

DESCRIPTION
PEPTIDE COMPOUNDS
TECHNICAL FIELD

This invention relates to new peptide compounds and
5 pharmaceutically acceptable salts thereof which are useful as a
medicament.

BACKGROUND ART

Some peptide compounds have been known as described in, for
example, EP 0 394 989 A2, WO96/16981 and JP-A-10-81671.

10 DISCLOSURE OF INVENTION

This invention relates to new peptide compounds.

One embodiment of this invention may provide new and
useful peptide compounds and pharmaceutically acceptable salts
thereof that possess a strong inhibitory activity on the
15 production of nitric oxide (NO).

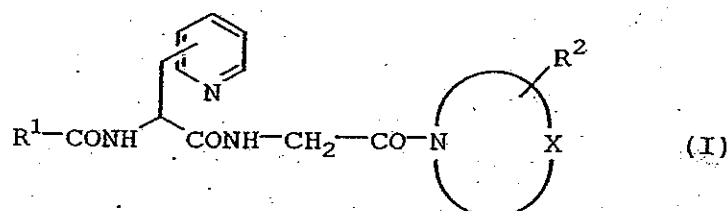
Another embodiment of this invention may provide a process
for the preparation of the peptide compounds and salts thereof.

A further embodiment of this invention may provide a
pharmaceutical composition comprising said peptide compound or a
20 pharmaceutically acceptable salt thereof.

Still further embodiment of this invention may provide a use
of said peptide compounds or pharmaceutically acceptable salts
thereof as a medicament for prophylactic and therapeutic
treatment of NO-mediated diseases including respiratory diseases
25 such as adult respiratory distress syndrome (ARDS) and asthma;
cardiovascular diseases such as cardiovascular ischemia,
myocarditis, heart failure, hypotension and atherosclerosis;
endocrine diseases such as diabetes (e.g., insulin-dependent
diabetes mellitus, etc.), complications of diabetes mellitus
30 (e.g., diabetic nephropathy, diabetic retinopathy, diabetic
neuropathy, etc.) and gout; renal diseases such as
glomerulonephritis and renal failure; gastrointestinal diseases
such as peptic ulcer and inflammatory bowel disease (e.g.,
ulcerative colitis, chronic colitis, etc.); pancreatic diseases
35 such as pancreatitis; hepatic diseases such as hepatitis and
liver cirrhosis; diseases of bone or joint such as synovitis,
arthritis, osteoarthritis, osteoporosis; autoimmune diseases such
as rheumatoid arthritis, systemic lupus erythematosus and

multiple sclerosis; dermal diseases such as dermatitis and eczema; cancer such as solid tumors and metastasis; rejection by organ transplantation; shock (e.g., septic shock, etc.); sepsis-induced systemic inflammatory response syndrome; and sexual dysfunction such as male sexual dysfunction (e.g., erectile dysfunction) and female sexual dysfunction (e.g., orgasmic dysfunction related to clitoral disturbances) in human being and animals.

- 10 Accordingly, a first aspect of the present invention provides a compound of the formula (I):



wherein

- 15 R^1 is benzofuranyl substituted by halogen, or styryl substituted by halogen;
 R^2 is substituted hydroxy; substituted mercapto or substituted sulfonyl; and
 X is



20 or pharmaceutically acceptable salts thereof.

A second aspect of the present invention provides a pharmaceutical composition comprising the compound of the first aspect or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier.

A third aspect of the present invention provides a compound of the first aspect or a pharmaceutically acceptable salt thereof for use as a medicament.

A fourth aspect of the present invention provides a use of the compound of the first aspect or a pharmaceutically

acceptable salt thereof in the manufacture of a medicament for prophylactic or therapeutic treatment of NO-mediated diseases.

A fifth aspect of the present invention provides a pharmaceutical composition comprising FK506 and the compound of the first aspect or a pharmaceutically acceptable salt thereof.

A sixth aspect of the present invention provides a use of a pharmaceutical composition comprising FK506 and the compound of the first aspect or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use as an immunosuppressant.

Suitable pharmaceutically acceptable salts of the object compound (I) may be conventional non-toxic salts and include, for example, a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g., sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g., triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.); an inorganic acid addition salt (e.g., hydrochloride,

hydrobromide, sulfate, phosphate, etc.); an organic carboxylic or sulfonic acid addition salt (e.g., formate, acetate, trifluoroacetate, maleate, tartrate, citrate, fumarate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.); and
5 a salt with a basic or acidic amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.).

In the above and subsequent descriptions of the present specification, suitable examples and illustration of the various
10 definitions which the present invention intends to include within the scope thereof are explained in detail as follows.

The term "lower" is used to intend a group having 1 to 6, preferably 1 to 4, carbon atom(s), unless otherwise provided.

15 Suitable "halogen" includes, for example, fluorine, bromine, chlorine and iodine.

"Styryl substituted by halogen" means styryl which has halogen atom as a substituent on the benzene ring. Suitable examples of "styryl substituted by halogen" include 2-(2-
20 chlorophenyl)ethenyl, 2-(3-chlorophenyl)ethenyl, 2-(4-chlorophenyl)ethenyl, 2-(2-bromophenyl)ethenyl, 2-(3-bromophenyl)ethenyl, 2-(4-bromophenyl)ethenyl, 2-(2-fluorophenyl)ethenyl, 2-(3-fluorophenyl)ethenyl, 2-(4-fluorophenyl)ethenyl, and the like.

25 "Substituted hydroxy" means a group of the formula: $-Y-R^3$ wherein Y is $-O-$ and R^3 is a suitable organic group.

"Substituted mercapto" means a group of the formula: $-Y-R^3$ wherein Y is $-S-$ and R^3 is a suitable organic group.

30 "Substituted sulfonyl" means a group of the formula: $-Y-R^3$ wherein Y is $-SO_2-$ and R^3 is a suitable organic group.

Examples of the above-mentioned "suitable organic group" include lower alkyl, halo(lower)alkyl, optionally substituted heterocyclic group and optionally substituted aryl. Each of said heterocyclic group and aryl is optionally substituted by one or
35 more, preferably one to three substituent(s) such as lower alkyl, lower alkoxy, halogen, halo(lower)alkyl, and the like.

In the formula: $-Y-R^3$, Y is preferably $-O-$.

"Heterocyclic group" includes saturated or unsaturated,

heteromonocyclic or fused heterocyclic group containing heteroatom(s) selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom.

Suitable examples of "heterocyclic group" include

5 unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, dihydropyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, tirazolyl, (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl), tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl),
10 etc.;

 saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl,
15 etc.;

 unsaturated fused heterocyclic group containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, indolinyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, etc.;

20 unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl) etc.;

25 saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, sydnonyl, etc.;

 unsaturated fused heterocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example,
30 benzoxazolyl, benzoxadiazolyl, etc.;

 unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl (e.g., 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl), dihydrothiazinyl, etc.;

35 saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolidinyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 sulfur atom(s), for example, thienyl, dihydrodithiinyl, etc.;

5 unsaturated fused heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, imidazothiadiazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom, for example, furyl, etc.;

10 saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom, for example, tetrahydrofuranlyl, tetrahydropyranlyl, etc.;

15 saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom and 1 or 2 sulfur atom(s), for example, dihydrooxathiinyl, etc.;

unsaturated fused heterocyclic group containing 1 or 2 sulfur atom(s), for example, benzothienyl, benzodithiinyl, etc.;

20 unsaturated fused heterocyclic group containing an oxygen atom and 1 or 2 sulfur atom(s), for example, benzoxathiinyl, etc.; and the like.

Preferable examples of heterocyclic group include unsaturated 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s); and unsaturated 5 or 6-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 25 3 nitrogen atom(s).

More preferable examples of heterocyclic group include pyridyl, pyrazinyl, thiazolyl, pyridazinyl and pyrimidinyl, and particularly preferable examples of heterocyclic group are pyridyl, pyrazinyl and thiazolyl.

30 Suitable "aryl" includes C₆-C₁₂ aryl such as phenyl and naphthyl, in which more preferred one is phenyl.

Suitable "lower alkyl" and "lower alkyl" moiety in the term "halo(lower)alkyl" include straight or branched alkyl having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, 35 isobutyl, sec-butyl, tert-butyl, pentyl, tert-pentyl and hexyl, in which more preferred one is C₁-C₄ alkyl.

Suitable "lower alkoxy" includes straight or branched alkoxy having 1 to 6 carbon atom(s), such as methoxy, ethoxy,

propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, tert-pentyloxy and hexyloxy, in which more preferred one is C₁-C₄ alkoxy.

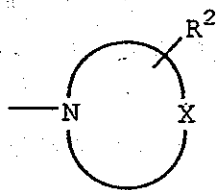
Suitable "halo(lower)alkyl" includes lower alkyl

- 5 substituted by one or more, preferably one to three halogen atom(s) such as trifluoromethyl, trichloromethyl, tribromomethyl, 2,2,2-trifluoroethyl and 3,3,3-trifluoropropyl, in which more preferred one is trihalo(lower)alkyl.

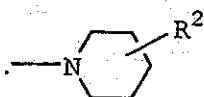
- Suitable examples of optionally substituted heterocyclic group include 2-pyridyl, 3-pyridyl, 4-pyridyl, 6-methoxy-2-pyridyl, 6-methyl-2-pyridyl, 5-chloro-2-pyridyl, 6-chloro-2-pyridyl, 3-chloro-2-pyridyl, 3,5-dichloro-2-pyridyl, 3-(trifluoromethyl)-2-pyridyl, 5-(trifluoromethyl)-2-pyridyl, 2-pyrazinyl, 5-chloro-2-pyrazinyl, 6-chloro-2-pyrazinyl, 1,3-thiazol-2-yl, 1,3-thiazol-4-yl, 1,3-thiazol-5-yl, 5-methyl-1,3-thiazol-2-yl, 5-chloro-1,3-thiazol-2-yl, 3-pyridazinyl, 4-pyridazinyl, 6-chloro-3-pyridazinyl, 6-methoxy-3-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-chloro-4-pyrimidinyl, 6-(trifluoromethyl)-4-pyrimidinyl, 2-(trifluoromethyl)-4-pyrimidinyl, and the like.
- 10
15
20

- Suitable examples of optionally substituted aryl include phenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-(trifluoromethyl)phenyl, 3-(trifluoromethyl)phenyl, 4-(trifluoromethyl)phenyl, and the like.
- 25

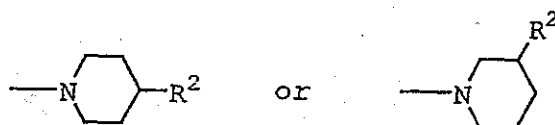
In the formula (I), a group of the formula:



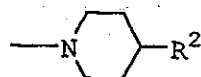
is preferably



more preferably



and particularly preferably

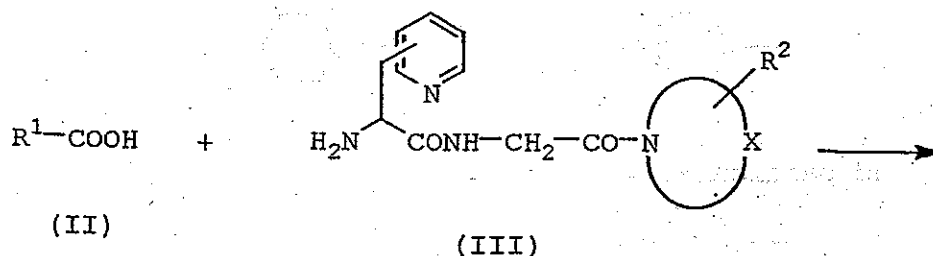


5

Suitable "amino-protecting group" includes, for example, acyl and conventional protecting group such as mono(or di or tri)aryl(lower)alkyl, for example, mono(or di or tri)phenyl(lower)alkyl (e.g., benzyl, trityl, etc.). Suitable examples of
 10 said acyl include aliphatic acyl such as lower alkanoyl which may be substituted by one to three halogen atoms (e.g., formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, trichloroacetyl, trifluoroacetyl, etc.), lower alkoxycarbonyl (e.g., methoxycarbonyl,
 15 ethoxycarbonyl, tert-butoxycarbonyl, tert-pentyloxycarbonyl, etc.), aryl(lower)alkoxycarbonyl [e.g., phenyl(lower)-alkoxycarbonyl (e.g., benzyloxycarbonyl, etc.), etc.] and the like.

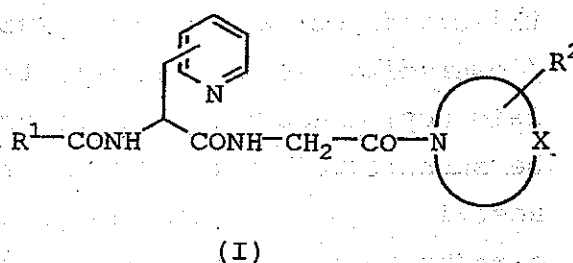
Suitable "carboxy-protecting group" includes, for example,
 20 lower alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, tert-butyl, pentyl, neopentyl, hexyl, etc.), optionally substituted phenyl(lower)alkyl, for example, mono(or di or tri)phenyl(lower)alkyl which may be substituted by nitro (e.g., benzyl, 4-nitrobenzyl, benzhydryl, trityl, etc.) and the
 25 like.

The object compound (I) of the present invention can be prepared by the following processes.

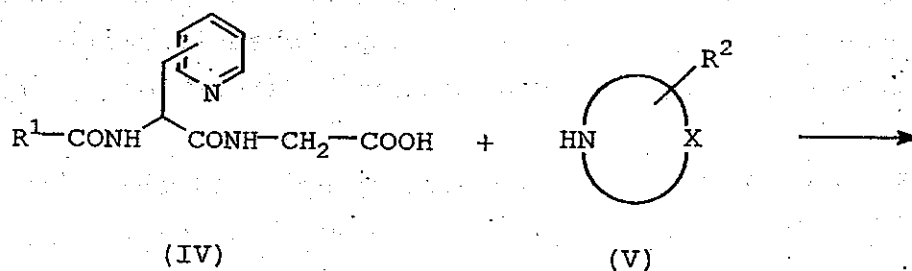
Process (1)

or its reactive derivative
at the carboxy group,
or a salt thereof

or its reactive derivative
at the amino group,
or a salt thereof

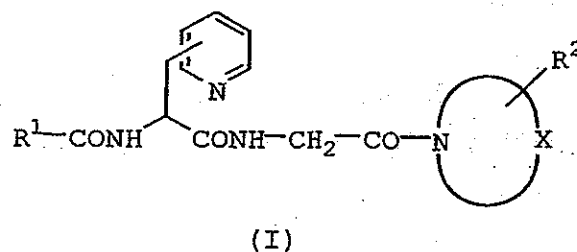


or a salt thereof

Process (2)

or its reactive derivative
at the carboxy group,
or a salt thereof

or a salt thereof

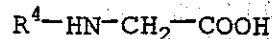


or a salt thereof

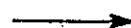
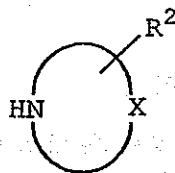
5 wherein R¹, R² and X are each as defined above.

The starting compounds can be prepared by the following processes.

Process (A)



+

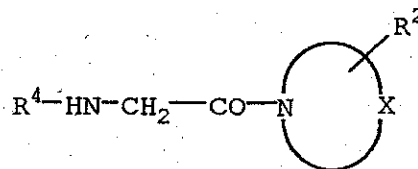


(VI)

(V)

or its reactive derivative
at the carboxy group,
or a salt thereof

or a salt thereof

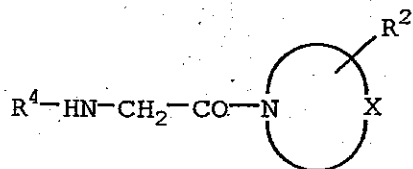


(VII)

or a salt thereof

5

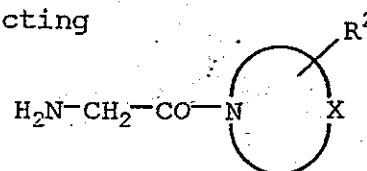
Process (B)



(VII)

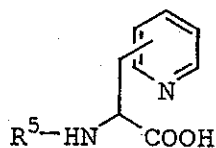
or a salt thereof

elimination reaction
of the amino-protecting
group



(VIII)

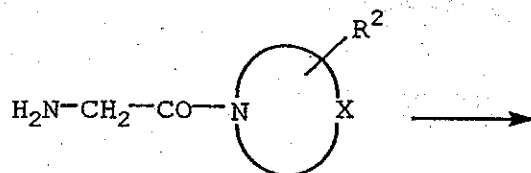
or a salt thereof

Process (C)

(IX)

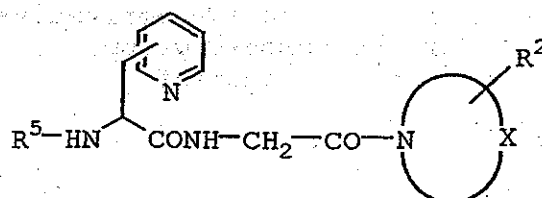
or its reactive derivative
at the carboxy group,
or a salt thereof

+



(VIII)

or its reactive derivative
at the amino group,
or a salt thereof

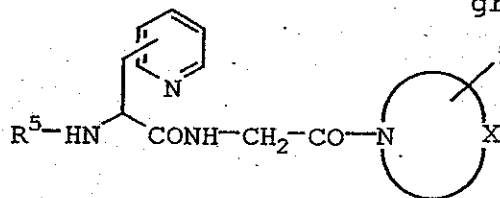


(X)

or a salt thereof

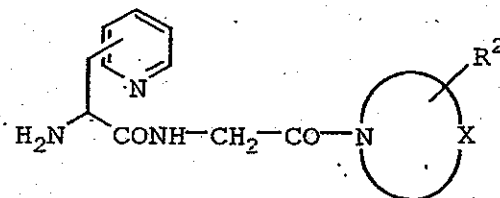
Process (D)

elimination reaction
of the amino-protecting
group



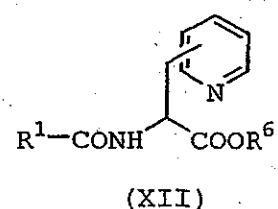
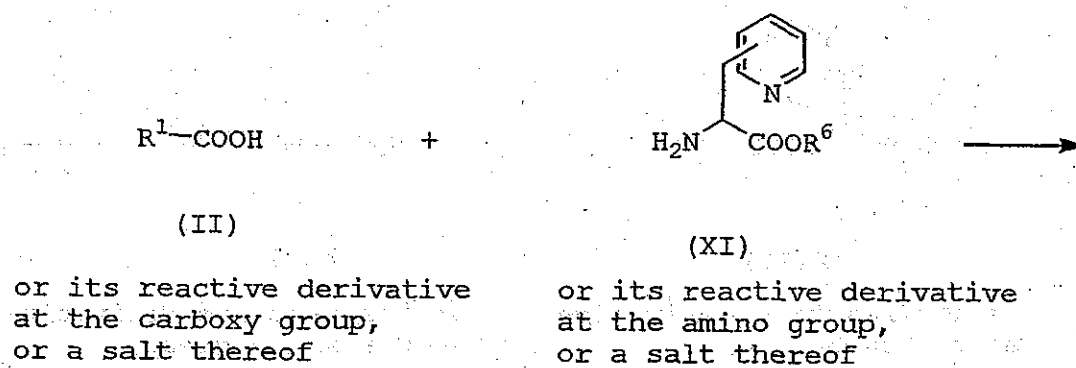
(X)

or a salt thereof

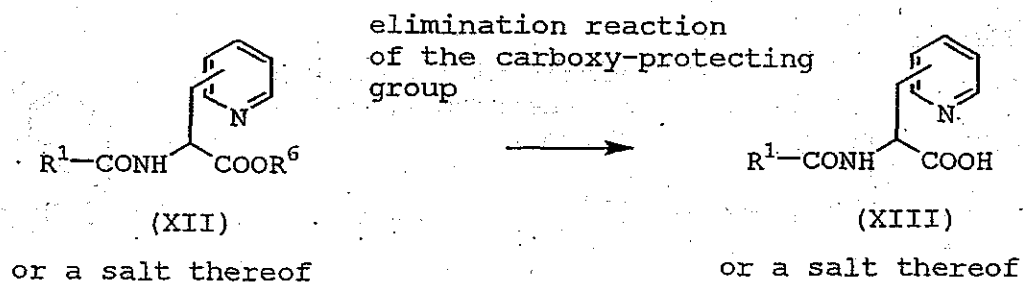


(III)

or a salt thereof

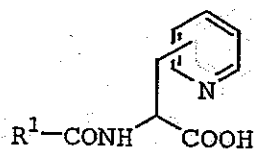
Process (E)

or a salt thereof

Process (F)

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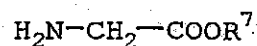
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Process (G)

(XIII)

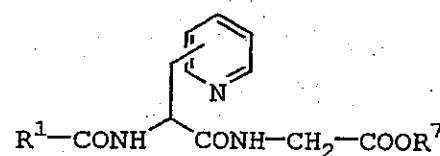
or its reactive derivative
at the carboxy group,
or a salt thereof

+



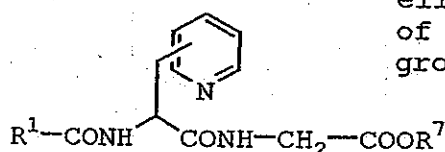
(XIV)

or its reactive derivative
at the amino group,
or a salt thereof



(XV)

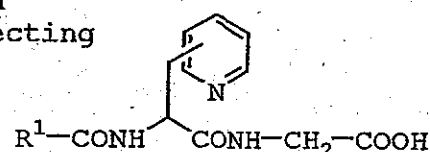
or a salt thereof

Process (H)

(XV)

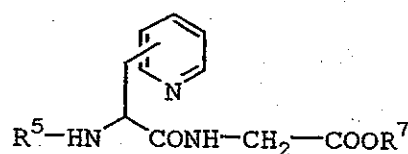
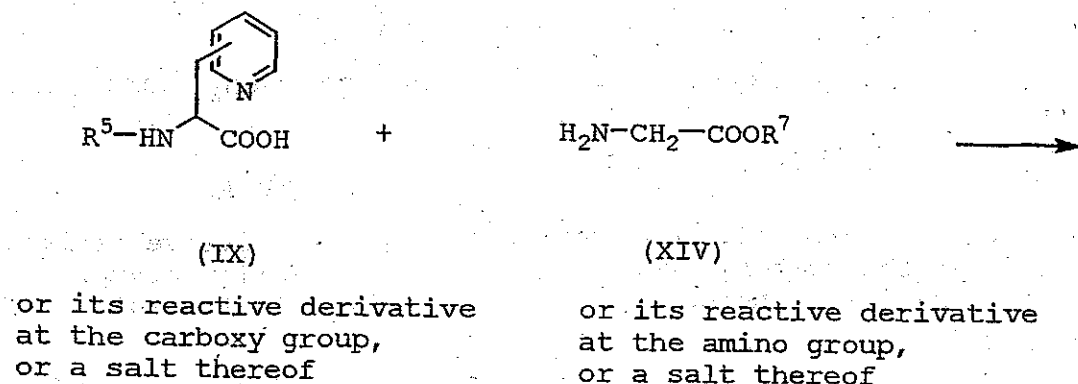
or a salt thereof

elimination reaction
of the carboxy-protecting
group

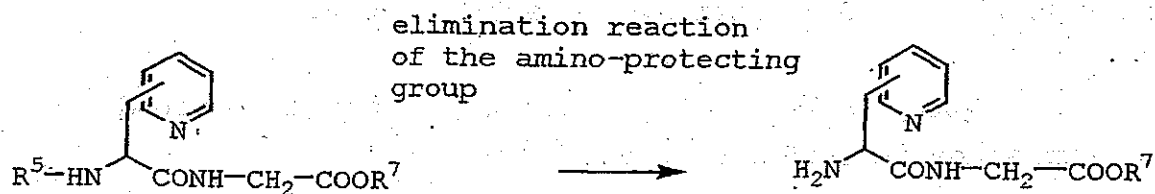


(IV)

or a salt thereof

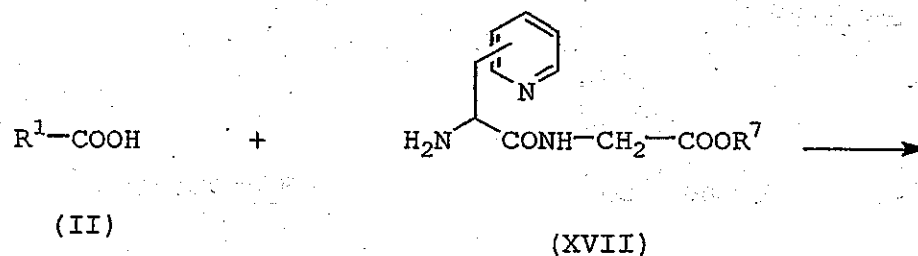
Process (I)

(XVI)
or a salt thereof

Process (J)

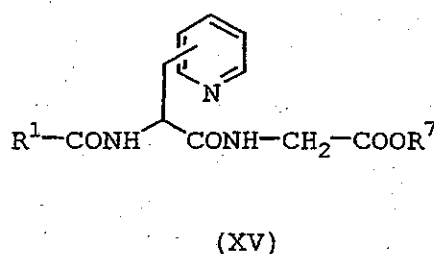
(XVI)
or a salt thereof

(XVII)
or a salt thereof

Process (K)

or its reactive derivative
at the carboxy group,
or a salt thereof

or its reactive derivative
at the amino group,
or a salt thereof



or a salt thereof

wherein R^1 , R^2 and X are each as defined above,

R^4 and R^5 are each amino-protecting group, and

5 R^6 and R^7 are each carboxy-protecting group.

The processes for preparing the object compound are explained in detail in the following.

