Compounds represented by the formulas (I) and (II) wherein each symbol is as defined in the specification, and a pro-drug thereof have a superior renin inhibitory activity, and are useful as agents for the prophylaxis or treatment of hypertension, various organ damages attributable to hypertension and the like.
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DESCRIPTION

HETEROCYCLIC CARBOXAMIDE COMPOUNDS AND THEIR USE IN THE PROPHYLAXIS OR TREATMENT OF HYPERTENSION

TECHNICAL FIELD OF THE INVENTION

[0001]

The present invention relates to a heterocyclic compound and the like, which has a superior renin inhibitory activity and is useful as an agent for the prophylaxis or treatment of hypertension, various organ damages attributable to hypertension, and the like.

[0002]

(Background of the Invention)

Hypertension is one of representative lifestyle-related diseases. Hypertension which is left untreated for long time lays a heavy burden on the cardiovascular system and results in arteriosclerosis to progress, thus causing various disorders in important organs, such as cerebral hemorrhage, cerebral infarction, cardiac failure, angina pectoris, myocardial infarction, renal failure and the like. Accordingly, the purpose of treating hypertension lies not only in lowering the blood pressure, but also in improving and/or preventing disorders in important organs including brain, heart and kidney, by controlling the blood pressure. As a method of treating hypertension, there are available fundamental treatments based on improvement in the lifestyle, such as dietetic therapy, exercise therapy and the like, as well as an attempt to control the blood pressure by positive pharmaceutical intervention.

[0003]

The renin-angiotensin (RA) system is a system of biosynthesis of angiotensin II (AII), which is a major vasopressor factor, and takes an important role in the control of the blood pressure and the amount of body fluid. AII exhibits a strong vasoconstrictive effect brought by the intervention of AII receptors on the cellular membrane, thus raising the blood pressure, and also promotes cellular
propagation or production of extracellular matrix by directly acting on the AII receptors in the cardiac cells or renal cells. Therefore, drugs inhibiting increase in the activity of the RA system can be expected to have a blood pressure lowering action as well as a powerful organ protecting action, and thus active researches on such drugs have been conducted so far.

[0004]

The method of inhibiting the AII action is broadly classified into methods of inhibiting the biosynthesis of AII and methods of inhibiting the binding of AII to AII receptors. For the drugs inhibiting the biosynthesis of AII, angiotensin converting enzyme (ACE) inhibitory drugs have been already put to practical use and are being confirmed to have a blood pressure lowering action as well as an effect for protecting various organs. However, since ACE is an enzyme identical to kininase II, which is a bradykinin degrading enzyme, ACE inhibitory drug inhibits the biosynthesis of AII as well as the degradation of bradykinin. As a result, ACE inhibitory drugs are believed to induce side effects such as dry cough, angioedema and the like, which are considered to be caused by accumulation of bradykinin.

[0005]

As the drugs inhibiting the binding of AII to AII receptors, AII type 1 receptor blockers (ARB) have been developed. ARB has a merit in that it can inhibit, at the receptor level, the action of AII that is biosynthesized by not only ACE but also an enzyme other than ACE, such as chymase and the like. It is known that administration of ACE inhibitors and ARB increases the plasma renin activity (PRA) as a compensatory feedback effect, since these drugs act on a more peripheral region of the RA system.

[0006]

Renin is an enzyme occupying a position at the uppermost stream of the RA system, and converts angiotensinogen to
angiotensin I. A renin inhibitory drug inhibits the RA system by inhibiting the biosynthesis of AII in the same manner as the ACE inhibitory drugs do, and thus can be expected to have a blood pressure lowering action or an effect of protecting various organs. Since the renin inhibitory drug does not have influence on the metabolism of bradykinin, it is believed to have no risk of side effects such as dry cough and the like, that are observed with the ACE inhibitory drugs. Furthermore, while the ACE inhibitory drugs or ARB increase the PRA level, the renin inhibitory drugs are the only drugs that can reduce PRA.


As other renin inhibitors, the following compounds have been reported.

