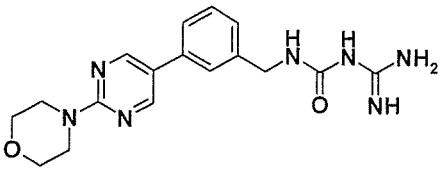
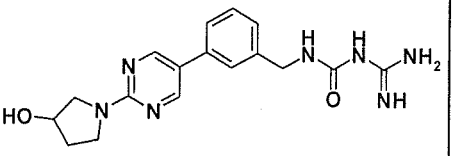
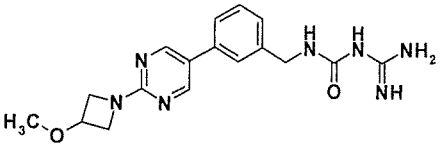
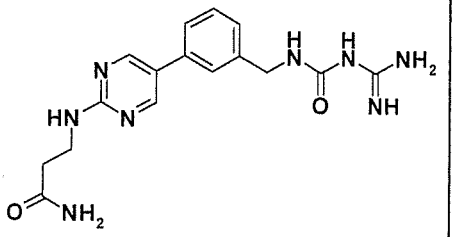
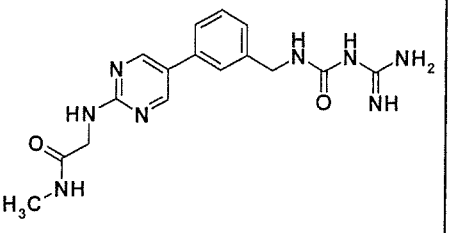
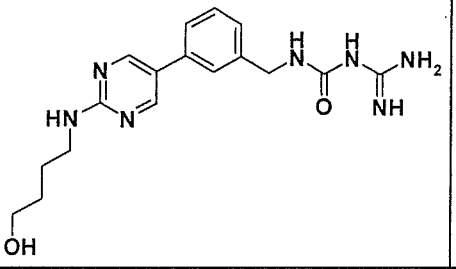
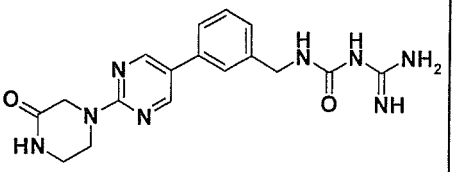
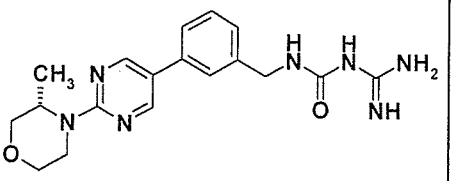
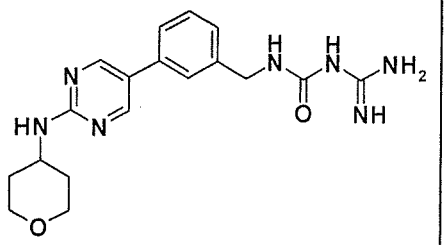
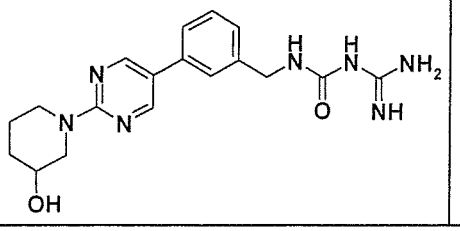
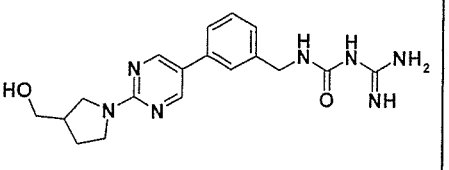
[0345]

[Table 105]

Ex	Syn	Structure	Ex	Syn	Structure
385	3		386	3	
387	3		388	3	
389	3		390	3	
391	3		392	3	
393	3		394	3	
395	3		396	3	
397	397		398	398	
399	546		400	546	

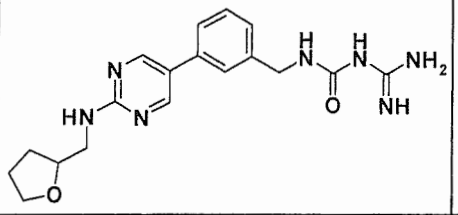
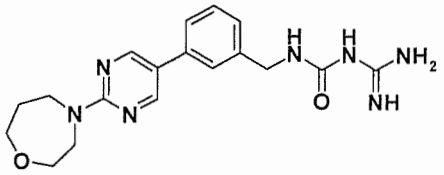
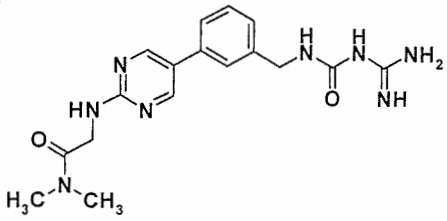
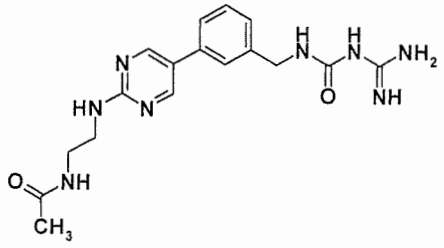
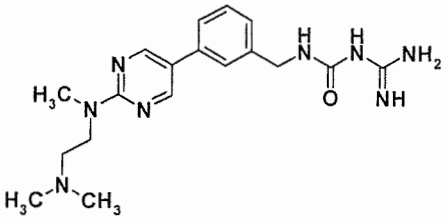
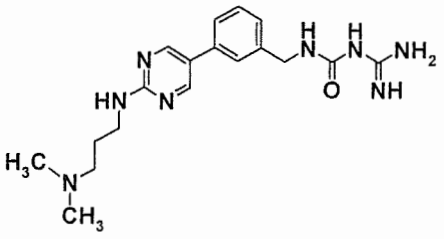
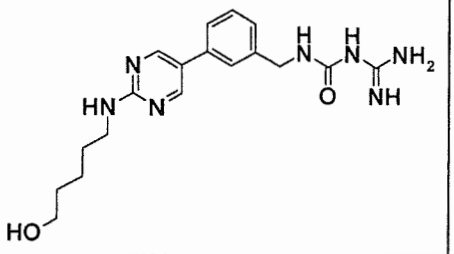
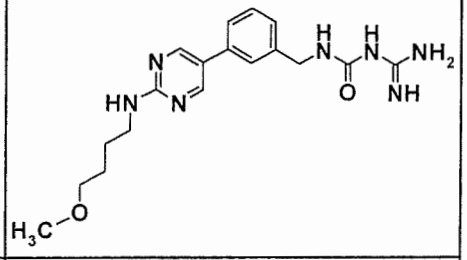
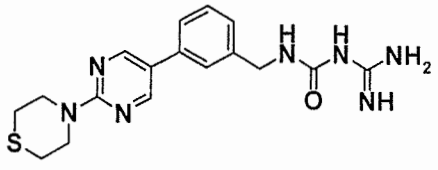
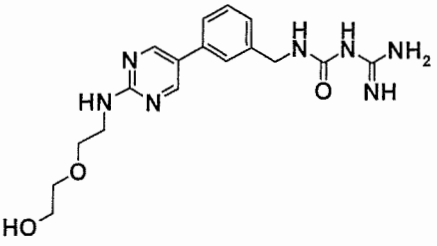
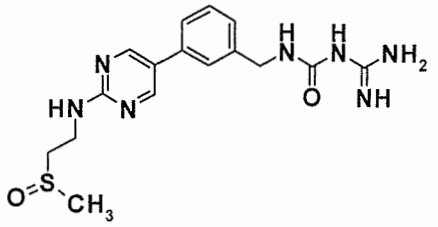
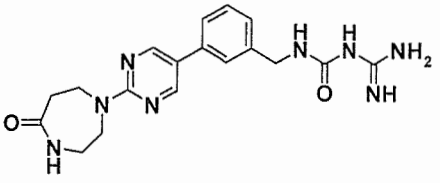
[0346]

[Table 106]

Ex	Syn	Structure	Ex	Syn	Structure
401	546		402	546	
403	546		404	546	
405	546		406	546	
407	546		408	546	
409	546		410	546	
411	546		412	546	
413	546		414	546	

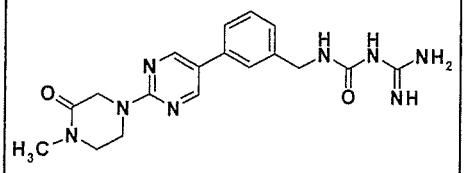
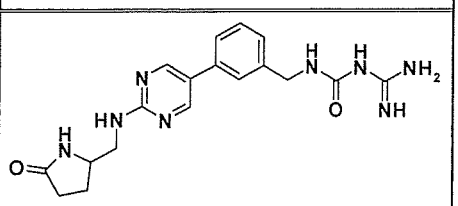
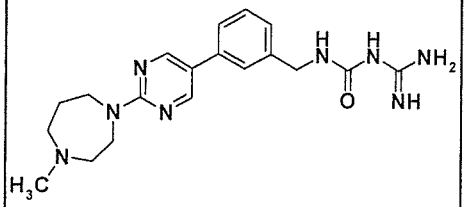
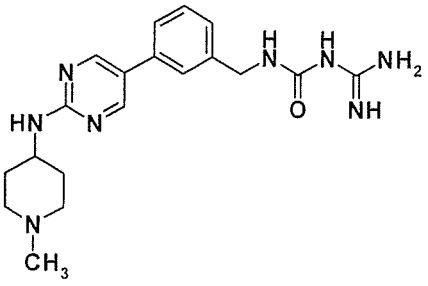
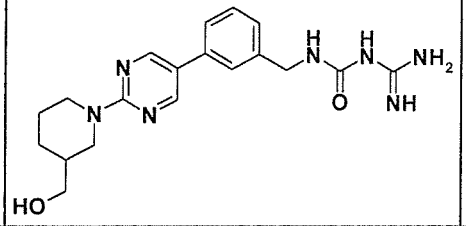
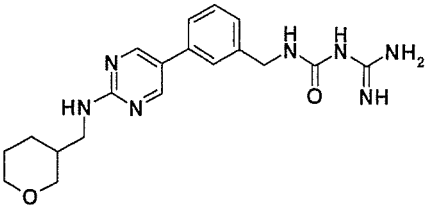
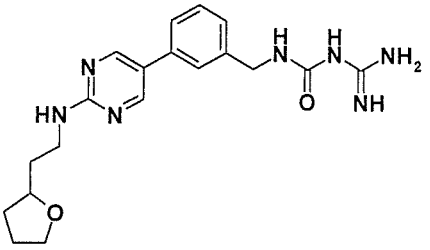
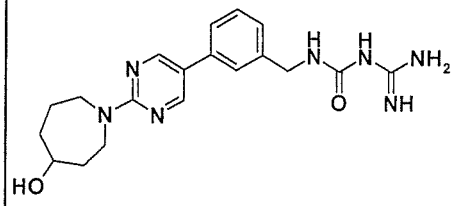
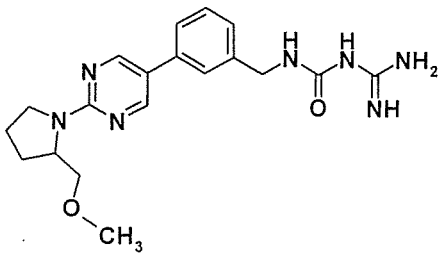
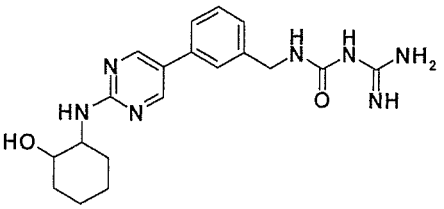
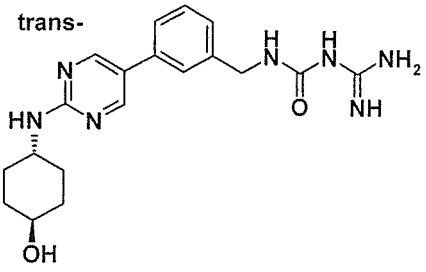
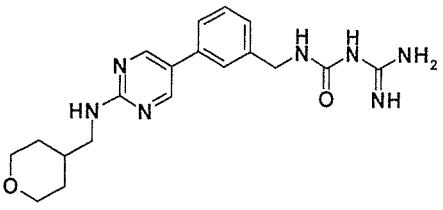
[0347]

[Table 107]

Ex	Syn	Structure	Ex	Syn	Structure
415	546		416	546	
417	546		418	546	
419	546		420	546	
421	546		422	546	
423	546		424	546	
425	546		426	546	

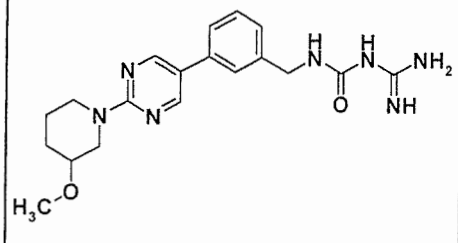
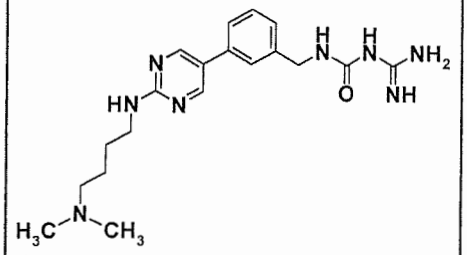
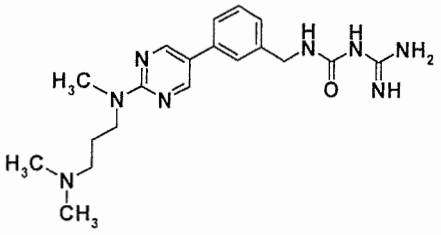
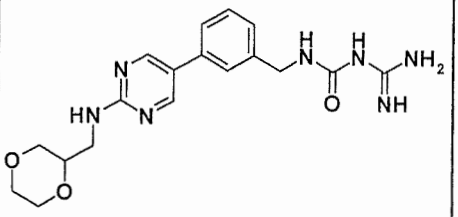
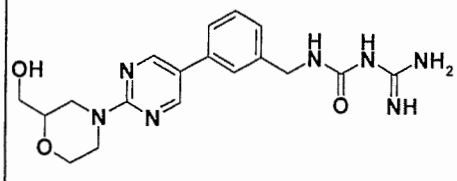
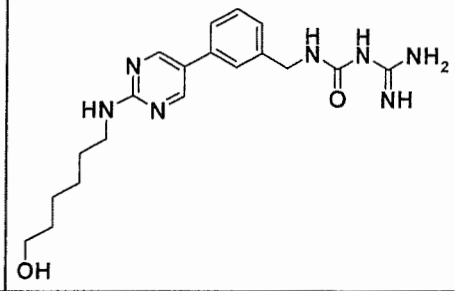
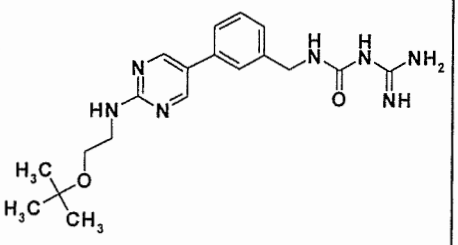
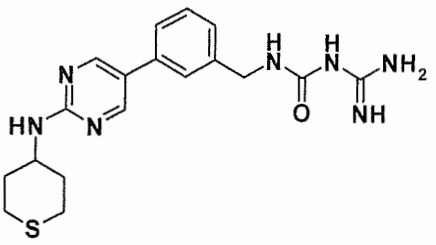
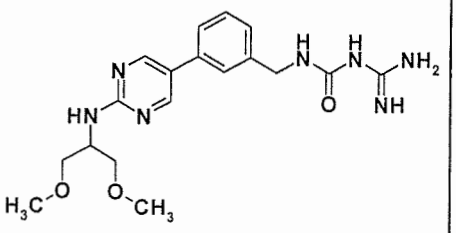
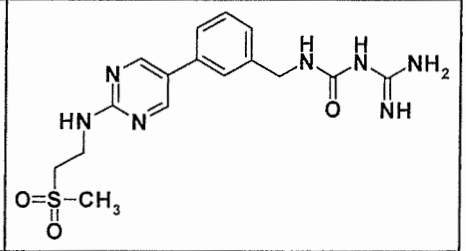
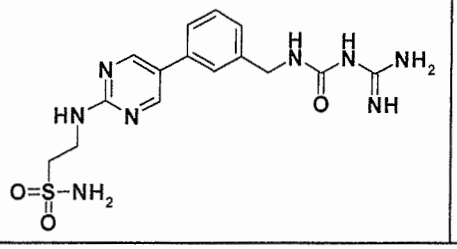
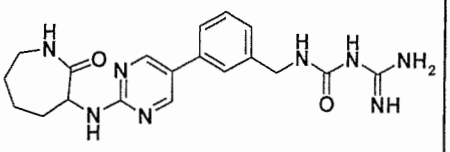
[0348]

[Table 108]

Ex	Syn	Structure	Ex	Syn	Structure
427	546		428	546	
429	546		430	546	
431	546		432	546	
433	546		434	546	
435	546		436	546	
437	546		438	546	