10 Process (1)

The compound (I) or a salt thereof can be prepared by reacting the compound (II) or its reactive derivative at the carboxy group, or a salt thereof with the compound (III) or its reactive derivative at the amino group, or a salt thereof.

15 Suitable reactive derivative of the compound (III) includes Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (III) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (III) with a silyl
20 compound such as N,O-bis(trimethylsilyl)acetamide, N-trimethylsilylacetamide or the like; a derivative formed by the reaction of the compound (III) with phosphorus trichloride or phosgene.

Suitable reactive derivative of the compound (II) includes an acid halide, an acid anhydride and an activated ester. The suitable example may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid (e.g., dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.), dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, alkanesulfonic acid (e.g., methanesulfonic acid, ethanesulfonic acid, etc.), sulfuric acid, alkylcarbonic acid, aliphatic carboxylic acid (e.g., pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.); aromatic carboxylic acid (e.g., benzoic acid, etc.); a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; an activated ester (e.g., cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl $[(CH_3)_2N^+=CH-]$ ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranil ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.); or an ester with an N-hydroxy compound (e.g., N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxybenzotriazole, N-hydroxyphthalimide, 1-hydroxy-6-chloro-1H-benzotriazole, etc.). These reactive derivatives can optionally be selected from them according to the kind of the compound (II) to be used.

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvents which do not adversely affect the reaction, or the mixture thereof.

When the compound (II) is used in free acid form or its salt form in the reaction, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)-

carbodiimide; N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N-carbonyl-bis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; thionyl chloride; oxalyl chloride; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, phosphorus oxychloride, etc.; or the like.

The reaction may also be carried out in the presence of an organic or inorganic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

20 Process (2)

The compound (I) or a salt thereof can be prepared by reacting the compound (IV) or its reactive derivative at the carboxy group, or a salt thereof with the compound (V) or a salt thereof.

25 This reaction can be carried out in a similar manner to the reaction in the aforementioned Process (1), and therefore the reagents to be used and reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of Process (1).

30

Process (A)

The compound (VII) or a salt thereof can be prepared by reacting the compound (VI) or its reactive derivative at the carboxy group, or a salt thereof with the compound (V) or a salt thereof.

35

This reaction can be carried out in a similar manner to the reaction in the aforementioned Process (1), and therefore the reagents to be used and reaction conditions (e.g., solvent,

reaction temperature, etc.) can be referred to those of Process (1).

Process (B)

The compound (VIII) or a salt thereof can be prepared by
5 subjecting the compound (VII) or a salt thereof to elimination
 reaction of the amino-protecting group.

Suitable method of this elimination reaction includes
conventional one such as hydrolysis, reduction and the like.

(i) For hydrolysis:

10 The hydrolysis is preferably carried out in the presence of
 a base or an acid including Lewis acid.

Suitable base includes an inorganic base and an organic
base such as an alkali metal (e.g., sodium, potassium, etc.), an
alkaline earth metal (e.g., magnesium, calcium, etc.), the
15 hydroxide or carbonate or hydrogencarbonate thereof,
 trialkylamine (e.g., trimethylamine, triethylamine, etc.),
 picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, or the like.

Suitable acid includes an organic acid (e.g., formic acid,
acetic acid, propionic acid, trichloroacetic acid,
20 trifluoroacetic acid, etc.), and an inorganic acid (e.g.,
 hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen
 chloride, hydrogen bromide, etc.).

The elimination using Lewis acid such as trihaloacetic acid
(e.g., trichloroacetic acid, trifluoroacetic acid, etc.), or the
25 like is preferably carried out in the presence of a cation
 trapping agent (e.g., anisole, phenol, etc.). This reaction is
 usually carried out without solvent.

The reaction may be carried out in a conventional solvent
such as water, alcohol (e.g., methanol, ethanol, isopropyl
30 alcohol, etc.), tetrahydrofuran, dioxane, toluene, methylene
 chloride, ethylene dichloride, chloroform, N,N-dimethylformamide,
 N,N-dimethylacetamide or any other organic solvents which do not
 adversely affect the reaction, or a mixture thereof.

The reaction temperature is not critical and the reaction
35 is usually carried out under cooling to warming.

(ii) For reduction:

Reduction is carried out in a conventional manner,
including chemical reduction and catalytic reduction.

Suitable reducing reagent to be used in chemical reduction are hydrides (e.g., hydrogen iodide, hydrogen sulfide, lithium aluminum hydride, sodium borohydride, sodium cyanoborohydride, etc.), or a combination of a metal (e.g., tin, zinc, iron, etc.)
5 or metallic compound (e.g., chromium chloride, chromium acetate, etc.) and an organic acid or inorganic acid (e.g., formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.).

Suitable catalysts to be used in catalytic reduction are
10 conventional ones such as platinum catalysts (e.g., platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.), palladium catalysts (e.g., spongy palladium, palladium black, palladium oxide, palladium on carbon, palladium hydroxide on carbon, colloidal palladium,
15 palladium on barium sulfate, palladium on barium carbonate, etc.), nickel catalysts (e.g., reduced nickel, nickel oxide, Raney nickel, etc.), cobalt catalysts (e.g., reduced cobalt, Raney cobalt, etc.), iron catalysts (e.g., reduced iron, Raney iron, Ullman iron, etc.), and the like.

20 The reduction is usually carried out in a conventional solvent such as water, alcohol (e.g., methanol, ethanol, isopropyl alcohol, etc.), tetrahydrofuran, dioxane, toluene, methylene chloride, ethylene dichloride, chloroform, N,N-dimethylformamide, N,N-dimethylacetamide or any other organic
25 solvents which do not adversely affect the reaction, or a mixture thereof.

Additionally, in case that the above-mentioned acids to be used in chemical reduction are in a liquid state, they can also be used as a solvent.

30 The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.
Process (C)

The compound (X) or a salt thereof can be prepared by reacting the compound (IX) or its reactive derivative at the
35 carboxy group, or a salt thereof with the compound (VIII) or its reactive derivative at the amino group, or a salt thereof.

This reaction can be carried out in a similar manner to the reaction in the aforementioned Process (1), and therefore the

reagents to be used and reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of Process (1).

Process (D)

- 5 The compound (III) or a salt thereof can be prepared by subjecting the compound (X) or a salt thereof to elimination reaction of the amino-protecting group.

 This reaction can be carried out in a similar manner to the reaction in the aforementioned Process (B), and therefore the
10 reagents to be used and reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of Process (B).

Process (E)

- The compound (XII) or a salt thereof can be prepared by
15 reacting the compound (II) or its reactive derivative at the carboxy group, or a salt thereof with the compound (XI) or its reactive derivative at the amino group, or a salt thereof.

 This reaction can be carried out in a similar manner to the reaction in the aforementioned Process (1), and therefore the
20 reagents to be used and reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of Process (1).

Process (F)

- The compound (XIII) or a salt thereof can be prepared by
25 subjecting the compound (XII) or a salt thereof to elimination reaction of the carboxy-protecting group.

 This reaction can be carried out in a similar manner to the reaction in the aforementioned Process (B), and therefore the
30 reagents to be used and reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of Process (B).

Process (G)

- The compound (XV) or a salt thereof can be prepared by
35 reacting the compound (XIII) or its reactive derivative at the carboxy group, or a salt thereof with the compound (XIV) or its reactive derivative at the amino group, or a salt thereof.

 This reaction can be carried out in a similar manner to the reaction in the aforementioned Process (1), and therefore the

reagents to be used and reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of Process (1).

Process (H)

- 5 The compound (IV) or a salt thereof can be prepared by subjecting the compound (XV) or a salt thereof to elimination reaction of the carboxy-protecting group.

 This reaction can be carried out in a similar manner to the reaction in the aforementioned Process (B), and therefore the
10 reagents to be used and reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of Process (B).

Process (I)

- 15 The compound (XVI) or a salt thereof can be prepared by reacting the compound (IX) or its reactive derivative at the carboxy group, or a salt thereof with the compound (XIV) or its reactive derivative at the amino group, or a salt thereof.

 This reaction can be carried out in a similar manner to the reaction in the aforementioned Process (1), and therefore the
20 reagents to be used and reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of Process (1).

Process (J)

- 25 The compound (XVII) or a salt thereof can be prepared by subjecting the compound (XVI) or a salt thereof to elimination reaction of the amino-protecting group.

 This reaction can be carried out in a similar manner to the reaction in the aforementioned Process (B), and therefore the
30 reagents to be used and reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of Process (B).

Process (K)

- 35 The compound (XV) or a salt thereof can be prepared by reacting the compound (II) or its reactive derivative at the carboxy group, or a salt thereof with the compound (XVII) or its reactive derivative at the amino group, or a salt thereof.

 This reaction can be carried out in a similar manner to the reaction in the aforementioned Process (1), and therefore the

reagents to be used and reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of Process (1).

5 Suitable salts of the starting compounds and their reactive derivatives in Processes (1) and (2) and Processes (A) to (K) can be referred to the ones as exemplified for the compound (I).

10 The compounds obtained by the above process can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography, reprecipitation, or the like.

15 It is to be noted that the compound (I) and the other compounds may include one or more stereoisomer(s) such as optical isomer(s) and geometrical isomer(s) due to asymmetric carbon atom(s) and double bond(s), and all of such isomers and mixtures thereof are included within the scope of this invention.

 The object compounds (I) and pharmaceutically acceptable salts thereof include solvates [e.g., enclosure compounds (e.g., hydrate, etc.)].

20 The object compounds (I) and pharmaceutically acceptable salts thereof possess a strong inhibitory activity on the production of nitric oxide (NO).

25 Accordingly, the object compounds (I) and pharmaceutically acceptable salts thereof are expected to possess a nitric oxide synthase (NOS)-inhibitory activity or a NOS-production inhibitory activity.

30 Accordingly, the object compounds (I) and pharmaceutically acceptable salts thereof are useful for prevention and/or treatment of NO-mediated diseases in human being and animals, including respiratory diseases such as adult respiratory distress syndrome (ARDS) and asthma; cardiovascular diseases such as cardiovascular ischemia, myocarditis, heart failure, hypotension and atherosclerosis; endocrine diseases such as diabetes (e.g., insulin-dependent diabetes mellitus, etc.), complications of
35 diabetes mellitus (e.g., diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, etc.) and gout; renal diseases such as glomerulonephritis and renal failure; gastrointestinal diseases such as peptic ulcer and inflammatory bowel disease

(e.g., ulcerative colitis, chronic colitis, etc.); pancreatic diseases such as pancreatitis; hepatic diseases such as hepatitis and liver cirrhosis; diseases of bone or joint such as synovitis, arthritis, osteoarthritis, osteoporosis; autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus and multiple sclerosis; dermal diseases such as dermatitis and eczema; cancer such as solid tumors and metastasis; rejection by organ transplantation; shock (e.g., septic shock, etc.); and sepsis-induced systemic inflammatory response syndrome.

10 The object compounds (I) and pharmaceutically acceptable salts thereof are also useful for prevention and/or treatment of NO-mediated nervous diseases including central nervous system diseases such as CNS disorders, cerebrovascular diseases (e.g., cerebral infarction, cerebral ischemia, cerebral hemorrhage, etc.), migraine, Alzheimer's disease; peripheral nervous system diseases such as neuritis, pain (e.g., postherpetic neuralgia, reflex sympathetic dystrophy (RSD), causalgia, deafferentation pain syndrome, neuropathic pain, etc.), allodynia, hyperalgesia, neurological disorders and neuroprotection; Parkinson's disease; and amyotrophic lateral sclerosis....

20 Additionally, the object compounds (I) and pharmaceutically acceptable salts thereof are useful for treatment of sexual dysfunction such as male sexual dysfunction including erectile dysfunction, and female sexual dysfunction including orgasmic dysfunction related to clitoral disturbances.

25 Further, the object compounds (I) and pharmaceutically acceptable salts thereof are useful for prevention and/or treatment of NO-mediated ophthalmic diseases, including conjunctive diseases such as conjunctivitis (e.g., allergic conjunctivitis, vernal conjunctivitis, keratoconjunctivitis sicca, viral conjunctivitis, bacterial conjunctivitis, etc.); uveal diseases such as uveitis (e.g., Behcet disease, Harada disease, sympathetic ophthalmia, sarcoidosis, diabetic iritis, etc.); scleral diseases such as scleritis; corneal diseases such as corneal neovascularization, keratitis, corneal edema, corneal opacity, corneal dystrophy, keratoconus and neuroparalytic keratitis; retinal, vitreous diseases such as diabetic retinopathy, retinal artery occlusion, retinal vein occlusion,

central serous chorioretinopathy, central hemorrhagic chorioretinitis, macular degeneration (e.g., age-related macular degeneration, etc.), retinal detachment, retinal pigmentary degeneration, macular neovascularization, macular hole, proliferative vitreoretinopathy, vitreous hemorrhage and vitreous opacity; lens diseases such as cataract (e.g., senile cataract, traumatic cataract, diabetic cataract, atopic cataract, etc.); glaucoma such as primary open-angle glaucoma, primary angle-closure glaucoma, normal tension glaucoma and neovascular glaucoma; ocular hypertension; vision disorders such as amblyopia, color vision defect and night blindness; refractive errors such as astigmatism, hyperopia, myopia and presbyopia; and lacrimal apparatus diseases such as dry eye syndromes, lacrimal duct obstruction and dacryocystitis.

15

In order to illustrate the usefulness of the object compound (I), the pharmacological test result of the compound (I) is shown in the following.

20 Test Compound:

Compound (a): 5-Chloro-N-[(1S)-2-oxo-2-({2-oxo-2-[4-(1,3-thiazol-2-yloxy)-1-piperidinyl]ethyl}amino)-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide

Compound (b): (2E)-3-(4-Chlorophenyl)-N-[(1S)-2-oxo-2-({2-oxo-2-[4-(2-pyrazinyloxy)-1-piperidinyl]ethyl}amino)-1-(2-pyridylmethyl)ethyl]acrylamide

Compound (c): 5-Chloro-N-[(1S)-2-[(2-{4-[(6-methoxy-2-pyridyl)oxy]-1-piperidinyl}-2-oxoethyl)amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide

Compound (d): 5-Chloro-N-[(1S)-2-oxo-2-({2-oxo-2-[4-(2-pyridyloxy)-1-piperidinyl]ethyl}amino)-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide

Compound (e): (2E)-3-(4-Chlorophenyl)-N-[(1S)-2-oxo-2-([2-oxo-2-(4-phenoxy-1-piperidinyl)ethyl]amino)-1-(2-pyridylmethyl)ethyl]acrylamide

Compound (f): 5-Chloro-N-[(1S)-2-oxo-2-({2-oxo-2-[4-(2,2,2-trifluoroethoxy)-1-piperidinyl]ethyl}amino)-1-(2-pyridylmethyl)-ethyl]-1-benzofuran-2-carboxamide

Compound (g): (2E)-3-(4-Chlorophenyl)-N-[(1S)-2-{[2-(4-isopropoxy-1-piperidinyl)-2-oxoethyl]amino}-2-oxo-1-(2-pyridylmethyl)ethyl]acrylamide

5 Test 1: Assay for inhibitory activity on the production of nitric oxide

The murine macrophage cell line RAW264.7 (American Type Culture Collection, No. TIB71) was used in this study. RAW264.7 cells were grown on F75 plastic culture flasks at 37°C, 5% in 10 Dulbecco's modified Eagle's medium (DMEM) supplemented with L-glutamine, penicillin, streptomycin and 10% heat-inactivated fetal bovine serum. They were removed from culture flasks by rubber cell scraper and were centrifuged and resuspended in DMEM without phenol red. They were plated in 96-well microtiter plates. 15 (10⁵ cells per well) and allowed to adhere over 2 hours. The test samples were added and the cells were preincubated for 1 hour. Thereafter the cells were activated with both of lipopolysaccharide (LPS) (1 µg/ml) and interferon γ (INF γ) (3 u/ml) for 18-24 hours. An equal volume of Griess reagent (1% 20 sulfanilamide/0.1% N-naphthylethylenediamine dihydrochloride/2.5% H₃PO₄) was added and the cells were incubated at room temperature for 10 minutes. The absorbance was read at 570 nm using microplate reader and NO₂⁻ was measured using NaNO₂ as a standard.

25 Test result:

Table 1

Test compound (10 ⁻⁶ M)	Inhibition (%)
(a)	100
(b)	97.6
(c)	100
(d)	100
(e)	100
(f)	100
(g)	100

Test 2: Protective effect of the compound (I) combined with FK506 on rat cardiac allograft

30 Method:

Experiments were performed on male Lewis and ACI rats weighing 175-200 g. Rats were anesthetized with sodium pentobarbital (50 mg/kg, i.p.), and underwent allogeneic (Lewis donor to ACI recipient) heterotopic cardiac transplantation.

5 Experimental groups were divided into single-drug group and combined-drug group. Single-drug dose of FK506, which was prepared in a manner similar to that disclosed in EP-0184162, was 0.32 mg/kg. Combined-drug dose was FK506 (0.32 mg/kg) + the compound (I) (10 mg/kg). The grafted hearts were monitored by
10 daily palpation where complete rejection was defined as the cessation of palpable contractile activity. Each drug was suspended in a solution of 0.5% methylcellulose, and administered by daily gastric intubation in a volume of 5 ml/kg of body weight for 14 days.

15 The combination of the compound (I) and FK506 dramatically prolonged the graft survival.

The above experimental results indicate that the activity and/or efficacy of an immunosuppressant in rejection of transplantation can be remarkably and synergistically increased
20 by administering compound (I) in combination, which has a strong inhibitory activity on the production of nitric oxide.

For therapeutic administration, the object compound (I) of the present invention and pharmaceutically acceptable salts
25 thereof are used in the form of a conventional pharmaceutical preparation in admixture with a conventional pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient which is suitable for oral, parenteral or external administration. The pharmaceutical preparation may be
30 compounded in a solid form such as granule, capsule, tablet, dragee, suppository or ointment, or in a liquid form such as solution, suspension or emulsion for injection, intravenous drip, ingestion, eye drop, etc. If needed, there may be included in the above preparation auxiliary substance such as stabilizing agent,
35 wetting or emulsifying agent, buffer or any other commonly used additives.

The effective ingredient may usually be administered in a unit dose of 0.001 mg/kg to 500 mg/kg, preferably 0.01 mg/kg to

10 mg/kg, 1 to 4 times a day. However, the above dosage may be increased or decreased according to age, body weight and conditions of the patient or administering method.

According to the present invention, a pharmaceutical
5 composition comprising FK506 and the compound (I) or a pharmaceutically acceptable salt thereof is provided. A pharmaceutical composition comprising FK506 and the compound (I) or a pharmaceutically acceptable salt thereof is useful as an immunosuppressant. For example, the pharmaceutical composition of
10 the present invention is useful as a medicament for the prevention or treatment of rejection by organ transplantation.

When the compound (I) is used in combination with FK506, a ratio by weight of the compound (I) or a pharmaceutically acceptable salt thereof to FK506 is in the range of 0.1/1 -
15 1000/1, preferably in the range of 1/1 - 100/1.

The preferred embodiments of the compound of the present invention represented by the general formula (I) are as follows.

- (1) The compound of the formula (I), wherein R^2 is a group of the formula: $-Y-R^3$ wherein R^3 is lower alkyl, halo(lower)alkyl,
20 optionally substituted heterocyclic group or optionally substituted aryl, and Y is -O-, -S- or $-SO_2-$, or a pharmaceutically acceptable salt thereof.
- (2) The compound of (1) mentioned above, wherein R^3 is lower alkyl; halo(lower)alkyl; heterocyclic group optionally
25 substituted by one or more substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, halogen and halo(lower)alkyl; or aryl optionally substituted by one or more substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, halogen and halo(lower)alkyl, or a pharmaceutically
30 acceptable salt thereof.
- (3) The compound of (2) mentioned above, wherein R^3 is lower alkyl; halo(lower)alkyl; heterocyclic group selected from the group consisting of pyridyl, pyrazinyl, thiazolyl, pyridazinyl and pyrimidinyl, said heterocyclic group is optionally
35 substituted by one or more substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, halogen and halo(lower)alkyl; or phenyl optionally substituted by one or more substituent(s) selected from the group consisting of lower alkyl,

lower alkoxy, halogen and halo(lower)alkyl, or a pharmaceutically acceptable salt thereof.

(4) The compound of the formula (I), wherein X is



5 or a pharmaceutically acceptable salt thereof.

(5) The compound of (4) mentioned above, wherein R² is substituted hydroxy, or a pharmaceutically acceptable salt thereof.

(6) The compound of (5) mentioned above, wherein R² is a group of the formula: -O-R³ wherein R³ is lower alkyl, halo(lower)alkyl, optionally substituted heterocyclic group or optionally substituted aryl, or a pharmaceutically acceptable salt thereof.

(7) The compound of (6) mentioned above, wherein R³ is lower alkyl, halo(lower)alkyl, pyridyl, pyrazinyl, thiazolyl or phenyl, each of said pyridyl, pyrazinyl, thiazolyl and phenyl is optionally substituted by one or more substituents selected from the group consisting of lower alkyl, lower alkoxy, halogen and halo(lower)alkyl, or a pharmaceutically acceptable salt thereof.

(8) The compound of (7) mentioned above, wherein R³ is lower alkyl, halo(lower)alkyl, pyridyl, pyrazinyl, thiazolyl or phenyl, said pyridyl is optionally substituted by a substituent selected from the group consisting of lower alkyl, lower alkoxy, halogen and halo(lower)alkyl, or a pharmaceutically acceptable salt thereof.

(9) The compound of the formula (I), wherein R¹ is benzofuranyl substituted by chlorine, or styryl substituted by chlorine, or a pharmaceutically acceptable salt thereof.

(10) The compound of the formula (I), wherein R¹ is 5-chloro-1-benzofuran-2-yl or 2-(4-chlorophenyl)ethenyl, or a pharmaceutically acceptable salt thereof.

30 The following Preparations and Examples are given for the purpose of illustrating the present invention in detail.

Preparation 1

Benzyl ((2S)-2-[(tert-butoxycarbonyl)amino]-3-(2-pyridyl)propanoyl)amino)acetate

35 To a solution of (2S)-2-[(tert-butoxycarbonyl)amino]-3-(2-pyridyl)propanoic acid (55.0 g), glycine benzyl ester tosylate (69.7 g), and diphenylphosphoryl azide (46.7 ml) in N,N-

dimethylformamide (550 ml) was added dropwise N,N-diisopropyl-ethylamine (75.6 ml) at 4°C. The mixture was warmed to room temperature and stirred for 3 hours. The resulting mixture was poured into ice-cold saturated aqueous sodium hydrogencarbonate solution (700 ml). The mixture was extracted twice with ethyl acetate (total 1.3 L) and washed successively with water (400 ml x 2), saturated aqueous ammonium chloride solution (200 ml), aqueous sodium hydrogencarbonate solution (300 ml x 2), and brine (40 ml). The organic layer was dried over anhydrous magnesium sulfate and concentrated to give the title compound (77.4 g) as pale brown crystals.

ESI-MS: 414.3 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.48(dd, J=5,2Hz, 1H), 7.82(br, 1H), 7.60(td, J=8,2Hz, 1H), 7.40-7.29(m, 5H), 7.21(d, J=8Hz, 1H), 7.14(dd, J=8,5Hz, 1H), 6.33(br, 1H), 5.15(s, 2H), 4.62(br, 1H), 4.04(d, J=6Hz, 2H), 3.36-3.18(m, 2H), 1.43(s, 9H).