(1) A compound represented by the formula

![Chemical structure]

wherein G is any one of groups represented by the following formulas (a) to (c)
R^{1a} is an optionally substituted C_{1-6} alkyl group, an optionally substituted C_{2-6} alkenyl group, an optionally substituted C_{2-6} alkynyl group, an optionally substituted C_{3-10} cycloalkyl group, an optionally substituted C_{5-6} cycloalkenyl group or an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl-C_{1-4} alkyl group; R^{1b}, R^{1c}, R^{1d} and R^{1e} are the same or different and each independently is a hydrogen atom, a halogen atom, a hydroxyl group, a formyl group, a carboxyl group, a cyano group, an optionally substituted C_{1-6} alkyl group, an optionally substituted C_{2-6} alkenyl group, an optionally substituted C_{2-6} alkynyl group, an optionally substituted C_{3-10} cycloalkenyl group, an optionally substituted C_{3-6} cycloalkenyl group, an optionally substituted C_{5-6} cycloalkenyl group, an optionally substituted C_{5-6} cycloalkenyl group, an optionally substituted C_{6-10} aryl group, an optionally substituted C_{7-14} aralkyl group, an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl group, an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl C_{1-4} alkyl group, an optionally substituted saturated heterocyclic group, an optionally substituted C_{1-6} alkylthio group, an optionally substituted C_{1-6} alkylsulfenyl group, an optionally substituted C_{1-6} alkylsulfonyl group, an optionally substituted C_{6-10} arylthio group, an optionally substituted C_{6-10} arylsulfenyl group, an optionally substituted C_{6-10} arylsulfonyl group, an optionally substituted C_{1-6} alkoxy group, an optionally substituted C_{3-6} alkynyloxy group, an optionally substituted C_{3-6} cycloalkyloxy group, an optionally substituted C_{6-10} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally 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optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substitute
substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryloxy group, an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl C$_{1-4}$ alkyloxy group, an optionally substituted amino group, an optionally substituted aminocarbonyl group, an optionally substituted aminocarbonyloxy group, an optionally substituted aminosulfonyl group, an optionally substituted C$_{1-6}$ alkoxy carbonyl group, an optionally substituted C$_{3-6}$ cycloalkyloxycarbonyl group, an optionally substituted C$_{1-4}$ alkylcarbonyl group, an optionally substituted C$_{3-6}$ cycloalkyl carbonyl group, an optionally substituted C$_{6-10}$ aryl carbonyl group or an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl carbonyl group; R$^{1'}$ is a hydrogen atom, a halogen atom, a hydroxyl group, a cyano group, an optionally substituted C$_{1-6}$ alkyl group, an optionally substituted C$_{2-6}$ alkenyl group, an optionally substituted C$_{2-6}$ alkynyl group, an optionally substituted C$_{3-10}$ cycloalkyl group, an optionally substituted C$_{3-6}$ cycloalkenyl group, an optionally substituted C$_{6-10}$ aryl group, an optionally substituted C$_{7-14}$ aralkyl group, an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl group, an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl C$_{1-4}$ alkyl group, an optionally substituted saturated heterocyclic group, an optionally substituted C$_{1-6}$ alkylthio group, an optionally substituted C$_{1-6}$ alkylsulfinyl group, an optionally substituted C$_{1-6}$ alkylsulffonyl group, an optionally substituted C$_{1-6}$ alkoxy group, an optionally substituted C$_{3-6}$ alkynloxy group, an optionally substituted C$_{3-6}$ cycloalkyloxy group, an optionally substituted C$_{6-10}$ aryloxy group, an optionally substituted C$_{7-14}$ aralkyloxy group, an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl C$_{1-4}$ aryloxy group, an optionally substituted amino group, an optionally substituted aminocarbonyl group, an optionally substituted aminosulfonyl group, an optionally substituted C$_{1-4}$
alkoxy carbonyl group, an optionally substituted C₃-₆
cycloalkyloxycarbonyl group, an optionally substituted C₁-₄
alkyl carbonyl group, an optionally substituted C₃-₆
cycloalkyl carbonyl group, an optionally substituted C₆-₁₀
aryl carbonyl group or an optionally substituted 5-membered to
10-membered monocyclic or polycyclic heteroaryl carbonyl group;
R² is an optionally substituted C₁-₆ alkyl group, an optionally
substituted C₂-₆ alkenyl group, an optionally substituted C₂-₆
alkynyl group, an optionally substituted C₃-₆ cycloalkyl group,
an optionally substituted C₅-₆ cycloalkenyl group, an optionally
substituted C₆-₁₀ aryl group, an optionally substituted C₇-₁₄
aralkyl group or an optionally substituted 5-membered to 10-
membered monocyclic or polycyclic heteroaryl group;
R¹ₐ, R¹ₐ, R³c and R³d are the same or different and each
independently is a halogen atom, a cyano group or a group: -A-
B (wherein A is a single bond, -(CH₂)₆O-, -(CH₂)₆N(R⁴)-, -(CH₂)₆SO₂-, -(CH₂)₆CO-, -(CH₂)₆COO-, -(CH₂)₆N(R⁴)CO-, -(CH₂)₆N(R⁴)SO₂-, -(CH₂)₆N(R⁴)COO-, -(CH₂)₆OCON(R⁴)-, -(CH₂)₆O-CO-, -(CH₂)₆ON(R⁴)-, -(CH₂)₆N(R⁴)CON(R⁴)- or -(CH₂)₆SΟ₂N(R⁴)-,
B is a hydrogen atom, an optionally substituted C₁-₆ alkyl group,
an optionally substituted C₂-₆ alkenyl group, an optionally
substituted C₂-₆ alkynyl group, an optionally substituted C₃-₆
cycloalkyl group, an optionally substituted C₅-₆ cycloalkenyl
group, an optionally substituted C₆-₁₀ aryl group, an optionally
substituted C₇-₁₄ aralkyl group, an optionally substituted 5-
membered to 10-membered monocyclic or polycyclic heteroaryl
group, an optionally substituted 5-membered to 10-membered
monocyclic or polycyclic heteroaryl C₁-₄ alkyl group or an
optionally substituted 5-membered or 6-membered saturated
heterocyclic group (when A is -(CH₂)₆N(R⁴)-, -(CH₂)₆OCON(R⁴)-, -(CH₂)₆CON(R⁴)-, -(CH₂)₆N(R⁴)CON(R⁴)- or -(CH₂)₆SO₂N(R⁴)-, R⁴ and B
may be bonded to each other to form a ring), or two of R¹ₐ, R¹ₐ,
R³c and R³d are hydrogen atoms, and the other two are bonded to
each other to form a bridged ring together with the hetero
R^4 is a hydrogen atom, an optionally substituted C_{1-6} alkyl group, an optionally substituted C_{3-6} cycloalkyl group, an optionally substituted C_{6-10} aryl group, an optionally substituted C_{7-14} aralkyl group or an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl group;
s is 0, 1 or 2 (when A is -(CH_{2})_{s}N(R^4)-, s is 0 or 2, and when A is -(CH_{2})_{s}CON(R^4)-, s is 1 or 2); and
n is 0, 1 or 2, or a salt thereof (see WO2009/14217).