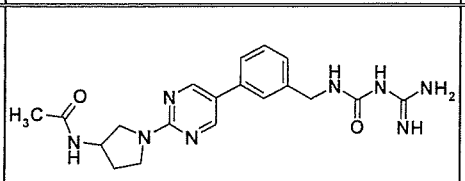
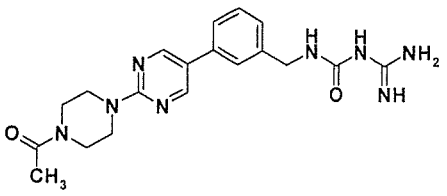
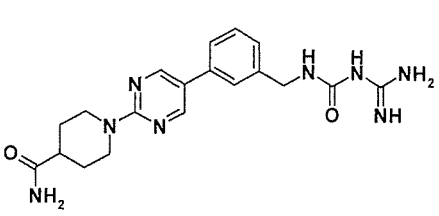
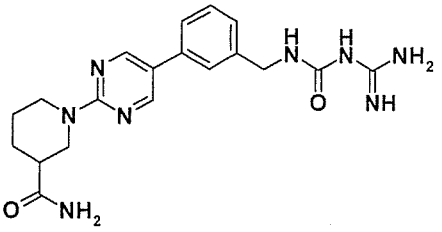
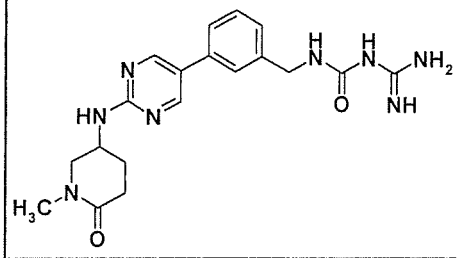
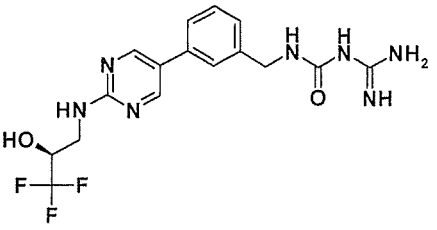
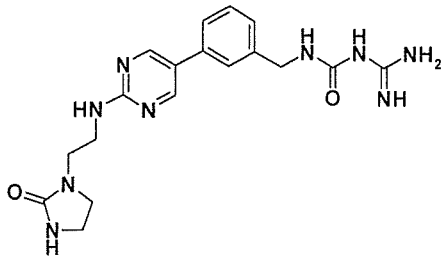
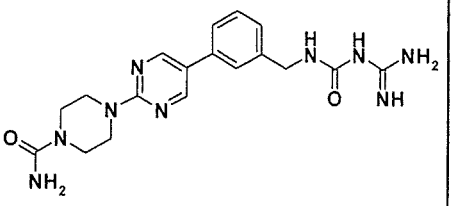
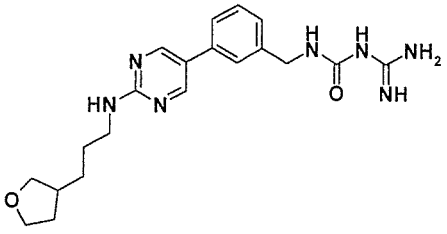
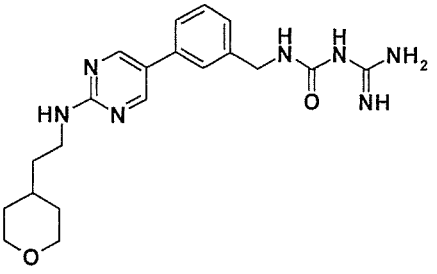
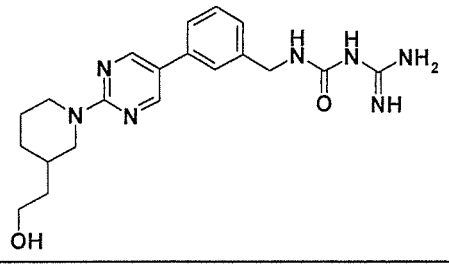
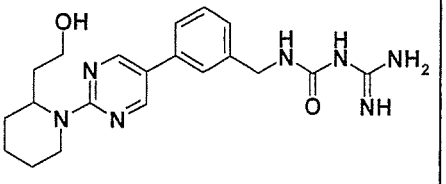
[0349]

[Table 109]

Ex	Syn	Structure	Ex	Syn	Structure
439	546		440	546	
441	546		442	546	
443	546		444	546	
445	546		446	546	
447	546		448	546	
449	546		450	546	

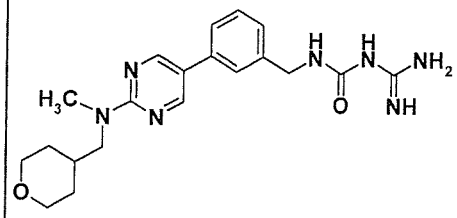
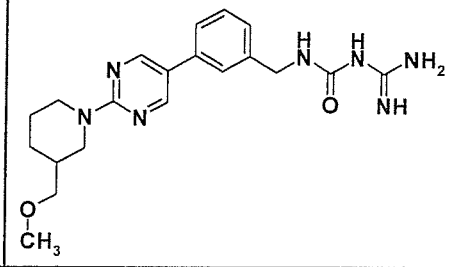
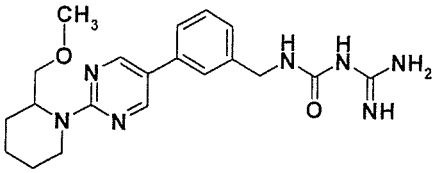
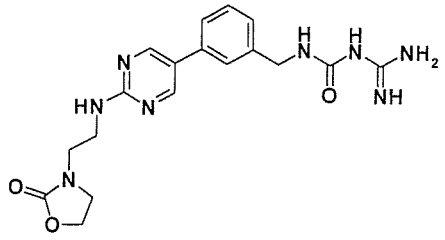
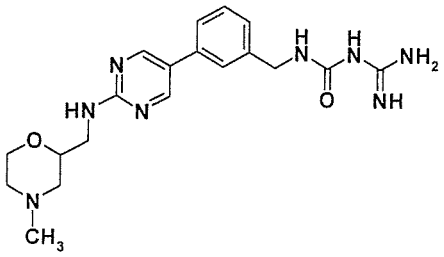
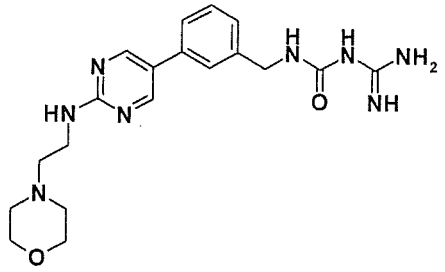
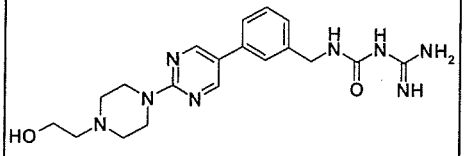
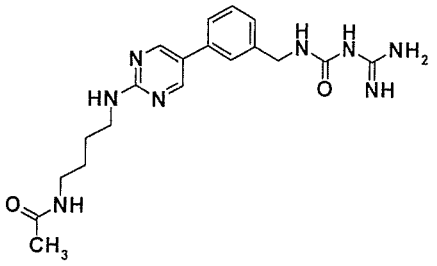
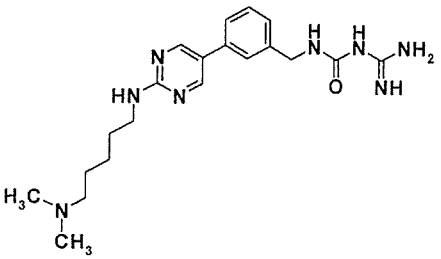
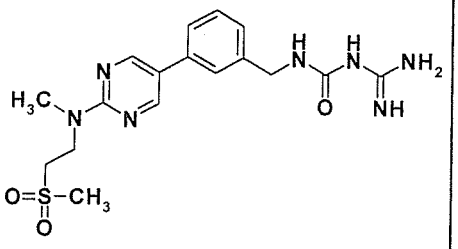
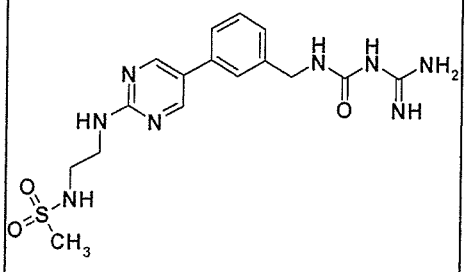
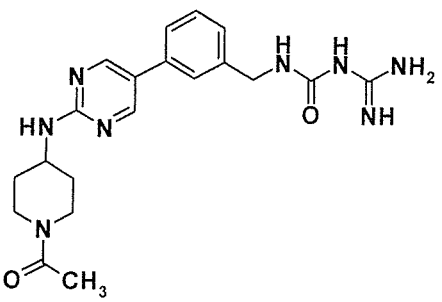
[0350]

[Table 110]

Ex	Syn	Structure	Ex	Syn	Structure
451	546		452	546	
453	546		454	546	
455	546		456	546	
457	546		458	546	
459	546		460	546	
461	546		462	546	

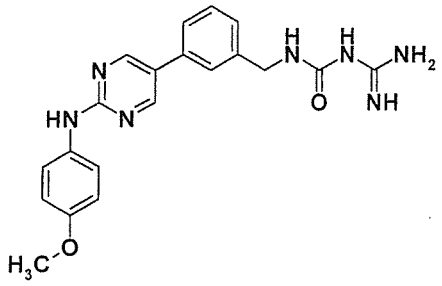
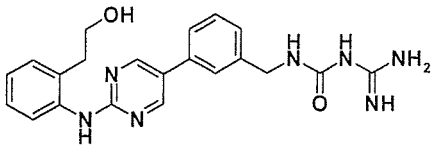
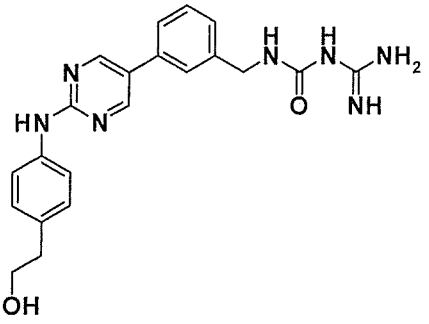
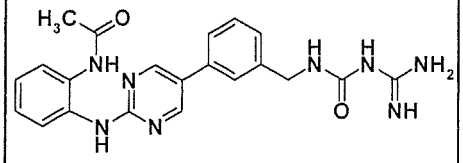
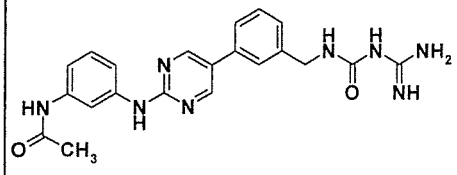
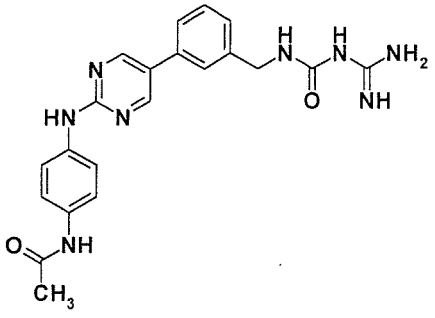
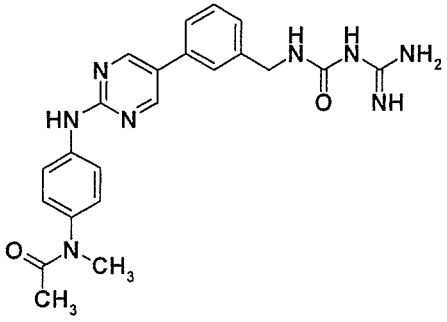
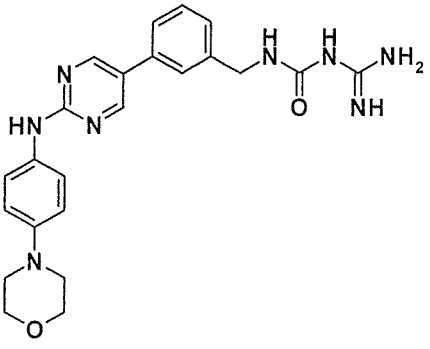
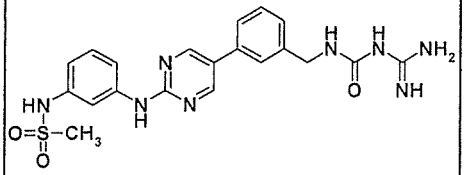
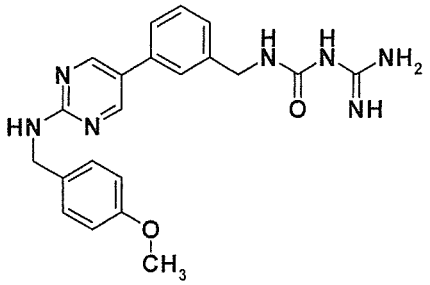
[0351]

[Table 111]

Ex	Syn	Structure	Ex	Syn	Structure
463	546		464	546	
465	546		466	546	
467	546		468	546	
469	546		470	546	
471	546		472	546	
473	546		474	546	

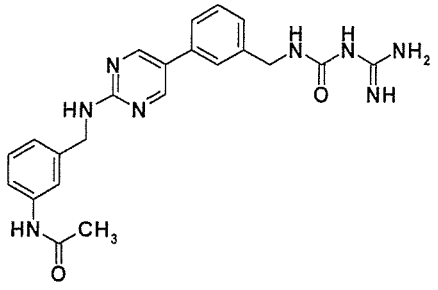
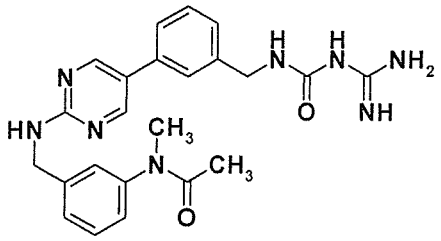
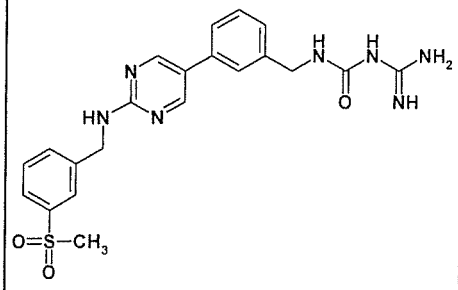
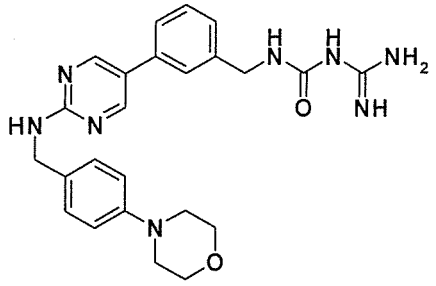
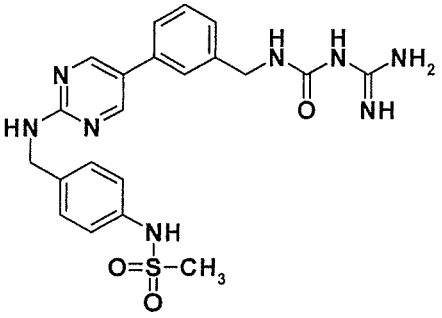
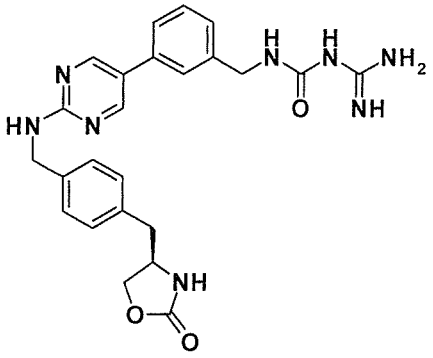
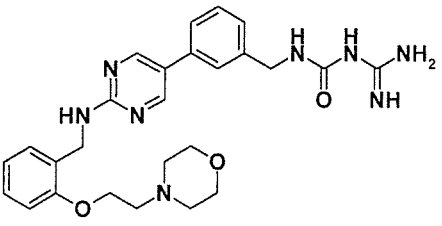
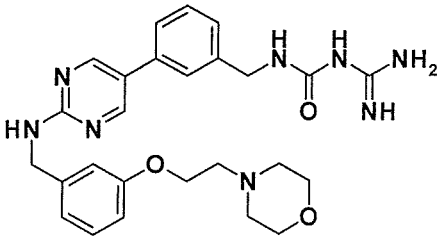
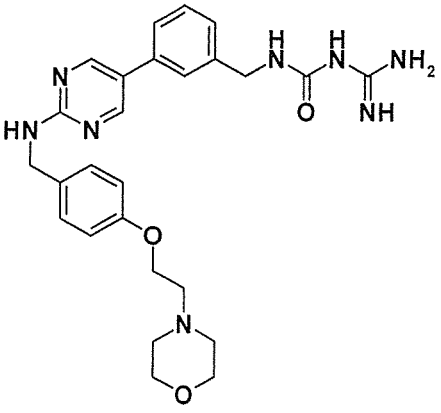
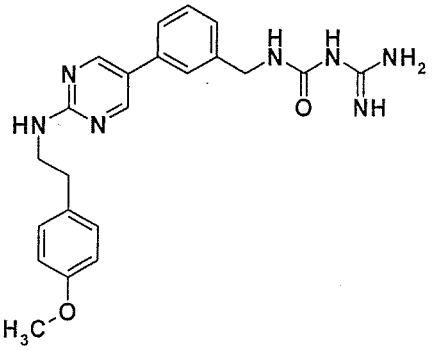
[0352]

[Table 112]

Ex	Syn	Structure	Ex	Syn	Structure
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477	546		478	546	
479	546		480	546	
481	546		482	546	
483	546		484	546	