Preparation 2

Benzyl {[(2S)-2-amino-3-(2-pyridyl)propanoyl]amino}acetate dihydrochloride

To a solution of benzyl {[(2S)-2-[(tert-butoxycarbonyl)-amino]-3-(2-pyridyl)propanoyl]amino}acetate (73.8 g) in ethyl acetate (150 ml) was added dropwise 4N hydrogen chloride in ethyl acetate (669 ml) at 10°C over 30 minutes. The mixture was warmed to room temperature and stirred for 3 hours. The mixture was diluted with ethyl acetate (300 ml). The resulting precipitate was collected by filtration, washed with ethyl acetate (700 ml), and dried in vacuo to give the title compound.

¹H-NMR (300MHz, DMSO-d₆) δ 9.31(t, J=6Hz, 1H), 8.83(d, J=5Hz, 1H), 8.70(br, 3H), 8.40(t, J=8Hz, 1H), 7.96(d, J=8Hz, 1H), 7.87(t, J=5Hz, 1H), 7.41-7.30(m, 5H), 5.14(s, 2H), 4.53(br, 1H), 4.05(dd, J=18,6Hz, 1H), 3.99(dd, J=18,6Hz, 1H), 3.64(dd, J=15,5Hz, 1H), 3.54(dd, J=15,8Hz, 1H).

Preparation 3

Benzyl {[(2S)-2-[[(2E)-3-(4-chlorophenyl)-2-propenoyl]-amino]-3-(2-pyridyl)propanoyl]amino}acetate

To a solution of 4-chlorocinnamic acid (49.2 g) in dichloromethane (400 ml) were added oxalyl chloride (30.5 ml) and 1 drop of N,N-dimethylformamide, and the mixture was stirred at

room temperature for 6 hours. The reaction mixture was evaporated to dryness, and the residual acid chloride was dissolved in dichloromethane (900 ml). To this solution was added benzyl

- 5 dihydrochloride (104 g) at 10°C followed by addition of triethylamine (116 ml) over 40 minutes. The mixture was allowed to warm to room temperature and stirred for 2 hours. The reaction mixture was evaporated to dryness, and the residue was washed successively with water (500 ml x 5) and tetrahydrofuran-n-hexane
10 (1:2, 500 ml x 10), and dried in vacuo to give the title compound (115 g) as a white solid.

ESI-MS: 478.3 (M+H)

- ¹H-NMR (300MHz, CDCl₃) δ 8.51 (dd, J=5,2Hz, 1H), 8.27 (t, J=5Hz, 1H), 7.83 (d, J=6Hz, 1H), 7.64 (td, J=8,2Hz, 1H), 7.57 (d, J=16Hz, 1H),
15 7.44 (d, J=9Hz, 2H), 7.39-7.28 (m, 8H), 7.19 (dd, J=8,5Hz, 1H), 6.47 (d, J=16Hz, 1H), 5.14 (s, 2H), 4.98 (app q, J=6Hz, 1H), 4.07 (d, J=5Hz, 2H), 3.36 (dd, J=15,5Hz, 1H), 3.26 (dd, J=15,6Hz, 1H).

Preparation 4

- 20 [[(2S)-2-[[[(2E)-3-(4-Chlorophenyl)-2-propenoyl]amino]-3-(2-pyridyl)propanoyl]amino]acetic acid

- To a suspension of benzyl [[(2S)-2-[[[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino]-3-(2-pyridyl)propanoyl]amino]acetate (10.8 g) in methanol (200 ml) was added 1N aqueous sodium hydroxide solution (22.6 ml), and the mixture was stirred at room
25 temperature for 5 hours. The reaction mixture was concentrated in vacuo, and the residue was treated with aqueous citric acid solution (10%, 100 ml). The resulting white precipitate was collected by filtration, washed with tetrahydrofuran-hexane (1:1, 150 ml), and dried in vacuo to give the title compound (8.25 g)
30 as a white solid.

ESI-MS: 388.2 (M+H)

- ¹H-NMR (300MHz, DMSO-d₆) δ 12.6 (br, 1H), 8.50-8.36 (m, 3H), 7.68 (td, J=8,2Hz, 1H), 7.56 (d, J=9Hz, 2H), 7.47 (d, J=9Hz, 2H), 7.34 (d, J=16Hz, 1H), 7.30 (d, J=8Hz, 1H), 7.20 (dd, J=8,5Hz, 1H), 6.68 (d, J=16Hz, 1H), 4.96-4.86 (m, 1H), 3.78 (dd, J=18,6Hz, 1H), 3.74 (dd, J=18,6Hz, 1H), 3.24 (dd, J=14,5Hz, 1H), 2.99 (dd, J=14,10Hz, 1H).
35

Preparation 5

Benzyl [[(2S)-2-[[[(5-chloro-1-benzofuran-2-yl)carbonyl]-

amino}-3-(2-pyridyl)propanoyl]amino}acetate

The title compound was obtained from benzyl {[(2S)-2-amino-3-(2-pyridyl)propanoyl]amino}acetate dihydrochloride and 5-chloro-1-benzofuran-2-carboxylic acid in the same manner as in Preparation 3.

ESI-MS: 492.3 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.70-8.49 (m, 3H), 7.71-7.62 (m, 2H), 7.52-7.18 (m, 10H), 5.16 (s, 2H), 5.11-5.02 (m, 1H), 4.19-4.03 (m, 2H), 3.44 (dd, J=15, 4Hz, 1H), 3.35 (dd, J=15, 7Hz, 1H).

10 Preparation 6

{[(2S)-2-[(5-Chloro-1-benzofuran-2-yl)carbonyl]amino}-3-(2-pyridyl)propanoyl]amino}acetic acid

The title compound was obtained from benzyl {[(2S)-2-[(5-chloro-1-benzofuran-2-yl)carbonyl]amino}-3-(2-pyridyl)propanoyl]-amino}acetate in the same manner as in Preparation 4.

ESI-MS: 402.2 (M+H)

¹H-NMR (300MHz, DMSO-d₆) δ 12.6 (br, 1H), 9.00 (d, J=8Hz, 1H), 8.49 (dd, J=5, 2Hz, 1H), 8.46 (t, J=6Hz, 1H), 7.88 (d, J=2Hz, 1H), 7.72 (d, J=9Hz, 1H), 7.67 (td, J=8, 2Hz, 1H), 7.53 (d, J=1Hz, 1H), 7.48 (dd, J=9, 2Hz, 1H), 7.33 (d, J=8Hz, 1H), 7.20 (dd, J=8, 5Hz, 1H), 5.04-4.94 (m, 1H), 3.80 (dd, J=18, 6Hz, 1H), 3.74 (dd, J=18, 6Hz, 1H), 3.32 (dd, J=14, 4Hz, 1H), 3.22 (dd, J=14, 10Hz, 1H).

Preparation 7

tert-Butyl 4-(1,3-thiazol-2-yloxy)-1-piperidinecarboxylate

To a slurry of sodium hydride (about 60% oil suspension, 5.67g) in dimethoxyethane (40 ml) was added a solution of tert-butyl 4-hydroxy-1-piperidinecarboxylate (23.9 g) in dimethoxyethane (60 ml) over 30 minutes, and the mixture was stirred for an additional 1 hour. To the mixture was added 2-bromothiazole (15.0 g), and the mixture was refluxed for 4 hours. After cooling, the resulting pale brown suspension was diluted with ether (300 ml) and the mixture was filtered through a pad of Celite. The filtrate was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residual oil was purified by silica gel column chromatography (eluent; 15% ethyl acetate in n-hexane) to give the title compound (22.1 g) as a yellow oil.

ESI-MS: 285.2 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 7.11(d, J=4Hz, 1H), 6.67(d, J=4Hz, 1H), 5.13(septet, J=4Hz, 1H), 3.73(ddd, J=14,7,4Hz, 2H), 3.32(ddd, J=14,8,4Hz, 2H), 2.08-1.96(m, 2H), 1.88-1.74(m, 2H), 1.47(s, 9H).

Example 1

- 5 (2E)-3-(4-Chlorophenyl)-N-[(1S)-2-oxo-2-({2-oxo-2-[4-(1,3-thiazol-2-yloxy)-1-piperidinyl]ethyl}amino)-1-(2-pyridylmethyl)-ethyl]acrylamide

To a solution of tert-butyl 4-(1,3-thiazol-2-yloxy)-1-piperidinecarboxylate (2.93 g) in ethyl acetate (12 ml) was added
10 dropwise 4N hydrogen chloride in ethyl acetate (15 ml) at 10°C. The mixture was warmed to room temperature and stirred for 1 hour. The mixture was concentrated and dried in vacuo. The residual yellow solid was added to an ice-cold mixture of {(2S)-2-[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino}-3-(2-pyridyl)propanoyl]-
15 amino}acetic acid (4.0 g), 1-hydroxybenzotriazole (1.53 g), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.17 g) in N,N-dimethylformamide (40 ml). To the mixture was added dropwise N,N-diisopropylethylamine (3.9 ml). The mixture was warmed to room temperature and stirred for 2 hours. The resulting
20 mixture was poured into ice-cold saturated aqueous sodium hydrogencarbonate solution (200 ml). The mixture was extracted three times with ethyl acetate (total 400 ml) and washed successively with saturated aqueous ammonium chloride solution (100 ml), water (70 ml x 3), and brine (20 ml). The organic layer
25 was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (eluent; 1% methanol in chloroform) to give the title compound (4.57 g) as a pale yellow solid, which was recrystallized from ethyl acetate. ESI-MS: 554.2 (M+H)

- 30 ¹H-NMR (300MHz, CDCl₃) δ 8.55(dd, J=5,2Hz, 1H), 8.04-7.97(m, 1H), 7.96-7.88(m, 1H), 7.63(td, J=8,2Hz, 1H), 7.60(d, J=16Hz, 1H), 7.45(d, J=9Hz, 2H), 7.34(d, J=9Hz, 2H), 7.25(d, J=8Hz, 1H), 7.18(dd, J=8,5Hz, 1H), 7.10(d, J=4Hz, 1H), 6.68(d, J=4Hz, 1H), 6.50(d, J=16Hz, 1H), 5.25-5.15(br m, 1H), 5.06-4.99(m, 1H),
35 4.03(d, J=4Hz, 2H), 3.83-3.52(m, 3H), 3.43(dd, J=15,5Hz, 1H), 3.37-3.31(m, 1H), 3.26(dd, J=15,6Hz, 1H), 2.08-1.81(m, 4H).

Example 2

5-Chloro-N-[(1S)-2-oxo-2-({2-oxo-2-[4-(1,3-thiazol-2-

xyloxy)-1-piperidinyl]ethyl}amino)-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide

The title compound was obtained from tert-butyl 4-(1,3-thiazol-2-yloxy)-1-piperidinecarboxylate and [(2S)-2-[(5-chloro-1-benzofuran-2-yl)carbonyl]amino]-3-(2-pyridyl)propanoyl]-amino}acetic acid in the same manner as in Example 1.

ESI-MS: 568.3 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.80-8.72 (m, 1H), 8.62 (d, J=5,2Hz, 1H), 8.19-8.11 (m, 1H), 7.65 (td, J=8,2Hz, 1H), 7.65 (d, J=2Hz, 1H), 7.49 (d, J=9Hz, 1H), 7.42 (s, 1H), 7.39 (dd, J=9,2Hz, 1H), 7.27 (d, J=8Hz, 1H), 7.20 (dd, J=8,5Hz, 1H), 7.10 (d, J=4Hz, 1H), 6.68 (d, J=4Hz, 1H), 5.25-5.16 (m, 1H), 5.15-5.07 (m, 1H), 4.07 (d, J=4Hz, 2H), 3.83-3.53 (m, 3H), 3.48 (dd, J=15,5Hz, 1H), 3.40-3.29 (m, 2H), 2.08-1.81 (m, 4H).

15 Preparation 8

tert-Butyl 4-(2-pyrazinyloxy)-1-piperidinecarboxylate

To a slurry of sodium hydride (about 60% oil suspension, 114 mg) in dimethyl sulfoxide (5 ml) was added dropwise tert-butyl 4-hydroxy-1-piperidinecarboxylate (576 mg). Considerable foaming occurred and the solution turned pale orange. To this solution was added chloropyrazine (377 mg) and the mixture was stirred at room temperature for 12 hours. The resulting mixture was partitioned between saturated aqueous sodium hydrogen-carbonate solution and ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residual solid was triturated with a mixture of ethyl acetate and n-hexane to give the title compound (472 mg) as white crystals.

ESI-MS: 280.2 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.20 (d, J=1Hz, 1H), 8.10 (d, J=3Hz, 1H), 8.05 (dd, J=3,1Hz, 1H), 5.20 (septet, J=4Hz, 1H), 3.84-3.72 (m, 2H), 3.30 (ddd, J=14,8,4Hz, 2H), 2.05-1.93 (m, 2H), 1.81-1.68 (m, 2H), 1.48 (s, 9H).

Example 3

(2E)-3-(4-Chlorophenyl)-N-[(1S)-2-oxo-2-[(2-oxo-2-[4-(2-pyrazinyloxy)-1-piperidinyl]ethyl}amino)-1-(2-pyridylmethyl)-ethyl]acrylamide

The title compound was obtained from tert-butyl 4-(2-

pyrazinyloxy)-1-piperidinecarboxylate and {[(2S)-2-[[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino]-3-(2-pyridyl)propanoyl]amino}-acetic acid in the same manner as in Example 1.

ESI-MS: 549.4 (M+H)

- 5 ¹H-NMR (300MHz, CDCl₃) δ 8.56(dd, J=5,2Hz, 1H), 8.22-8.20(m, 1H), 8.13(d, J=3Hz, 1H), 8.05(dd, J=3,1Hz, 1H), 8.03-7.88(m, 2H), 7.64(td, J=8,2Hz, 1H), 7.61(d, J=16Hz, 1H), 7.46(d, J=8Hz, 2H), 7.35(d, J=8Hz, 2H), 7.27(d, J=8Hz, 1H), 7.19(dd, J=8,5Hz, 1H), 6.50(d, J=16Hz, 1H), 5.33-5.22(m, 1H), 5.07-4.99(m, 1H), 4.05(app
10 d, J=4Hz, 2H), 3.92-3.78(m, 1H), 3.68-3.52(m, 2H), 3.48-3.22(m, 3H), 2.07-1.92(m, 2H), 1.88-1.78(m, 2H).

Example 4

- 5-Chloro-N-[(1S)-2-oxo-2-({2-oxo-2-[4-(2-pyrazinyloxy)-1-piperidinyl]ethyl}amino)-1-(2-pyridylmethyl)ethyl]-1-benzofuran-
15 2-carboxamide

The title compound was obtained from tert-butyl 4-(2-pyrazinyloxy)-1-piperidinecarboxylate and {[(2S)-2-[[(5-chloro-1-benzofuran-2-yl)carbonyl]amino]-3-(2-pyridyl)propanoyl]amino}-acetic acid in the same manner as in Example 1.

- 20 ESI-MS: 563.2 (M+H)

- ¹H-NMR (300MHz, CDCl₃) δ 8.81-8.71(m, 1H), 8.62(dd, J=5,2Hz, 1H), 8.22-8.14(m, 2H), 8.13(d, J=3Hz, 1H), 8.05(dd, J=3,1Hz, 1H), 7.65(td, J=8,2Hz, 1H), 7.65(d, J=2Hz, 1H), 7.49(dd, J=9,1Hz, 1H), 7.43(d, J=1Hz, 1H), 7.39(dd, J=9,2Hz, 1H), 7.27(d, J=8Hz, 1H),
25 7.20(dd, J=8,5Hz, 1H), 5.32-5.21(m, 1H), 5.16-5.06(m, 1H), 4.15-4.00(m, 2H), 3.92-3.76(m, 1H), 3.69-3.54(m, 2H), 3.49(dd, J=15,5Hz, 1H), 3.40-3.28(m, 2H), 2.07-1.90(m, 2H), 1.89-1.74(m, 2H).

Preparation 9

- 30 tert-Butyl 4-(4-pyridyloxy)-1-piperidinecarboxylate

The title compound was obtained from tert-butyl 4-hydroxy-1-piperidinecarboxylate and 4-chloropyridine hydrochloride in the same manner as in Preparation 8.

ESI-MS: 279.2 (M+H)

- 35 ¹H-NMR (300MHz, CDCl₃) δ 8.42(d, J=6Hz, 2H), 6.80(d, J=6Hz, 2H), 4.58(septet, J=4Hz, 1H), 3.69(ddd, J=14,8,4Hz, 2H), 3.37(ddd, J=14,8,4Hz, 2H), 2.01-1.88(m, 2H), 1.84-1.69(m, 2H), 1.47(s, 9H).

Example 5

(2E)-3-(4-Chlorophenyl)-N-[(1S)-2-oxo-2-({2-oxo-2-[4-(4-pyridyloxy)-1-piperidinyl]ethyl}amino)-1-(2-pyridylmethyl)ethyl]-acrylamide

The title compound was obtained from tert-butyl 4-(4-pyridyloxy)-1-piperidinecarboxylate and {[(2S)-2-{{(2E)-3-(4-chlorophenyl)-2-propenoyl}amino}-3-(2-pyridyl)propanoyl}amino]-acetic acid in the same manner as in Example 1.

ESI-MS: 548.3 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.55 (dd, J=5, 2Hz, 1H), 8.43 (dd, J=5, 2Hz, 2H), 8.04-7.86 (m, 2H), 7.64 (td, J=8, 2Hz, 1H), 7.60 (d, J=16Hz, 1H), 7.45 (d, J=8Hz, 2H), 7.35 (d, J=8Hz, 2H), 7.26 (d, J=8Hz, 1H), 7.18 (dd, J=8, 5Hz, 1H), 6.79 (dd, J=5, 2Hz, 2H), 6.50 (d, J=16Hz, 1H), 5.06-4.98 (m, 1H), 4.70-4.62 (m, 1H), 4.12-3.96 (m, 2H), 3.84-3.22 (m, 6H), 1.98-1.79 (m, 4H).

15 Example 6

5-Chloro-N-[(1S)-2-oxo-2-({2-oxo-2-[4-(4-pyridyloxy)-1-piperidinyl]ethyl}amino)-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide

The title compound was obtained from tert-butyl 4-(4-pyridyloxy)-1-piperidinecarboxylate and {[(2S)-2-{{(5-chloro-1-benzofuran-2-yl)carbonyl}amino}-3-(2-pyridyl)propanoyl}amino]-acetic acid in the same manner as in Example 1.

ESI-MS: 562.3 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.83-8.71 (m, 1H), 8.62 (dd, J=5, 2Hz, 1H), 8.43 (d, J=6Hz, 2H), 8.22-8.12 (m, 1H), 7.65 (td, J=8, 2Hz, 1H), 7.65 (d, J=2Hz, 1H), 7.49 (d, J=9Hz, 1H), 7.42 (s, 1H), 7.39 (dd, J=9, 2Hz, 1H), 7.28 (d, J=8Hz, 1H), 7.20 (dd, J=8, 5Hz, 1H), 6.79 (d, J=6Hz, 2H), 5.15-5.07 (m, 1H), 4.71-4.62 (m, 1H), 4.16-3.99 (m, 2H), 3.83-3.29 (m, 6H), 2.00-1.77 (m, 4H).

30 Preparation 10

tert-Butyl 4-(3-pyridyloxy)-1-piperidinecarboxylate

The title compound was obtained from tert-butyl 4-hydroxy-1-piperidinecarboxylate and 3-fluoropyridine in the same manner as in Preparation 8.

35 ESI-MS: 279.2 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.33-8.30 (m, 1H), 8.22 (dd, J=4, 3Hz, 1H), 7.23-7.20 (m, 2H), 4.51 (septet, J=4Hz, 1H), 3.71 (ddd, J=14, 7, 4Hz, 2H), 3.35 (ddd, J=14, 8, 4Hz, 2H), 2.00-1.88 (m, 2H), 1.83-1.70 (m,

2H), 1.47(s, 9H).

Example 7

(2E)-3-(4-Chlorophenyl)-N-[(1S)-2-oxo-2-({2-oxo-2-[4-(3-pyridyloxy)-1-piperidinyl]ethyl}amino)-1-(2-pyridylmethyl)ethyl]-acrylamide

The title compound was obtained from tert-butyl 4-(3-pyridyloxy)-1-piperidinecarboxylate and {[(2S)-2-{{ (2E)-3-(4-chlorophenyl)-2-propenoyl}amino}-3-(2-pyridyl)propanoyl}amino}-acetic acid in the same manner as in Example 1.

ESI-MS: 548.3 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.56(dd, J=5,2Hz, 1H), 8.33-8.30(m, 1H), 8.24(dd, J=4,1Hz, 1H), 8.06-7.87(m, 2H), 7.64(td, J=8,2Hz, 1H), 7.61(d, J=16Hz, 1H), 7.46(d, J=8Hz, 2H), 7.35(d, J=8Hz, 2H), 7.29-7.16(m, 5H), 6.50(d, J=16Hz, 1H), 5.06-4.99(m, 1H), 4.63-4.57(m, 1H), 4.13-3.97(m, 2H), 3.81-3.23(m, 6H), 1.99-1.81(m, 4H).

Example 8

5-Chloro-N-[(1S)-2-oxo-2-({2-oxo-2-[4-(3-pyridyloxy)-1-piperidinyl]ethyl}amino)-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide

The title compound was obtained from tert-butyl 4-(3-pyridyloxy)-1-piperidinecarboxylate and {[(2S)-2-{{ (5-chloro-1-benzofuran-2-yl)carbonyl}amino}-3-(2-pyridyl)propanoyl}amino}-acetic acid in the same manner as in Example 1.

ESI-MS: 562.3 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.83-8.70(m, 1H), 8.62(dd, J=5,2Hz, 1H), 8.33-8.29(m, 1H), 8.25-8.22(m, 1H), 8.21-8.10(m, 1H), 7.65(td, J=8,2Hz, 1H), 7.65(d, J=2Hz, 1H), 7.49(d, J=9Hz, 1H), 7.42(s, 1H), 7.39(dd, J=9,2Hz, 1H), 7.30-7.16(m, 4H), 5.16-5.07(m, 1H), 4.64-4.55(m, 1H), 4.15-3.98(m, 2H), 3.80-3.28(m, 6H), 1.98-1.80(m, 4H).

Preparation 11

tert-Butyl 4-[(6-methoxy-2-pyridyl)oxy]-1-piperidine-carboxylate

The title compound was obtained from tert-butyl 4-hydroxy-1-piperidinecarboxylate and 2-chloro-6-methoxypyridine in the same manner as in Preparation 8.

ESI-MS: 309.2 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 7.49(t, J=8Hz, 1H), 6.29(d, J=8Hz, 2H), 5.17(septet, J=4Hz, 1H), 3.88(s, 3H), 3.81-3.70(m, 2H), 3.31(ddd,

J=14,8,4Hz, 2H), 2.04-1.92 (m, 2H), 1.82-1.67 (m, 2H), 1.47 (s, 9H).

Example 9

(2E)-3-(4-Chlorophenyl)-N-[(1S)-2-[(2-{4-[(6-methoxy-2-pyridyl)oxy]-1-piperidinyl}-2-oxoethyl)amino]-2-oxo-1-(2-pyridylmethyl)ethyl]acrylamide

The title compound was obtained from tert-butyl 4-[(6-methoxy-2-pyridyl)oxy]-1-piperidinecarboxylate and {[(2S)-2-[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino]-3-(2-pyridyl)-propanoyl]amino}acetic acid in the same manner as in Example 1.

ESI-MS: 578.3 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.56 (dd, J=5,2Hz, 1H), 8.04-7.86 (m, 2H), 7.63 (td, J=8,2Hz, 1H), 7.61 (d, J=16Hz, 1H), 7.53-7.42 (m, 3H), 7.35 (d, J=8Hz, 2H), 7.26 (d, J=8Hz, 1H), 7.18 (dd, J=8,5Hz, 1H), 6.50 (d, J=16Hz, 1H), 6.29 (d, J=8Hz, 2H), 5.32-5.20 (m, 1H), 5.06-4.98 (m, 1H), 4.03 (app d, J=4Hz, 2H), 3.86 (s, 3H), 3.82-3.21 (m, 6H), 2.02-1.74 (m, 4H).

Example 10

5-Chloro-N-[(1S)-2-[(2-{4-[(6-methoxy-2-pyridyl)oxy]-1-piperidinyl}-2-oxoethyl)amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide

The title compound was obtained from tert-butyl 4-[(6-methoxy-2-pyridyl)oxy]-1-piperidinecarboxylate and {[(2S)-2-[(5-chloro-1-benzofuran-2-yl)carbonyl]amino]-3-(2-pyridyl)propanoyl]-amino}acetic acid in the same manner as in Example 1.