(2) A compound represented by the formula

[0013]

[0014]

wherein R^{1a} is an optionally substituted C_{1-6} alkyl group, an optionally substituted C_{2-10} alkenyl group, an optionally substituted C_{2-6} alkynyl group, an optionally substituted C_{3-6} cycloalkyl group, an optionally substituted C_{3-6} cycloalkenyl group, an optionally substituted C_{1-6} alkylsulfinyl group, an optionally substituted C_{1-6} alkylsulfonyl group, an optionally substituted aminocarbonyl group, an optionally substituted C_{1-4} alkoxy carbonyl group or an optionally substituted C_{1-4} alkyl carbonyl group;
R^{1b} and R^{1e} are the same or different and each independently is a hydrogen atom, a halogen atom, a cyano group, an optionally substituted C_{1-6} alkyl group, an optionally substituted C_{1-6} alkoxy group, an optionally substituted C_{3-6} cycloalkyloxy group or an optionally substituted aminocarbonyl group;
R^{2c} and R^{1d} are the same or different and each independently is a hydrogen atom, a halogen atom, a hydroxyl group, a formyl
group, a carboxy group, a cyano group, an optionally substituted C<sub>1-6</sub> alkyl group, an optionally substituted C<sub>2-6</sub> alkenyl group, an optionally substituted C<sub>2-6</sub> alkynyl group, an optionally substituted C<sub>3-10</sub> cycloalkyl group, an optionally substituted C<sub>5-6</sub> cycloalkenyl group, an optionally substituted C<sub>6-10</sub> aryl group, an optionally substituted C<sub>7-14</sub> aralkyl group, an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl group, an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl C<sub>1-4</sub> alkyl group, an optionally substituted saturated heterocyclic group, an optionally substituted C<sub>1-6</sub> alkylthio group, an optionally substituted C<sub>1-6</sub> alkylsulfanyl group, an optionally substituted C<sub>1-6</sub> alkylsulfonyl group, an optionally substituted C<sub>6-10</sub> arylthio group, an optionally substituted C<sub>6-10</sub> arylsulfinyl group, an optionally substituted C<sub>6-10</sub> arylsulfonyl group, an optionally substituted C<sub>1-6</sub> alkoxy group, an optionally substituted C<sub>3-6</sub> alkynyl group, an optionally substituted C<sub>3-10</sub> cycloalkyl group, an optionally substituted C<sub>6-10</sub> aryloxy group, an optionally substituted C<sub>7-14</sub> aralkyloxy group, an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl oxy group, an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl C<sub>1-4</sub> aryloxy group, an optionally substituted amino group, an optionally substituted aminocarbonyl group, an optionally substituted aminosulfonyl group, an optionally substituted C<sub>1-4</sub> alkoxy carbonyl group, an optionally substituted C<sub>3-6</sub> cyclo alkyl oxycarbonyl group, an optionally substituted C<sub>1-4</sub> alky carbonyl group, an optionally substituted C<sub>3-6</sub> cycloalkyl carbonyl group, an optionally substituted C<sub>6-10</sub> alky carbonyl group or an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl carbonyl group; R<sup>1f</sup> are the same or different and each independently is a hydrogen atom, a halogen atom, a cyano group, an optionally substituted C<sub>1-6</sub> alkyl group, an optionally substituted C<sub>1-6</sub> alkoxy group, an optionally substituted C<sub>3-10</sub> cycloalkyl group,
an optionally substituted C₂⁻₆ alkenyl group, an optionally substituted C₂⁻₆ alkenyloxy group, an optionally substituted C₃⁻₆ alkynyl group, an optionally substituted C₃⁻₆ alkyloxy group or an optionally substituted C₃⁻₁₀ cycloalkyloxy group;

R² is an optionally substituted C₁⁻₆ alkyl group, an optionally substituted C₂⁻₆ alkenyl group, an optionally substituted C₂⁻₆ alkynyl group, an optionally substituted C₃⁻₁₀ cycloalkyl group, an optionally substituted C₅⁻₆ cycloalkenyl group, an optionally substituted C₆⁻₁₀ aryl group, an optionally substituted C₇⁻₁₄ aralkyl group or an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl group;

R³a, R³b, R³c and R³d are the same or different and each independently is a halogen atom, a cyano group or a group: -A-B (wherein A is a single bond, -(CH₂)₈0-, -(CH₂)₈N(R⁴)-, -(CH₂)₈SO₂-, -(CH₂)₈CO-, -(CH₂)₈COO-, -(CH₂)₈NO₂-, -(CH₂)₈N(R⁴)SO₂-, -(CH₂)₈N(R⁴)CO-, -(CH₂)₈N(R⁴)CON(R⁴)-, -(CH₂)₈O-CO-, -(CH₂)₈ON(R⁴)-, -(CH₂)₈N(R⁴)CON(R⁴)- or -(CH₂)₈SO₂N(R⁴)-,

B is a hydrogen atom, an optionally substituted C₁⁻₆ alkyl group, an optionally substituted C₂⁻₆ alkenyl group, an optionally substituted C₃⁻₆ cycloalkyl group, an optionally substituted C₅⁻₆ cycloalkenyl group, an optionally substituted C₆⁻₁₀ aryl group, an optionally substituted C₇⁻₁₄ aralkyl group, an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl group, an optionally substituted C₂⁻₆ alkynyl group, an optionally substituted C₃⁻₆ cycloalkynyl group, an optionally substituted C₅⁻₆ cycloalkynyl group, an optionally substituted C₆⁻₁₀ aryl group, an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl group or an optionally substituted saturated heterocyclic group (when A is -(CH₂)₈N(R⁴)-, -(CH₂)₈OCON(R⁴)-, -(CH₂)₈CON(R⁴)-, -(CH₂)₈N(R³)CON(R⁴)- or -(CH₂)₈SO₂N(R⁴)-, R⁴ and B may be bonded to each other to form a ring), or two of R³a, R³b, R³c and R³d are hydrogen atoms, and the other two are bonded to each other to form a bridged ring together with the hetero ring;

R⁴ is a hydrogen atom, an optionally substituted C₁⁻₆ alkyl group, an optionally substituted C₃⁻₆ cycloalkyl group, an optionally substituted C₅⁻₆ cycloalkenyl group, an optionally substituted C₆⁻₁₀ aryl group, an optionally
substituted C₇₋₁₄ aralkyl group or an optionally substituted 5-membered to 10-membered monocyclic or a polycyclic heteroaryl group;

s is 0, 1 or 2 (when A is -(CH₂)ₓN(R⁴)₋, s is 0 or 2, and when A is -(CH₂)ₓCON(R⁴)₋, s is 1 or 2); and

n is 0, 1 or 2, or a salt thereof (see WO2009/05002).