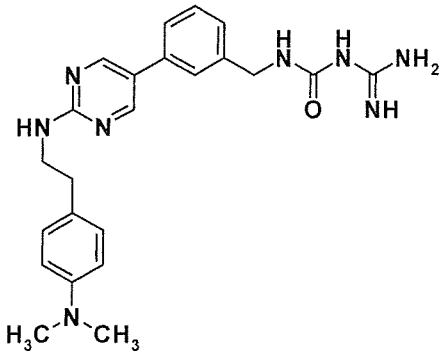
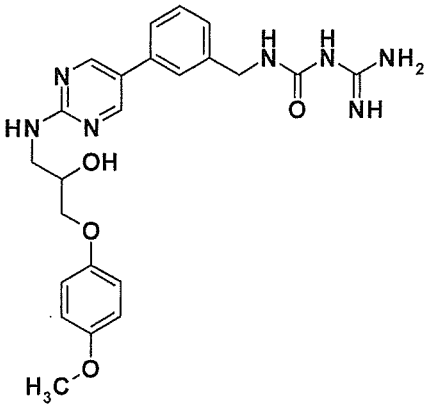
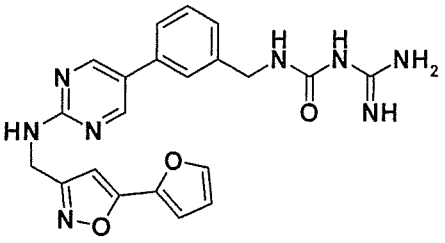
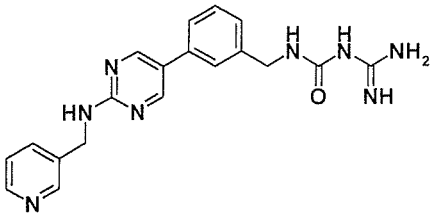
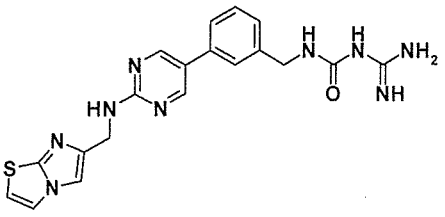
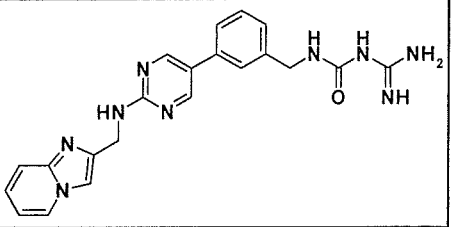
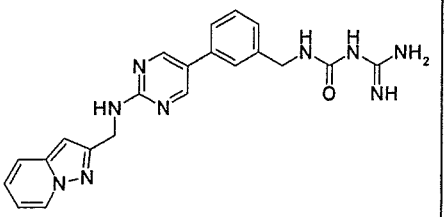
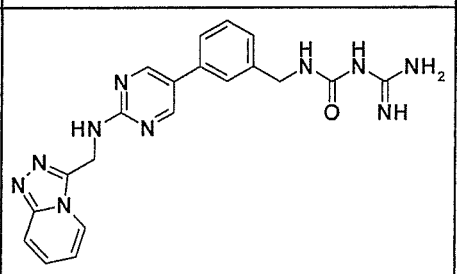
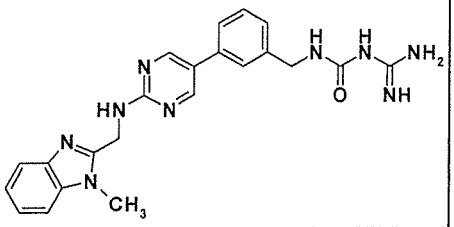
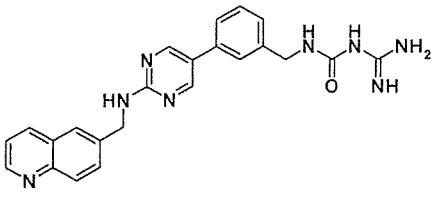
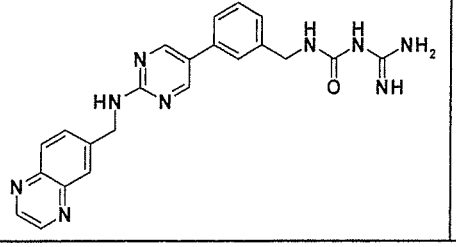
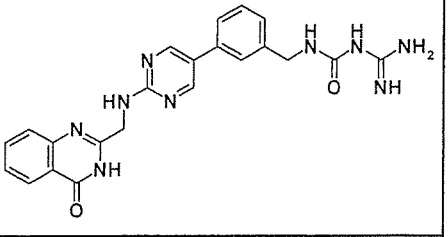
[0353]

[Table 113]

Ex	Syn	Structure	Ex	Syn	Structure
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487	546		488	546	
489	546		490	546	
491	546		492	546	
493	546		494	546	

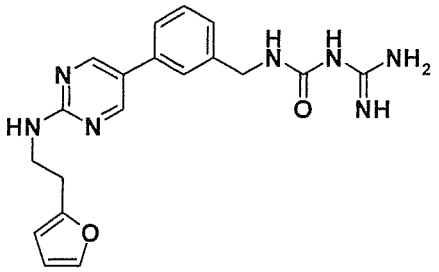
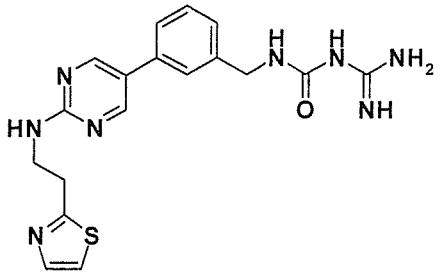
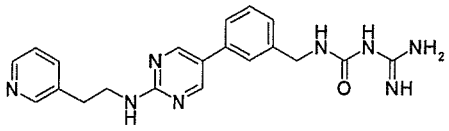
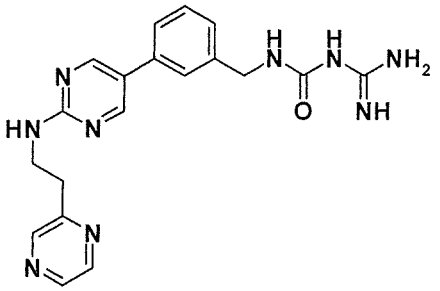
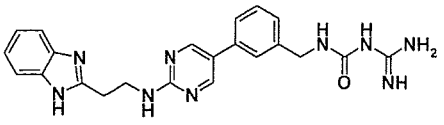
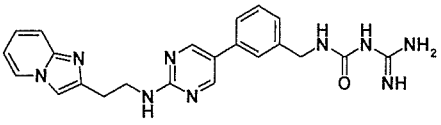
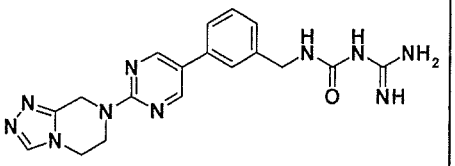
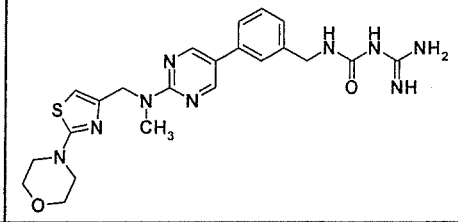
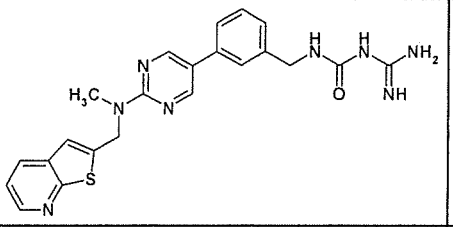
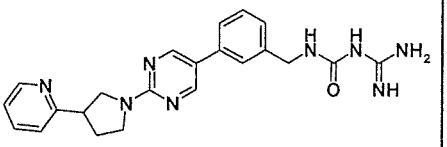
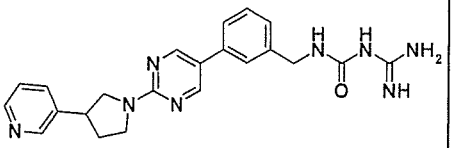
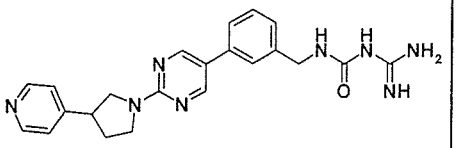
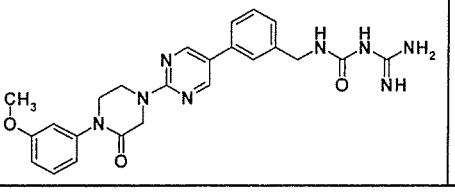
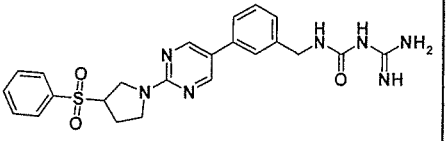
[0354]

[Table 114]

Ex	Syn	Structure	Ex	Syn	Structure
495	546		496	546	
497	546		498	546	
499	546		500	546	
501	546		502	546	
503	546		504	546	
505	546		506	546	

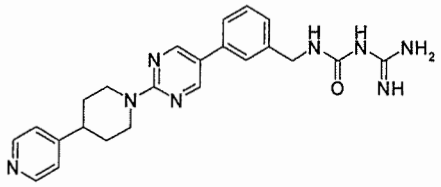
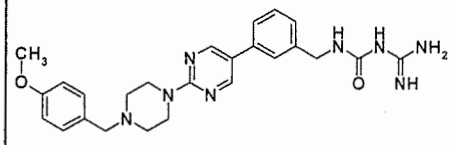
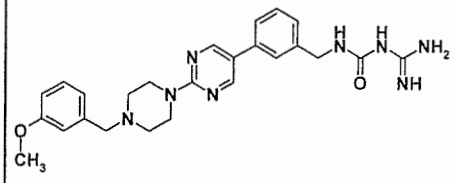
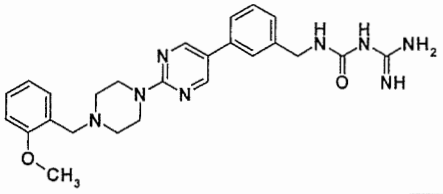
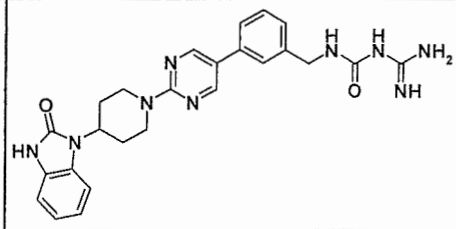
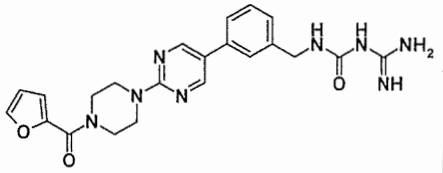
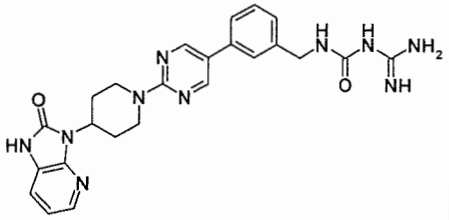
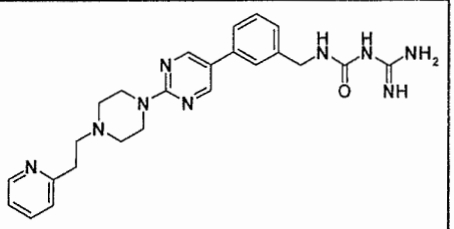
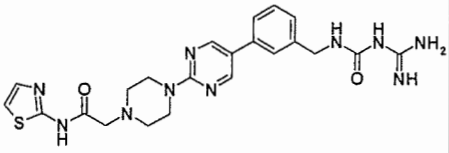
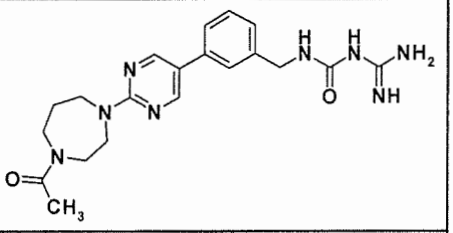
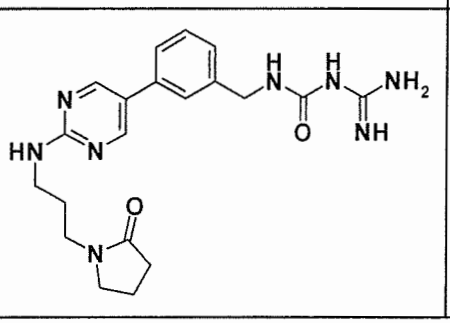
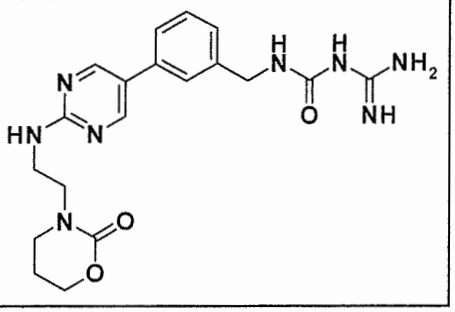
[0355]

[Table 115]

Ex	Syn	Structure	Ex	Syn	Structure
507	546		508	546	
509	546		510	546	
511	546		512	546	
513	546		514	546	
515	546		516	546	
517	546		518	546	
519	546		520	546	

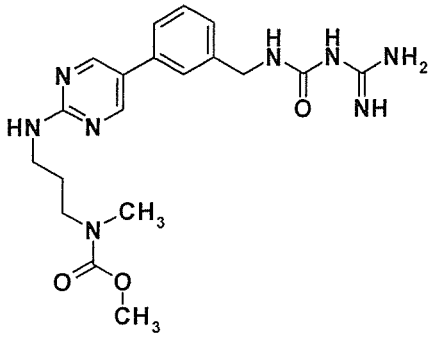
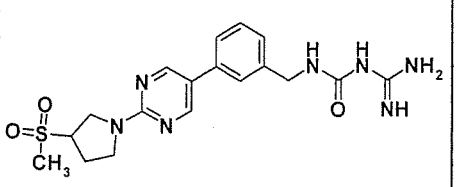
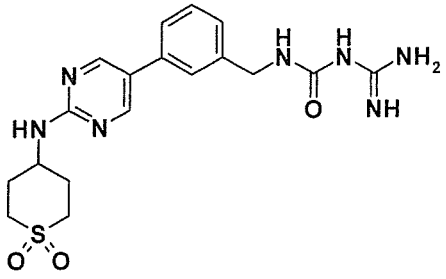
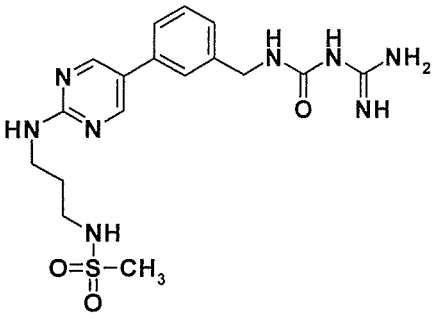
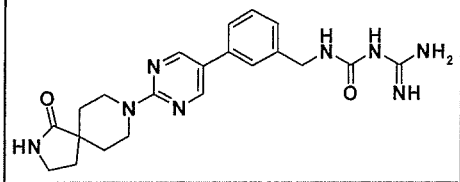
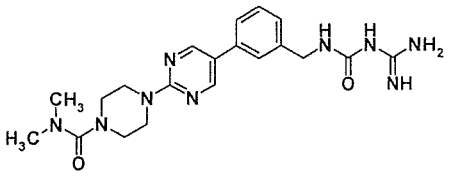
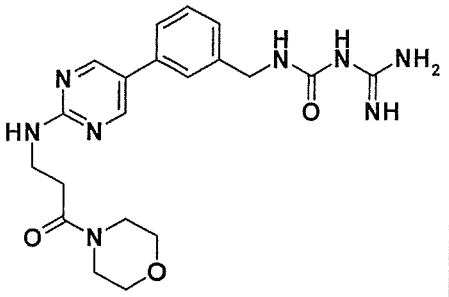
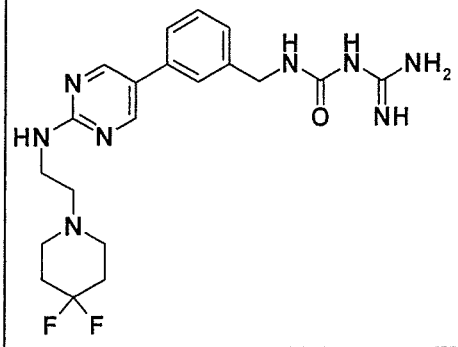
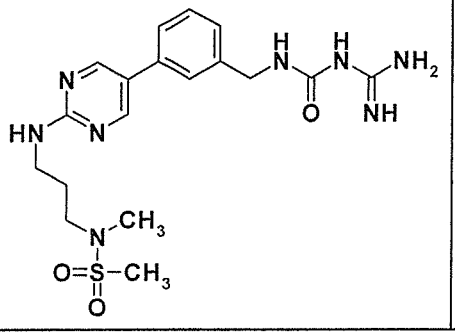
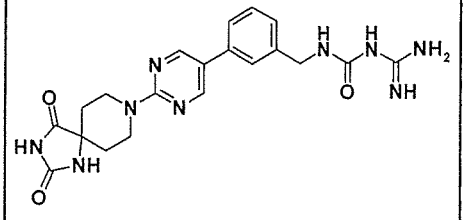
[0356]

[Table 116]

Ex	Syn	Structure	Ex	Syn	Structure
521	546		522	546	
523	546		524	546	
525	546		526	546	
527	546		528	546	
529	546		530	546	
531	546		532	546	

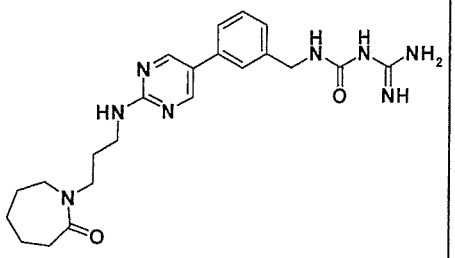
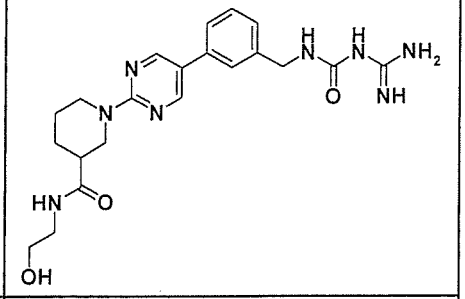
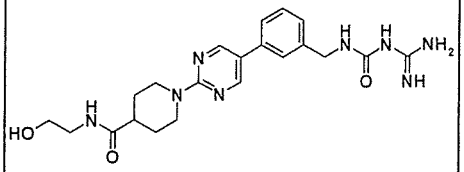
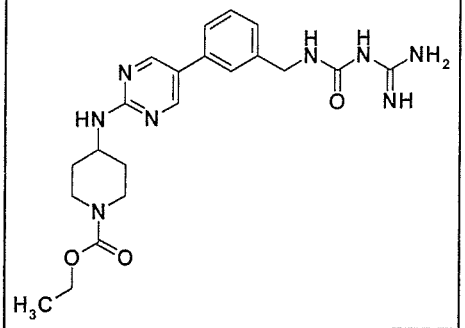
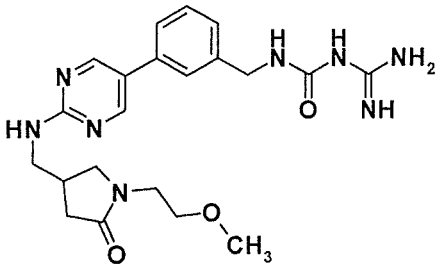
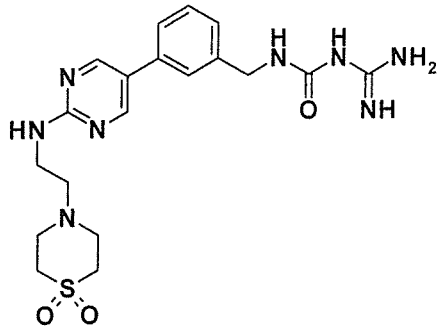
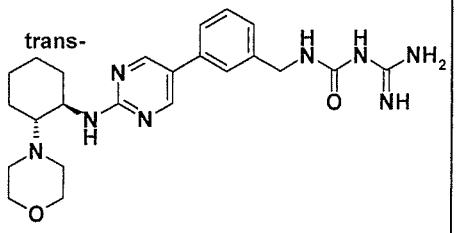
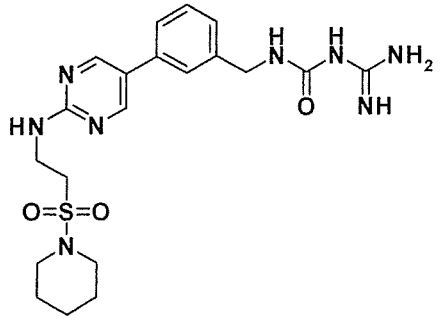
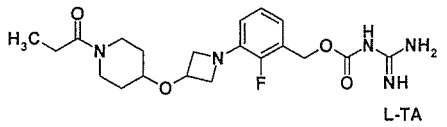
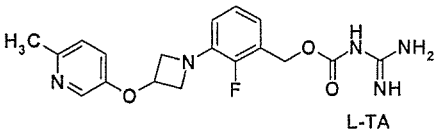
[0357]