ESI-MS: 592.4 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.82-8.71 (m, 1H), 8.62 (dd, J=5,2Hz, 1H), 8.19-8.09 (m, 1H), 7.65 (td, J=8,2Hz, 1H), 7.65 (d, J=2Hz, 1H), 7.52-7.45 (m, 2H), 7.42 (s, 1H), 7.38 (dd, J=9,2Hz, 1H), 7.27 (d, J=8Hz, 1H), 7.20 (dd, J=8,5Hz, 1H), 6.29 (d, J=8Hz, 2H), 5.31-5.21 (m, 1H), 5.16-5.08 (m, 1H), 4.07 (app d, J=4Hz, 2H), 3.86 (s, 3H), 3.82-3.44 (m, 4H), 3.40-3.28 (m, 2H), 2.03-1.70 (m, 4H).

Preparation 12

tert-Butyl 3-[(5-chloro-2-pyridyl)oxy]-1-piperidinecarboxylate

The title compound was obtained from tert-butyl 3-hydroxy-1-piperidinecarboxylate and 2,5-dichloropyridine in the same manner as in Preparation 8.

ESI-MS: 313.2 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.07(d, J=3Hz, 1H), 7.52(dd, J=9,3Hz, 1H), 6.66(d, J=9Hz, 1H), 4.99(br s, 1H), 3.90-3.10(br m, 4H), 2.10-1.70(br m, 3H), 1.60-1.50(m, 1H), 1.34(br s, 9H).

Example 11

5 (2E)-3-(4-Chlorophenyl)-N-[(1S)-2-[(2-{3-[(5-chloro-2-pyridyl)oxy]-1-piperidinyl)-2-oxoethyl]amino]-2-oxo-1-(2-pyridylmethyl)ethyl]acrylamide

The title compound was obtained from tert-butyl 3-[(5-chloro-2-pyridyl)oxy]-1-piperidinecarboxylate and {[(2S)-2-
10 {[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino}-3-(2-pyridyl)-propanoyl]amino}acetic acid in the same manner as in Example 1.
ESI-MS: 582.3(M+H).

¹H-NMR (300MHz, CDCl₃) δ 8.58-8.51(m, 1H), 8.10-7.81(m, 3H), 7.66-7.41(m, 5H), 7.34(d, J=8Hz, 2H), 7.25(d, J=8Hz, 1H), 7.20-7.14(m,
15 1H), 6.69-6.60(m, 1H), 6.53-6.44(m, 1H), 5.10-4.96(m, 2H), 4.16-3.80(m, 2H), 3.77-3.20(m, 6H), 2.10-1.50(m, 4H).

Example 12

5-Chloro-N-[(1S)-2-[(2-{3-[(5-chloro-2-pyridyl)oxy]-1-piperidinyl)-2-oxoethyl]amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-1-
20 benzofuran-2-carboxamide

The title compound was obtained from tert-butyl 3-[(5-chloro-2-pyridyl)oxy]-1-piperidinecarboxylate and {[(2S)-2-[(5-chloro-1-benzofuran-2-yl)carbonyl]amino}-3-(2-pyridyl)propanoyl]-
amino}acetic acid in the same manner as in Example 1.

25 ESI-MS: 596.3(M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.84-8.69(m, 1H), 8.65-8.58(m, 1H), 8.17-7.97(m, 2H), 7.68-7.60(m, 2H), 7.56-7.46(m, 2H), 7.43-7.36(m, 2H), 7.29-7.24(m, 1H), 7.23-7.16(m, 1H), 6.70-6.60(m, 1H), 5.15-4.98(m, 2H), 4.20-3.85(m, 2H), 3.76-3.27(m, 6H), 2.09-1.50(m, 4H).

30 Preparation 13

tert-Butyl 4-(2-pyridyloxy)-1-piperidinecarboxylate

To a solution of 2-hydroxypyridine (2.0 g), tert-butyl 4-hydroxy-1-piperidinecarboxylate (5.3 g) and triphenylphosphine (8.3 g) in tetrahydrofuran (63 ml) was slowly added diethyl
35 azodicarboxylate (5.5 g) at 8°C, and the mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated in vacuo to give the crude product of the title compound and the crude product was purified by chromatography on

silica gel.

¹H-NMR (300MHz, CDCl₃) δ 8.16-8.10 (m, 1H), 7.60-7.52 (m, 1H), 6.88-6.81 (m, 1H), 6.71 (d, J=8Hz, 1H), 5.27-5.17 (m, 1H), 3.85-3.70 (m, 2H), 3.35-3.23 (m, 2H), 2.05-1.90 (m, 2H), 1.80-1.65 (m, 2H), 1.47 (s, 9H).

Example 13

(2E)-3-(4-Chlorophenyl)-N-[(1S)-2-oxo-2-({2-oxo-2-[4-(2-pyridyloxy)-1-piperidinyl]ethyl}amino)-1-(2-pyridylmethyl)ethyl]-acrylamide

The title compound was obtained from tert-butyl 4-(2-pyridyloxy)-1-piperidinecarboxylate and {[(2S)-2-[[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino]-3-(2-pyridyl)propanoyl]amino}-acetic acid in the same manner as in Example 1.

ESI-MS: m/z 548 (M+1)

¹H-NMR (300MHz, CDCl₃) δ 8.55 (d, J=5Hz, 1H), 8.01 (d, J=5Hz, 1H), 8.04-7.85 (m, 2H), 7.67-7.53 (m, 3H), 7.45 (d, J=8Hz, 2H), 7.35 (d, J=8Hz, 2H), 7.28-7.15 (m, 2H), 6.85 (dd, J=8,8Hz, 1H), 6.70 (d, J=8Hz, 1H), 6.50 (d, J=16Hz, 1H), 5.34-5.25 (m, 1H), 5.06-4.98 (m, 1H), 4.06-4.01 (m, 2H), 3.91-3.77 (m, 1H), 3.66-3.50 (m, 2H), 3.48-3.20 (m, 3H), 2.05-1.90 (m, 2H), 1.86-1.71 (m, 2H).

Example 14

5-Chloro-N-[(1S)-2-oxo-2-({2-oxo-2-[4-(2-pyridyloxy)-1-piperidinyl]ethyl}amino)-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide

The title compound was obtained from tert-butyl 4-(2-pyridyloxy)-1-piperidinecarboxylate and {[(2S)-2-[[(5-chloro-1-benzofuran-2-yl)carbonyl]amino]-3-(2-pyridyl)propanoyl]amino}-acetic acid in the same manner as in Example 1.

ESI-MS: m/z 562 (M+1)

¹H-NMR (300MHz, CDCl₃) δ 8.80-8.71 (m, 1H), 8.62 (d, J=5Hz, 1H), 8.16-8.07 (m, 2H), 7.68-7.52 (m, 3H), 7.48 (d, J=8Hz, 1H), 7.40 (d, J=8Hz, 1H), 7.37 (dd, J=2,8Hz, 1H), 7.30-7.15 (m, 2H), 6.85 (dd, J=8,8Hz, 1H), 6.70 (d, J=8Hz, 1H), 5.35-5.24 (m, 1H), 5.15-5.07 (m, 1H), 4.09-4.02 (m, 2H), 3.90-3.71 (m, 1H), 3.67-3.44 (m, 3H), 3.39-3.26 (m, 2H), 2.05-1.70 (m, 4H).

Preparation 14

tert-Butyl 4-[(6-methyl-2-pyridyl)oxy]-1-piperidinecarboxylate

The title compound was obtained from tert-butyl 4-hydroxy-1-piperidinecarboxylate and 2-hydroxy-6-methylpyridine in the same manner as in Preparation 13.

¹H-NMR (300MHz, CDCl₃) δ 7.44(dd, J=8,8Hz, 1H), 6.68(d, J=8Hz, 1H), 6.49(d, J=8Hz, 1H), 5.26-5.16(m, 1H), 3.82-3.68(m, 2H), 3.35-3.24(m, 2H), 2.42(s, 3H), 2.02-1.90(m, 2H), 1.79-1.64(m, 2H), 1.47(s, 9H).

Example 15

(2E)-3-(4-Chlorophenyl)-N-[(1S)-2-[(2-{4-[(6-methyl-2-pyridyl)oxy]-1-piperidinyl})-2-oxoethyl]amino]-2-oxo-1-(2-pyridylmethyl)ethyl]acrylamide

The title compound was obtained from tert-butyl 4-[(6-methyl-2-pyridyl)oxy]-1-piperidinecarboxylate and {[(2S)-2-[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino]-3-(2-pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 1.

ESI-MS: m/z 562 (M+1)

¹H-NMR (300MHz, CDCl₃) δ 8.55(d, J=5Hz, 1H), 8.04-7.85(m, 2H), 7.63(dd, J=2,16Hz, 1H), 7.61(d, J=16Hz, 1H), 7.50-7.40(m, 3H), 7.35(d, J=8Hz, 2H), 7.30-7.15(m, 2H), 6.70(d, J=8Hz, 1H), 6.55-6.45(m, 2H), 5.35-5.25(m, 1H), 5.07-4.98(m, 1H), 4.07-4.00(m, 2H), 3.86-3.72(m, 1H), 3.70-3.52(m, 2H), 3.48-3.20(m, 3H), 2.41(s, 3H), 2.01-1.71(m, 4H).

Example 16

5-Chloro-N-[(1S)-2-[(2-{4-[(6-methyl-2-pyridyl)oxy]-1-piperidinyl})-2-oxoethyl]amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide

The title compound was obtained from tert-butyl 4-[(6-methyl-2-pyridyl)oxy]-1-piperidinecarboxylate and {[(2S)-2-[(5-chloro-1-benzofuran-2-yl)carbonyl]amino]-3-(2-pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 1.

ESI-MS: m/z 576 (M+1)

¹H-NMR (300MHz, CDCl₃) δ 8.80-8.70(m, 1H), 8.62(d, J=5Hz, 1H), 8.16-8.07(m, 1H), 7.69-7.60(m, 2H), 7.51-7.35(m, 4H), 7.30-7.16(m, 2H), 6.70(d, J=8Hz, 1H), 6.49(d, J=8Hz, 1H), 5.35-5.25(m, 1H), 5.16-5.06(m, 1H), 4.10-4.02(m, 2H), 3.85-3.27(m, 6H), 2.41(s, 3H), 2.02-1.70(m, 4H).

Preparation 15

tert-Butyl 4-[(6-chloro-2-pyridyl)oxy]-1-piperidine-

carboxylate

The title compound was obtained from tert-butyl 4-hydroxy-1-piperidinecarboxylate and 6-chloro-2-hydroxypyridine in the same manner as in Preparation 13.

- 5 ¹H-NMR (300MHz, CDCl₃) δ 7.50 (dd, J=8,8Hz, 1H), 6.87 (d, J=8Hz, 1H), 6.61 (d, J=8Hz, 1H), 5.26-5.15 (m, 1H), 3.80-3.68 (m, 2H), 3.35-3.25 (m, 2H), 2.03-1.90 (m, 2H), 1.78-1.65 (m, 2H), 1.47 (s, 9H).

Example 17

- 10 (2E)-3-(4-Chlorophenyl)-N-[(1S)-2-[(2-{4-[(6-chloro-2-pyridyl)oxy]-1-piperidinyl}-2-oxoethyl)amino]-2-oxo-1-(2-pyridylmethyl)ethyl]acrylamide

- The title compound was obtained from tert-butyl 4-[(6-chloro-2-pyridyl)oxy]-1-piperidinecarboxylate and {[(2S)-2-{[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino}-3-(2-pyridyl)-propanoyl]amino}acetic acid in the same manner as in Example 1.

ESI-MS: m/z 582 (M+1)

- ¹H-NMR (300MHz, CDCl₃) δ 8.56 (d, J=5Hz, 1H), 8.04-7.87 (m, 2H), 7.69-7.49 (m, 3H), 7.46 (d, J=8Hz, 2H), 7.36 (d, J=8Hz, 2H), 7.30-7.15 (m, 2H), 6.90 (d, J=8Hz, 1H), 6.64 (dd, J=2,8Hz, 1H), 6.50 (d, J=16Hz, 1H), 5.35-5.25 (m, 1H), 5.07-4.99 (m, 1H), 4.08-4.00 (m, 2H), 3.90-3.75 (m, 1H), 3.67-3.50 (m, 2H), 3.49-3.20 (m, 3H), 2.06-1.90 (m, 2H), 1.87-1.73 (m, 2H).

Example 18

- 25 5-Chloro-N-[(1S)-2-[(2-{4-[(6-chloro-2-pyridyl)oxy]-1-piperidinyl}-2-oxoethyl)amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide

- The title compound was obtained from tert-butyl 4-[(6-chloro-2-pyridyl)oxy]-1-piperidinecarboxylate and {[(2S)-2-{[(5-chloro-1-benzofuran-2-yl)carbonyl]amino}-3-(2-pyridyl)propanoyl]-amino}acetic acid in the same manner as in Example 1.

ESI-MS: m/z 596 (M+1)

- ¹H-NMR (300MHz, CDCl₃) δ 8.80-8.71 (m, 1H), 8.62 (d, J=5Hz, 1H), 8.14 (d, J=2Hz, 1H), 7.69-7.60 (m, 2H), 7.56-7.45 (m, 2H), 7.41 (d, J=8Hz, 1H), 7.34 (dd, J=2,8Hz, 1H), 7.30-7.16 (m, 2H), 6.90 (d, J=8Hz, 1H), 6.67 (dd, J=2,8Hz, 1H), 5.35-5.24 (m, 1H), 5.15-5.07 (m, 1H), 4.10-4.03 (m, 2H), 3.89-3.75 (m, 1H), 3.66-3.44 (m, 3H), 3.40-3.28 (m, 2H), 2.05-1.89 (m, 2H), 1.86-1.69 (m, 2H).

Preparation 16

tert-Butyl 4-[[5-(trifluoromethyl)-2-pyridyl]oxy]-1-piperidinecarboxylate

The title compound was obtained from tert-butyl 4-hydroxy-1-piperidinecarboxylate and 5-trifluoromethyl-2-hydroxypyridine in the same manner as in Preparation 13.

¹H-NMR (300MHz, CDCl₃) δ 8.40(br s, 1H), 7.76(dd, J=2,8Hz, 1H), 6.69(d, J=8Hz, 1H), 5.33-5.23(m, 1H), 3.84-3.70(m, 2H), 3.35-3.23(m, 2H), 2.05-1.92(m, 2H), 1.80-1.66(m, 2H), 1.48(s, 9H).

Example 19

(2E)-3-(4-Chlorophenyl)-N-[(1S)-2-oxo-2-[[2-oxo-2-(4-[[5-(trifluoromethyl)-2-pyridyl]oxy]-1-piperidinyl)ethyl]amino]-1-(2-pyridylmethyl)ethyl]acrylamide

The title compound was obtained from tert-butyl 4-[[5-(trifluoromethyl)-2-pyridyl]oxy]-1-piperidinecarboxylate and [[(2S)-2-[[[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino]-3-(2-pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 1.

ESI-MS: m/z 616(M+1)

¹H-NMR (300MHz, CDCl₃) δ 8.55(d, J=5Hz, 1H), 8.40 (br s, 1H), 8.04-7.95(m, 1H), 7.91(d, J=8Hz, 1H), 7.77(dd, J=2,8Hz, 1H), 7.63(dd, J=2,16Hz, 1H), 7.60(d, J=16Hz, 1H), 7.45(d, J=8Hz, 2H), 7.35(d, J=8Hz, 2H), 7.29-7.15(m, 2H), 6.80(dd, J=2,8Hz, 1H), 6.50(d, J=16Hz, 1H), 5.41-5.30(m, 1H), 5.06-4.97(m, 1H), 4.08-4.00(m, 2H), 3.92-3.20(m, 6H), 2.06-1.92(m, 2H), 1.86-1.71(m, 2H).

Example 20

5-Chloro-N-[(1S)-2-oxo-2-[[2-oxo-2-(4-[[5-(trifluoromethyl)-2-pyridyl]oxy]-1-piperidinyl)ethyl]amino]-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide

The title compound was obtained from tert-butyl 4-[[5-(trifluoromethyl)-2-pyridyl]oxy]-1-piperidinecarboxylate and [[(2S)-2-[[[(5-chloro-1-benzofuran-2-yl)carbonyl]amino]-3-(2-pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 1.

ESI-MS: m/z 630(M+1)

¹H-NMR (300MHz, CDCl₃) δ 8.75(d, J=8Hz, 1H), 8.62(d, J=5Hz, 1H), 8.40(br s, 1H), 8.18-8.10(m, 1H), 7.77(dd, J=2,8Hz, 1H), 7.69-7.60(m, 2H), 7.49(d, J=8Hz, 1H), 7.41(d, J=8Hz, 1H), 7.39(dd, J=2,8Hz, 1H), 7.30-7.15(m, 2H), 6.80(dd, J=2,8Hz, 1H), 5.41-

5.30 (m, 1H), 5.15-5.07 (m, 1H), 4.10-4.03 (m, 2H), 3.90-3.80 (m, 1H), 3.70-3.27 (m, 5H), 2.07-1.91 (m, 2H), 1.87-1.72 (m, 2H).

Preparation 17

tert-Butyl 4-[(5-chloro-2-pyridyl)oxy]-1-piperidine-
5 carboxylate

The title compound was obtained from tert-butyl 4-hydroxy-1-piperidinecarboxylate and 5-chloro-2-hydroxypyridine in the same manner as in Preparation 13.

¹H-NMR (300MHz, CDCl₃) δ 8.06 (d, J=2Hz, 1H), 7.51 (dd, J=2,8Hz, 1H),
10 6.67 (d, J=8Hz, 1H), 5.20-5.10 (m, 1H), 3.83-3.70 (m, 2H), 3.33-3.20 (m, 2H), 2.02-1.90 (m, 2H), 1.77-1.64 (m, 2H), 1.47 (s, 9H).

Example 21

(2E)-3-(4-Chlorophenyl)-N-[(1S)-2-[(2-{4-[(5-chloro-2-
pyridyl)oxy]-1-piperidinyl)-2-oxoethyl]amino]-2-oxo-1-(2-
15 pyridylmethyl)ethyl]acrylamide

The title compound was obtained from tert-butyl 4-[(5-chloro-2-pyridyl)oxy]-1-piperidinecarboxylate and {[(2S)-2-[[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino]-3-(2-pyridyl)-propanoyl]amino}acetic acid in the same manner as in Example 1.

20 ESI-MS: m/z 582 (M+1)

¹H-NMR (300MHz, CDCl₃) δ 8.55 (d, J=5Hz, 1H), 8.05 (d, J=2Hz, 1H),
7.98 (br s, 1H), 7.90 (d, J=8Hz, 1H), 7.63 (dd, J=2,16Hz, 1H),
7.60 (d, J=16Hz, 1H), 7.52 (dd, J=2,8Hz, 1H), 7.45 (d, J=8Hz, 2H),
7.35 (d, J=8Hz, 2H), 7.28-7.14 (m, 2H), 6.66 (dd, J=2,8Hz, 1H),
25 6.50 (d, J=16Hz, 1H), 5.27-5.17 (m, 1H), 5.06-4.97 (m, 1H), 4.06-3.98 (m, 2H), 3.90-3.75 (m, 1H), 3.70-3.20 (m, 5H), 2.03-1.70 (m, 4H).

Example 22

5-Chloro-N-[(1S)-2-[(2-{4-[(5-chloro-2-pyridyl)oxy]-1-piperidinyl)-2-oxoethyl]amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-1-
30 benzofuran-2-carboxamide

The title compound was obtained from tert-butyl 4-[(5-chloro-2-pyridyl)oxy]-1-piperidinecarboxylate and {[(2S)-2-[[(5-chloro-1-benzofuran-2-yl)carbonyl]amino]-3-(2-pyridyl)propanoyl]-amino}acetic acid in the same manner as in Example 1.

35 ESI-MS: m/z 596 (M+1)

¹H-NMR (300MHz, CDCl₃) δ 8.75 (d, J=8Hz, 1H), 8.62 (d, J=5Hz, 1H),
8.17-8.09 (m, 1H), 8.05 (d, J=2Hz, 1H), 7.69-7.60 (m, 2H), 7.52 (dd,
J=2,8Hz, 1H), 7.49 (d, J=8Hz, 1H), 7.41 (d, J=8Hz, 1H), 7.39 (dd,

J=2,8Hz, 1H), 7.30-7.17(m, 2H), 6.67(dd, J=2,8Hz, 1H), 5.27-5.17(m, 1H), 5.16-5.07(m, 1H), 4.10-4.02(m, 2H), 3.90-3.76(m, 1H), 3.65-3.43(m, 3H), 3.39-3.26(m, 2H), 2.05-1.87(m, 2H), 1.85-1.70(m, 2H).

5 Preparation 18

tert-Butyl 4-phenoxy-1-piperidinecarboxylate

The title compound was obtained from tert-butyl 4-hydroxy-1-piperidinecarboxylate and phenol in the same manner as in Preparation 13.

10 $^1\text{H-NMR}$ (300MHz, CDCl_3) δ 7.32-7.20(m, 2H), 6.98-6.80(m, 3H), 4.50-4.41(m, 1H), 3.75-3.64(m, 2H), 3.39-3.27(m, 2H), 1.99-1.66(m, 4H), 1.47(s, 9H).

Example 23

15 (2E)-3-(4-Chlorophenyl)-N-[(1S)-2-oxo-2-[[2-oxo-2-(4-phenoxy-1-piperidinyl)ethyl]amino]-1-(2-pyridylmethyl)ethyl]-acrylamide

The title compound was obtained from tert-butyl 4-phenoxy-1-piperidinecarboxylate and {[(2S)-2-[[[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino]-3-(2-pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 1.

ESI-MS: m/z 547 (M+1)

25 $^1\text{H-NMR}$ (300MHz, CDCl_3) δ 8.55(d, J=5Hz, 1H), 8.05-7.82(m, 2H), 7.62(dd, J=2,16Hz, 1H), 7.60(d, J=16Hz, 1H), 7.45(d, J=8Hz, 2H), 7.12-7.38(m, 6H), 6.96(dd, J=8,8Hz, 1H), 6.90(d, J=8Hz, 2H), 6.49(dd, J=2,16Hz, 1H), 5.06-4.97(m, 1H), 4.60-4.50(m, 1H), 4.06-3.99(m, 2H), 3.81-3.52(m, 3H), 3.48-3.20(m, 3H), 1.90-1.79(m, 4H).

Example 24

30 5-Chloro-N-[(1S)-2-oxo-2-[[2-oxo-2-(4-phenoxy-1-piperidinyl)ethyl]amino]-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide

The title compound was obtained from tert-butyl 4-phenoxy-1-piperidinecarboxylate and {[(2S)-2-[[[(5-chloro-1-benzofuran-2-yl)carbonyl]amino]-3-(2-pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 1.

35 ESIMS: m/z 561 (M+1)

$^1\text{H-NMR}$ (300MHz, CDCl_3) δ 8.84-8.69(m, 1H), 8.61(d, J=5Hz, 1H), 8.19-8.08(m, 1H), 7.67-7.60(m, 2H), 7.49(d, J=8Hz, 1H), 7.41(d, J=8Hz, 1H), 7.38(dd, J=2,8Hz, 1H), 7.32-7.15(m, 4H), 6.96(dd,

J=8,8Hz, 1H), 6.90(d, J=8Hz, 2H), 5.15-5.06(m, 1H), 4.61-4.51(m, 1H), 4.09-4.02(m, 2H), 3.80-3.44(m, 4H), 3.40-3.28(m, 2H), 1.92-1.80(m, 4H).

Preparation 19

- 5 tert-Butyl 4-(2,2,2-trifluoroethoxy)-1-piperidine-carboxylate

To a solution of tert-butyl 4-hydroxy-1-piperidine-carboxylate (30.0 g), 2,2,2-trifluoroethanol (149 g) and triphenylphosphine (58.6 g) in tetrahydrofuran (450 ml) was

- 10 slowly added diethyl azodicarboxylate (38.9 g) at 8°C. The mixture was stirred at room temperature for 2 hours, and at 60°C for 8 hours. The reaction mixture was concentrated in vacuo to give the crude product of the title compound. The crude product was purified by chromatography on silica gel.

- 15 ¹H-NMR (300MHz, CDCl₃) δ 3.90-3.58(m, 5H), 3.20-3.10(m, 2H), 1.90-1.78(m, 2H), 1.65-1.50(m, 2H), 1.46(s, 9H).