(3) A compound represented by the formula

\[
\begin{array}{c}
\text{[0015]}
\end{array}
\]

\[
\begin{array}{c}
\text{[0016]}
\end{array}
\]

wherein

R¹ is a substituent;
R² is a cyclic group optionally having substituent(s), a C₁₋₁₀ alkyl optionally having substituent(s), a C₂₋₁₀ alkenyl optionally having substituent(s) or a C₂₋₁₀ alkynyl optionally having substituent(s);
R³ is a hydrogen atom, a halogen atom, a C₁₋₆ alkyl or C₁₋₆ alkoxy;
ring A is a nitrogen-containing heterocycle optionally having substituent(s); and

ring B is a piperazine optionally further having substituent(s) besides R¹, or a salt thereof (see WO2009/001915).

(4) A compound represented by the formula

\[
\begin{array}{c}
\text{[0017]}
\end{array}
\]

\[
\begin{array}{c}
\text{[0018]}
\end{array}
\]
wherein R¹ is A) an alkyl group substituted by the group selected from
1) an optionally substituted alkoxy group, 2) a hydroxyl group, 3) a halogen atom, 4) an optionally substituted aryl group, 5) an optionally substituted
tetrahydronaphthyl group, 6) an optionally substituted indolyl group, 7) an optionally substituted benzofuranyl group, 8) an optionally substituted benzothienyl group, 9) an optionally substituted quinolyl group, 10) an optionally substituted dihydrochromenyl group, 11) an optionally substituted
dihydrobenzofuranyl group, 12) an optionally substituted indazolyl group, 13) an optionally substituted pyrrolopyridinyl group, 14) an optionally substituted benzoxazinyl group, 15) an optionally substituted xanthenyl group, 16) an optionally substituted indolinyl group and 17) an optionally substituted imidazopyridinyl group, B) an optionally substituted aryl group, C) an optionally substituted heterocyclic group, D) a cycloalkyl group or E) an alkyl group,
R² is A) an alkyl group substituted by the group selected from
1) an optionally substituted alkoxy group, 2) a hydroxyl group,
3) a halogen atom, 4) an optionally substituted aryl group, 5) an optionally substituted tetrahydronaphthyl group, 6) an optionally substituted indolyl group, 7) an optionally substituted benzofuranyl group, 8) an optionally substituted benzothienyl group, 9) an optionally substituted quinolyl group, 10) an optionally substituted dihydrochromenyl group, 11) an optionally substituted dihydrobenzofuranyl group, 12) an optionally substituted indazolyl group, 13) an optionally substituted pyrrolopyridinyl group, 14) an optionally substituted benzoxazinyl group, 15) an optionally substituted xanthenyl group, 16) an optionally substituted indolinyl group and 17) an optionally substituted alkylcarbonyl group, E) an optionally substituted arylcarbonyl
group, F) an optionally substituted heterocyclic group—substituted carbonyl group or G) a cycloalkylcarbonyl group, T is a methylene group or a carbonyl group, and R³, R⁴, R⁵ and R⁶ are the same or different and each is a hydrogen atom, an optionally substituted carbamoyl group or an optionally a substituted alkyl group, or a salt thereof (see WO2008/153182).