[Table 117]

Ex	Syn	Structure	Ex	Syn	Structure
533	546		534	546	
535	546		536	546	
537	546		538	546	
539	546		540	546	
541	546		542	546	

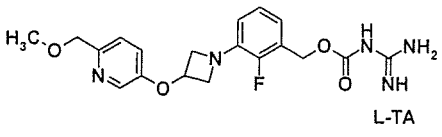
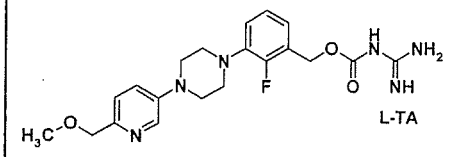
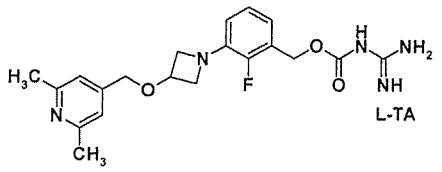
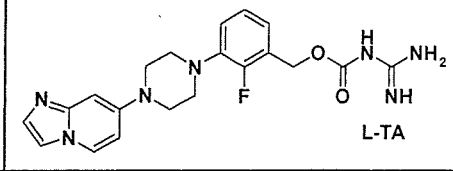
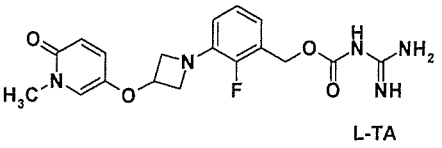
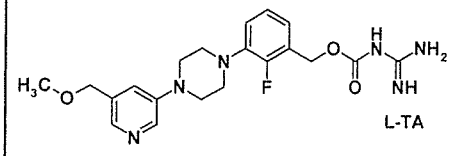
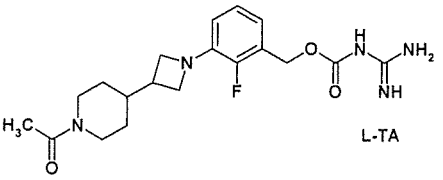
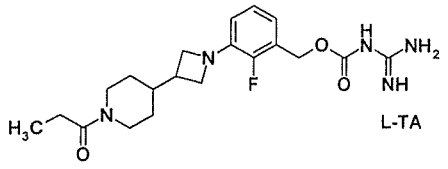
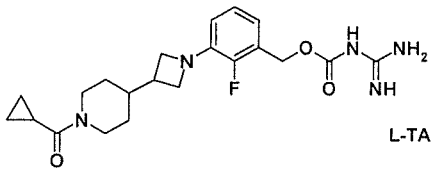
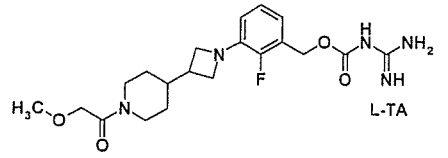
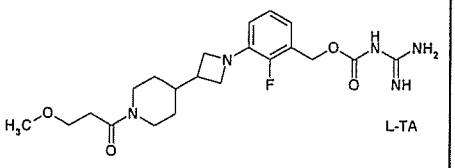
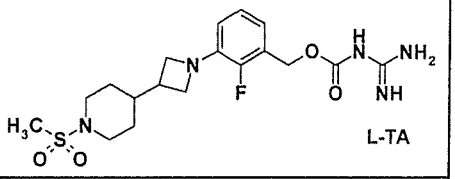
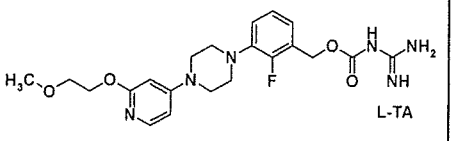
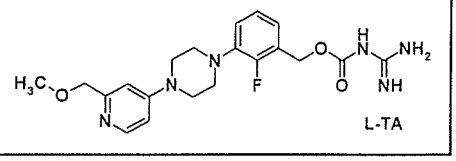
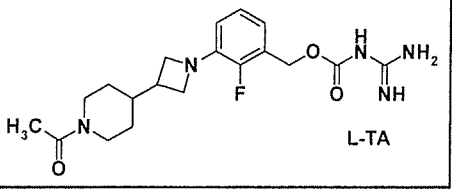
[0358]

[Table 118]

Ex	Syn	Structure	Ex	Syn	Structure
543	546		544	546	
545	546		546	546	
547	546		548	546	
549	546		550	546	
551	112		552	112	

[0359]

[Table 119]

Ex	Syn	Structure	Ex	Syn	Structure
553	112	 L-TA	554	112	 L-TA
555	112	 L-TA	556	112	 L-TA
557	112	 L-TA	558	112	 L-TA
559	567	 L-TA	560	112	 L-TA
561	112	 L-TA	562	112	 L-TA
563	112	 L-TA	564	112	 L-TA
565	112	 L-TA	566	112	 L-TA
567	567	 L-TA			

[0360]

[Table 120]

Ex	Data
1	ESI+: 384
2	ESI+: 401
3	ESI+: 388
4	ESI+: 417
5	ESI+: 418
6	ESI+: 426
7	ESI+: 430
8	ESI+: 443
9	ESI+: 431
10	ESI+: 487 NMR-DMSO-d_6: 1.37-1.50 (2H, m), 1.83-1.94 (2H, m), 3.21-3.50 (14H, m), 4.06-4.18 (2H, m), 5.29 (2H, s), 7.08-7.22 (3H, m), 8.49 (2H, s)
11	ESI+: 445 NMR-DMSO-d_6: 1.06-1.34 (2H, m), 1.71-1.85 (2H, m), 2.00 (3H, s), 2.01-2.14 (1H, m), 2.50-2.60 (1H, m), 3.00-3.11 (1H, m), 3.80-3.90 (1H, m), 4.25 (2H, d, J = 6.4 Hz), 4.36-4.46 (1H, m), 5.37 (2H, s), 7.39 (1H, t, J = 7.6 Hz), 7.55-7.63 (1H, m), 7.64-7.72 (1H, m), 8.78-8.83 (2H, m)
12	ESI+: 475
13	ESI+: 390
14	ESI+: 390
15	ESI+: 440
16	ESI+: 430
17	ESI+: 430
18	ESI+: 430
19	ESI+: 401
20	ESI+: 401
21	ESI+: 401
22	ESI+: 507
23	ESI+: 459 NMR-DMSO-d_6: 0.99 (3H, t, J = 7.4 Hz), 1.03-1.32 (2H, m), 1.71-1.87 (2H, m), 2.00-2.13 (1H, m), 2.32 (2H, q, J = 7.4 Hz), 2.50-2.62 (1H, m), 2.96-3.08 (1H, m), 3.84-3.95 (1H, m), 4.24 (2H, d, J = 6.25 Hz), 4.38-4.48 (1H, m), 5.37 (2H, s), 7.39 (1H, t, J = 7.7 Hz), 7.55-7.62 (1H, m), 7.64-7.71 (1H, m), 8.77-8.83 (2H, m)
24	ESI+: 473

[0361]

[Table 121]

Ex	Data
25	ESI+: 503
26	ESI+: 489
27	ESI+: 489
28	ESI+: 508
29	ESI+: 508
30	ESI+: 508
31	ESI+: 474
32	ESI+: 461
33	ESI+: 507
34	ESI+: 481
35	ESI+: 495
36	ESI+: 474
37	ESI+: 502
38	ESI+: 486
39	ESI+: 488
40	ESI+: 488
41	ESI+: 362
42	ESI+: 362
43	ESI+: 354
44	ESI+: 441
45	ESI+: 369
46	ESI+: 416 NMR-DMSO-d_6: 2.06 (3H, s), 3.54-3.56 (4H, m), 3.77-3.86 (4H, m), 5.35 (2H, s), 7.33-7.37 (1H, m), 7.49-7.54 (1H, m), 7.60-7.64 (1H, m), 8.61 (2H, s)
47	ESI+: 404
48	ESI+: 416
49	ESI+: 412
50	ESI+: 355
51	ESI+: 355 NMR-DMSO-d_6: 3.36-3.38 (4H, m), 3.59-3.62 (4H, m), 5.20 (2H, s), 6.91 (1H, d, J = 7.6 Hz), 7.06-7.08 (1H, m), 7.13 (1H, s), 7.28-7.32 (1H, m), 7.87 (1H, dd, J = 9.0,5.4 Hz), 8.15-8.18 (1H, m), 8.22 (1H, d, J = 5.3 Hz), 8.53 (1H, d)

[0362]

[Table 122]

Ex	Data
52	ESI+: 372 NMR-DMSO-d_6: 1.88-2.01 (4H, m), 2.83-2.89 (2H, m), 3.04-3.12 (1H, m), 3.49-3.52 (2H, m), 5.28 (2H, s), 7.08-7.12 (1H, m), 7.16-7.18 (2H, m), 8.08-8.09 (2H, m), 8.87-8.88 (2H, m)
53	ESI+: 373 NMR-DMSO-d_6: 3.17-3.19 (4H, m), 3.85-3.88 (4H, m), 5.29 (2H, s), 7.11-7.20 (3H, m), 7.27-7.28 (2H, m), 8.27-8.30 (2H, m)
54	ESI+: 459
55	ESI+: 416
56	ESI+: 430
57	ESI+: 402
58	ESI+: 372
59	ESI+: 449
60	ESI+: 391, 393
61	ESI+: 397
62	ESI+: 421
63	ESI+: 375 NMR-DMSO-d_6: 3.27 (3H, s), 3.89-3.95 (2H, m), 4.27-4.39 (3H, m), 5.35 (2H, s), 7.31-7.38 (1H, m), 7.48-7.55 (1H, m), 7.57-7.64 (1H, m), 8.53-8.58 (2H, m)
64	ESI+: 403 NMR-DMSO-d_6: 1.17 (3H, s), 1.41-1.60 (4H, m), 3.41-3.54 (2H, m), 4.20-4.29 (2H, m), 5.35 (2H, s), 7.31-7.37 (1H, m), 7.46-7.54 (1H, m), 7.57-7.64 (1H, m), 8.53-8.58 (2H, m)
65	ESI+: 389
66	ESI+: 403
67	ESI+: 403
68	ESI+: 445
69	ESI+: 493
70	ESI+: 494
71	ESI+: 473
72	ESI+: 499
73	ESI+: 487

[0363]

[Table 123]

Ex	Data
74	ESI+: 471 NMR-DMSO-d_6: 0.61-0.78 (4H, m), 1.00-1.35 (2H, m), 1.66-1.91 (2H, m), 1.92-2.02 (1H, m), 2.02-2.17 (1H, m), 2.53-2.69 (1H, m), 3.00-3.21 (1H, m), 4.15-4.48 (4H, m), 5.37 (2H, s), 7.33-7.43 (1H, m), 7.52-7.63 (1H, m), 7.63-7.72 (1H, m), 8.74-8.84 (2H, m)
75	ESI+: 483
76	ESI+: 490
77	ESI+: 464
78	ESI+: 478
79	ESI+: 417
80	ESI+: 427
81	ESI+: 375 NMR-DMSO-d_6: 3.67-3.71 (4H, m), 3.74-3.78 (4H, m), 5.35 (2H, s), 7.34 (1H, dd, J = 7.7, 7.7 Hz), 7.49-7.53 (1H, m), 7.59-7.63 (1H, m), 8.59-8.60 (2H, m)
82	ESI+: 375
83	ESI+: 361
84	ESI+: 509
85	ESI+: 510
86	ESI+: 362
87	ESI+: 402
88	ESI+: 403
89	ESI+: 419
90	ESI+: 402
91	ESI+: 473
92	ESI+: 428
93	ESI+: 458
94	ESI+: 396
95	ESI+: 387
96	ESI+: 374
97	ESI+: 387
98	ESI+: 387
99	ESI+: 465
100	ESI+: 419
101	ESI+: 457

[0364]

[Table 124]

Ex	Data
102	ESI+: 441
103	ESI+: 432
104	ESI+: 426
105	ESI+: 444 NMR-DMSO-d_6: 1.09-1.18 (1H, m), 1.22-1.32 (1H, m), 1.78 (2H, t, J = 16 Hz), 2.00 (3H, s), 2.01-2.11 (1H, m), 2.52-2.59 (1H, m), 3.00-3.09 (1H, m), 3.85 (1H, d, J = 14 Hz), 4.09 (2H, s), 4.24 (2H, d, J = 6 Hz), 4.40-4.42 (3H, m), 7.31 (1H, t, J = 7 Hz), 7.41 (1H, t, J = 7 Hz), 7.52 (1H, t, J = 7 Hz), 8.78-8.79 (2H, m)
106	ESI+: 470 NMR-DMSO-d_6: 0.62-0.75 (4H, m), 1.08-1.34 (2H, m), 1.72-1.89 (2H, m), 1.93-2.01 (1H, m), 2.05-2.15 (1H, m), 2.55-2.66 (1H, m), 3.05-3.17 (1H, m), 4.09 (2H, s), 4.20-4.45 (6H, m), 7.31 (1H, t, J = 7 Hz), 7.41 (1H, t, J = 7 Hz), 7.52 (1H, t, J = 7 Hz), 8.78-8.79 (2H, m)
107	ESI+: 413
108	ESI+: 415
109	ESI+: 459
110	ESI+: 487
111	ESI+: 458
112	FAB+: 428
113	ESI+: 503 NMR-DMSO-d_6: 3.10-3.19 (8H, m), 3.25 (3H, s), 3.42-3.55 (4H, m), 3.73-3.80 (2H, m), 4.12-4.21 (3H, m), 4.35-4.43 (1H, m), 5.04 (2H, s), 6.98-7.15 (3H, m), 8.25 (2H, s)
114	ESI+: 459
115	ESI+: 446
116	ESI+: 443
117	ESI+: 487
118	ESI+: 461
119	ESI+: 461
120	ESI+: 458
121	ESI+: 479
122	ESI+: 473
123	ESI+: 500
124	ESI+: 441

[0365]

[Table 125]

Ex	Data
125	ESI+: 447
126	ESI+: 404
127	ESI+: 367
128	ESI+: 382
129	ESI+: 408
130	ESI+: 338
131	ESI+: 297
132	ESI+: 474
133	ESI+: 404
134	ESI+: 366
135	ESI+: 394
136	ESI+: 334
137	ESI+: 449
138	ESI+: 436
139	ESI+: 411
140	EI: 431
141	ESI+: 433
142	ESI+: 450
143	ESI+: 464
144	ESI+: 450 NMR-DMSO-d_6: 1.11 (3H, t, J = 7 Hz), 1.31-1.51 (4H, m), 1.59-1.73 (2H, m), 1.77-1.88 (2H, m), 2.59-2.70 (1H, m), 2.88-3.04 (4H, m), 3.39 (2H, q, J = 7 Hz), 3.47-3.53 (1H, m), 3.55-3.70 (4H, m), 4.21 (2H, s), 5.05 (2H, s), 6.97-7.05 (2H, m), 7.05-7.13 (1H, m)
145	ESI+: 464
146	ESI+: 297
147	ESI+: 341
148	ESI+: 422
149	ESI+: 352
150	ESI+: 414
151	ESI+: 400
152	ESI+: 436
153	ESI+: 436
154	ESI+: 489

[0366]

[Table 126]

Ex	Data
155	ESI+: 487
156	ESI+: 374
157	ESI+: 388
158	ESI+: 400
159	ESI+: 402
160	ESI+: 402
161	ESI+: 442
162	ESI+: 421
163	ESI+: 449
164	ESI+: 403
165	ESI+: 431
166	ESI+: 443
167	ESI+: 529
168	ESI+: 555
169	ESI+: 445
170	ESI+: 458
171	ESI+: 466
172	ESI+: 493
173	ESI+: 371
174	ESI+: 362
175	ESI+: 358
176	ESI+: 371
177	ESI+: 385
178	ESI+: 359
179	ESI+: 341
180	ESI+: 431
181	ESI+: 405
182	ESI+: 458
183	ESI+: 458 NMR-DMSO-d_6: 1.76-1.92 (4H, m), 2.66-2.78 (2H, m), 2.87-2.98 (1H, m), 3.24 (3H, s), 3.50-3.60 (2H, m), 3.72-3.80 (2H, m), 4.10-4.18 (2H, m), 4.24 (1H, s), 4.25-4.31 (1H, m), 5.10 (2H, s), 7.13-7.21 (1H, m), 7.25-7.32 (1H, m), 7.32-7.40 (1H, m), 8.22 (2H, s)
184	ESI+: 458

[0367]

[Table 127]

Ex	Data
185	ESI+: 458
186	ESI+: 374
187	ESI+: 374
188	ESI+: 474
189	ESI+: 474
190	ESI+: 474
191	ESI+: 380
192	ESI+: 473
193	ESI+: 473
194	ESI+: 420
195	ESI+: 483
196	ESI+: 483
197	ESI+: 364
198	ESI+: 320
199	ESI+: 390
200	ESI+: 431
201	ESI+: 363
202	ESI+: 461
203	ESI+: 460
204	ESI+: 325
205	ESI+: 408
206	ESI+: 406
207	ESI+: 490
208	ESI+: 422
209	ESI+: 420
210	ESI+: 383
211	ESI+: 403
212	ESI+: 453
213	ESI+: 467
214	ESI+: 433
215	ESI+: 447
216	ESI+: 448
217	ESI+: 450

[0368]

[Table 128]