Example 25

- (2E)-3-(4-Chlorophenyl)-N-[(1S)-2-oxo-2-({2-oxo-2-[4-(2,2,2-trifluoroethoxy)-1-piperidinyl]ethyl}amino)-1-(2-pyridylmethyl)ethyl]acrylamide
- 20

The title compound was obtained from tert-butyl 4-(2,2,2-trifluoroethoxy)-1-piperidinecarboxylate and {[(2S)-2-{{(2E)-3-(4-chlorophenyl)-2-propenoyl}amino}-3-(2-pyridyl)propanoyl]-amino}acetic acid in the same manner as in Example 1.

- 25 ESI-MS: m/z 553 (M+1)

- ¹H-NMR (300MHz, CDCl₃) δ 8.55(d, J=5Hz, 1H), 8.05-7.82(m, 2H), 7.62(dd, J=2,16Hz, 1H), 7.60(d, J=16Hz, 1H), 7.45(d, J=8Hz, 2H), 7.34(d, J=8Hz, 2H), 7.28-7.13(m, 2H), 6.49(dd, J=2,16Hz, 1H), 5.05-4.95(m, 1H), 4.10-3.92(m, 2H), 3.90-3.63(m, 4H), 3.60-3.35(m, 3H), 3.30-3.16(m, 2H), 1.88-1.56(m, 4H).
- 30

Example 26

5-Chloro-N-[(1S)-2-oxo-2-({2-oxo-2-[4-(2,2,2-trifluoroethoxy)-1-piperidinyl]ethyl}amino)-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide

- 35 The title compound was obtained from tert-butyl 4-(2,2,2-trifluoroethoxy)-1-piperidinecarboxylate and {[(2S)-2-{{(5-chloro-1-benzofuran-2-yl)carbonyl}amino}-3-(2-pyridyl)propanoyl]-amino}acetic acid in the same manner as in Example 1.

ESI-MS: m/z 567 (M+1)

¹H-NMR (300MHz, CDCl₃) δ 8.83-8.67 (m, 1H), 8.61 (d, J=5Hz, 1H), 8.19-8.05 (m, 1H), 7.69-7.59 (m, 2H), 7.49 (d, J=8Hz, 1H), 7.40 (d, J=8Hz, 1H), 7.39 (dd, J=2,8Hz, 1H), 7.30-7.16 (m, 2H), 5.15-5.05 (m, 1H), 4.12-3.94 (m, 2H), 3.90-3.64 (m, 4H), 3.60-3.42 (m, 3H), 3.39-3.17 (m, 2H), 1.90-1.58 (m, 4H).

Preparation 20

tert-Butyl 4-isopropoxy-1-piperidinecarboxylate

The title compound was obtained from tert-butyl 4-hydroxy-1-piperidinecarboxylate and 2-iodopropane in the same manner as in Preparation 7.

¹H-NMR (300MHz, CDCl₃) δ 3.87-3.73 (m, 2H), 3.75-3.65 (m, 1H), 3.55-3.45 (m, 1H), 3.10-2.47 (m, 2H), 1.85-1.40 (m, 4H), 1.26 (s, 9H), 1.15 (d, J=7Hz, 6H).

Example 27

(2E)-3-(4-Chlorophenyl)-N-[(1S)-2-[[2-(4-isopropoxy-1-piperidinyl)-2-oxoethyl]amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-acrylamide

The title compound was obtained from tert-butyl 4-isopropoxy-1-piperidinecarboxylate and {[(2S)-2-[[[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino]-3-(2-pyridyl)propanoyl]amino]-acetic acid in the same manner as in Example 1.

ESI-MS: m/z 513 (M+1)

¹H-NMR (300MHz, CDCl₃) δ 8.55 (d, J=5Hz, 1H), 8.01-7.81 (m, 2H), 7.66-7.55 (m, 2H), 7.45 (d, J=8Hz, 2H), 7.35 (d, J=8Hz, 2H), 7.14-7.27 (m, 2H), 6.49 (dd, J=2,16Hz, 1H), 5.05-4.97 (m, 1H), 4.04-3.96 (m, 2H), 3.90-3.31 (m, 6H), 3.29-3.10 (m, 2H), 1.82-1.45 (m, 4H), 1.14 (d, J=7Hz, 6H).

Example 28

5-Chloro-N-[(1S)-2-[[2-(4-isopropoxy-1-piperidinyl)-2-oxoethyl]amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide

The title compound was obtained from tert-butyl 4-isopropoxy-1-piperidinecarboxylate and {[(2S)-2-[[[(5-chloro-1-benzofuran-2-yl)carbonyl]amino]-3-(2-pyridyl)propanoyl]amino]-acetic acid in the same manner as in Example 1.

ESI-MS: m/z 527 (M+1)

¹H-NMR (300MHz, CDCl₃) δ 8.83-8.68 (m, 1H), 8.61 (d, J=5Hz, 1H),

8.15-8.05(m, 1H), 7.68-7.60(m, 2H), 7.48(d, J=8Hz, 1H), 7.44-7.35(m, 2H), 7.30-7.15(m, 2H), 5.15-5.05(m, 1H), 4.06-4.00(m, 2H), 3.89-3.75(m, 1H), 3.78-3.28(m, 6H), 3.23-3.10(m, 1H), 1.82-1.45(m, 4H), 1.14(d, J=7Hz, 6H).

5 Preparation 21

tert-Butyl 4-butoxy-1-piperidinecarboxylate

The title compound was obtained from tert-butyl 4-hydroxy-1-piperidinecarboxylate and 1-iodobutane in the same manner as in Preparation 7.

10 ¹H-NMR (300MHz, CDCl₃) δ 3.82-3.70(m, 2H), 3.48-3.36(m, 3H), 3.12-3.00(m, 2H), 1.87-1.76(m, 2H), 1.46(s, 9H), 1.60-1.30(m, 4H), 0.98-0.80(m, 5H).

Example 29

15 (2E)-N-[(1S)-2-[[2-(4-Butoxy-1-piperidinyl)-2-oxoethyl]-amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-3-(4-chlorophenyl)-acrylamide

The title compound was obtained from tert-butyl 4-butoxy-1-piperidinecarboxylate and {[(2S)-2-[[2-(4-chlorophenyl)-2-propenoyl]amino]-3-(2-pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 1.

ESI-MS: m/z 527 (M+1)

25 ¹H-NMR (300MHz, CDCl₃) δ 8.55(d, J=5Hz, 1H), 8.01-7.82(m, 2H), 7.62(dd, J=2,16Hz, 1H), 7.60(d, J=16Hz, 1H), 7.45(d, J=8Hz, 2H), 7.35(d, J=8Hz, 2H), 7.32-7.14(m, 2H), 6.49(dd, J=2,16Hz, 1H), 5.05-4.95(m, 1H), 4.05-3.95(m, 2H), 3.84-3.69(m, 1H), 3.59-3.11(m, 8H), 1.84-1.70(m, 2H), 1.44-1.29(m, 4H), 0.91(t, J=7Hz, 3H).

Example 30

30 N-[(1S)-2-[[2-(4-Butoxy-1-piperidinyl)-2-oxoethyl]amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-5-chloro-1-benzofuran-2-carboxamide

The title compound was obtained from tert-butyl 4-butoxy-1-piperidinecarboxylate and {[(2S)-2-[[5-chloro-1-benzofuran-2-yl]carbonyl]amino]-3-(2-pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 1.

ESI-MS: m/z 541 (M+1)

35 ¹H-NMR (300MHz, CDCl₃) δ 8.87-8.55(m, 2H), 8.17-8.04(m, 1H), 7.71-7.59(m, 2H), 7.51-7.15(m, 5H), 5.15-5.04(m, 1H), 4.07-3.99(m, 2H), 3.83-3.69(m, 1H), 3.60-3.27(m, 7H), 3.24-3.11(m, 1H), 1.85-1.47(m, 6H), 1.44-1.29(m, 2H), 0.91(t, J=7Hz, 3H).

Preparation 22

tert-Butyl 4-[(6-chloro-2-pyrazinyl)oxy]-1-piperidinecarboxylate

The title compound was obtained from tert-butyl 4-hydroxy-1-piperidinecarboxylate and 2,6-dichloropyrazine in the same manner as in Preparation 8.

ESI-MS: 314.2 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.13(s, 1H), 8.10(s, 1H), 5.21(septet, J=4Hz, 1H), 3.82-3.70(m, 2H), 3.32(ddd, J=14,9,4Hz, 2H), 2.05-1.93(m, 2H), 1.82-1.68(m, 2H), 1.48(s, 9H).

Example 31

(2E)-3-(4-Chlorophenyl)-N-[(1S)-2-[(2-{4-[(6-chloro-2-pyrazinyl)oxy]-1-piperidinyl}-2-oxoethyl)amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-2-propenamide

The title compound was obtained from tert-butyl 4-[(6-chloro-2-pyrazinyl)oxy]-1-piperidinecarboxylate and {[(2S)-2-[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino]-3-(2-pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 1.

ESI-MS: 583.2 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.56(dd, J=5,2Hz, 1H), 8.16(s, 1H), 8.11(d, J=1.5Hz, 1H), 8.02(s, 1H), 7.96-7.89(m, 1H), 7.64(td, J=8,2Hz, 1H), 7.61(d, J=16Hz, 1H), 7.46(d, J=9Hz, 2H), 7.35(d, J=9Hz, 2H), 7.26(d, J=8Hz, 1H), 7.19(dd, J=8,5Hz, 1H), 6.50(d, J=16Hz, 1H), 5.33-5.22(m, 1H), 5.07-4.99(m, 1H), 4.05(app d, J=4Hz, 2H), 3.92-3.76(m, 1H), 3.67-3.51(m, 2H), 3.48-3.21(m, 3H), 2.06-1.92(m, 2H), 1.88-1.73(m, 2H).

Example 32

5-Chloro-N-[(1S)-2-[(2-{4-[(6-chloro-2-pyrazinyl)oxy]-1-piperidinyl}-2-oxoethyl)amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide

The title compound was obtained from tert-butyl 4-[(6-chloro-2-pyrazinyl)oxy]-1-piperidinecarboxylate and {[(2S)-2-[(5-chloro-1-benzofuran-2-yl)carbonyl]amino]-3-(2-pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 1.

ESI-MS: 597.2 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.81-8.75(m, 1H), 8.62(dd, J=5,2Hz, 1H),

8.20-8.09(m, 3H), 7.65(td, J=8,2Hz, 1H), 7.65(d, J=2H, 1H),
 7.49(d, J=9Hz, 1H), 7.43(s, 1H), 7.39(dd, J=9,2Hz, 1H), 7.28(d,
 J=8Hz, 1H), 7.20(dd, J=8,5Hz, 1H), 5.33-5.23(m, 1H), 5.16-5.07(m,
 1H), 4.07(app d, J=4Hz, 2H), 3.91-3.76(m, 1H), 3.67-3.28(m, 5H),
 5 2.07-1.91(m, 2H), 1.89-1.72(m, 2H).

Preparation 23

tert-Butyl 4-[(6-chloro-3-pyridazinyl)oxy]-1-
 piperidinecarboxylate

10 The title compound was obtained from tert-butyl 4-hydroxy-
 1-piperidinecarboxylate and 3,6-dichloropyridazine in the same
 manner as in Preparation 8.

ESI-MS: 314.2 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 7.38(d, J=9Hz, 1H), 6.94(d, J=9Hz, 1H),
 5.44(septet, J=4Hz, 1H), 3.87-3.73(br m, 2H), 3.26(ddd,
 15 J=14,9,4Hz, 2H), 2.13-2.02(m, 2H), 1.83-1.67(m, 2H), 1.48(s, 9H).

Example 33

(2E)-3-(4-Chlorophenyl)-N-[(1S)-2-[(2-{4-[(6-chloro-3-
 pyridazinyl)oxy]-1-piperidinyl}-2-oxoethyl)amino]-2-oxo-1-(2-
 pyridylmethyl)ethyl]-2-propenamide

20 The title compound was obtained from tert-butyl 4-[(6-
 chloro-3-pyridazinyl)oxy]-1-piperidinecarboxylate and {[(2S)-2-
 {[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino}-3-(2-
 pyridyl)propanoyl]amino}acetic acid in the same manner as in
 Example 1.

25 ESI-MS: 583.2 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.51-8.46(m, 2H), 8.15-8.08(m, 1H), 7.82-
 7.78(m, 1H), 7.69(td, J=8,2Hz, 1H), 7.56(d, J=9Hz, 2H), 7.47(d,
 J=9Hz, 2H), 7.39-7.29(m, 3H), 7.20(dd, J=8,5Hz, 1H), 6.68(d,
 J=16Hz, 1H), 5.43-5.32(m, 1H), 5.00-4.90(m, 1H), 4.04-3.97(m, 2H),
 30 3.95-3.84(m, 1H), 3.73-3.62(m, 1H), 3.41-3.22(m, 3H), 3.07-2.96(m,
 1H), 2.14-1.95(m, 2H), 1.80-1.53(m, 2H).

Example 34

5-Chloro-N-[(1S)-2-[(2-{4-[(6-chloro-3-pyridazinyl)oxy]-1-
 piperidinyl}-2-oxoethyl)amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-1-
 35 benzofuran-2-carboxamide

The title compound was obtained from tert-butyl 4-[(6-
 chloro-3-pyridazinyl)oxy]-1-piperidinecarboxylate and {[(2S)-2-
 {[(5-chloro-1-benzofuran-2-yl)carbonyl]amino}-3-(2-

pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 1.

ESI-MS: 597.2 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.84-8.70(m, 1H), 8.65-8.60(m, 1H), 7.69-7.61(m, 2H), 7.52-7.46(m, 1H), 7.44-7.36(m, 3H), 7.30-7.25(m, 1H), 7.23-7.18(m, 1H), 6.97-6.91(m, 1H), 5.54-5.43(m, 1H), 5.16-5.07(m, 1H), 4.11-4.03(m, 2H), 4.02-3.89(m, 1H), 3.68-3.56(m, 1H), 3.53-3.26(m, 4H), 2.17-2.00(m, 2H), 1.89-1.73(m, 2H).

Preparation 24

10 tert-Butyl 4-[(6-methoxy-3-pyridazinyl)oxy]-1-piperidinecarboxylate

The title compound was obtained from tert-butyl 4-hydroxy-1-piperidinecarboxylate and 3-chloro-6-methoxypyridazine in the same manner as in Preparation 7.

15 ESI-MS: 310.2 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 6.96-6.88(m, 2H), 5.31(tt, J=8,4Hz, 1H), 4.04(s, 3H), 3.89-3.75(br m, 2H), 3.22(ddd, J=14,8,4Hz, 2H), 2.13-2.01(m, 2H), 1.81-1.66(m, 2H), 1.47(s, 9H).

Example 35

20 (2E)-3-(4-Chlorophenyl)-N-[(1S)-2-[(2-{4-[(6-methoxy-3-pyridazinyl)oxy]-1-piperidinyl}-2-oxoethyl)amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-2-propenamide

The title compound was obtained from tert-butyl 4-[(6-methoxy-3-pyridazinyl)oxy]-1-piperidinecarboxylate and [(2S)-2-
25 {[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino}-3-(2-pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 1.

ESI-MS: 579.1 (M+H)

30 ¹H-NMR (300MHz, CDCl₃) δ 8.56(dd, J=5,2Hz, 1H), 8.06-7.84(m, 2H), 7.64(td, J=8,2Hz, 1H), 7.61(d, J=16Hz, 1H), 7.46(d, J=8Hz, 2H), 7.35(d, J=8Hz, 2H), 7.26(d, J=8Hz, 1H), 7.18(dd, J=8,5Hz, 1H), 6.97-6.86(m, 2H), 6.50(d, J=16Hz, 1H), 5.42-5.31(m, 1H), 5.06-4.98(m, 1H), 4.06-3.89(m, 3H), 4.04(s, 3H), 3.66-3.56(m, 1H), 3.51-3.36(m, 2H), 3.35-3.20(m, 2H), 2.16-2.00(m, 2H), 1.87-1.72(m, 35 2H).

Example 36

5-Chloro-N-[(1S)-2-[(2-{4-[(6-methoxy-3-pyridazinyl)oxy]-1-piperidinyl}-2-oxoethyl)amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-1-

benzofuran-2-carboxamide

The title compound was obtained from tert-butyl 4-[(6-methoxy-3-pyridazinyl)oxy]-1-piperidinecarboxylate and {(2S)-2-[(5-chloro-1-benzofuran-2-yl)carbonyl]amino}-3-(2-

- 5 pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 1.

ESI-MS: 593.2 (M+H)

- ¹H-NMR (300MHz, CDCl₃) δ 8.81-8.71 (m, 1H), 8.62 (dd, J=5, 2Hz, 1H), 8.20-8.10 (m, 2H), 7.65 (td, J=8, 2Hz, 1H), 7.65 (d, J=2Hz, 1H), 10 7.49 (d, J=9Hz, 1H), 7.42 (s, 1H), 7.39 (dd, J=9, 2Hz, 1H), 7.27 (d, J=8Hz, 1H), 7.20 (dd, J=8, 5Hz, 1H), 6.97-6.87 (m, 2H), 5.42-5.32 (m, 1H), 5.16-5.08 (m, 1H), 4.07 (app d, J=4Hz, 2H), 4.04 (s, 3H), 4.01-3.90 (m, 1H), 3.67-3.57 (m, 1H), 3.53-3.25 (m, 4H), 2.17-2.00 (m, 2H), 1.87-1.73 (m, 2H).

15 Preparation 25

tert-Butyl 4-[(3-chloro-2-pyridyl)oxy]-1-piperidinecarboxylate

- The title compound was obtained from tert-butyl 4-hydroxy-1-piperidinecarboxylate and 2,3-dichloropyridine in the same 20 manner as in Preparation 7.

ESI-MS: 313.1 (M+H)

- ¹H-NMR (300MHz, CDCl₃) δ 8.02 (dd, J=5, 2Hz, 1H), 7.63 (dd, J=8, 2Hz, 1H), 6.83 (dd, J=8, 5Hz, 1H), 5.32 (tt, J=8, 4Hz, 1H); 3.71 (ddd, J=14, 8, 4Hz, 2H), 3.41 (ddd, J=14, 8, 4Hz, 2H), 2.02-1.89 (m, 2H), 25 1.87-1.74 (m, 2H), 1.48 (s, 9H).

Example 37

(2E)-3-(4-Chlorophenyl)-N-[(1S)-2-[(2-{4-[(3-chloro-2-pyridyl)oxy]-1-piperidinyl}-2-oxoethyl)amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-2-propenamide

- 30 The title compound was obtained from tert-butyl 4-[(3-chloro-2-pyridyl)oxy]-1-piperidinecarboxylate and {(2S)-2-[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino}-3-(2-pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 1.

- 35 ESI-MS: 582.2 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.56 (dd, J=5, 2Hz, 1H), 8.06-7.86 (m, 3H), 7.68-7.57 (m, 3H), 7.46 (d, J=8Hz, 2H), 7.35 (d, J=8Hz, 2H), 7.29-7.23 (m, 1H), 7.18 (dd, J=8, 5Hz, 1H), 6.85 (dd, J=8, 5Hz, 1H), 6.50 (d,

J=16Hz, 1H), 5.44-5.34(m, 1H), 5.08-4.99(m, 1H), 4.14-3.95(m, 2H), 3.85-3.54(m, 3H), 3.49-3.20(m, 3H), 2.01-1.80(m, 4H).

Example 38

5-Chloro-N-[(1S)-2-[(2-{4-[(3-chloro-2-pyridyl)oxy]-1-piperidinyl}-2-oxoethyl)amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide

The title compound was obtained from tert-butyl 4-[(3-chloro-2-pyridyl)oxy]-1-piperidinecarboxylate and {[(2S)-2-[(5-chloro-1-benzofuran-2-yl)carbonyl]amino}-3-(2-pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 1.

ESI-MS: 596.2 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.86-8.71(m, 1H), 8.63(dd, J=5,2Hz, 1H), 8.21-8.09(m, 1H), 8.02(dd, J=5,2Hz, 1H), 7.70-7.60(m, 3H), 7.50(d, J=9Hz, 1H), 7.43(s, 1H), 7.40(dd, J=9,2Hz, 1H), 7.28(d, J=8Hz, 1H), 7.21(dd, J=8,5Hz, 1H), 6.86(dd, J=8,5Hz, 1H), 5.44-5.36(m, 1H), 5.17-5.08(m, 1H), 4.15-4.00(m, 2H), 3.85-3.56(m, 3H), 3.55-3.28(m, 3H), 2.00-1.81(m, 2H), 1.65-1.56(m, 2H).

Preparation 26

tert-Butyl 4-[(6-chloro-4-pyrimidinyl)oxy]-1-piperidinecarboxylate

The title compound was obtained from tert-butyl 4-hydroxy-1-piperidinecarboxylate and 4,6-dichloropyrimidine in the same manner as in Preparation 7.

ESI-MS: 314.2 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.55(s, 1H), 6.76(s, 1H), 5.31(tt, J=8,4Hz, 1H), 3.84-3.70(m, 2H), 3.29(ddd, J=14,8,4Hz, 2H), 2.05-1.93(m, 2H), 1.81-1.66(m, 2H), 1.47(s, 9H).

Example 39

(2E)-3-(4-Chlorophenyl)-N-[(1S)-2-[(2-{4-[(6-chloro-4-pyrimidinyl)oxy]-1-piperidinyl}-2-oxoethyl)amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-2-propenamide

The title compound was obtained from tert-butyl 4-[(6-chloro-4-pyrimidinyl)oxy]-1-piperidinecarboxylate and {[(2S)-2-[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino}-3-(2-pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 1.

ESI-MS: 583.1 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.57-8.56(m, 1H), 8.55(s, 1H), 8.05-7.99(m, 1H), 7.96-7.89(m, 1H), 7.64(td, J=8,2Hz, 1H), 7.61(d, J=16Hz, 1H), 7.46(d, J=9Hz, 2H), 7.96-7.89(m, 1H), 7.64(td, J=8,2Hz, 1H), 7.61(d, J=16Hz, 1H), 7.46(d, J=9Hz, 2H), 7.35(d, J=9Hz, 2H), 7.26(d, J=8Hz, 1H), 7.19(dd, J=8,5Hz, 1H), 6.76(app d, J=2Hz, 1H), 6.50(d, J=16Hz, 1H), 5.42-5.32(m, 1H), 5.07-4.98(m, 1H), 4.05(d, J=4Hz, 2H), 3.93-3.77(m, 1H), 3.65-3.47(m, 2H), 3.47-3.21(m, 3H), 2.07-1.91(m, 2H), 1.87-1.71(m, 2H).

Example 40

10 5-Chloro-N-[(1S)-2-[(2-{4-[(6-chloro-4-pyrimidinyl)oxy]-1-piperidinyl}-2-oxoethyl)amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide

The title compound was obtained from tert-butyl 4-[(6-chloro-4-pyrimidinyl)oxy]-1-piperidinecarboxylate and [(2S)-2-
15 {[(5-chloro-1-benzofuran-2-yl)carbonyl]amino}-3-(2-pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 1.

ESI-MS: 597.1(M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.81-8.74(m, 1H), 8.63(dd, J=5,2Hz, 1H),
20 8.56(s, 1H), 8.17(br. s, 1H), 7.66(td, J=8,2Hz, 1H), 7.66(d, J=2Hz, 1H), 7.50(d, J=9Hz, 1H), 7.43(s, 1H), 7.40(dd, J=9,2Hz, 1H), 7.29(d, J=8Hz, 1H), 7.22(dd, J=8,5Hz, 1H), 6.77(app d, J=2Hz, 1H), 5.44-5.33(m, 1H), 5.16-5.08(m, 1H), 4.09(app d, 2H), 3.92-3.78(m, 1H), 3.67-3.44(m, 3H), 3.41-3.29(m, 2H), 2.08-1.92(m, 2H), 1.88-
25 1.72(m, 2H).

Preparation 27

tert-Butyl 4-[[6-(trifluoromethyl)-4-pyrimidinyl]oxy]-1-piperidinecarboxylate

The title compound was obtained from tert-butyl 4-hydroxy-
30 1-piperidinecarboxylate and 6-(trifluoromethyl)-4-pyrimidinol in the same manner as in Preparation 13.

ESI-MS: 348.3(M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.86(s, 1H), 7.06(s, 1H), 5.39(tt, J=8,4Hz, 1H), 3.85-3.72(m, 2H), 3.30(ddd, J=14,8,4Hz, 2H), 2.08-
35 1.95(m, 2H), 1.84-1.68(m, 2H), 1.48(s, 9H).

Example 41

(2E)-3-(4-Chlorophenyl)-N-[(1S)-2-oxo-2-{[2-oxo-2-(4-[[6-(trifluoromethyl)-4-pyrimidinyl]oxy]-1-piperidinyl)ethyl]amino}-

1-(2-pyridylmethyl)ethyl]-2-propenamide

The title compound was obtained from tert-butyl 4-{{6-(trifluoromethyl)-4-pyrimidinyl}oxy}-1-piperidinecarboxylate and
 5 [[(2S)-2-{{[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino}-3-(2-pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 1.