(5) A compound represented by the formula

![Chemical Structure]

[0019]

wherein R¹a is an optionally substituted C₁-₆ alkyl group, a C₃-₆ cycloalkyl group substituted by C₁-₄ alkoxy, an optionally substituted C₂-₆ alkenyl group, an optionally substituted C₂-₆ alkenyloxy group, an optionally substituted C₃-₆ alkynyl group, an optionally substituted C₃-₆ alkynyloxy group, an optionally substituted C₁-₆ alkylsulfinyl group, an optionally substituted C₁-₆ alkylsulfonil group, an optionally substituted C₁-₆ alkoxy group, an optionally substituted amino group, an optionally substituted aminocarbonyl group, an optionally substituted C₁-₄ alkoxy carbonyl group or an optionally substituted C₁-₄ alkyl carbonyl group; R₁b and R¹e are each a hydrogen atom, a halogen atom, a cyano group, an optionally substituted C₁-₆ alkyl group, an optionally substituted C₁-₆ alkoxy group, an optionally substituted C₃-₆ cycloalkyloxy group or an optionally substituted aminocarbonyl group;

R¹c and R¹d are the same or different and each independently is a hydrogen atom, a halogen atom, a hydroxyl group, a formyl
group, a carboxy group, a cyano group, an optionally substituted C$_{1-6}$ alkyl group, an optionally substituted C$_{2-6}$ alkenyl group, an optionally substituted C$_{2-6}$ alkynyl group, an optionally substituted C$_{3-10}$ cycloalkyl group, an optionally substituted C$_{5-6}$ cycloalkenyl group, an optionally substituted C$_{6-10}$ aryl group, an optionally substituted C$_{7-14}$ aralkyl group, an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl group, an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl C$_{1-4}$ alkyl group, an optionally substituted saturated heterocyclic group, an optionally substituted C$_{1-6}$ alkylthio group, an optionally substituted C$_{1-6}$ alkylsulfinyl group, an optionally substituted C$_{1-6}$ alkylsulfonyl group, an optionally substituted C$_{5-10}$ arylthio group, an optionally substituted C$_{6-10}$ arylsulfinyl group, an optionally substituted C$_{6-10}$ arylsulfonyl group, an optionally substituted C$_{1-6}$ alkoxy group, an optionally substituted C$_{3-6}$ alkynyl group, an optionally substituted C$_{3-10}$ cycloalkyl group, an optionally substituted C$_{5-10}$ aryloxy group, an optionally substituted C$_{7-14}$ aralkyloxy group, an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl group, an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl C$_{1-4}$ aryloxy group, an optionally substituted amino group, an optionally substituted aminocarbonyl group, an optionally substituted aminosulfonyl group, an optionally substituted C$_{1-4}$ alkoxy group, an optionally substituted C$_{3-10}$ cycloalkyl group, an optionally substituted C$_{1-4}$ alkylcarbonyl group, an optionally substituted C$_{3-10}$ cycloalkylcarbonyl group, an optionally substituted C$_{6-10}$ aryloxycarbonyl group or an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroarylcarbonyl group; R$^{1f}$ and R$^{1g}$ are the same or different and each independently is a hydrogen atom, a halogen atom, a cyano group, an optionally substituted C$_{1-6}$ alkyl group, an optionally substituted C$_{1-6}$ alkoxy group, an optionally substituted C$_{3-10}$ cycloalkyl group,
an optionally substituted C2-6 alkenyl group, an optionally substituted C2-6 alkenyloxy group, an optionally substituted C3-6 alkynyl group, an optionally substituted C3-6 alkynlyloxy group or an optionally substituted C3-10 cycloalkyloxy group;

R² is an optionally substituted C1-6 alkyl group, an optionally substituted C2-6 alkenyl group, an optionally substituted C2-6 alkynyl group, an optionally substituted C3-10 cycloalkyl group, an optionally substituted C5-8 cycloalkenyl group, an optionally substituted C6-10 aryl group, an optionally substituted C7-14 aralkyl group or an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl group;

R³a, R³b, R³c and R³d are the same or different and each independently is a halogen atom, a cyano group or a group: -A-B (wherein A is a single bond, -(CH₂)₆O-, -(CH₂)₆N(R⁴)-, -(CH₂)₆SO₂-, -(CH₂)₆CO-, -(CH₂)₆OCON(R⁴)-, -(CH₂)₆SO₂N(R⁴)-, -(CH₂)₆COO-, -(CH₂)₆N(R⁴)CO-, -(CH₂)₆SO₂N(R⁴)-, -(CH₂)₆SO₂CO-, -(CH₂)₆SO₂(O)CO-, -(CH₂)₆SO₂N(R⁴)CO-, -(CH₂)₆SO₂N(R⁴)CON(R⁴)- or -(CH₂)₆SO₂N(R⁴)CON(R⁴)-, B is a hydrogen atom, an optionally substituted C1-6 alkyl group, an optionally substituted C2-6 alkenyl group, an optionally substituted C2-6 alkynyl group, an optionally substituted C3-6 cycloalkyl group, an optionally substituted C4-8 cycloalkenyl group, an optionally substituted C6-10 aryl group, an optionally substituted C7-14 aralkyl group, an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl group, an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl C1-4 alkyl group or an optionally substituted saturated heterocyclic group (when A is -(CH₂)₆N(R⁴)-, -(CH₂)₆OCON(R⁴)-, -(CH₂)₆CON(R⁴)-, -(CH₂)₆N(R⁴)CON(R⁴)- or -(CH₂)₆SO₂N(R⁴)-, R⁴ and B may be bonded to each other to form a ring) or two of R³a, R³b, R³c and R³d are hydrogen atoms, and the other two are bonded to each other to form a bridged ring together with the hetero ring;