Ex	Data
218	ESI+: 450
219	ESI+: 409
220	ESI+: 436
221	ESI+: 409
222	ESI+: 422
223	ESI+: 381
224	ESI+: 407
225	ESI+: 408
226	ESI+: 458
227	ESI+: 478
228	ESI+: 422
229	ESI+: 462
230	ESI+: 388
231	ESI+: 388
232	ESI+: 360
233	ESI+: 374
234	ESI+: 374
235	ESI+: 402
236	ESI+: 416
237	ESI+: 374 NMR-DMSO-d_6: 2.39 (3H, s), 3.84-3.92 (2H, m), 4.21 (1H, s), 4.40-4.48 (2H, m), 5.03 (2H, s), 5.12-5.21 (1H, m), 6.56-6.64 (1H, m), 6.75-6.82 (1H, m), 6.98-7.04 (1H, m), 7.13-7.22 (2H, m), 8.02-8.08 (1H, m)
238	ESI+: 388
239	ESI+: 445
240	ESI+: 514
241	ESI+: 460 NMR-DMSO-d_6: 2.63 (2H, t, J = 6.7 Hz), 3.24 (3H, s), 3.57-3.60 (6H, m), 3.76-3.85 (4H, m), 5.14 (2H, s), 7.29 (1H, t, J = 7.6 Hz), 7.41-7.45 (1H, m), 7.50-7.55 (1H, m), 8.59-8.60 (2H, m)
242	ESI+: 460
243	ESI+: 390

[0369]

[Table 129]

Ex	Data
244	ESI+: 374 NMR-DMSO-d_6: 3.67-3.70 (4H, m), 3.74-3.78 (4H, m), 4.40 (2H, d, J = 5.7 Hz), 7.26 (1H, t, J = 7.6 Hz), 7.31-7.35 (1H, m), 7.44-7.48 (1H, m), 7.58-7.59 (2H, m)
245	ESI+: 382
246	ESI+: 362
247	ESI+: 375
248	ESI+: 402
249	ESI+: 393
250	ESI+: 458
251	ESI+: 389
252	ESI+: 405
253	ESI+: 418
254	ESI+: 492
255	ESI+: 459
256	ESI+: 464
257	ESI+: 459
258	ESI+: 423
259	ESI+: 423
260	ESI+: 486
261	ESI+: 486
262	ESI+: 458
263	ESI+: 488
264	ESI+: 487
265	ESI+: 487
266	ESI+: 474
267	ESI+: 496
268	ESI+: 429
269	ESI+: 455
270	ESI+: 410
271	ESI+: 412
272	ESI+: 422
273	ESI+: 422
274	ESI+: 436
275	ESI+: 394

[0370]

[Table 130]

Ex	Data
276	ESI+: 431
277	ESI+: 431
278	ESI+: 450
279	ESI+: 476
280	ESI+: 410
281	ESI+: 436
282	ESI+: 461
283	ESI+: 422
284	ESI+: 396
285	ESI+: 422
286	ESI+: 382
287	ESI+: 473
288	ESI+: 381
289	ESI+: 408
290	ESI+: 428
291	ESI+: 394
292	ESI+: 408
293	ESI+: 373 NMR-DMSO-d_6: 3.15-3.17 (4H, m), 3.35-3.37 (4H, m), 5.07 (2H, s), 7.01-7.14 (3H, m), 7.24 (1H, dd, J = 4.6, 8.4 Hz), 7.37-7.40 (1H, m), 8.03 (1H, dd, J = 1.3, 4.6 Hz), 8.36 (1H, d, J = 2.8 Hz)
294	ESI+: 373
295	ESI+: 387 NMR-DMSO-d_6: 2.37 (3H, s), 3.14-3.17 (4H, m), 3.28-3.30 (4H, m), 5.06 (2H, s), 7.01-7.14 (4H, m), 7.31 (1H, dd, J = 3.0, 8.5 Hz), 8.21 (1H, d, J = 2.9 Hz)
296	ESI+: 387
297	ESI+: 527
298	ESI+: 435
299	ESI+: 387
300	ESI+: 387 NMR-DMSO-d_6: 2.37 (3H, s), 3.14-3.17 (4H, m), 3.28-3.30 (4H, m), 5.06 (2H, s), 7.01-7.14 (4H, m), 7.31 (1H, dd, J = 3.0, 8.5 Hz), 8.21 (1H, d, J = 2.9 Hz)
301	ESI+: 379
302	ESI+: 387

[0371]

[Table 131]

Ex	Data
303	ESI+: 430
304	ESI+: 387
305	ESI+: 374
306	ESI+: 401
307	ESI+: 398
308	ESI+: 400
309	ESI+: 370
310	ESI+: 384
311	ESI+: 372
312	ESI+: 386
313	ESI+: 388
314	ESI+: 374
315	ESI+: 473
316	ESI+: 459 NMR-DMSO-d_6: 3.20-3.29 (8H, m), 3.30-3.39 (3H, m), 3.88-3.98 (2H, m), 4.28-4.37 (3H, m), 5.29 (2H, s), 7.09-7.22 (3H, m), 8.48 (2H, s)
317	ESI+: 457
318	ESI+: 509
319	ESI+: 357 NMR-DMSO-d_6: 3.67-3.70 (4H, m), 3.74-3.77 (4H, m), 5.09 (2H, s), 7.33 (1H, d, J = 7.6 Hz), 7.44 (1H, dd, J = 7.6,7.6 Hz), 7.58 (1H, d, J = 7.6 Hz), 7.62 (1H, s), 8.71 (2H, s)
320	ESI+: 355
321	ESI+: 370
322	ESI+: 356 NMR-DMSO-d_6: 3.64-3.71 (4H, m), 3.72-3.78 (4H, m), 4.02 (1H, s), 4.27-4.38 (2H, m), 7.21-7.29 (1H, m), 7.35-7.43 (1H, m), 7.46-7.57 (2H, m), 8.70 (2H, s)
323	ESI+: 354
324	FAB+: 446
325	ESI+: 500
326	FAB+: 529
327	ESI+: 417
328	ESI+: 417
329	ESI+: 489

[0372]

[Table 132]

Ex	Data
330	ESI+: 412
331	ESI+: 444
332	ESI+: 398
333	ESI+: 443
334	ESI+: 447
335	ESI+: 522 NMR-DMSO-d_6: 2.51-2.59 (3H, m), 2.77-2.86 (3H, m), 3.42-3.60 (4H, br s), 4.00-4.40 (4H, br s), 7.30-7.40 (3H, m), 7.50-7.60 (3H, m), 7.61-7.68 (1H, m), 8.65-8.70 (2H, m)
336	ESI+: 489
337	ESI+: 490
338	ESI+: 431 NMR-DMSO-d_6: 1.09-1.20 (2H, m), 1.75-1.78 (2H, m), 1.93-2.04 (1H, m), 2.20 (2H, d, J = 6.9 Hz), 2.92-2.99 (2H, m), 4.67-4.72 (2H, m), 4.84 and 5.35 (2H, s and s), 7.28-7.35 (1H, m), 7.48-7.62 (2H, m), 8.55-8.56 (2H, m)
339	ESI+: 446
340	ESI+: 422
341	ESI+: 422
342	ESI+: 489
343	ESI+: 433
344	ESI+: 459 NMR-DMSO-d_6: 1.00-1.11 (2H, m), 1.21-1.26 (2H, m), 1.51-1.59 (3H, m), 1.72-1.76 (2H, m), 2.21 (2H, t, J = 7.3 Hz), 2.87-2.94 (2H, m), 4.68-4.73 (2H, m), 5.11 (2H, s), 7.27 (1H, dd, J = 7.6, 7.6 Hz), 7.38-7.42 (1H, m), 7.48-7.52 (1H, m), 8.53-8.54 (2H, m)
345	ESI+: 389
346	ESI+: 385
347	ESI+: 384
348	ESI+: 340
349	ESI+: 439
350	ESI+: 389
351	ESI+: 432
352	FAB+: 439
353	ESI+: 384

[0373]

[Table 133]

Ex	Data
354	ESI+: 359
355	ESI+: 385
356	ESI+: 399
357	ESI+: 413
358	ESI+: 433
359	ESI+: 377
360	ESI+: 377
361	ESI+: 359
362	ESI+: 373
363	ESI+: 371
364	ESI+: 333
365	ESI+: 403 NMR-DMSO-d_6: 1.37-1.52 (2H, m), 1.85-1.97 (2H, m), 3.29 (3H, s), 3.40-3.52 (3H, m), 4.16-4.27 (3H, m), 5.11 (2H, s), 7.23-7.32 (1H, m), 7.36-7.43 (1H, m), 7.46-7.54 (1H, m), 8.52-8.57 (2H, m)
366	ESI+: 373
367	ESI+: 391
368	ESI+: 458
369	ESI+: 391
370	ESI+: 389
371	ESI+: 375
372	ESI+: 489
373	ESI+: 355
374	ESI+: 375
375	ESI+: 528
376	ESI+: 557
377	APCI/ESI+: 459
378	APCI/ESI+: 526
379	APCI/ESI+: 526
380	APCI/ESI+: 517
381	ESI+: 579
382	ESI+: 517
383	ESI+: 517
384	ESI+: 580

[0374]

[Table 134]

Ex	Data
385	ESI+: 459
386	ESI+: 474
387	ESI+: 461
388	ESI+: 487
389	ESI+: 431
390	ESI+: 431
391	ESI+: 472
392	APCI/ESI+: 457
393	APCI/ESI+: 471
394	APCI/ESI+: 475
395	APCI/ESI+: 550
396	ESI+: 493
397	ESI+: 523, 525
398	ESI+: 426
399	ESI+: 330
400	ESI+: 342
401	ESI+: 343
402	ESI+: 344
403	ESI+: 344
404	ESI+: 356
405	ESI+: 356
406	ESI+: 356
407	ESI+: 357
408	ESI+: 357
409	ESI+: 358
410	ESI+: 369
411	ESI+: 370
412	ESI+: 370
413	ESI+: 370
414	ESI+: 370
415	ESI+: 370
416	ESI+: 370
417	ESI+: 371

[0375]

[Table 135]

Ex	Data
418	ESI+: 371
419	ESI+: 371
420	ESI+: 371
421	ESI+: 372
422	ESI+: 372
423	ESI+: 372
424	ESI+: 374
425	ESI+: 376
426	ESI+: 383
427	ESI+: 383
428	ESI+: 383
429	ESI+: 383
430	ESI+: 383
431	ESI+: 384
432	ESI+: 384
433	ESI+: 384
434	ESI+: 384
435	ESI+: 384
436	ESI+: 384
437	ESI+: 384
438	ESI+: 384
439	ESI+: 384
440	ESI+: 385
441	ESI+: 385
442	ESI+: 386
443	ESI+: 386
444	ESI+: 386
445	ESI+: 386
446	ESI+: 386
447	ESI+: 388
448	ESI+: 392
449	ESI+: 393
450	ESI+: 397

[0376]

[Table 136]

Ex	Data
451	ESI+: 397
452	ESI+: 397
453	ESI+: 397
454	ESI+: 397
455	ESI+: 397
456	ESI+: 398
457	ESI+: 398
458	ESI+: 398
459	ESI+: 398
460	ESI+: 398
461	ESI+: 398
462	ESI+: 398
463	ESI+: 398
464	ESI+: 398
465	ESI+: 398
466	ESI+: 399
467	ESI+: 399
468	ESI+: 399
469	ESI+: 399
470	ESI+: 399
471	ESI+: 399
472	ESI+: 406
473	ESI+: 407
474	ESI+: 411
475	ESI+: 392
476	ESI+: 406
477	ESI+: 406
478	ESI+: 419
479	ESI+: 419
480	ESI+: 419
481	ESI+: 433
482	ESI+: 447
483	ESI+: 455

[0377]

[Table 137]

Ex	Data
484	ESI+: 406
485	ESI+: 433
486	ESI+: 447
487	ESI+: 454
488	ESI+: 461
489	ESI+: 469
490	ESI+: 475
491	ESI+: 505
492	ESI+: 505
493	ESI+: 505
494	ESI+: 420
495	ESI+: 433
496	ESI+: 466
497	ESI+: 433
498	ESI+: 377
499	ESI+: 422
500	ESI+: 416
501	ESI+: 416
502	ESI+: 417
503	ESI+: 430
504	ESI+: 427
505	ESI+: 428
506	ESI+: 444
507	ESI+: 380
508	ESI+: 397
509	ESI+: 391
510	ESI+: 392
511	ESI+: 430
512	ESI+: 430
513	ESI+: 393
514	ESI+: 482
515	ESI+: 447
516	ESI+: 417

[0378]

[Table 138]

Ex	Data
517	ESI+: 417
518	ESI+: 417
519	ESI+: 475
520	ESI+: 480
521	ESI+: 431
522	ESI+: 475
523	ESI+: 475
524	ESI+: 475
525	ESI+: 486
526	ESI+: 449
527	ESI+: 487
528	ESI+: 460
529	ESI+: 495
530	ESI+: 411
531	ESI+: 411
532	ESI+: 413
533	ESI+: 415
534	ESI+: 418
535	ESI+: 418
536	ESI+: 421
537	ESI+: 423
538	ESI+: 426
539	ESI+: 427
540	ESI+: 433
541	ESI+: 435
542	ESI+: 438
543	ESI+: 439
544	ESI+: 441
545	ESI+: 441
546	ESI+: 441
547	ESI+: 441
548	ESI+: 447
549	ESI+: 453
550	ESI+: 461

[0379]

[Table 139]

Ex	Data
551	ESI+: 422 NMR-DMSO-d_6: 1.02 (3H, t, J = 7.4 Hz), 1.27-1.50 (2H, m), 1.77-1.93 (2H, m), 2.35 (2H, q, J = 7.4 Hz), 3.03 (1H, t, J = 9.9 Hz), 3.19 (1H, t, J = 9.9 Hz), 3.57-3.80 (4H, m), 3.91-4.04 (1H, m), 4.19-4.27 (3H, m), 4.54-4.63 (1H, m), 5.05 (2H, s), 6.57 (1H, t, J = 8.0 Hz), 6.79 (1H, t, J = 6.4 Hz), 7.03 (tH, 1, J = 7.8 Hz).
552	ESI+: 374 NMR-DMSO-d_6: 2.40 (3H, s), 3.82-3.89 (2H, m), 4.21 (2H, s), 4.37-4.44 (2H, m), 5.03 (2H, s), 5.13-5.20 (1H, m), 6.55-6.61 (1H, m), 6.74-6.81 (1H, m), 7.01 (1H, t, J = 7.8 Hz), 7.17-7.27 (2H, m), 8.12 (1H, d, J = 2.7 Hz).
553	ESI+: 404 NMR-DMSO-d_6: 3.28 (3H, s), 3.84-3.91 (2H, m), 4.21 (2H, s), 4.38-4.45 (4H, m), 5.02 (2H, s), 5.18-5.24 (1H, m), 6.55-6.62 (1H, m), 6.75-6.80 (1H, m), 7.01 (1H, t, J = 7.8 Hz), 7.34-7.37 (2H, m), 8.19-8.22 (1H, m).
554	ESI+: 417 NMR-DMSO-d_6: 3.13-3.20 (4H, m), 3.31 (3H, s), 3.32-3.39 (4H, m), 4.21 (2H, s), 4.39 (2H, s), 5.07 (2H, s), 7.00-7.15 (3H, m), 7.26 (1H, d, J = 7.6 Hz), 7.37-7.42 (1H, m), 8.29 (1H, d, J = 2.8 Hz).
555	ESI+: 402 NMR-DMSO-d_6: 2.41 (6H, s), 3.72-3.78 (2H, m), 4.12-4.19 (2H, m), 4.20 (2H, s), 4.45 (2H, s), 4.46-4.51 (1H, m), 5.01 (2H, s), 6.50-6.56 (1H, m), 6.71-6.77 (1H, m), 6.95-7.02 (3H, m).
556	ESI+: 412 NMR-DMSO-d_6: 3.12-3.20 (4H, m), 3.37-3.45 (4H, m), 4.06 (1H, s), 5.03 (2H, s), 6.77 (1H, d, J = 2.2 Hz), 6.94-7.14 (4H, m), 7.42 (1H, d, J = 1.4 Hz), 7.69 (1H, d, J = 0.8 Hz), 8.37 (1H, d, J = 7.6 Hz).
557	ESI+: 390 NMR-DMSO-d_6: 3.39 (3H, s), 3.79-3.86 (2H, m), 4.20 (2H, s), 4.29-4.37 (2H, m), 4.87-4.94 (1H, m), 5.02 (2H, s), 6.35-6.40 (1H, m), 6.57 (1H, t, J = 8.0 Hz), 6.77 (1H, t, J = 6.4 Hz), 7.01 (1H, t, J = 7.8 Hz), 7.29-7.35 (2H, m).
558	ESI+: 417 NMR-DMSO-d_6: 3.13-3.19 (4H, m), 3.30 (3H, s), 3.33-3.40 (4H, m), 4.21 (2H, s), 4.41 (2H, s), 5.08 (2H, s), 7.01-7.15 (3H, m), 7.31 (1H, s), 7.99 (1H, d, J = 1.4 Hz), 8.29 (1H, d, J = 2.7 Hz).

[0380]

[Table 140]

Ex	Data
559	ESI+: 392 NMR-DMSO-d_6: 0.81-1.09 (2H, m), 1.59-1.75 (3H, m), 1.98 (3H, s), 2.39-2.52 (2H, m), 2.93-3.03 (1H, m), 3.58-3.65 (2H, m), 3.77-3.85 (1H, m), 3.93-4.01 (2H, m), 4.21 (2H, s), 4.34-4.42 (1H, m), 5.01 (2H, s), 6.46-6.52 (1H, m), 6.69-6.74 (1H, m), 6.97 (1H, t, J = 7.8 Hz).
560	ESI+: 406 NMR-DMSO-d_6: 0.82-1.04 (5H, m), 1.59-1.78 (3H, m), 2.29 (2H, q, J = 7.4 Hz), 2.37-2.49 (2H, m), 2.89-2.99 (1H, m), 3.57-3.65 (2H, m), 3.79-3.89 (1H, m), 3.93-4.00 (2H, m), 4.18 (1H, s), 4.34-4.43 (1H, m), 4.98 (2H, s), 6.44-6.52 (1H, m), 6.67-6.74 (1H, m), 6.97 (1H, t, J = 7.8 Hz).
561	ESI+: 418 NMR-DMSO-d_6: 0.63-0.75 (4H, m), 0.83-1.07 (2H, m), 1.56-1.80 (3H, m), 1.89-2.00 (1H, m), 2.38-2.59 (2H, m), 2.99-3.11 (1H, m), 3.57-3.65 (2H, m), 3.92-4.01 (2H, m), 4.18 (1H, s), 4.19-4.22 (2H, m), 4.98 (2H, s), 6.44-6.52 (1H, m), 6.67-6.73 (1H, m), 6.97 (1H, t, J = 7.7 Hz).
562	ESI+: 422 NMR-DMSO-d_6: 0.85-1.09 (2H, m), 1.62-1.76 (3H, m), 2.38-2.59 (2H, m), 2.87-2.97 (1H, m), 3.27 (3H, s), 3.58-3.65 (2H, m), 3.72-3.80 (1H, m), 3.93-4.11 (4H, m), 4.20 (2H, m), 4.30-4.38 (1H, m), 5.00 (2H, s), 6.45-6.52 (1H, m), 6.68-6.74 (1H, m), 6.97 (1H, t, J = 7.7 Hz).
563	ESI+: 436 NMR-DMSO-d_6: 0.83-1.52 (2H, m), 1.60-1.75 (3H, m), 2.37-2.58 (5H, m), 2.90-3.00 (1H, m), 3.22 (3H, s), 3.53 (2H, t, J = 6.4 Hz), 3.58-3.65 (2H, m), 3.85-3.92 (1H, m), 3.93-4.01 (2H, m), 4.18 (1H, s), 4.34-4.42 (1H, m), 4.98 (2H, s), 4.45-4.50 (1H, m), 6.67-6.73 (1H, m), 6.97 (1H, t, J = 7.8 Hz).
564	ESI+: 428 NMR-DMSO-d_6: 1.08-1.19 (2H, m), 1.53-1.64 (1H, m), 1.70-1.80 (2H, m), 2.41-2.51 (2H, m), 2.62-2.72 (2H, m), 2.84 (3H, s), 3.53-3.65 (4H, m), 3.94-4.01 (2H, m), 4.18 (1H, s), 4.98 (1H, s), 6.44-6.52 (1H, m), 6.67-6.73 (1H, m), 6.97 (1H, t, J = 7.8 Hz).
565	ESI+: 447 NMR-DMSO-d_6: 3.05-3.12 (4H, m), 3.28 (3H, s), 3.41-3.47 (4H, m), 3.59-3.63 (2H, m), 4.18 (1H, s), 4.28-4.33 (2H, m), 5.04 (2H, s), 6.19 (1H, d, J = 2.2 Hz), 6.59-6.63 (1H, m), 6.98-713 (3H, m), 7.81 (1H, d, J = 6.1 Hz).