ESI-MS: 617.1 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.86(s, 1H), 8.57(dd, J=5,2Hz, 1H), 8.08-8.01(m, 1H), 7.98-7.89(m, 1H), 7.64(td, J=8,2Hz, 1H), 7.61(d, J=16Hz, 1H), 7.46(d, J=9Hz, 2H), 7.35(d, J=9Hz, 2H), 7.27(d, J=8Hz, 1H), 7.19(dd, J=8,5Hz, 1H), 7.07(s, 1H), 6.50(d, J=16Hz, 1H), 5.51-5.41(m, 1H), 5.06-4.98(m, 1H), 4.05(d, J=4Hz, 2H), 3.96-3.80(m, 1H), 3.68-3.50(m, 2H), 3.50-3.21(m, 3H), 2.10-1.95(m, 2H), 1.90-1.74(m, 2H).

15 Example 42

5-Chloro-N-[(1S)-2-oxo-2-{{2-oxo-2-(4-{{6-(trifluoromethyl)-4-pyrimidinyl}oxy}-1-piperidinyl)ethyl]amino}-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide

The title compound was obtained from tert-butyl 4-{{6-(trifluoromethyl)-4-pyrimidinyl}oxy}-1-piperidinecarboxylate and
 20 [[(2S)-2-{{[(5-chloro-1-benzofuran-2-yl)carbonyl]amino}-3-(2-pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 1.

ESI-MS: 631.1 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.86(s, 1H), 8.84-8.75(m, 1H), 8.63(dd, J=5,2Hz, 1H), 8.20(br s, 1H), 7.65(td, J=8,2Hz, 1H), 7.65(d, J=2Hz, 1H), 7.49(dd, J=9,1Hz, 1H), 7.43(d, J=1Hz, 1H), 7.39(dd, J=9,2Hz, 1H), 7.28(d, J=8Hz, 1H), 7.21(dd, J=8,5Hz, 1H), 7.07(s, 1H), 5.52-5.41(m, 1H), 5.16-5.07(m, 1H), 4.09(app d, J=4Hz, 2H),
 30 3.95-3.80(m, 1H), 3.69-3.45(m, 3H), 3.42-3.30(m, 2H), 2.11-1.95(m, 2H), 1.90-1.75(m, 2H).

Preparation 28

tert-Butyl 4-{{2-(trifluoromethyl)-4-pyrimidinyl}oxy}-1-piperidinecarboxylate

35 The title compound was obtained from tert-butyl 4-hydroxy-1-piperidinecarboxylate and 4-hydroxy-2-(trifluoromethyl)-pyrimidine in the same manner as in Preparation 13.

ESI-MS: 348.3 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.56(d, J=6Hz, 1H), 6.86(d, J=6Hz, 1H), 5.39(tt, J=8,4Hz, 1H), 3.83-3.71(m, 2H), 3.33(ddd, J=14,8,4Hz, 2H), 2.08-1.96(m, 2H), 1.84-1.68(m, 2H), 1.48(s, 9H).

Example 43

5 5-Chloro-N-[(1S)-2-oxo-2-[[2-oxo-2-(4-[[2-(trifluoromethyl)-4-pyrimidinyl]oxy]-1-piperidinyl)ethyl]amino]-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide

The title compound was obtained from tert-butyl 4-[[2-(trifluoromethyl)-4-pyrimidinyl]oxy]-1-piperidinecarboxylate and
10 [[(2S)-2-[[[(5-chloro-1-benzofuran-2-yl)carbonyl]amino]-3-(2-pyridyl)propanoyl]amino]acetic acid in the same manner as in Example 1.

ESI-MS: 631.1 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.84-8.74(m, 1H), 8.63(dd, J=5,2Hz, 1H),
15 8.58(d, J=6Hz, 1H), 8.24-8.14(m, 1H), 7.65(td, J=8,2Hz, 1H), 7.65(d, J=2Hz, 1H), 7.49(d, J=9Hz, 1H), 7.43(s, 1H), 7.39(dd, J=9,2Hz, 1H), 7.28(d, J=8Hz, 1H), 7.21(dd, J=8,5Hz, 1H), 6.87(d, J=6Hz, 1H), 5.51-5.41(m, 1H), 5.16-5.08(m, 1H), 4.08(app d, 2H), 3.94-3.80(m, 1H), 3.68-3.44(m, 3H), 3.44-3.29(m, 2H), 2.11-1.95(m,
20 2H), 1.90-1.74(m, 2H).

Preparation 29

tert-Butyl 4-[(5-chloro-2-pyrazinyl)oxy]-1-piperidinecarboxylate

The title compound was obtained from tert-butyl 4-hydroxy-
25 1-piperidinecarboxylate and 5-chloro-2-pyrazinol in the same manner as in Preparation 13. 5-Chloro-2-pyrazinol was prepared according to the method described in J. Org. Chem. 29, 2491-2492 (1964).

ESI-MS: 314.2 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.07(d, J=1Hz, 1H), 7.99(d, J=1Hz, 1H),
30 5.14(tt, J=8,4Hz, 1H), 3.83-3.70(m, 2H), 3.29(ddd, J=14,8,4Hz, 2H), 2.03-1.91(m, 2H), 1.66-1.80(m, 2H), 1.48(s, 9H).

Example 44

5-Chloro-N-[(1S)-2-[(2-[4-[(5-chloro-2-pyrazinyl)oxy]-1-piperidinyl]-2-oxoethyl)amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide

The title compound was obtained from tert-butyl 4-[(5-chloro-2-pyrazinyl)oxy]-1-piperidinecarboxylate and [[(2S)-2-

{[(5-chloro-1-benzofuran-2-yl)carbonyl]amino}-3-(2-pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 1.

ESI-MS: 597.1 (M+H)

- 5 $^1\text{H-NMR}$ (300MHz, CDCl_3) δ 8.82-8.72 (m, 1H), 8.62 (dd, $J=5,2\text{Hz}$, 1H), 8.21-8.13 (m, 1H), 8.06 (s, 1H), 7.99 (s, 1H), 7.65 (td, $J=8,2\text{Hz}$, 1H), 7.65 (d, $J=2\text{Hz}$, 1H), 7.49 (d, $J=9\text{Hz}$, 1H), 7.42 (s, 1H), 7.39 (dd, $J=9,2\text{Hz}$, 1H), 7.27 (d, $J=8\text{Hz}$, 1H), 7.21 (dd, $J=8,5\text{Hz}$, 1H), 5.26-5.16 (m, 1H), 5.15-5.07 (m, 1H), 4.08 (app d, 2H), 3.90-3.75 (m, 1H),
10 3.67-3.43 (m, 3H), 3.40-3.28 (m, 2H), 2.06-1.90 (m, 2H), 1.87-1.71 (m, 2H).

Preparation 30

2-Bromo-5-methyl-1,3-thiazole

- To a solution of 2-amino-5-methyl-1,3-thiazole (11.7 g) in
15 acetonitrile (200 ml) was added dropwise tert-butyl nitrite (8.33 ml) at 0°C followed by addition of copper(II) bromide (5 g) over 5 minutes. After stirring at 0°C for 3 hours, the mixture was concentrated and partitioned between 1N hydrochloric acid and ethyl acetate. The organic layer was washed with water, saturated
20 aqueous sodium hydrogencarbonate solution and brine, dried over anhydrous magnesium sulfate, filtered through a pad of Celite, and concentrated in vacuo to give the title compound (3.24 g) as an oil.

ESI-MS: 177.8 (M+H)

- 25 $^1\text{H-NMR}$ (300MHz, CDCl_3) δ 7.25 (s, 1H), 2.44 (s, 3H).

Preparation 31

tert-Butyl 4-[(5-methyl-1,3-thiazol-2-yl)oxy]-1-piperidinecarboxylate

- The title compound was obtained from tert-butyl 4-hydroxy-
30 1-piperidinecarboxylate and 2-bromo-5-methyl-1,3-thiazole in the same manner as in Preparation 7.

ESI-MS: 299.3 (M+H)

- $^1\text{H-NMR}$ (300MHz, CDCl_3) δ 6.74 (s, 1H), 5.06 (tt, $J=8,4\text{Hz}$, 1H), 3.78-3.66 (m, 2H), 3.30 (ddd, $J=14,8,4\text{Hz}$, 2H), 2.31 (s, 3H), 2.06-1.95 (m,
35 2H), 1.85-1.72 (m, 2H), 1.47 (s, 9H).

Example 45

(2E)-3-(4-Chlorophenyl)-N-[(1S)-2-[(2-{4-[(5-methyl-1,3-thiazol-2-yl)oxy]-1-piperidinyl}-2-oxoethyl)amino]-2-oxo-1-(2-

pyridylmethyl)ethyl]-2-propenamide

The title compound was obtained from tert-butyl 4-[(5-methyl-1,3-thiazol-2-yl)oxy]-1-piperidinecarboxylate and {[(2S)-2-[[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino]-3-(2-pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 1.

ESI-MS: 568.2 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.55 (dd, J=5,2Hz, 1H), 8.04-7.97 (m, 1H), 7.96-7.87 (m, 1H), 7.63 (td, J=8,2Hz, 1H), 7.61 (d, J=16Hz, 1H), 7.45 (d, J=8Hz, 2H), 7.34 (d, J=8Hz, 2H), 7.25 (d, J=8Hz, 1H), 7.18 (dd, J=8,5Hz, 1H), 6.73 (app s, 1H), 6.50 (d, J=16Hz, 1H), 5.13 (br s, 1H), 5.06-4.98 (m, 1H), 4.03 (app d, J=4Hz, 2H), 3.83-3.49 (m, 3H), 3.43 (dd, J=15,5Hz, 1H), 3.37-3.20 (m, 2H), 2.31 (d, J=1Hz, 3H), 2.05-1.79 (m, 4H).

Example 46

5-Chloro-N-[(1S)-2-[(2-{4-[(5-methyl-1,3-thiazol-2-yl)oxy]-1-piperidinyl}-2-oxoethyl)amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide

The title compound was obtained from tert-butyl 4-[(5-methyl-1,3-thiazol-2-yl)oxy]-1-piperidinecarboxylate and {[(2S)-2-[[(5-chloro-1-benzofuran-2-yl)carbonyl]amino]-3-(2-pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 1.

ESI-MS: 582.2 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.81-8.73 (m, 1H), 8.63 (dd, J=5,2Hz, 1H), 8.19-8.11 (m, 1H), 7.66 (td, J=8,2Hz, 1H), 7.66 (d, J=2Hz, 1H), 7.50 (d, J=9Hz, 1H), 7.43 (s, 1H), 7.39 (dd, J=9,2Hz, 1H), 7.28 (d, J=8Hz, 1H), 7.21 (dd, J=8,5Hz, 1H), 7.43 (s, 1H), 7.39 (dd, J=9,2Hz, 1H), 7.28 (d, J=8Hz, 1H), 7.21 (dd, J=8,5Hz, 1H), 6.75-6.71 (m, 1H), 5.19-5.07 (m, 2H), 4.07 (app d, J=4Hz, 2H), 3.81-3.44 (m, 4H), 3.39-3.27 (m, 2H), 2.31 (d, J=1Hz, 3H), 2.07-1.78 (m, 4H).

Preparation 32

tert-Butyl 4-[(5-chloro-1,3-thiazol-2-yl)oxy]-1-piperidinecarboxylate

To a solution of tert-butyl 4-[(1,3-thiazol-2-yl)oxy]-1-piperidinecarboxylate (8.0 g) in acetic acid (80 ml) was added dropwise N-chlorosuccinimide (4.5 g). The mixture was warmed to 60-70°C and stirred for 5 hours. The resulting mixture was poured

into a mixture of ice (80 g) and water (80 ml), and extracted with ethyl acetate. The organic layer was concentrated in vacuo, and the residue was dissolved in ethyl acetate. The solution was basified with 1N sodium hydroxide solution. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent; 9% ethyl acetate in n-hexane) to give the title compound (5.56 g) as white crystals.

ESI-MS: 319.2 (M+H)

- 10 $^1\text{H-NMR}$ (300MHz, CDCl_3) δ 6.93(s, 1H), 5.11(tt, J=8,4Hz, 1H), 3.79-3.63(m, 2H), 3.31(ddd, J=14,8,4Hz, 2H), 2.07-1.94(m, 2H), 1.87-1.72(m, 2H), 1.47(s, 9H).

Example 47

- 15 (2E)-3-(4-Chlorophenyl)-N-[(1S)-2-[(2-{4-[(5-chloro-1,3-thiazol-2-yl)oxy]-1-piperidinyl}-2-oxoethyl)amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-2-propenamide

- The title compound was obtained from tert-butyl 4-[(5-chloro-1,3-thiazol-2-yl)oxy]-1-piperidinecarboxylate and [(2S)-2-[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino]-3-(2-pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 1.

ESI-MS: 588.1 (M+H)

- 25 $^1\text{H-NMR}$ (300MHz, CDCl_3) δ 8.55(dd, J=5,2Hz, 1H), 8.06-7.98(m, 1H), 7.95-7.88(m, 1H), 7.63(td, J=8,2Hz, 1H), 7.61(d, J=16Hz, 1H), 7.46(d, J=8Hz, 2H), 7.35(d, J=8Hz, 2H), 7.25(d, J=8Hz, 1H), 7.18(dd, J=8,5Hz, 1H), 6.92(s, 1H), 6.50(d, J=16Hz, 1H), 5.23-5.13(m, 1H), 5.05-4.97(m, 1H), 4.03(app d, J=4Hz, 2H), 3.83-3.49(m, 3H), 3.48-3.20(m, 3H), 2.06-1.78(m, 4H).

Example 48

- 30 5-Chloro-N-[(1S)-2-[(2-{4-[(5-chloro-1,3-thiazol-2-yl)oxy]-1-piperidinyl}-2-oxoethyl)amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide

- The title compound was obtained from tert-butyl 4-[(5-chloro-1,3-thiazol-2-yl)oxy]-1-piperidinecarboxylate and [(2S)-2-[(5-chloro-1-benzofuran-2-yl)carbonyl]amino]-3-(2-pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 1.

ESI-MS: 602.1 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.81-8.73(m, 1H), 8.63(dd, J=5,2Hz, 1H), 8.21-8.13(m, 1H), 7.65(td, J=8,2Hz, 1H), 7.65(d, J=2Hz, 1H), 7.49(d, J=9Hz, 1H), 7.42(s, 1H), 7.39(dd, J=9,2Hz, 1H), 7.27(d, J=8Hz, 1H), 7.20(dd, J=8,5Hz, 1H), 6.92(s, 1H), 5.23-5.06(m, 2H), 4.06(app d, J=4Hz, 2H), 3.81-3.43(m, 4H), 3.40-3.27(m, 2H), 2.06-1.78(m, 4H).

Preparation 33

tert-Butyl (3R)-3-[(5-chloro-2-pyridyl)oxy]-1-pyrrolidinecarboxylate

The title compound was obtained from tert-butyl (3R)-3-hydroxy-1-pyrrolidinecarboxylate and 2,5-dichloropyridine in the same manner as in Preparation 7.

ESI-MS: 299.1 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.08(s, 1H), 7.53(d, J=9Hz, 1H), 6.69(d, J=9Hz, 1H), 5.49(br s, 1H), 3.71-3.40(m, 4H), 2.14(br s, 2H), 1.47(s, 9H).

Example 49

(2E)-3-(4-Chlorophenyl)-N-[(1S)-2-[(2-{(3R)-3-[(5-chloro-2-pyridyl)oxy]-1-pyrrolidinyl)-2-oxoethyl]amino}-2-oxo-1-(2-pyridylmethyl)ethyl)-2-propenamide

The title compound was obtained from tert-butyl (3R)-3-[(5-chloro-2-pyridyl)oxy]-1-pyrrolidinecarboxylate and {[(2S)-2-[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino]-3-(2-pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 1.

ESI-MS: 568.1 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.58-8.53(m, 1H), 8.08-8.05(m, 1H), 8.03-7.98(m, 1H), 7.90-7.83(m, 1H), 7.66-7.50(m, 3H), 7.45(d, J=8Hz, 2H), 7.34(d, J=8Hz, 2H), 7.28-7.22(m, 1H), 7.21-7.14(m, 1H), 6.69-6.61(m, 1H), 6.49(d, J=16Hz, 1H), 5.58-5.49(m, 1H), 5.06-4.97(m, 1H), 3.99(d, J=4Hz, 1H), 3.91(d, J=4Hz, 1H), 3.83-3.51(m, 4H), 3.46-3.37(m, 1H), 3.30-3.21(m, 1H), 2.34-2.06(m, 2H).

Example 50

5-Chloro-N-[(1S)-2-[(2-{(3R)-3-[(5-chloro-2-pyridyl)oxy]-1-pyrrolidinyl)-2-oxoethyl]amino}-2-oxo-1-(2-pyridylmethyl)ethyl)-1-benzofuran-2-carboxamide

The title compound was obtained from tert-butyl (3R)-3-[(5-chloro-2-pyridyl)oxy]-1-pyrrolidinecarboxylate and {[(2S)-2-[(5-

chloro-1-benzofuran-2-yl)carbonyl]amino}-3-(2-pyridyl)propanoyl]-amino}acetic acid in the same manner as in Example 1.

ESI-MS: 582.2 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.75-8.69 (m, 1H), 8.69-8.65 (m, 1H), 8.21-8.14 (m, 1H), 8.08-8.04 (m, 1H), 7.68-7.60 (m, 2H), 7.57-7.45 (m, 2H), 7.43-7.35 (m, 2H), 7.30-7.16 (m, 2H), 6.69-6.62 (m, 1H), 5.58-5.49 (m, 1H), 5.15-5.06 (m, 1H), 4.02 (d, J=4Hz, 1H), 3.94 (d, J=4Hz, 1H), 3.84-3.28 (m, 6H), 2.35-2.07 (m, 2H).

Preparation 34

10 tert-Butyl (3S)-3-[(5-chloro-2-pyridyl)oxy]-1-pyrrolidinecarboxylate

The title compound was obtained from tert-butyl (3S)-3-hydroxy-1-pyrrolidinecarboxylate and 5-chloro-2-pyridinol in the same manner as in Preparation 13.

15 ESI-MS: 299.1 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.08 (s, 1H), 7.53 (d, J=9Hz, 1H), 6.68 (d, J=9Hz, 1H), 5.48 (br s, 1H), 3.69-3.42 (m, 4H), 2.14 (br s, 2H), 1.46 (s, 9H).

Example 51

20 (2E)-3-(4-Chlorophenyl)-N-[(1S)-2-[(2-[(3S)-3-[(5-chloro-2-pyridyl)oxy]-1-pyrrolidinyl)-2-oxoethyl]amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-2-propenamide

The title compound was obtained from tert-butyl (3S)-3-[(5-chloro-2-pyridyl)oxy]-1-pyrrolidinecarboxylate and {[(2S)-2-
25 {[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino}-3-(2-pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 1.

ESI-MS: 568.2 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.60-8.51 (m, 1H), 8.11-7.95 (m, 2H), 7.93-7.84 (m, 1H), 7.68-7.40 (m, 5H), 7.39-7.12 (m, 4H), 6.70-6.61 (m, 1H), 6.55-6.43 (m, 1H), 5.59-5.47 (m, 1H), 5.07-4.95 (m, 1H), 4.04-3.88 (m, 1H), 3.86-3.18 (m, 6H), 2.38-2.02 (m, 2H).

Example 52

35 5-Chloro-N-[(1S)-2-[(2-[(3S)-3-[(5-chloro-2-pyridyl)oxy]-1-pyrrolidinyl)-2-oxoethyl]amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide

The title compound was obtained from tert-butyl (3S)-3-[(5-chloro-2-pyridyl)oxy]-1-pyrrolidinecarboxylate and {[(2S)-2-[(5-

chloro-1-benzofuran-2-yl)carbonyl]amino}-3-(2-pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 1.

ESI-MS: 582.2 (M+H)

- 5 ¹H-NMR (300MHz, CDCl₃) δ 8.77-8.71 (m, 1H), 8.64-8.59 (m, 1H), 8.21-8.12 (m, 1H), 8.08-8.04 (m, 1H), 7.68-7.60 (m, 2H), 7.56-7.45 (m, 2H), 7.41 (s, 1H), 7.38 (dd, J=9,2Hz, 1H), 7.30-7.23 (m, 1H), 7.22-7.16 (m, 1H), 6.65 (d, J=9Hz, 1H), 5.58-5.49 (m, 1H), 5.15-5.07 (m, 1H), 4.02 (d, J=4Hz, 1H), 3.94 (d, J=4Hz, 1H), 3.84-3.42 (m, 5H), 3.33 (dd, J=15,6Hz, 1H), 2.36-2.07 (m, 2H).

Preparation 35

tert-Butyl (3R)-3-[(6-chloro-2-pyrazinyl)oxy]-1-pyrrolidinecarboxylate

- 15 The title compound was obtained from tert-butyl (3R)-3-hydroxy-1-pyrrolidinecarboxylate and 2,6-dichloropyrazine in the same manner as in Preparation 7.

¹H-NMR (300MHz, CDCl₃) δ 8.17 (s, 1H), 7.12 (s, 1H), 5.54 (br s, 1H), 3.73-3.43 (m, 4H), 2.26-2.12 (m, 2H), 1.48 (s, 9H).

Example 53

- 20 (2E)-3-(4-Chlorophenyl)-N-[(1S)-2-[(2-[(3R)-3-[(6-chloro-2-pyrazinyl)oxy]-1-pyrrolidinyl)-2-oxoethyl]amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-2-propenamide

- 25 The title compound was obtained from tert-butyl (3R)-3-[(6-chloro-2-pyrazinyl)oxy]-1-pyrrolidinecarboxylate and [(2S)-2-[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino}-3-(2-pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 1.

ESI-MS: 569.1 (M+H)

- 30 ¹H-NMR (300MHz, CDCl₃) δ 8.59-8.53 (m, 1H), 8.22-8.00 (m, 3H), 7.91-7.84 (m, 1H), 7.67-7.56 (m, 2H), 7.46 (d, J=8Hz, 2H), 7.35 (d, J=8Hz, 2H), 7.29-7.24 (m, 1H), 7.22-7.14 (m, 1H), 6.49 (d, J=16Hz, 1H), 5.65-5.53 (m, 1H), 5.07-4.97 (m, 1H), 4.02 (d, J=4Hz, 1H), 3.94 (d, J=4Hz, 1H), 3.88-3.54 (m, 4H), 3.47-3.36 (m, 1H), 3.31-3.21 (m, 1H), 2.39-2.12 (m, 2H).

35 Example 54

5-Chloro-N-[(1S)-2-[(2-[(3R)-3-[(6-chloro-2-pyrazinyl)oxy]-1-pyrrolidinyl)-2-oxoethyl]amino]-2-oxo-1-(2-pyridylmethyl)-ethyl]-1-benzofuran-2-carboxamide

The title compound was obtained from tert-butyl (3R)-3-[(6-chloro-2-pyrazinyl)oxy]-1-pyrrolidinecarboxylate and {[(2S)-2-[(5-chloro-1-benzofuran-2-yl)carbonyl]amino}-3-(2-pyridyl)propanoyl]amino}acetic acid in the same manner as in

5 Example 1.

ESI-MS: 583.1 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.68-8.60 (m, 2H), 8.36-8.28 (m, 1H), 8.21-8.10 (m, 2H), 7.77-7.69 (m, 1H), 7.65-7.63 (m, 1H), 7.50-7.45 (m, 1H), 7.42-7.24 (m, 4H), 5.65-5.54 (m, 1H), 5.20-5.11 (m, 1H), 4.09-4.02 (m, 1H), 4.01-3.95 (m, 1H), 3.88-3.58 (m, 4H), 3.51-3.44 (m, 2H), 2.38-2.10 (m, 2H).

10 Preparation 36

tert-Butyl (3R)-3-[(5-methyl-1,3-thiazol-2-yl)oxy]-1-pyrrolidinecarboxylate

15 The title compound was obtained from tert-butyl (3R)-3-hydroxy-1-pyrrolidinecarboxylate and 2-bromo-5-methyl-1,3-thiazole in the same manner as in Preparation 7.

ESI-MS: 285.1 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 6.75 (s, 1H), 5.46-5.40 (m, 1H), 3.77-3.38 (m, 4H), 2.31 (s, 3H), 2.40-2.00 (m, 2H), 1.47 (s, 9H).