R⁴ is a hydrogen atom, an optionally substituted C1-6 alkyl group, an optionally substituted C3-6 cycloalkyl group, an optionally substituted C6-10 aryl group, an optionally substituted C8-14 aralkyl group or an optionally substituted C8-14 aralkenyl group.
substituted C₇₋₁₄ aralkyl group or an optionally substituted 5-membered to 10-membered monocyclic or a polycyclic heteroaryl group;
s is 0, 1 or 2 (when A is -(CH₂)ₖN(R⁴)⁻, s is 0 or 2, and
when A is -(CH₂)ₖCON(R⁴)⁻, s is 1 or 2); and
n is 0, 1 or 2, or a salt thereof (see WO2008/153135).
(6) A compound represented by the formula

![Chemical Structure](image)

10 [0022]
wherein
R¹ is a substituent,
R² is a cyclic group optionally having substituent(s), C₁⁻₁₀ alkyl optionally having substituent(s), C₂⁻₁₀ alkenyl optionally having substituent(s),
R³ is a hydrogen atom, a halogen atom, C₁⁻₆ alkyl or C₁⁻₆ alkoxy, X is a bond or a spacer having 1 to 6 atoms in the main chain, ring A is a C₅⁻₇ cycloalkane optionally having substituent(s),
and
ring B is a piperazine optionally further having substituent(s) besides R¹, or a salt thereof (see WO2008/139941).
(7) A compound represented by the formula

![Chemical Structure](image)
[0024] wherein \( R^1 \) and \( R^2 \) are each a hydrocarbon group optionally having substituent(s) or a heterocyclic group optionally having substituent(s), or

\( R^1 \) and \( R^2 \) may form, together with the nitrogen atom bonded thereto, a nitrogen-containing heterocycle optionally having substituent(s), 

\( R^3 \) is a substituent, 

ring A is a homocycle optionally having substituent(s) or a heterocycle optionally having substituent(s), or a salt thereof (see WO2009/051112).

(8) A compound represented by the formula

![Chemical Structure](image)

[0025]

15 [0026] wherein G is one group selected from the group consisting of the following formulas (a) to (d)

![Chemical Structures](images)

[0027]

20 [0028] wherein \( R^{1a} \) is an optionally substituted \( C_{1-6} \) alkyl group, a \( C_{3-6} \) cycloalkoxy group substituted by \( C_{1-4} \) alkoxy, an optionally substituted \( C_{2-6} \) alkenyl group, an optionally substituted \( C_{2-6} \) alkenyloxy group, an optionally substituted \( C_{3-6} \) alkynyl group,
an optionally substituted C₃₋₅ alkynylxylo group, an optionally substituted C₁₋₆ alkylsulfinyl group, an optionally substituted C₁₋₆ alkylsulfonyl group, an optionally substituted C₁₋₆ alkoxy group, an optionally substituted amino group, an optionally substituted aminocarbonyl group, an optionally substituted C₁₋₄ alkoxycarbonyl group or an optionally substituted C₁₋₄ alkylcarbonyl group;

R¹ᵇ and R¹ᶜ are the same or different and each independently is a hydrogen atom, a cyano group, an optionally substituted C₁₋₆ alkyl group, an optionally substituted C₁₋₆ alkoxy group, an optionally substituted C₂₋₆ alkenyl group, C₁₋₆ alkylsulfonyl group, or a halogen atom;