[0381]

[Table 141]

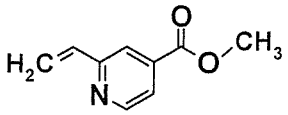
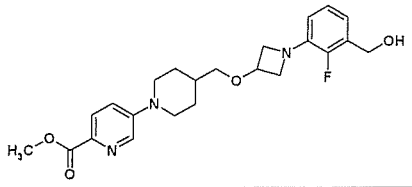
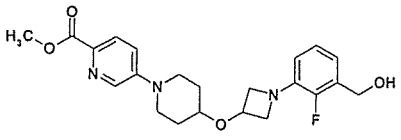
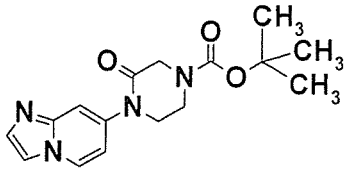
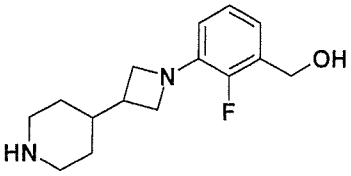
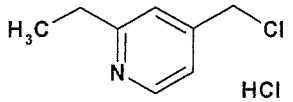
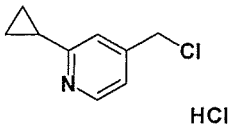
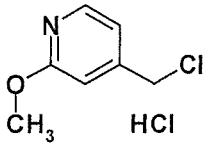
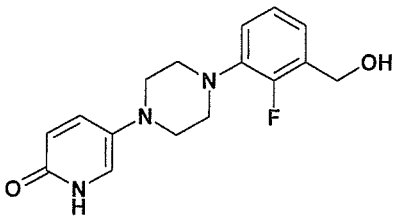
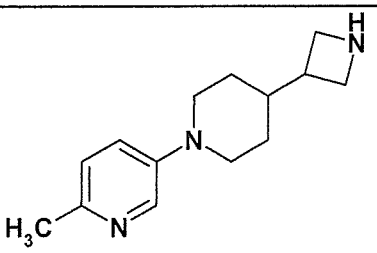
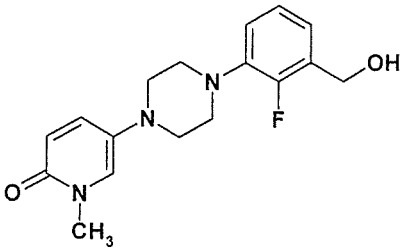
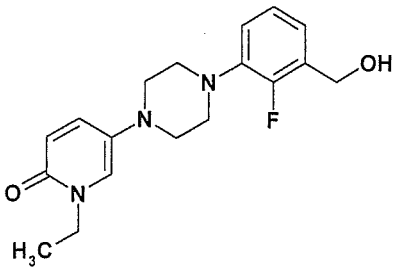
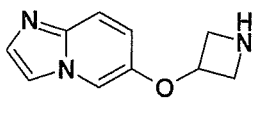
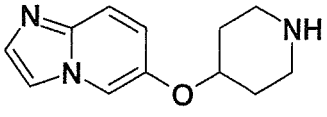
Ex	Data
566	**ESI+: 417** **NMR-DMSO-d_6: 3.10-3.15 (4H, m), 3.36 (3H, s), 3.49-3.55 (4H, m), 4.15 (2H, s), 4.39 (2H, s), 5.04 (2H, s), 6.82-6.86 (1H, m), 6.91 (1H, d, J = 2.4 Hz), 7.00-7.14 (3H, m), 8.15 (1H, d, J = 6.1 Hz).**
567	**ESI+: 392** **NMR-DMSO-d6: 0.81-1.09 (2H, m), 1.59-1.75 (3H, m), 1.98 (3H, s), 2.39-2.52 (2H, m), 2.93-3.03 (1H, m), 3.58-3.65 (2H, m), 3.77-3.85 (1H, m), 3.93-4.01 (2H, m), 4.21 (2H, s), 4.34-4.42 (1H, m), 5.01 (2H, s), 6.46-6.52 (1H, m), 6.69-6.74 (1H, m), 6.97 (1H, t, J = 7.8 Hz).**

[0382]

The compounds of Preparation Examples shown in the tables below were prepared using the respective corresponding starting materials in the same manner as the methods of Preparation Examples above. The structures, the preparation methods, and the physicochemical data for the compounds of Preparation Examples are shown in the tables below.

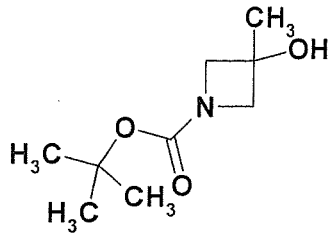
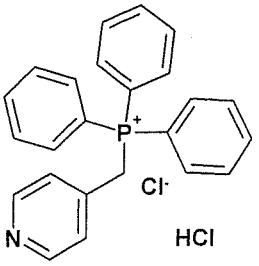
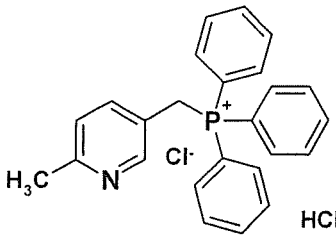
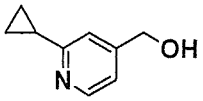
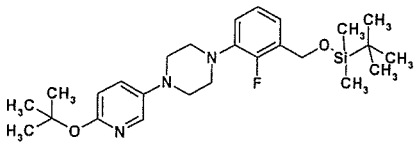
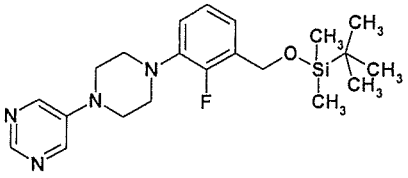
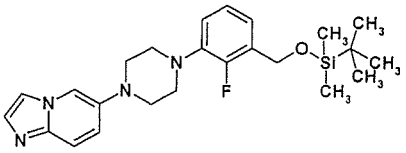
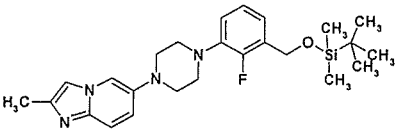
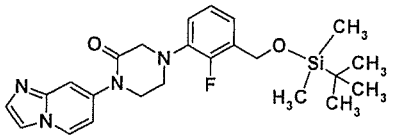
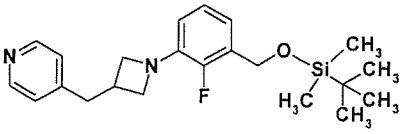
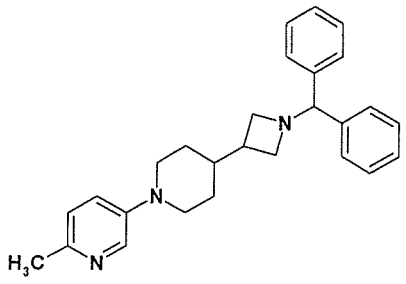
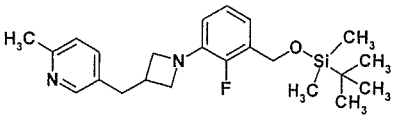
[0383]

[Table 142]

Rf	Syn	Structure	Rf	Syn	Structure
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845	R845		846	R70	
847	R847		848	R806	
849	R806		850	R806	
851	R807		852	R809	
853	R853		854	R853	
855	R855		856	R855	

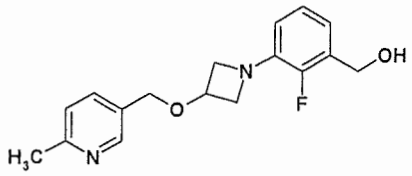
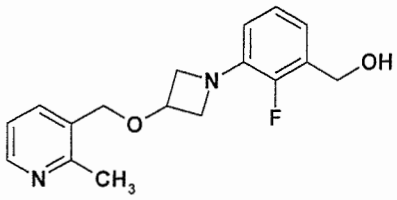
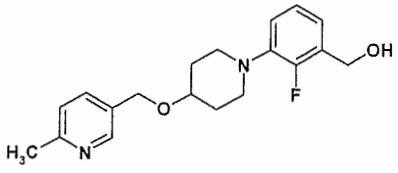
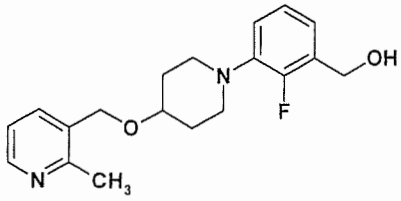
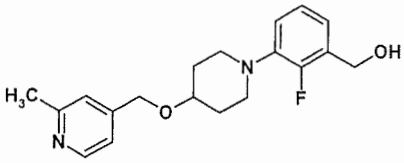
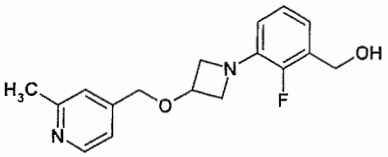
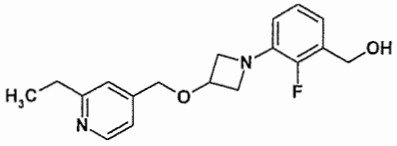
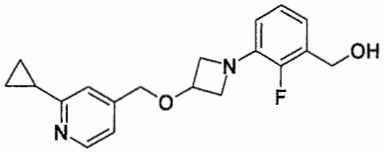
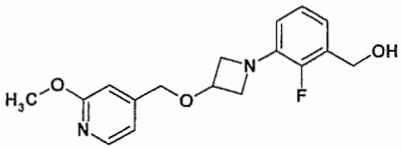
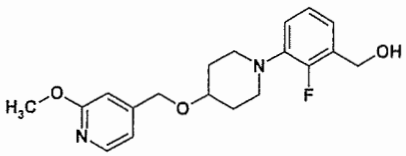
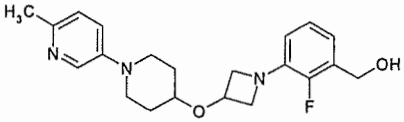
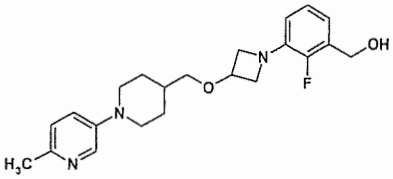
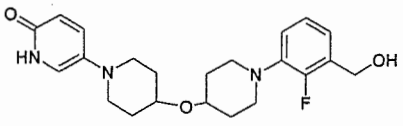
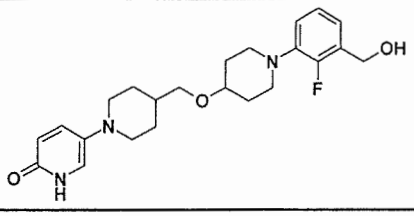
[0384]

[Table 143]

Rf	Syn	Structure	Rf	Syn	Structure
857	R857		858	R859	
859	R859		860	R860	
861	R228		862	R228	
863	R228		864	R228	
865	R228		866	R228	
867	R228		868	R228	

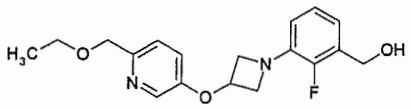
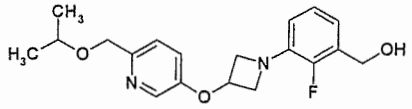
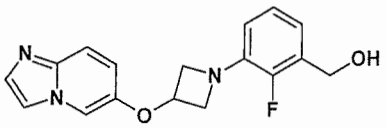
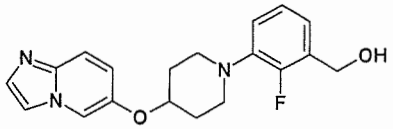
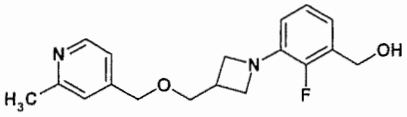
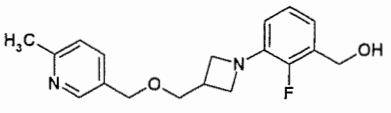
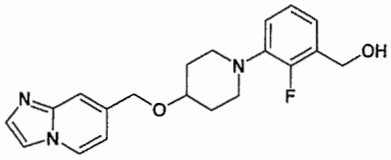
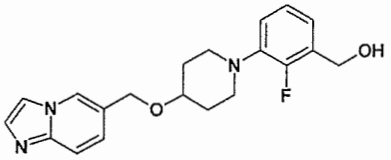
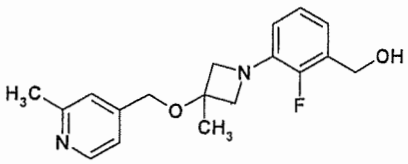
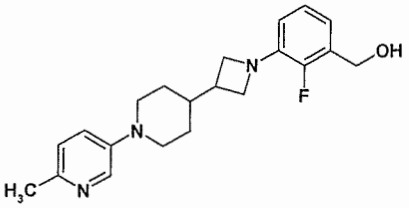
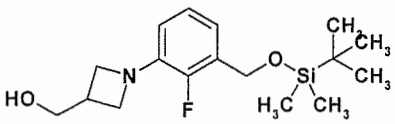
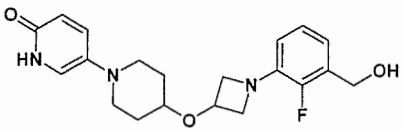
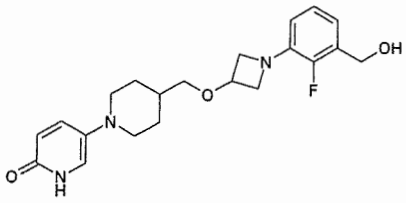
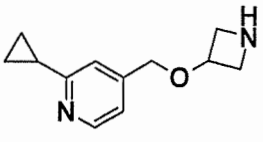
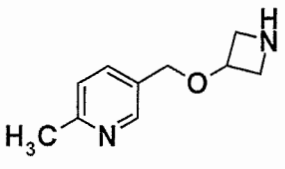
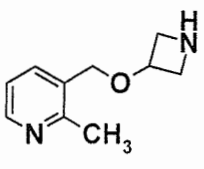
[0385]

[Table 144]

Rf	Syn	Structure	Rf	Syn	Structure
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871	R285		872	R285	
873	R285		874	R285	
875	R285		876	R285	
877	R285		878	R285	
879	R285		880	R285	
881	R285		882	R285	

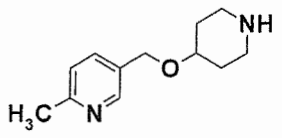
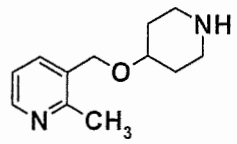
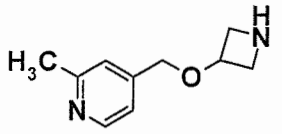
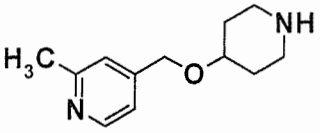
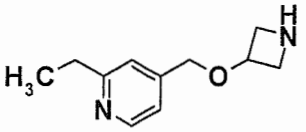
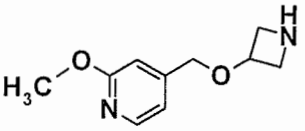
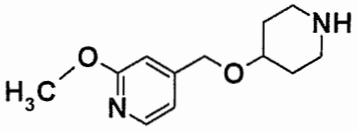
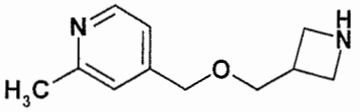
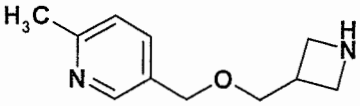
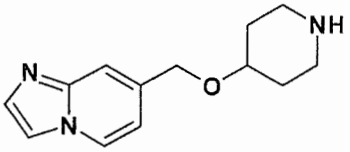
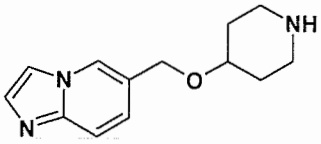
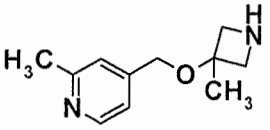
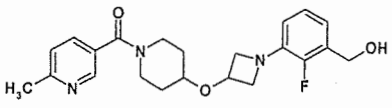
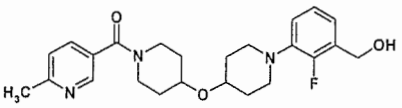
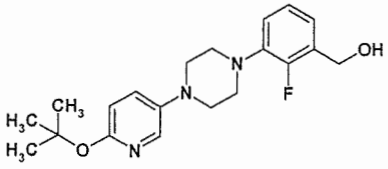
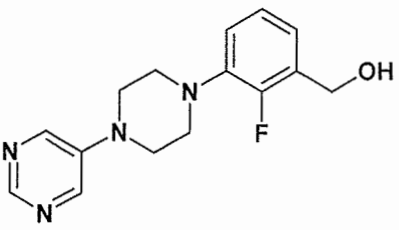
[0386]