20 Example 55

(2E)-3-(4-Chlorophenyl)-N-[(1S)-2-[(2-[(3R)-3-[(5-methyl-1,3-thiazol-2-yl)oxy]-1-pyrrolidinyl]-2-oxoethyl)amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-2-propenamide

25 The title compound was obtained from tert-butyl (3R)-3-[(5-methyl-1,3-thiazol-2-yl)oxy]-1-pyrrolidinecarboxylate and {[(2S)-2-[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino}-3-(2-pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 1.

30 ESI-MS: 554.1 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.58-8.52 (m, 1H), 8.06-7.95 (m, 1H), 7.93-7.80 (m, 1H), 7.67-7.55 (m, 2H), 7.45 (d, J=8Hz, 2H), 7.34 (d, J=8Hz, 2H), 7.28-7.22 (m, 1H), 7.21-7.14 (m, 1H), 6.74 (s, 1H), 6.49 (d, J=16Hz, 1H), 5.53-5.43 (m, 1H), 5.06-4.97 (m, 1H), 4.01-3.90 (m, 2H), 3.79-3.19 (m, 6H), 2.33-2.03 (m, 5H).

35 Example 56

5-Chloro-N-[(1S)-2-[(2-[(3R)-3-[(5-methyl-1,3-thiazol-2-yl)oxy]-1-pyrrolidinyl]-2-oxoethyl)amino]-2-oxo-1-(2-

pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide

The title compound was obtained from tert-butyl (3R)-3-[(5-methyl-1,3-thiazol-2-yl)oxy]-1-pyrrolidinecarboxylate and {[(2S)-2-[[5-chloro-1-benzofuran-2-yl)carbonyl]amino]-3-(2-pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 1.

ESI-MS: 568.1 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.77-8.67 (m, 1H), 8.64-8.59 (m, 1H), 8.23-8.13 (m, 1H), 7.64 (td, J=8,2Hz, 1H), 7.64 (d, J=2Hz, 1H), 7.48 (d, J=9Hz, 1H), 7.41 (s, 1H), 7.38 (dd, J=9,2Hz, 1H), 7.30-7.24 (m, 1H), 7.23-7.16 (m, 1H), 6.76-6.71 (m, 1H), 5.53-5.43 (m, 1H), 5.15-5.07 (m, 1H), 4.05-3.99 (m, 1H), 3.98-3.93 (m, 1H), 3.79-3.28 (m, 6H), 2.33-2.05 (m, 5H).

Preparation 37

tert-Butyl 3-[[6-(trifluoromethyl)-4-pyrimidinyl]oxy]-1-azetidinecarboxylate

The title compound was obtained from tert-butyl 3-hydroxy-1-azetidinecarboxylate and 6-(trifluoromethyl)-4-pyrimidinol in the same manner as in Preparation 13.

ESI-MS: 320.2 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.87 (s, 1H), 7.14 (s, 1H), 5.44 (tt, J=7,4Hz, 1H), 4.37 (dd, J=10,7Hz, 2H), 4.01 (dd, J=10,4Hz, 2H), 1.45 (s, 9H).

Example 57

(2E)-3-(4-Chlorophenyl)-N-[(1S)-2-oxo-2-[[2-oxo-2-(3-[[6-(trifluoromethyl)-4-pyrimidinyl]oxy]-1-azetidiny]ethyl]amino]-1-(2-pyridylmethyl)ethyl]-2-propenamide

The title compound was obtained from tert-butyl 3-[[6-(trifluoromethyl)-4-pyrimidinyl]oxy]-1-azetidinecarboxylate and {[(2S)-2-[[2E)-3-(4-chlorophenyl)-2-propenoyl]amino]-3-(2-pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 1.

ESI-MS: 589.2 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.88 (s, 1H), 8.55 (dd, J=5,2Hz, 1H), 8.06 (br s, 1H), 7.91-7.84 (m, 1H), 7.64 (td, J=8,2Hz, 1H), 7.59 (d, J=16Hz, 1H), 7.45 (d, J=8Hz, 2H), 7.35 (d, J=8Hz, 2H), 7.26 (d, J=8Hz, 1H), 7.19 (dd, J=8,5Hz, 1H), 7.15 (s, 1H), 6.48 (d, J=16Hz, 1H), 5.57-5.47 (m, 1H), 5.05-4.96 (m, 1H), 4.64-4.42 (m, 2H), 4.24-

4.06(m, 2H), 3.89(app d, J=4Hz, 2H), 3.41(dd, J=15,5Hz, 1H),
3.26(dd, J=15,6Hz, 1H).

Example 58

5-Chloro-N-[(1S)-2-oxo-2-[[2-oxo-2-(4-[[6-(trifluoromethyl)-4-pyrimidinyl]oxy)-1-azetidiny]ethyl]amino]-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide

The title compound was obtained from tert-butyl 3-[[6-(trifluoromethyl)-4-pyrimidinyl]oxy]-1-azetidinecarboxylate and [(2S)-2-[[[(5-chloro-1-benzofuran-2-yl) carbonyl]amino]-3-(2-pyridyl)propanoyl]amino]acetic acid in the same manner as in Example 1.

ESI-MS: 603.1 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.88(s, 1H), 8.74-8.67(m, 1H), 8.61(dd, J=5,2Hz, 1H), 8.26(br s, 1H), 7.65(td, J=8,2Hz, 1H), 7.65(d, J=2Hz, 1H), 7.49(d, J=9Hz, 1H), 7.41(s, 1H), 7.39(dd, J=9,2Hz, 1H), 7.28(d, J=8Hz, 1H), 7.21(dd, J=8,5Hz, 1H), 7.15(s, 1H), 5.58-5.48(m, 1H), 5.14-5.05(m, 1H), 4.65-4.55(m, 1H), 4.52-4.43(m, 1H), 4.25-4.06(m, 2H), 3.89(app d, J=4Hz, 2H), 3.47(dd, J=15,4Hz, 1H), 3.33(dd, J=15,7Hz, 1H).

20 Preparation 38

3,5-Dichloro-2-(4-piperidinyloxy)pyridine dihydrochloride

To a solution of tert-butyl 4-hydroxy-1-piperidinecarboxylate (0.5 g), 3,5-dichloro-2-pyridone (0.41 g) and triphenylphosphine (0.98 g) in tetrahydrofuran was slowly added diethyl azodicarboxylate (0.65 g) at 8°C, and the mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated in vacuo to give the crude product.

To a solution of the crude product in methanol (5 ml) was added 4N hydrogen chloride in ethyl acetate (6.2 ml) at 8°C. The mixture was stirred at room temperature for 1 hour and concentrated in vacuo. The residual solid was washed with ethyl acetate to give the title compound (585 mg).

¹H-NMR (300MHz, CDCl₃) δ 7.99(d, J=2Hz, 1H), 7.68(d, J=2Hz, 1H), 5.45-5.37(m, 1H), 3.45-3.29(m, 4H), 2.44-2.13(m, 4H).

35 Example 59

(2E)-3-(4-Chlorophenyl)-N-[(1S)-2-[(2-{4-[(3,5-dichloro-2-pyridyl)oxy]-1-piperidinyl}-2-oxoethyl)amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-2-propenamide

To a mixture of {[(2S)-2-[[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino]-3-(2-pyridyl)propanoyl]amino}acetic acid (0.19 g), 3,5-dichloro-2-(4-piperidinyloxy)pyridine dihydrochloride (0.16 g), 1-hydroxybenzotriazole (0.084 g) and 1-(3-

- 5 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.11 g) in N,N-dimethylformamide (2.5 ml) was added dropwise N,N-diisopropylethylamine (0.27 ml) at 8°C. The mixture was warmed to room temperature and stirred for 6 hours. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The
10 organic layer was washed with saturated aqueous sodium hydrogencarbonate solution and brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography to give the title compound (231 mg).

- 15 ¹H-NMR (300MHz, CDCl₃) δ 8.61-8.53(m, 1H), 8.07-7.85(m, 3H), 7.70-7.57(m, 3H), 7.45(d, J=8Hz, 2H), 7.35(d, J=8Hz, 2H), 7.30-7.15(m, 2H), 6.51(dd, J=2,15Hz, 1H), 5.38-5.28(m, 1H), 5.07-4.98(m, 1H), 4.13-3.95(m, 2H), 3.85-3.20(m, 6H), 2.00-1.79(m, 4H).

ESI-MS: m/z 616 (M+1)

20 Example 60

5-Chloro-N-[(1S)-2-[(2-{4-[(3,5-dichloro-2-pyridyl)oxy]-1-piperidinyl}-2-oxoethyl)amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide

- The title compound was obtained from 3,5-dichloro-2-(4-piperidinyloxy)pyridine dihydrochloride and {[(2S)-2-[[(5-chloro-1-benzofuran-2-yl)carbonyl]amino]-3-(2-pyridyl)propanoyl]-
25 amino}acetic acid in the same manner as in Example 59.

ESI-MS: m/z 630 (M+1)

- ¹H-NMR (300MHz, CDCl₃) δ 8.85-8.70(m, 1H), 8.67-8.59(m, 1H), 8.22-8.10(m, 1H), 7.96(d, J=2Hz, 1H), 7.70-7.60(m, 3H), 7.49(d, J=8Hz, 1H), 7.42(s, 1H), 7.39(dd, J=8,2Hz, 1H), 7.32-7.16(m, 2H), 5.39-5.28(m, 1H), 5.17-5.06(m, 1H), 4.15-3.98(m, 2H), 3.83-3.28(m, 6H),
30 2.01-1.79(m, 4H).

Preparation 39

- 35 tert-Butyl 4-[[3-(trifluoromethyl)-2-pyridyl]oxy]-1-piperidinecarboxylate

The title compound was obtained from tert-butyl 4-hydroxy-1-piperidinecarboxylate and 3-(trifluoromethyl)-2-hydroxypyridine

in the same manner as in Preparation 13.

¹H-NMR (300MHz, CDCl₃) δ 8.33-8.24 (m, 1H), 7.90-7.81 (m, 1H), 6.99-6.90 (m, 1H), 5.48-5.33 (m, 1H), 3.63-3.44 (m, 4H), 1.99-1.77 (m, 4H), 1.47 (s, 9H).

5. Example 61

(2E)-3-(4-Chlorophenyl)-N-[(1S)-2-oxo-2-{{2-oxo-2-(4-{{3-(trifluoromethyl)-2-pyridyl}oxy)-1-piperidinyl}ethyl}amino}-1-(2-pyridylmethyl)ethyl]-2-propenamide

The title compound was obtained from tert-butyl 4-{{3-(trifluoromethyl)-2-pyridyl}oxy}-1-piperidinecarboxylate and
10 {{[(2S)-2-{{[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino}-3-(2-pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 1.

ESI-MS: m/z 616 (M+1)

15 ¹H-NMR (300MHz, CDCl₃) δ 8.59-8.53 (m, 1H), 8.30-8.25 (m, 1H), 8.06-7.83 (m, 3H), 7.66-7.55 (m, 2H), 7.45 (d, J=8Hz, 2H), 7.35 (d, J=8Hz, 2H), 7.29-7.14 (m, 2H), 7.00-6.93 (m, 1H), 6.50 (dd, J=15, 3Hz, 1H), 5.55-5.45 (m, 1H), 5.06-4.98 (m, 1H), 4.14-3.90 (m, 3H), 3.60-3.35 (m, 4H), 3.30-3.20 (m, 1H), 2.00-1.79 (m, 4H).

20 Example 62

5-Chloro-N-[(1S)-2-oxo-2-{{2-oxo-2-(4-{{3-(trifluoromethyl)-2-pyridyl}oxy)-1-piperidinyl}ethyl}amino}-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide

The title compound was obtained from tert-butyl 4-{{3-(trifluoromethyl)-2-pyridyl}oxy}-1-piperidinecarboxylate and
25 {{[(2S)-2-{{[(5-chloro-1-benzofuran-2-yl)carbonyl]amino}-3-(2-pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 1.

ESI-MS: m/z 630 (M+1)

30 ¹H-NMR (300MHz, CDCl₃) δ 8.85-8.67 (m, 1H), 8.62 (d, J=5Hz, 1H), 8.28 (d, J=5Hz, 1H), 8.20-8.07 (m, 1H), 7.86 (d, J=8Hz, 1H), 7.69-7.59 (m, 2H), 7.49 (d, J=8Hz, 1H), 7.42 (s, 1H), 7.38 (dd, J=8, 2Hz, 1H), 7.30-7.15 (m, 2H), 7.00-6.92 (m, 1H), 5.50 (br s, 1H), 5.16-5.05 (m, 1H), 4.16-3.89 (m, 3H), 3.61-3.27 (m, 5H), 2.00-1.79 (m, 4H).

35 Preparation 40

4-(4-Fluorophenoxy)piperidine

To a solution of tert-butyl 4-hydroxy-1-piperidinecarboxylate (2.0 g), 4-fluorophenol (1.1 g) and

triphenylphosphine (3.9 g) in tetrahydrofuran was slowly added diethyl azodicarboxylate (2.6 g) at 8°C, and the mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated in vacuo to give the crude product.

- 5 To a solution of the crude product in ethyl acetate (5 ml) and methanol (5 ml) was added 4N hydrogen chloride in ethyl acetate (25 ml) at 8°C. The mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution and extracted
10 with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo to give the title compound (1.08 g).

Example 63

- (2E)-3-(4-Chlorophenyl)-N-[(1S)-2-({2-[4-(4-fluorophenoxy)-
15 1-piperidinyl]-2-oxoethyl}amino)-2-oxo-1-(2-pyridylmethyl)ethyl]-2-propenamide

- The title compound was obtained from 4-(4-fluorophenoxy)piperidine and {[(2S)-2- {[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino}-3-(2-pyridyl)propanoyl]amino}acetic acid in
20 the same manner as in Example 59.

ESI-MS: m/z 565 (M+1)

- ¹H-NMR (300MHz, CDCl₃) δ 8.60-8.53(m, 1H), 8.07-7.85(2H, m), 7.68-7.56(m, 2H), 7.45(d, J=8Hz, 2H), 7.35(d, J=8Hz, 2H), 7.31-7.15(m, 2H), 7.04-6.93(m, 2H), 6.90-6.80(m, 2H), 6.50(dd, J=15,2Hz, 1H),
25 5.06-4.97(m, 1H), 4.50-4.40(m, 1H), 4.11-3.95(m, 2H), 3.79-3.20(m, 6H), 1.94-1.75(m, 4H).

Example 64

- 5-Chloro-N-[(1S)-2-({2-[4-(4-fluorophenoxy)-1-piperidinyl]-2-oxoethyl}amino)-2-oxo-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-
30 carboxamide

The title compound was obtained from 4-(4-fluorophenoxy)piperidine and {[(2S)-2- {[(5-chloro-1-benzofuran-2-yl)carbonyl]amino}-3-(2-pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 59.

- 35 ESI-MS: m/z 579 (M+1)

¹H-NMR (300MHz, CDCl₃) δ 8.85-8.70(m, 1H), 8.67-8.60(m, 1H), 8.22-8.09(m, 1H), 7.70-7.60(m, 2H), 7.49(d, J=8Hz, 1H), 7.42(s, 1H), 7.39(dd, J=2,8Hz, 1H), 7.32-7.16(m, 2H), 7.04-6.92(m, 2H), 6.90-

6.80 (m, 2H), 5.16-5.06 (m, 1H), 4.51-4.40 (m, 1H), 4.15-3.96 (m, 2H), 3.75-3.44 (m, 4H), 3.40-3.26 (m, 2H), 1.95-1.73 (m, 4H).

Preparation 41

4-[4-(Trifluoromethyl)phenoxy]piperidine hydrochloride

5 The title compound was obtained from tert-butyl 4-hydroxy-1-piperidinecarboxylate and 4-(trifluoromethyl)phenol in the same manner as in Preparation 38.

¹H-NMR (300MHz, DMSO-d₆) δ 7.67 (d, J=8Hz, 2H), 7.19 (d, J=8Hz, 2H), 4.85-4.737 (m, 1H), 3.29-3.00 (m, 4H), 2.20-2.05 (m, 2H), 1.98-1.78 (m, 2H).

Example 65

(2E)-3-(4-Chlorophenyl)-N-[(1S)-2-oxo-2-[(2-oxo-2-{4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl}ethyl)amino]-1-(2-pyridylmethyl)ethyl]-2-propenamide

15 The title compound was obtained from 4-[4-(trifluoromethyl)phenoxy]piperidine hydrochloride and {[(2S)-2-[[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino]-3-(2-pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 59.

20 ESI-MS: m/z 615 (M+1)

¹H-NMR (300MHz, CDCl₃) δ 8.60-8.53 (m, 1H), 8.10-7.85 (m, 2H), 7.68-7.51 (m, 4H), 7.45 (d, J=8Hz, 2H), 7.35 (d, J=8Hz, 2H), 7.30-7.15 (m, 2H), 6.95 (d, J=8Hz, 2H), 6.50 (dd, J=15, 2Hz, 1H), 5.07-4.97 (m, 1H), 4.68-4.58 (m, 1H), 4.09-3.97 (m, 2H), 3.86-3.20 (m, 6H), 1.99-1.78 (m, 4H).

Example 66

5-Chloro-N-[(1S)-2-oxo-2-[(2-oxo-2-{4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl}ethyl)amino]-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide

30 The title compound was obtained from 4-[4-(trifluoromethyl)phenoxy]piperidine hydrochloride and {[(2S)-2-[[(5-chloro-1-benzofuran-2-yl)carbonyl]amino]-3-(2-pyridyl)propanoyl]amino}acetic acid in the same manner as in Example 59.

35 ESI-MS: m/z 629 (M+1)

¹H-NMR (300MHz, CDCl₃) δ 8.85-8.71 (m, 1H), 8.66-8.59 (m, 1H), 8.24-8.10 (m, 1H), 7.70-7.60 (m, 2H), 7.55 (d, J=8Hz, 2H), 7.50 (d, J=8Hz, 1H), 7.43 (s, 1H), 7.39 (dd, J=8, 2Hz, 1H), 7.33-7.16 (m, 2H), 6.95 (d,

J=8Hz, 2H), 5.16-5.06(m, 1H), 4.69-4.59(m, 1H), 4.15-3.97(m, 2H), 3.87-3.29(m, 6H), 2.00-1.77(m, 4H).

Preparation 42

tert-Butyl 4-(4-chlorophenoxy)-1-piperidinecarboxylate

- 5 The title compound was obtained from tert-butyl 4-hydroxy-1-piperidinecarboxylate and 4-chlorophenol in the same manner as in Preparation 13.

¹H-NMR (300MHz, CDCl₃) δ 7.31-7.14(m, 2H), 6.74-6.60(m, 2H), 4.47-4.36(m, 1H), 3.75-3.61(m, 2H), 3.40-3.26(m, 2H), 1.97-1.84(m, 2H),
10 1.80-1.66(m, 2H), 1.47(s, 9H).

Example 67

(2E)-3-(4-Chlorophenyl)-N-[(1S)-2-({2-[4-(4-chlorophenoxy)-1-piperidinyl]-2-oxoethyl}amino)-2-oxo-1-(2-pyridylmethyl)ethyl]-2-propenamide

- 15 The title compound was obtained from tert-butyl 4-(4-chlorophenoxy)-1-piperidinecarboxylate and {[(2S)-2-{{ (2E)-3-(4-chlorophenyl)-2-propenoyl}amino}-3-(2-pyridyl)-propanoyl}amino}acetic acid in the same manner as in Example 1.

ESI-MS: m/z 581 (M+1)

20 ¹H-NMR (300MHz, CDCl₃) δ 8.60-8.51(m, 1H), 8.09-7.84(m, 2H), 7.68-7.55(m, 2H), 7.45(d, J=8Hz, 2H), 7.35(d, J=8Hz, 2H), 7.30-7.14(m, 4H), 6.83(d, J=8Hz, 2H), 6.50(d, J=15Hz, 1H), 5.05-4.97(m, 1H), 4.55-4.45(m, 1H), 4.11-3.94(m, 2H), 3.80-3.20(m, 6H), 1.91-1.73(m, 4H).

25 Example 68

5-Chloro-N-[(1S)-2-({2-[4-(4-chlorophenoxy)-1-piperidinyl]-2-oxoethyl}amino)-2-oxo-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide

- 30 The title compound was obtained from tert-butyl 4-(4-chlorophenoxy)-1-piperidinecarboxylate and {[(2S)-2-{{ (5-chloro-1-benzofuran-2-yl)carbonyl}amino}-3-(2-pyridyl)propanoyl}amino}acetic acid in the same manner as in Example 1.

ESI-MS: m/z 595 (M+1)

35 ¹H-NMR (300MHz, CDCl₃) δ 8.85-8.70(m, 1H), 8.65-8.60(m, 1H), 8.23-8.10(m, 1H), 7.70-7.60(m, 2H), 7.50(d, J=8Hz, 1H), 7.42(s, 1H), 7.39(dd, J=8, 2Hz, 1H), 7.17-7.31(m, 4H), 6.88(d, J=8Hz, 2H), 5.15-5.06(m, 1H), 4.55-4.46(m, 1H), 4.15-3.97(m, 2H), 3.29-3.28(m, 6H), 1.95-1.74(m, 4H).

Preparation 43

tert-Butyl 4-(2-pyridylthio)-1-piperidinecarboxylate

To a slurry of sodium hydride (about 60% oil suspension, 397 mg) in dimethoxyethane (4 ml) was added a solution of 2-pyridinethiol (1.05 g) in dimethoxyethane (6 ml) at 0°C, and the mixture was stirred at room temperature for 1 hour. To the mixture was added tert-butyl 4-bromo-1-piperidinecarboxylate (2.74 g), and the mixture was refluxed for 2 hours. After cooling, the resulting suspension was diluted with ether and filtered through a pad of Celite. The filtrate was washed with brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent; 14% ethyl acetate in n-hexane) to give the title compound (2.2 g) as a white solid.

ESI-MS: 295.1 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.42 (dd, J=5,2Hz, 1H), 7.47 (td, J=8,2Hz, 1H), 7.16 (d, J=8Hz, 1H), 6.99 (dd, J=8,5Hz, 1H), 4.06-3.83 (m, 3H), 3.16-3.02 (m, 2H), 2.12-2.00 (m, 2H), 1.71-1.56 (m, 2H), 1.46 (s, 9H).

Example 69

(2E)-3-(4-Chlorophenyl)-N-[(1S)-2-oxo-2-((2-oxo-2-[4-(2-pyridylthio)-1-piperidinyl]ethyl)amino)-1-(2-pyridylmethyl)ethyl]-2-propenamide

The title compound was obtained from tert-butyl 4-(2-pyridylthio)-1-piperidinecarboxylate and [(2S)-2-[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino]-3-(2-pyridyl)propanoyl]amino}-acetic acid in the same manner as in Example 1.

ESI-MS: 564.2 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.55 (dd, J=5,2Hz, 1H), 8.41 (dd, J=5,2Hz, 1H), 8.02-7.96 (m, 1H), 7.95-7.88 (m, 1H), 7.63 (td, J=8,2Hz, 1H), 7.61 (d, J=16Hz, 1H), 7.52-7.42 (m, 3H), 7.35 (d, J=8Hz, 2H), 7.28-7.23 (m, 1H), 7.18 (dd, J=8,5Hz, 1H), 7.15 (d, J=8Hz, 1H), 7.00 (dd, J=8,5Hz, 1H), 6.50 (d, J=16Hz, 1H), 5.06-4.97 (m, 1H), 4.26-4.04 (m, 2H), 4.02 (app d, J=4Hz, 2H), 3.70-3.59 (m, 1H), 3.43 (dd, J=15,5Hz, 1H), 3.30-3.10 (m, 3H), 2.19-2.02 (m, 2H), 1.73-1.54 (m, 2H).

Example 70

5-Chloro-N-[(1S)-2-oxo-2-((2-oxo-2-[4-(2-pyridylthio)-1-piperidinyl]ethyl)amino)-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide

The title compound was obtained from tert-butyl 4-(2-pyridylthio)-1-piperidinecarboxylate and {[(2S)-2-[[(5-chloro-1-benzofuran-2-yl) carbonyl] amino]-3-(2-pyridyl)propanoyl] amino}-acetic acid in the same manner as in Example 1.

5 ESI-MS: 578.1 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.80-8.73 (m, 1H), 8.62 (dd, J=5, 2Hz, 1H), 8.41 (dd, J=5, 2Hz, 1H), 8.18-8.10 (m, 1H), 7.65 (td, J=8, 2Hz, 1H), 7.65 (d, J=2Hz, 1H), 7.51-7.44 (m, 2H), 7.42 (s, 1H), 7.38 (dd, J=9, 2Hz, 1H), 7.27 (d, J=8Hz, 1H), 7.20 (dd, J=8, 5Hz, 1H), 7.15 (d, J=8Hz, 1H), 6.99 (dd, J=8, 5Hz, 1H), 5.15-5.06 (m, 1H), 4.25-4.00 (m, 4H), 3.71-3.59 (m, 1H), 3.49 (dd, J=15, 5Hz, 1H), 3.38-3.09 (m, 3H), 2.19-2.01 (m, 2H), 1.73-1.52 (m, 2H).