[Table 145]

Rf	Syn	Structure	Rf	Syn	Structure
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885	R285		886	R285	
887	R285		888	R285	
889	R285		890	R285	
891	R285		892	R285	
893	R893		894	R894	
895	R894		896	R821	
897	R821		898	R821	

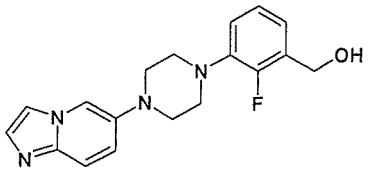
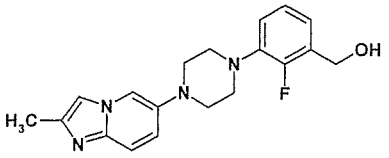
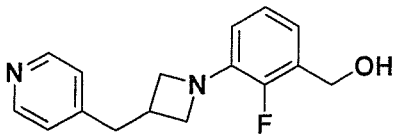
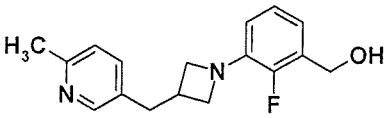
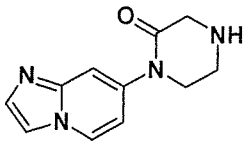
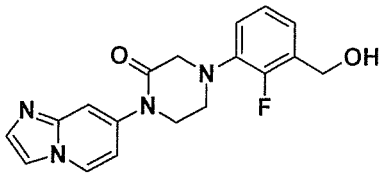
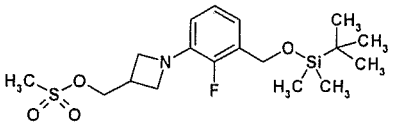
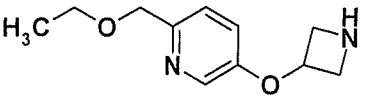
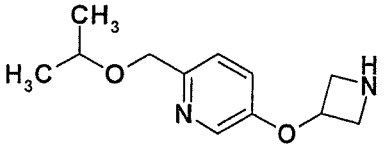
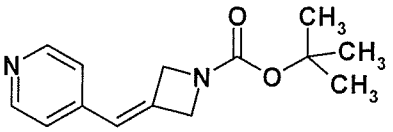
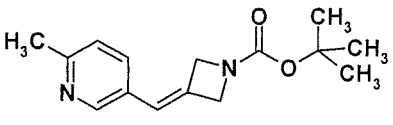
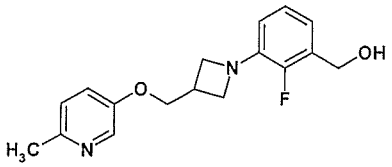
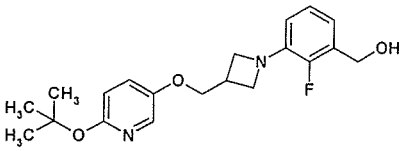
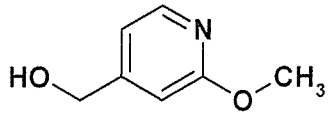
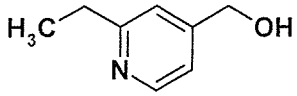
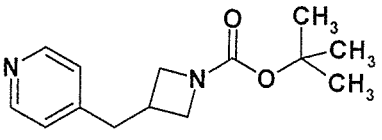
[0387]

[Table 146]

Rf	Syn	Structure	Rf	Syn	Structure
899	R821		900	R821	
901	R821		902	R821	
903	R821		904	R821	
905	R821		906	R821	
907	R821		908	R821	
909	R821		910	R821	
911	R343		912	R343	
913	R376		914	R376	

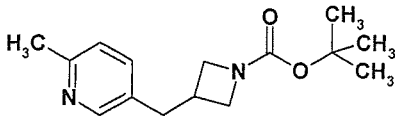
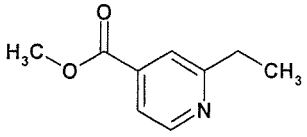
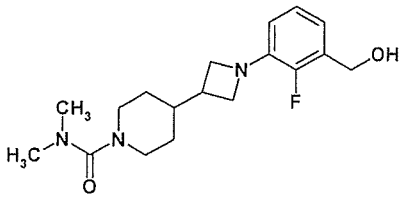
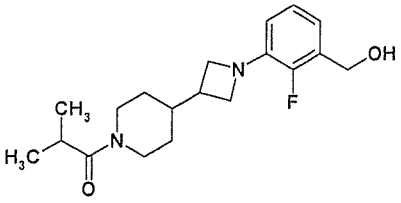
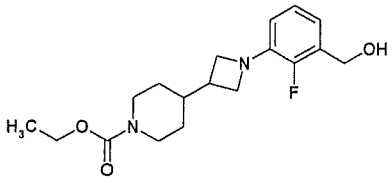
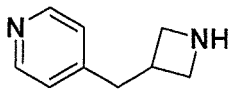
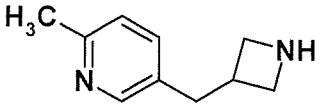
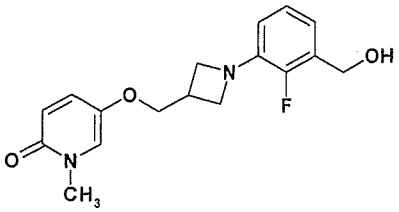
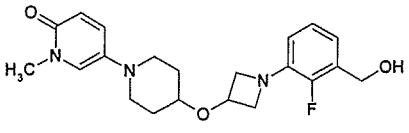
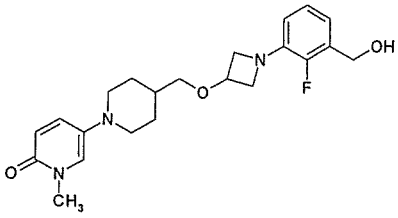
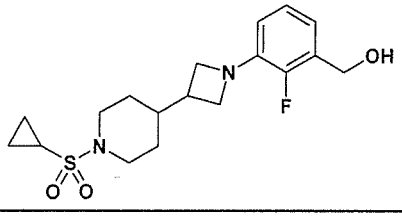
[0388]

[Table 147]

Rf	Syn	Structure	Rf	Syn	Structure
915	R376		916	R376	
917	R376		918	R376	
919	R478		920	R518	
921	R574		922	R922	
923	R922		924	R581	
925	R581		926	R926	
927	R926		928	R584	
929	R584		930	R603	

[0389]

[Table 148]

Rf	Syn	Structure	Rf	Syn	Structure
931	R603		932	R663	
933	R677		934	R680	
935	R686		936	R712	
937	R712		938	R938	
939	R758		940	R758	
941	R772				

[0390]

[Table 149]

Rf	Data
843	ESI+: 164
844	ESI+: 430
845	ESI+: 416
846	APCI/ESI+: 317
847	ESI+: 265
848	ESI+: 156, 158
849	ESI+: 168, 170
850	ESI+: 158, 160
851	ESI+: 304
852	ESI+: 232
853	ESI+: 318
854	ESI+: 332
855	ESI+: 190
856	ESI+: 218
857	NMR-$CDCl_3$: 1.44 (9H, s), 1.51 (3H, s), 3.81-3.87 (4H, m)
858	APCI/ESI+: 354
859	APCI/ESI+: 368
860	ESI+: 150
861	ESI+: 474
862	ESI+: 403
863	ESI+: 441
864	ESI+: 455
865	APCI/ESI+: 455
866	APCI/ESI+: 387
867	ESI+: 398
868	APCI/ESI+: 401
869	ESI+: 303
870	ESI+: 303
871	ESI+: 331
872	ESI+: 331
873	ESI+: 331
874	ESI+: 303
875	ESI+: 317

[0391]

[Table 150]

Rf	Data
876	ESI+: 329
877	ESI+: 319
878	ESI+: 347
879	ESI+: 372
880	ESI+: 386
881	ESI+: 402
882	ESI+: 416
883	ESI+: 333
884	ESI+: 347
885	ESI+: 314
886	ESI+: 342
887	ESI+: 317
888	ESI+: 317
889	ESI+: 356
890	ESI+: 356
891	ESI+: 317
892	ESI+: 356
893	ESI+: 326
894	ESI+: 374
895	ESI+: 388
896	ESI+: 205
897	ESI+: 179
898	ESI+: 179
899	ESI+: 207
900	ESI+: 207
901	ESI+: 179
902	ESI+: 207
903	ESI+: 193
904	ESI+: 195
905	ESI+: 223
906	ESI+: 193
907	ESI+: 193
908	ESI+: 232
909	ESI+: 232

[0392]

[Table 151]

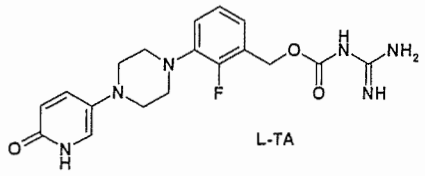
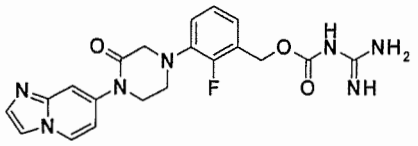
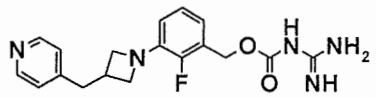
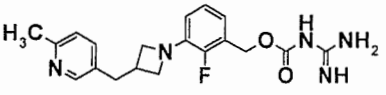
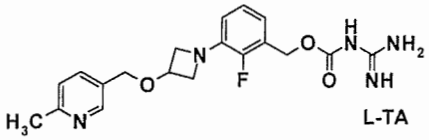
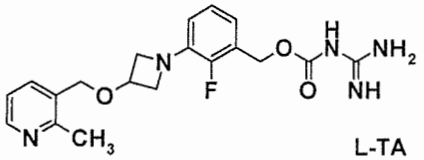
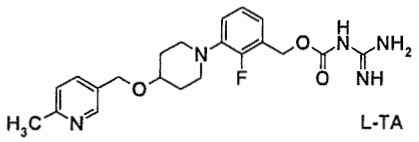
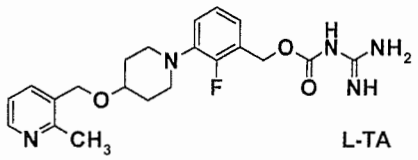
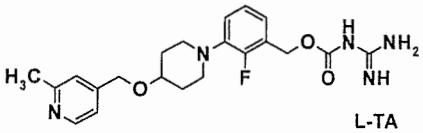
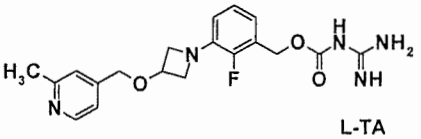
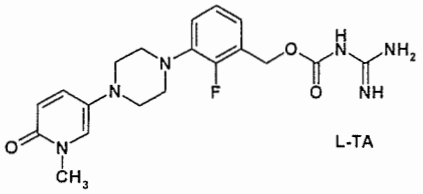
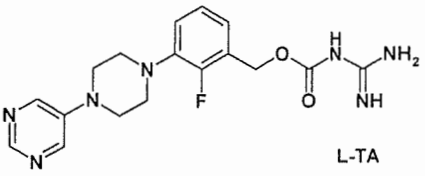
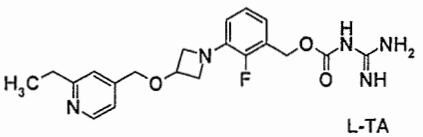
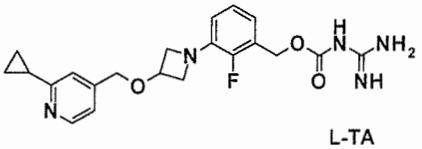
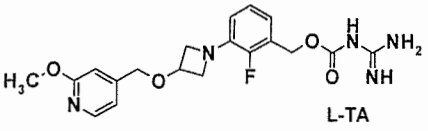
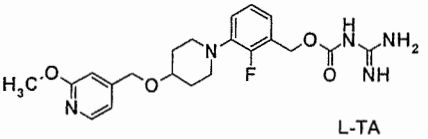
Rf	Data
910	ESI+: 193
911	ESI+: 400
912	ESI+: 428
913	ESI+: 360
914	ESI+: 289
915	ESI+: 327
916	ESI+: 341
917	APCI/ESI+: 273
918	APCI/ESI+: 287
919	NMR-$CDCl_3$: 1.80 (1H, br), 3.26 (2H, t, J = 5 Hz), 3.73 (2H, s), 3.77 (2H, t, J = 5
920	APCI/ESI+: 341
921	ESI+: 404
922	ESI+: 209
923	ESI+: 223
924	APCI/ESI+: 247
925	APCI/ESI+: 261
926	ESI+: 303
927	ESI+: 361
928	ESI+: 140
929	ESI+: 138
930	APCI/ESI+: 249
931	APCI/ESI+: 263
932	ESI+: 166
933	ESI+: 336
934	ESI+: 335
935	ESI+: 337
936	APCI/ESI+: 149
937	APCI/ESI+: 163
938	ESI+: 319
939	ESI+: 388
940	ESI+: 402
941	ESI+: 369

[0393]

The compounds of Examples shown in the tables below were prepared using the respective corresponding starting materials in the same manner as the methods of Examples above. The structures, the preparation methods, and the physicochemical data for the compounds of Examples are shown in the tables below.

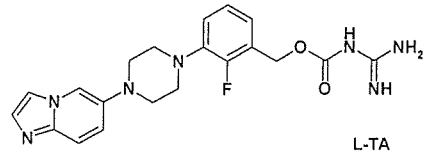
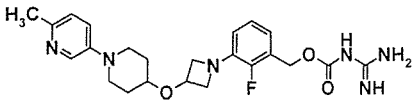
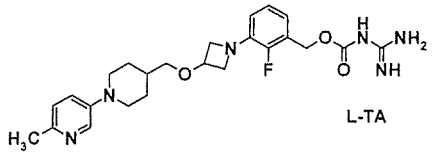
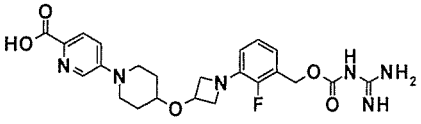
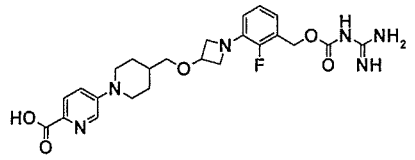
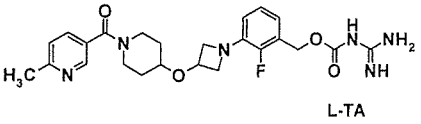
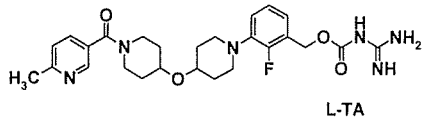
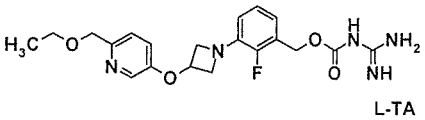
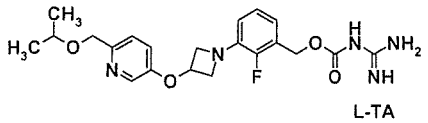
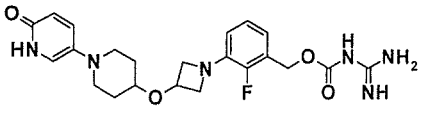
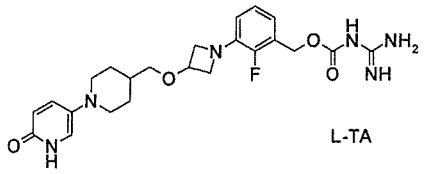
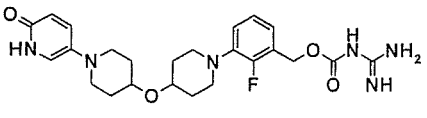
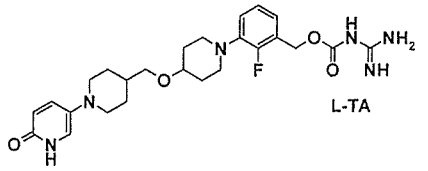
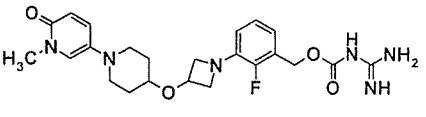
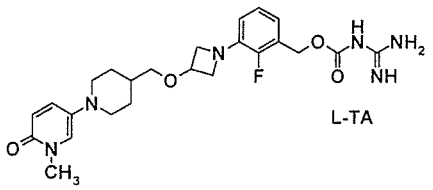
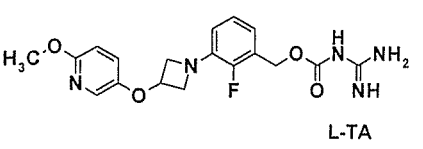
[0394]

[Table 152]

Ex	Syn	Structure	Ex	Syn	Structure
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570	112	 L-TA	571	112	 L-TA
572	112	 L-TA	573	112	 L-TA
574	112	 L-TA	575	112	 L-TA
576	112	 L-TA	577	112	 L-TA
578	112	 L-TA	579	112	 L-TA
580	112	 L-TA	581	112	 L-TA
582	112	 L-TA	583	112	 L-TA