Example 71

15 (2E)-3-(4-Chlorophenyl)-N-[(1S)-2-oxo-2-({2-oxo-2-[4-(2-pyridylsulfonyl)-1-piperidinyl]ethyl}amino)-1-(2-pyridylmethyl)ethyl]-2-propenamide

The title compound was obtained from 2-(4-piperidinylsulfonyl)pyridine hydrochloride and {[(2S)-2-[[(2E)-3-(4-chlorophenyl)-2-propenoyl] amino]-3-(2-pyridyl)propanoyl]-amino}acetic acid in the same manner as in Example 59.

20 ESI-MS: 596.2 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.75-8.80 (m, 1H), 8.58-8.52 (m, 1H), 8.12-7.82 (m, 4H), 7.68-7.55 (m, 3H), 7.45 (d, J=8Hz, 2H), 7.35 (d, J=8Hz, 2H), 7.28-7.15 (m, 2H), 6.54-6.44 (m, 1H), 5.04-4.96 (m, 1H), 4.68-4.56 (m, 1H), 3.99 (app d, J=4Hz, 2H), 3.88-3.67 (m, 2H), 3.47-3.35 (m, 1H), 3.29-3.19 (m, 1H), 3.11-2.97 (m, 1H), 2.74-2.61 (m, 1H), 2.12-1.90 (m, 2H), 1.86-1.68 (m, 2H).

Example 72

30 5-Chloro-N-[(1S)-2-oxo-2-({2-oxo-2-[4-(2-pyridylsulfonyl)-1-piperidinyl]ethyl}amino)-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide

The title compound was obtained from 2-(4-piperidinylsulfonyl)pyridine hydrochloride and {[(2S)-2-[[(5-chloro-1-benzofuran-2-yl) carbonyl] amino]-3-(2-pyridyl)propanoyl] amino}acetic acid in the same manner as in Example 59.

ESI-MS: 578.1 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.85-8.57 (m, 3H), 8.23-7.95 (m, 3H), 7.69-

7.55(m, 3H), 7.49(d, J=9Hz, 1H), 7.42(s, 1H), 7.38(dd, J=9, 2Hz, 1H), 7.29-7.16(m, 2H), 3.52-3.42(m, 1H), 3.37-3.26(m, 1H), 3.12-2.99(m, 1H), 2.74-2.61(m, 1H), 2.13-1.91(m, 2H), 1.88-1.65(m, 2H).

Preparation 44

- 5 tert-Butyl 4-[(5-chloro-2-pyridyl)thio]-1-piperidinecarboxylate

The title compound was obtained from tert-butyl 4-mercapto-1-piperidinecarboxylate and 2,5-dichloropyridine in the same manner as in Preparation 7.

- 10 ¹H-NMR (300MHz, CDCl₃) δ 8.38(dd, J=2, 1Hz, 1H), 7.45(dd, J=8, 2Hz, 1H), 7.10(dd, J=8, 1Hz, 1H), 4.01-3.85(m, 3H), 3.14-3.00(m, 2H), 2.10-1.98(m, 2H), 1.70-1.58(m, 2H), 1.46(s, 9H).

Example 73

- 15 (2E)-3-(4-Chlorophenyl)-N-[(1S)-2-[(2-{4-[(5-chloro-2-pyridyl)thio]-1-piperidinyl})-2-oxoethyl]amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-2-propenamide

The title compound was obtained from tert-butyl 4-[(5-chloro-2-pyridyl)thio]-1-piperidinecarboxylate and {[(2S)-2-{[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino}-3-(2-pyridyl)-propanoyl]amino}acetic acid in the same manner as in Example 1.

ESI-MS: 598.1 (M+H)

- 25 ¹H-NMR (300MHz, CDCl₃) δ 8.56(dd, J=5, 2Hz, 1H), 8.37(d, J=2Hz, 1H), 8.03-7.97(m, 1H), 7.95-7.89(m, 1H), 7.63(td, J=8, 2Hz, 1H), 7.61(d, J=16Hz, 1H), 7.49-7.42(m, 3H), 7.35(d, J=8Hz, 2H), 7.28-7.23(m, 1H), 7.18(dd, J=8, 5Hz, 1H), 7.09(d, J=8Hz, 1H), 6.50(d, J=16Hz, 1H), 5.06-4.97(m, 1H), 4.27-4.14(m, 1H), 4.10-3.97(m, 3H), 3.70-3.58(m, 1H), 3.43(dd, J=15, 5Hz, 1H), 3.30-3.07(m, 3H), 2.17-2.00(m, 2H), 1.72-1.54(m, 2H).

Example 74

- 30 5-Chloro-N-[(1S)-2-[(2-{4-[(5-chloro-2-pyridyl)thio]-1-piperidinyl})-2-oxoethyl]amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide

The title compound was obtained from tert-butyl 4-[(5-chloro-2-pyridyl)thio]-1-piperidinecarboxylate and {[(2S)-2-{[(5-chloro-1-benzofuran-2-yl)carbonyl]amino}-3-(2-pyridyl)propanoyl]-amino}acetic acid in the same manner as in Example 1.

ESI-MS: 612.1 (M+H)

- 35 ¹H-NMR (300MHz, CDCl₃) δ 8.81-8.73(m, 1H), 8.62(dd, J=5, 2Hz, 1H),

8.37(d, J=2Hz, 1H), 8.19-8.12(m, 1H), 7.65(td, J=8,2Hz, 1H),
 7.65(d, J=2Hz, 1H), 7.52-7.35(m, 4H), 7.30-7.24(m, 1H), 7.20(dd,
 J=8,5Hz, 1H), 7.09(d, J=8Hz, 1H), 5.15-5.07(m, 1H), 4.26-4.14(m,
 1H), 4.10-3.97(m, 3H), 3.71-3.60(m, 1H), 3.49(dd, J=15,4Hz, 1H),
 5 3.38-3.07(m, 3H), 2.18-2.01(m, 2H), 1.72-1.53(m, 2H).

Example 75

(2E)-3-(4-Chlorophenyl)-N-[(1S)-2-oxo-2-({2-oxo-2-[4-(4-
 pyridylthio)-1-piperidinyl]ethyl}amino)-1-(2-
 pyridylmethyl)ethyl]-2-propenamide

10 The title compound was obtained from 4-(4-
 piperidinylthio)pyridine dihydrochloride and {[(2S)-2-[[(2E)-3-
 (4-chlorophenyl)-2-propenoyl]amino]-3-(2-pyridyl)propanoyl]-
 amino}acetic acid in the same manner as in Example 59.

ESI-MS: 564.2 (M+H)

15 ¹H-NMR (300MHz, CDCl₃) δ 8.56(dd, J=5,2Hz, 1H), 8.45(d, J=6Hz, 2H),
 8.08-7.88(m, 1H), 7.65(td, J=8,2Hz, 1H), 7.62(d, J=16Hz, 1H),
 7.47(d, J=8Hz, 2H), 7.36(d, J=8Hz, 2H), 7.29-7.24(m, 1H), 7.20(dd,
 J=8,5Hz, 1H), 7.15(d, J=6Hz, 1H), 6.50(d, J=16Hz, 1H), 5.06-
 4.97(m, 1H), 4.27-4.13(m, 1H), 4.03(app d, J=4Hz, 2H), 3.75-
 20 3.52(m, 2H), 3.49-3.39(m, 1H), 3.31-3.11(m, 3H), 2.14-2.01(m, 2H),
 1.72-1.55(m, 2H).

Example 76

5-Chloro-N-[(1S)-2-oxo-2-({2-oxo-2-[4-(4-pyridylthio)-1-
 piperidinyl]ethyl}amino)-1-(2-pyridylmethyl)ethyl]-1-benzofuran-
 25 2-carboxamide

The title compound was obtained from 4-(4-
 piperidinylthio)pyridine dihydrochloride and {[(2S)-2-[[(5-
 chloro-1-benzofuran-2-yl)carbonyl]amino]-3-(2-
 pyridyl)propanoyl]amino}acetic acid in the same manner as in
 30 Example 59.

ESI-MS: 578.1 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.82-8.72(m, 1H), 8.62(dd, J=5,2Hz, 1H),
 8.44(d, J=6Hz, 2H), 8.22-8.12(m, 1H), 7.65(td, J=8,2Hz, 1H),
 7.65(d, J=2Hz, 1H), 7.49(d, J=9Hz, 1H), 7.42(s, 1H), 7.39(dd,
 35 J=9,2Hz, 1H), 7.27(d, J=8Hz, 1H), 7.20(dd, J=8,5Hz, 1H), 7.14(d,
 J=6Hz, 1H), 5.14-5.06(m, 1H), 4.25-4.12(m, 1H), 4.05(app d, J=4Hz,
 2H), 3.75-3.43(m, 3H), 3.38-3.10(m, 3H), 2.14-2.01(m, 2H), 1.73-
 1.55(m, 2H).

Preparation 45

tert-Butyl 4-[(4-chlorophenyl)thio]-1-piperidinecarboxylate

The title compound was obtained from tert-butyl 4-bromo-1-piperidinecarboxylate and 4-chlorobenzenethiol in the same manner as in Preparation 7.

¹H-NMR (300MHz, CDCl₃) δ 7.39-7.24 (m, 4H), 4.07-3.84 (m, 2H), 3.23-3.10 (m, 1H), 3.00-2.80 (m, 2H), 2.00-1.80 (m, 2H), 1.61-1.30 (m, 11H).

Example 77

(2E)-3-(4-Chlorophenyl)-N-[(1S)-2-[(2-{4-[(4-chlorophenyl)thio]-1-piperidinyl}-2-oxoethyl)amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-2-propenamide

The title compound was obtained from tert-butyl 4-[(4-chlorophenyl)thio]-1-piperidinecarboxylate and {[(2S)-2-[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino]-3-(2-pyridyl)-propanoyl]amino}acetic acid in the same manner as in Example 1.

ESI-MS: 597.2 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.55 (dd, J=5, 2Hz, 1H), 8.03-7.85 (m, 2H), 7.63 (td, J=8, 2Hz, 1H), 7.60 (d, 16Hz, 1H), 7.45 (d, J=8Hz, 2H), 7.37-7.22 (m, 7H), 7.18 (dd, J=8, 5Hz, 1H), 6.49 (d, J=16Hz, 1H), 5.04-4.96 (m, 1H), 4.30-4.16 (m, 1H), 3.99 (app d, d=4Hz, 2H), 3.71-3.59 (m, 1H), 3.47-3.37 (m, 1H), 3.29-3.16 (m, 2H), 3.15-2.91 (m, 2H), 2.00-1.88 (m, 2H), 1.59-1.42 (m, 2H).

Example 78

5-Chloro-N-[(1S)-2-[(2-{4-[(4-chlorophenyl)thio]-1-piperidinyl}-2-oxoethyl)amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide

The title compound was obtained from tert-butyl 4-[(4-chlorophenyl)thio]-1-piperidinecarboxylate and {[(2S)-2-[(5-chloro-1-benzofuran-2-yl)carbonyl]amino]-3-(2-pyridyl)propanoyl]-amino}acetic acid in the same manner as in Example 1.

ESI-MS: 611.1 (M+H)

¹H-NMR (300MHz, CDCl₃) δ 8.80-8.71 (m, 1H), 8.61 (dd, J=5, 2Hz, 1H), 8.18-8.08 (m, 1H), 7.65 (td, J=8, 2Hz, 1H), 7.65 (d, J=2Hz, 1H), 7.48 (d, J=9Hz, 1H), 7.41 (s, 1H), 7.40-7.15 (m, 7H), 5.13-5.04 (m, 1H), 4.29-4.17 (m, 1H), 4.02 (app d, J=4Hz, 2H), 3.71-3.60 (m, 1H), 3.48 (dd, J=15, 4Hz, 1H), 3.38-3.16 (m, 2H), 3.16-2.92 (m, 2H), 2.01-1.87 (m, 2H), 1.63-1.41 (m, 2H).

Example 79

(2E)-3-(4-Chlorophenyl)-N-[(1S)-2-[(2-{4-[(4-chlorophenyl)sulfonyl]-1-piperidinyl}-2-oxoethyl)amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-2-propenamide

5 The title compound was obtained from 4-[(4-chlorophenyl)sulfonyl]piperidine hydrochloride and {[(2S)-2-{[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino}-3-(2-pyridyl)-propanoyl]amino}acetic acid in the same manner as in Example 59.
ESI-MS: 629.1 (M+H)

10 ¹H-NMR (300MHz, CDCl₃) δ 8.57-8.51 (m, 1H), 8.05-7.83 (m, 2H), 7.82-7.74 (m, 2H), 7.67-7.52 (m, 4H), 7.45 (d, J=8Hz, 2H), 7.35 (d, J=8Hz, 2H), 7.28-7.13 (m, 2H), 6.53-6.43 (m, 1H), 5.03-4.93 (m, 1H), 4.71-4.57 (m, 1H), 3.98 (app d, J=4Hz, 2H), 3.86-3.75 (m, 1H), 3.46-3.34 (m, 1H), 3.29-3.19 (m, 1H), 3.16-2.90 (m, 2H), 2.65-2.50 (m, 1H),
15 2.15-1.95 (m, 2H), 1.69-1.49 (m, 2H).

Example 80

5-Chloro-N-[(1S)-2-[(2-{4-[(4-chlorophenyl)sulfonyl]-1-piperidinyl}-2-oxoethyl)amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide

20 The title compound was obtained from 4-[(4-chlorophenyl)sulfonyl]piperidine hydrochloride and {[(2S)-2-{[(5-chloro-1-benzofuran-2-yl)carbonyl]amino}-3-(2-pyridyl)propanoyl]-amino}acetic acid in the same manner as in Example 59.

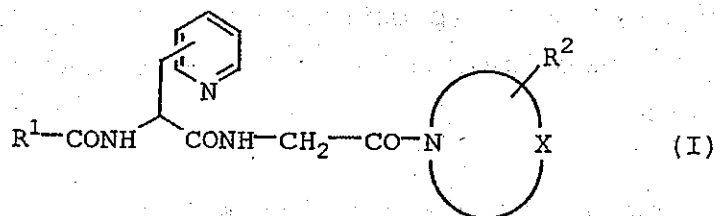
ESI-MS: 643.1 (M+H)

25 ¹H-NMR (300MHz, CDCl₃) δ 8.83-8.67 (m, 1H), 8.63-8.56 (m, 1H), 8.22-8.09 (m, 1H), 7.82-7.74 (m, 2H), 7.69-7.34 (m, 7H), 7.29-7.15 (m, 2H), 5.13-5.03 (m, 1H), 4.70-4.58 (m, 1H), 4.09-3.91 (m, 2H), 3.88-3.75 (m, 1H), 3.52-3.40 (m, 1H), 3.37-3.25 (m, 1H), 3.17-2.91 (m, 2H), 2.65-2.50 (m, 1H), 2.15-1.96 (m, 2H), 1.68-1.47 (m, 2H).

30

CLAIMS

1. A compound of the formula (I):

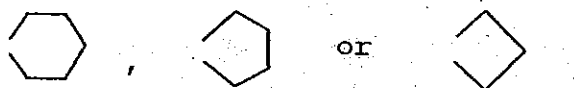


5 wherein

R^1 is benzofuranyl substituted by halogen, or styryl substituted by halogen;

R^2 is substituted hydroxy, substituted mercapto or substituted sulfonyl; and

10 X is



or pharmaceutically acceptable salts thereof.

2. The compound of claim 1, wherein R^2 is a group of the
 15 formula: $-Y-R^3$ wherein R^3 is lower alkyl, halo(lower)alkyl, optionally substituted heterocyclic group or optionally substituted aryl, and Y is $-O-$, $-S-$ or $-SO_2-$, or a pharmaceutically acceptable salt thereof.

20 3. The compound of claim 2, wherein R^3 is lower alkyl; halo(lower)alkyl; heterocyclic group optionally substituted by one or more substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, halogen and halo(lower)alkyl; or aryl
 25 optionally substituted by one or more substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, halogen and halo(lower)alkyl, or a pharmaceutically acceptable salt thereof.

4. The compound of claim 3, wherein R^3 is lower alkyl;
 30 halo(lower)alkyl; heterocyclic group selected from the group consisting of pyridyl, pyrazinyl, thiazolyl, pyridazinyl and pyrimidinyl, said heterocyclic group is optionally substituted by

one or more substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, halogen and halo(lower)alkyl; or phenyl optionally substituted by one or more substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, halogen and halo(lower)alkyl, or a pharmaceutically acceptable salt thereof.

5. The compound of claim 1, wherein X is



or a pharmaceutically acceptable salt thereof.

6. The compound of claim 5, wherein R^2 is substituted hydroxy, or a pharmaceutically acceptable salt thereof.

7. The compound of claim 6, wherein R^2 is a group of the formula: $-O-R^3$ wherein R^3 is lower alkyl, halo(lower)alkyl, optionally substituted heterocyclic group or optionally substituted aryl, or a pharmaceutically acceptable salt thereof.

8. The compound of claim 7, wherein R^3 is lower alkyl, halo(lower)alkyl, pyridyl, pyrazinyl, thiazolyl or phenyl, each of said pyridyl, pyrazinyl, thiazolyl and phenyl is optionally substituted by one or more substituents selected from the group consisting of lower alkyl, lower alkoxy, halogen and halo(lower)alkyl, or a pharmaceutically acceptable salt thereof.

9. The compound of claim 8, wherein R^3 is lower alkyl, halo(lower)alkyl, pyridyl, pyrazinyl, thiazolyl or phenyl, said pyridyl is optionally substituted by a substituent selected from the group consisting of lower alkyl, lower alkoxy, halogen and halo(lower)alkyl, or a pharmaceutically acceptable salt thereof.

10. The compound of claim 1, wherein R^1 is benzofuranyl substituted by chlorine, or styryl substituted by chlorine, or a pharmaceutically acceptable salt thereof.

11. The compound of claim 1, wherein R^1 is 5-chloro-1-

benzofuran-2-yl or 2-(4-chlorophenyl)ethenyl, or a pharmaceutically acceptable salt thereof.

5 12. A pharmaceutical composition comprising the compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier.

10 13. A compound of claim 1 or a pharmaceutically acceptable salt thereof for use as a medicament.

14. A compound of claim 1 or a pharmaceutically acceptable salt thereof for use as a medicament for prophylactic or therapeutic treatment of NO-mediated diseases.

15 15. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for prophylactic or therapeutic treatment of NO-mediated diseases.

20 16. A compound of claim 1 or a pharmaceutically acceptable salt thereof for use as a medicament for prophylactic or therapeutic treatment of NO-mediated disease selected from the group consisting of adult respiratory distress syndrome (ARDS); asthma; cardiovascular ischemia; myocarditis; heart failure; hypotension; atherosclerosis; diabetes including Insulin-dependent diabetes mellitus; complications of diabetes mellitus including diabetic nephropathy, diabetic retinopathy and diabetic neuropathy; 25 gout; glomerulonephritis; renal failure; peptic ulcer; inflammatory bowel diseases including ulcerative colitis and chronic colitis; pancreatitis; hepatitis; liver cirrhosis; synovitis; arthritis; osteoarthritis; osteoporosis; autoimmune diseases including rheumatoid arthritis, systemic lupus erythematosus and multiple sclerosis; dermatitis; eczema; cancer; solid tumors; metastasis; rejection by organ transplantation; shock 30 including septic shock; sepsis-induced systemic inflammatory response syndrome; CNS disorders; cerebral infarction; cerebral ischemia; cerebral hemorrhage; migraine; Alzheimer's disease; neuritis; postherpetic neuralgia; reflex sympathetic dystrophy (RSD); causalgia; deafferentation pain syndrome; neuropathic pain; allodynia; 35 hyperalgesia; neurological disorders; neuroprotection; Parkinson's disease; amyotrophic lateral sclerosis; male sexual dysfunction including erectile dysfunction; female sexual dysfunction including orgasmic dysfunction related to clitoral disturbances; conjunctivitis including allergic conjunctivitis, vernal conjunctivitis, keratoconjunctivitis sicca, viral

conjunctivitis and bacterial conjunctivitis; uveitis including Behcet disease, Harada disease, sympathetic ophthalmia, sarcoidosis and diabetic iritis; scleritis; corneal neovascularization; keratitis; corneal edema; corneal opacity; corneal dystrophy; keratoconus; neuroparalytic keratitis; diabetic retinopathy; retinal artery occlusion; retinal vein occlusion; central serous chorioretinopathy; central hemorrhagic chorioretinitis; macular degeneration including age-related macular degeneration; retinal detachment; retinal pigmentary degeneration; macular neovascularization; macular hole; proliferative vitreoretinopathy; vitreous hemorrhage; vitreous opacity; cataract including senile cataract, traumatic cataract, diabetic cataract and atopic cataract; glaucoma-including primary open-angle glaucoma, primary angle-closure glaucoma, normal tension glaucoma and neovascular glaucoma; ocular hypertension; vision disorders including amblyopia, color vision defect and night blindness; refractive errors including astigmatism, hyperopia, myopia and presbyopia; dry eye syndromes; lacrimal duct obstruction and dacryocystitis.

17. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for prophylactic or therapeutic treatment of NO-mediated disease selected from the group consisting of adult respiratory distress syndrome (ARDS); asthma; cardiovascular ischemia; myocarditis; heart failure; hypotension; atherosclerosis; diabetes including Insulin-dependent diabetes mellitus; complications of diabetes mellitus including diabetic nephropathy, diabetic retinopathy and diabetic neuropathy; gout; glomerulonephritis; renal failure; peptic ulcer; inflammatory bowel diseases including ulcerative colitis and chronic colitis; pancreatitis; hepatitis; liver cirrhosis; synovitis; arthritis; osteoarthritis; osteoporosis; autoimmune diseases including rheumatoid arthritis, systemic lupus erythematosus and multiple sclerosis; dermatitis; eczema; cancer; solid tumors; metastasis; rejection by organ transplantation; shock including septic shock; sepsis-induced systemic inflammatory response syndrome; CNS disorders; cerebral infarction; cerebral ischemia; cerebral hemorrhage; migraine; Alzheimer's disease; neuritis; postherpetic neuralgia; reflex sympathetic dystrophy (RSD); causalgia; deafferentation pain syndrome; neuropathic pain; allodynia; hyperalgesia; neurological disorders; neuroprotection; Parkinson's disease; amyotrophic lateral sclerosis; male sexual dysfunction including erectile dysfunction; female sexual dysfunction including orgasmic dysfunction related to clitoral disturbances; conjunctivitis including allergic conjunctivitis, vernal conjunctivitis, keratoconjunctivitis sicca, viral

conjunctivitis and bacterial conjunctivitis; uveitis including Behcet disease, Harada disease, sympathetic ophthalmia, sarcoidosis and diabetic iritis; scleritis; corneal neovascularization; keratitis; corneal edema; corneal opacity; corneal dystrophy; keratoconus; neuroparalytic keratitis; diabetic retinopathy; retinal artery occlusion; retinal vein occlusion; central serous chorioretinopathy; central hemorrhagic chorioretinitis; macular degeneration including age-related macular degeneration; retinal detachment; retinal pigmentary degeneration; macular neovascularization; macular hole; proliferative vitreoretinopathy; vitreous hemorrhage; vitreous opacity; cataract including senile cataract, traumatic cataract, diabetic cataract and atopic cataract; glaucoma-including primary open-angle glaucoma, primary angle-closure glaucoma, normal tension glaucoma and neovascular glaucoma; ocular hypertension; vision disorders including amblyopia, color vision defect and night blindness; refractive errors including astigmatism, hyperopia, myopia and presbyopia; dry eye syndromes; lacrimal duct obstruction and dacryocystitis.

18. A pharmaceutical composition comprising FK506 and the compound of claim 1 or a pharmaceutically acceptable salt thereof.

19. A pharmaceutical composition comprising FK506 and the compound of claim 1 or a pharmaceutically acceptable salt thereof for use as an immunosuppressant.

20. Use of a pharmaceutical composition comprising FK506 and the compound of claim 1 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use as an immunosuppressant.

21. A pharmaceutical composition comprising FK506 and the compound of claim 1 or a pharmaceutically acceptable salt thereof for use as a medicament for the prevention or treatment of rejection by organ transplantation.

22. Use of a pharmaceutical composition comprising FK506 and the compound of claim 1 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the prevention or treatment of rejection by organ transplantation.