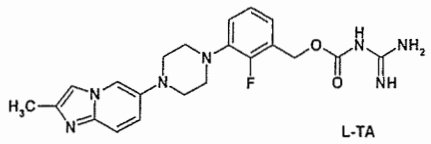
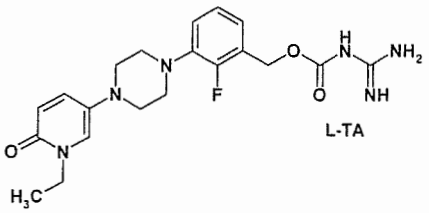
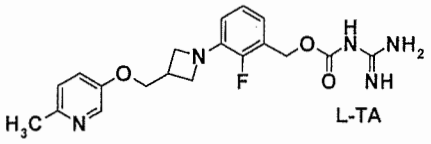
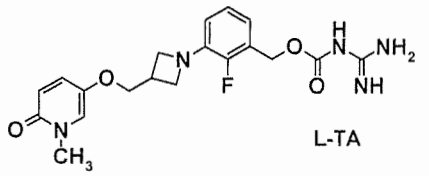
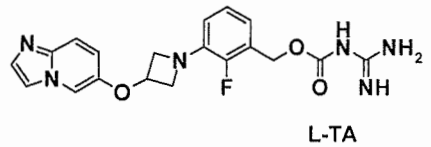
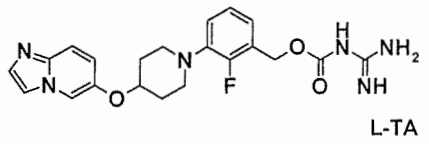
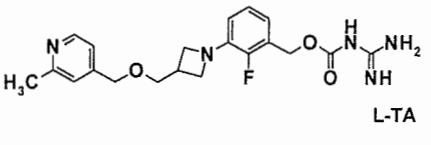
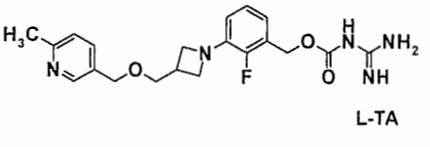
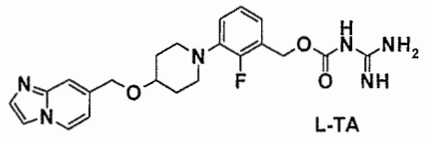
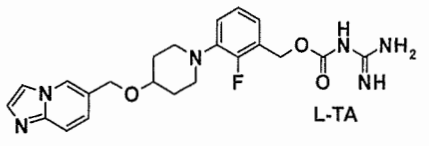
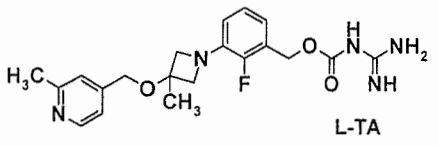
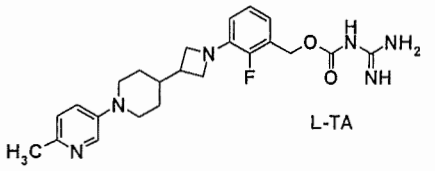
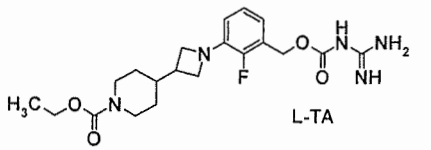
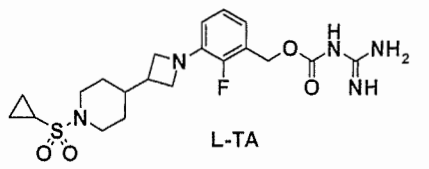
[0395]

[Table 153]

Ex	Syn	Structure	Ex	Syn	Structure
584	112	 L-TA	585	112	 L-TA
586	112	 L-TA	587	588	
588	588		589	112	 L-TA
590	112	 L-TA	591	112	 L-TA
592	112	 L-TA	593	112	 L-TA
594	112	 L-TA	595	112	 L-TA
596	112	 L-TA	597	112	 L-TA
598	112	 L-TA	599	112	 L-TA

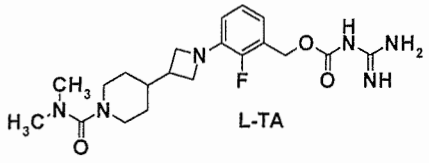
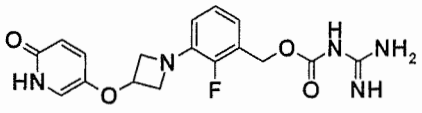
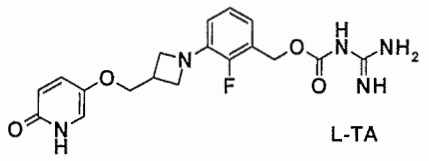
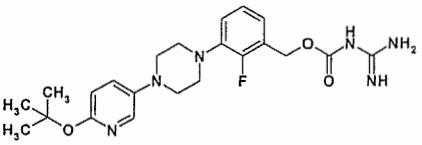
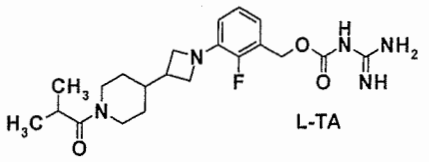
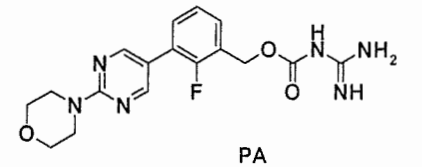
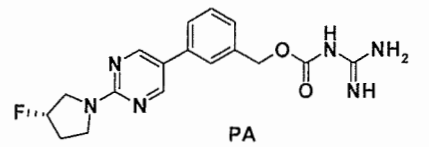
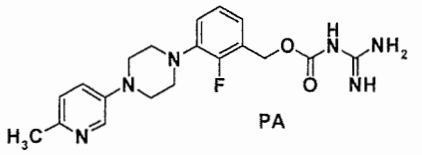
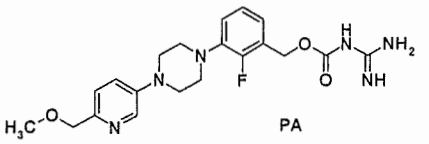
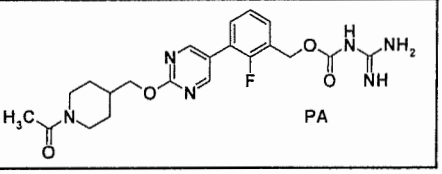
[0396]

[Table 154]

Ex	Syn	Structure	Ex	Syn	Structure
600	112	 L-TA	601	112	 L-TA
602	112	 L-TA	603	112	 L-TA
604	112	 L-TA	605	112	 L-TA
606	112	 L-TA	607	112	 L-TA
608	112	 L-TA	609	112	 L-TA
610	112	 L-TA	611	112	 L-TA
612	112	 L-TA	613	112	 L-TA

[0397]

[Table 155]

Ex	Syn	Structure	Ex	Syn	Structure
614	112	 L-TA	615	615	 L-TA
616	615	 L-TA	617	3	
618	112	 L-TA	619	619	 PA
620	619	 PA	621	619	 PA
622	619	 PA	623	619	 PA

[0398]

[Table 156]

Ex	Data
568	ESI+: 389
569	APCI/ESI+: 426
570	APCI/ESI+: 358
571	APCI/ESI+: 372
572	ESI+: 388
573	ESI+: 388
574	ESI+: 416
575	ESI+: 416
576	ESI+: 416
577	ESI+: 388
578	ESI+: 403
579	ESI+: 374
580	ESI+: 402
581	ESI+: 414
582	ESI+: 404
583	ESI+: 432
584	ESI+: 412
585	ESI+: 457
586	ESI+: 471
587	ESI+: 487
588	ESI+: 501
589	ESI+: 485
590	ESI+: 513
591	ESI+: 418
592	ESI+: 432
593	ESI+: 459
594	ESI+: 473
595	ESI+: 487
596	ESI+: 501
597	ESI+: 473
598	ESI+: 487
599	ESI+: 390
600	ESI+: 426

[0399]

[Table 157]

Ex	Data
601	ESI+: 417
602	ESI+: 388
603	ESI+: 404
604	ESI+: 399
605	ESI+: 427
606	ESI+: 402
607	ESI+: 402
608	ESI+: 441
609	ESI+: 441
610	ESI+: 402
611	ESI+: 441
612	ESI+: 422
613	ESI+: 454
614	ESI+: 421
615	ESI+: 376
616	ESI+: 390
617	ESI+: 445
618	ESI+: 420
619	ESI+: 375 DSC endothermic onset temperature: 197.4°C
620	ESI+: 359 DSC endothermic onset temperature: 184.7°C
621	ESI+: 387 DSC endothermic onset temperature: 173.0°C
622	ESI+: 417 DSC endothermic onset temperature: 207.8°C
623	ESI+: 445 DSC endothermic onset temperature: 204.0°C

Industrial Applicability

[0400]

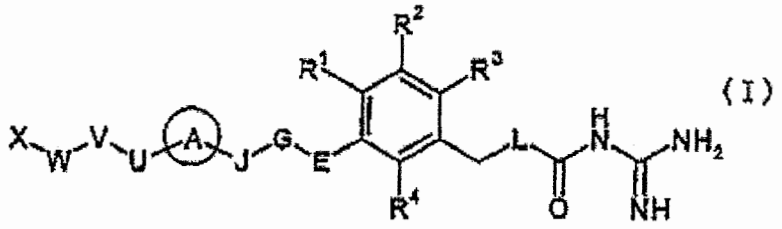
The compound of the formula (I) or a salt thereof has a VAP-1 inhibitory action, and can be used as an agent for preventing and/or treating VAP-1-related diseases.

CLAIMS

[Claim 1]

A compound represented by the formula (I) or a salt thereof:

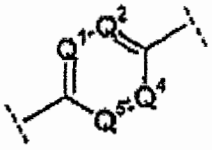
[Chem. 1]



(I)

wherein A is

[Chem. 2]



Q^1 is CR^{Q12} or N, Q^2 is CR^{Q22} or N, Q^4 is CR^{Q42} or N, Q^5 is CR^{Q52} or N, R^{Q12}, R^{Q22}, R^{Q42} and R^{Q52} are the same as or different from each other, and are H, lower alkyl, O-(lower alkyl), or $N(\text{lower alkyl})_2$,

R^1, R^2, R^3 and R^4 are the same as or different from each other, and are H, halogen, or lower alkyl,

E is a single bond,

G is a single bond,

J is a single bond,

L is O or NH, N(lower alkyl),

U is a single bond or O,

V is a single bond or lower alkylene which may be substituted with OH, O-(lower alkyl), or oxo (=O),

W is a single bond,

X is

H,

OH,

NH_2,

lower alkyl which may be substituted with halogen,

O-(lower alkyl which may be substituted with OH),

NH(lower alkyl which may be substituted with oxo (=O)),

$N(\text{lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O)})_2$,

$NH\text{-}SO_2\text{-}(\text{lower alkyl})$,

N(lower alkyl)-SO_2-(lower alkyl),

cycloalkyl which may be substituted with group(s) selected from Group G^{XA1} below,

O-(cycloalkyl),

cycloalkenyl which may be substituted with group(s) selected from Group G^{XA1} below,

aryl which may be substituted with group(s) selected from Group G^{XA1} below,

O-(aryl which may be substituted with O-(lower alkyl)), or

a hetero ring group which may be substituted with group(s) selected from Group G^{XA1} below, and

G^{XA1} is

i) halogen,

ii) OH,

iii) lower alkyl which may be substituted with group(s) selected from the group consisting of halogen; OH; O-(lower alkyl which may be substituted with OH, aryl, O-(lower alkyl), or oxo (=O)); NH_2; NH(lower alkyl which may be substituted with OH); N(lower alkyl)$_2$; NH(cycloalkyl); NH(hetero ring group); cycloalkyl which may be substituted with OH; aryl which may be substituted with O-(lower alkyl), COOH, or COO-(lower alkyl which may be substituted with aryl); hetero ring group(s) which may be substituted with O-(lower alkyl), oxo (=O), NH(lower alkyl which may be substituted with oxo (=O)), or lower alkyl; and oxo (=O),

iv) O-(lower alkyl which may be substituted with OH, O-(lower alkyl), aryl, hetero ring group(s) (in which the hetero ring group may be substituted with lower alkyl which may be substituted with cycloalkyl or oxo (=O)), or oxo (=O)),

v) NH-(lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O)),

vi) N(lower alkyl which may be substituted with oxo (=O))$_2$,

vii) NH-(aryl which may be substituted with COOH or COO-(lower alkyl)),

viii) cycloalkyl which may be substituted with group(s) selected from the group consisting of lower alkyl which may be substituted with OH; COOH; and COO-(lower alkyl),

ix) aryl which may be substituted with group(s) selected from the group consisting of halogen; lower alkyl (in which the lower alkyl may be substituted with COOH or COO-(lower alkyl)); O-(lower alkyl); COOH; and COO-(lower alkyl),

x) hetero ring group(s) which may be substituted with group(s) selected from the group consisting of OH; halogen; lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl which may be substituted with O-(lower alkyl)); and oxo (=O),

xi) O-(hetero ring group),

xii) SO_2-(lower alkyl which may be substituted with O-(lower alkyl)),

xiii) SO_2-(cycloalkyl),

xiv) SO_2-(aryl),

xv) $NHSO_2$-(lower alkyl), or

xvi) oxo (=O).

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

X is H,

lower alkyl, O-(lower alkyl), O-(cycloalkyl),

cycloalkyl which may be substituted with group(s) selected from Group G^{XB1} below,

cycloalkenyl which may be substituted with group(s) selected from Group G^{XB1} below,

aryl which may be substituted with group(s) selected from Group G^{XB1} below, or

a hetero ring group which may be substituted with group(s) selected from Group G^{XB1} below, and

G^{XB1} is

i) OH,

ii) lower alkyl which may be substituted with group(s) selected from the group consisting of OH; O-(lower alkyl which may be substituted with aryl); NH(lower alkyl); N(lower alkyl)$_2$; NH(cycloalkyl); cycloalkyl which may be substituted with OH; aryl; hetero ring group(s) which may be substituted with lower alkyl; and oxo (=O),

iii) O-(lower alkyl which may be substituted with O-(lower alkyl), aryl, hetero ring group(s) (in which the hetero ring group may be substituted with lower alkyl which may be substituted with cycloalkyl or oxo (=O)), or oxo (=O)),

iv) NH-(lower alkyl which may be substituted with O-(lower alkyl) or oxo (=O)),

v) cycloalkyl which may be substituted with COOH or COO-(lower alkyl),

vi) hetero ring group(s) which may be substituted with group(s) selected from the group consisting of OH; halogen; lower alkyl which may be substituted with OH, O-(lower alkyl), or oxo (=O); O-(lower alkyl which may be substituted with O-(lower alkyl)); and oxo (=O),

vii) O-(hetero ring group),

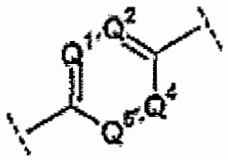
viii) SO_2-(lower alkyl),

ix) SO_2-(cycloalkyl), or

x) oxo (=O).

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

[Chem. 9]



Q^1 is N, Q^2 is CR^{Q22}, Q^4 is CR^{Q42}, Q^5 is N,

R^{Q22} and R^{Q42} is H,

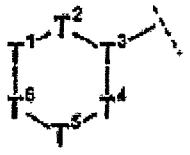
R^1, R^2 and R^3 is H, R^4 is halogen,

U is O,

V is lower alkylene which may be substituted with oxo (=O),

X is

[Chem. 10]



T^1 is a single bond or $CR^{T11}R^{T12}$, T^2 is $CR^{T21}R^{T22}$, T^3 is CR^{T31} or N, T^4 is $CR^{T41}R^{T42}$, T^5 is a single bond or $(CR^{T51}R^{T52})_m$, T^6 is NR^{T63},

R^{T11}, R^{T12}, R^{T21}, R^{T22}, R^{T31}, R^{T41}, R^{T42}, R^{T51} and R^{T52} is H,

R^{T63} is CO-(C_{1-6} alkyl which may be substituted with O-(lower alkyl) or nitrogen-containing monocyclic unsaturated hetero ring(s)), CO-(cycloalkyl), CO-(aryl), CO-(nitrogen-containing monocyclic unsaturated hetero ring group), CON(lower alkyl)$_2$, or SO_2-(lower alkyl), and

m is 1.

[Claim 4] The compound or a salt thereof according to claim 3, wherein T^1 is $CR^{T11}R^{T12}$, T^2 is $CR^{T21}R^{T22}$, T^3 is CR^{T31}, T^4 is $CR^{T41}R^{T42}$, T^5 is $(CR^{T51}R^{T52})_m$, T^6 is NR^{T63}, m is 1, and

L is O.

[Claim 5] The compound or a salt thereof according to claim 4, wherein R^{T63} is acetyl, propionyl, isobutyryl, pivaloyl, 2-ethoxy-1-oxoethyl, cyclopropylcarbonyl, benzoyl, pyridin-3-ylcarbonyl, dimethylaminocarbonyl, or methylsulfonyl.

[Claim 6] The compound according to claim 1, wherein said compound is selected from the group consisting of

2-fluoro-3-[2-(morpholin-4-yl)pyrimidin-5-yl]benzyl carbamimidoylcarbamate,

2-fluoro-3-[2-(3-methoxyazetidin-1-yl)pyrimidin-5-yl]benzyl carbamimidoylcarbamate,

3-{2-[(1-acetylpiperidin-4-yl)methoxy]pyrimidin-5-yl}-2-fluorobenzyl carbamimidoylcarbamate, and

3-(2-{[1-(cyclopropylcarbonyl)piperidin-4-yl]methoxy}pyrimidin-5-yl)-2-fluorobenzyl carbamimidoylcarbamate, or a salt thereof.

[Claim 7] 2-fluoro-3-[2-(morpholin-4-yl)pyrimidin-5-yl]benzyl carbamimidoylcarbamate, or a salt thereof.

[Claim 8] 2-fluoro-3-[2-(3-methoxyazetidin-1-yl)pyrimidin-5-yl]benzyl carbamimidoylcarbamate, or a salt thereof.

[Claim 9] 3-{2-[(1-acetylpiperidin-4-yl)methoxy]pyrimidin-5-yl}-2-fluorobenzyl carbamimidoylcarbamate, or a salt thereof.

[Claim 10] 3-(2-{[1-(cyclopropylcarbonyl)piperidin-4-yl]methoxy}pyrimidin-5-yl)-2-fluorobenzyl carbamimidoylcarbamate, or a salt thereof.

[Claim 11] 2-fluoro-3-[2-(morpholin-4-yl)pyrimidin-5-yl]benzyl carbamimidoylcarbamate monophosphate.

[Claim 12] 3-{2-[(1-acetylpiperidin-4-yl)methoxy]pyrimidin-5-yl}-2-fluorobenzyl carbamimidoylcarbamate monophosphate.

[Claim 13] A crystal of 2-fluoro-3-[2-(morpholin-4-yl)pyrimidin-5-yl]benzyl carbamimidoylcarbamate monophosphate.

[Claim 14] A crystal of 3-{2-[(1-acetylpiperidin-4-yl)methoxy]pyrimidin-5-yl}-2-fluorobenzyl carbamimidoylcarbamate monophosphate.

[Claim 15] A pharmaceutical composition comprising the compound or a salt thereof according to claim 6 and a pharmaceutically acceptable excipient.

[Claim 16] A pharmaceutical composition comprising the compound or a salt thereof according to claim 6 for use in the treatment or prevention of diabetic nephropathy or diabetic macular edema.

[Claim 17] Use of the compound or a salt thereof according to claim 6 for the manufacture of a medicament for the treatment or prevention of diabetic nephropathy or diabetic macular edema.

[Claim 18] The compound or a salt thereof according to claim 6 for use in the treatment or prevention of diabetic nephropathy or diabetic macular edema.