R³ᶜ and R¹ᵈ are the same or different and each independently is a hydrogen atom, a halogen atom, a hydroxyl group, a formyl group, a carboxy group, a cyano group, an optionally substituted C₁₋₆ alkyl group, an optionally substituted C₂₋₆ alkenyl group, an optionally substituted C₂₋₆ alkenyl group, an optionally substituted C₃₋₁₀ cycloalkyl group, an optionally substituted C₅₋₆ cycloalkenyl group, an optionally substituted C₆₋₁₀ aryl group, an optionally substituted C₇₋₁₄ aralkyl group, an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl group, an optionally substituted 5-membered or 6-membered saturated heterocyclic group, an optionally substituted C₁₋₆ alkylthio group, an optionally substituted C₁₋₆ alkylsulfinyl group, an optionally substituted C₁₋₆ alkylsulfonyl group, an optionally substituted C₆₋₁₀ arylthio group, an optionally substituted C₆₋₁₀ arylsulfinyl group, an optionally substituted C₆₋₁₀ arylsulfonyl group, an optionally substituted C₁₋₆ alkoxy group, an optionally substituted C₃₋₁₀ cycloalkylo group, an optionally substituted C₆₋₁₀ aryloxy group, an optionally substituted C₇₋₁₄ aralkylo group, an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroarylxy group, an optionally substituted amino group, an optionally substituted aminocarbonyl group, an
optionally substituted aminosulfanyl group, an optionally substituted C<sub>1-4</sub> alkoxy carbonyl group, an optionally substituted C<sub>3-10</sub> cycloalkyloxy carbonyl group, an optionally substituted C<sub>1-4</sub> alkyl carbonyl group, an optionally substituted C<sub>3-10</sub> cycloalkyl carbonyl group, an optionally substituted C<sub>6-10</sub> aryl carbonyl group or an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl carbonyl group; R<sup>1f</sup> is a hydrogen atom, a halogen atom, a cyano group, an optionally substituted C<sub>3-6</sub> cycloalkyl group, an optionally substituted C<sub>2-6</sub> alkenyl group, an optionally substituted C<sub>2-6</sub> alkenyloxy group, an optionally substituted C<sub>3-6</sub> alkynyl group, an optionally substituted C<sub>3-6</sub> alkynyloxy group, an optionally substituted C<sub>3-10</sub> cycloalkyloxy group, an optionally substituted C<sub>1-6</sub> alkoxy group or an optionally substituted C<sub>1-6</sub> alkyl group; R<sup>2</sup> is an optionally substituted C<sub>1-6</sub> alkyl group, an optionally substituted C<sub>2-6</sub> alkenyl group, an optionally substituted C<sub>2-6</sub> alkynyl group, an optionally substituted C<sub>2-6</sub> alkynyl group, an optionally substituted C<sub>3-10</sub> cycloalkyl group, an optionally substituted C<sub>6-10</sub> ary group, an optionally substituted C<sub>6-10</sub> cycloalkenyl group, an optionally substituted C<sub>7-14</sub> aralkyl group or an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl group; R<sup>3a</sup>, R<sup>3b</sup>, R<sup>3c</sup> and R<sup>3d</sup> are the same or different and each independently is a halogen atom, a hydroxyl group, a formyl group, a carboxyl group, a cyano group or a group: A-B

(wherein A is a single bond, -(CH<sub>2</sub>)<sub>5</sub>SO<sup>-</sup>, -(CH<sub>2</sub>)<sub>5</sub>N(R<sup>4</sup>)<sup>-</sup>, -(CH<sub>2</sub>)<sub>5</sub>S, -(CH<sub>2</sub>)<sub>5</sub>NO<sup>-</sup>, -(CH<sub>2</sub>)<sub>5</sub>COO<sup>-</sup>, -(CH<sub>2</sub>)<sub>5</sub>N(R<sup>4</sup>)CO-, -(CH<sub>2</sub>)<sub>5</sub>N(R<sup>4</sup>)SO<sup>-</sup>, -(CH<sub>2</sub>)<sub>5</sub>N(R<sup>4</sup>)COO-, -(CH<sub>2</sub>)<sub>5</sub>OCON(R<sup>4</sup>)<sup>-</sup>, -(CH<sub>2</sub>)<sub>5</sub>OCON(R<sup>4</sup>)<sup>-</sup>, -(CH<sub>2</sub>)<sub>5</sub>SO<sub>2</sub>N(R<sup>4</sup>)<sup>-</sup>, B is a hydrogen atom, an optionally substituted C<sub>1-6</sub> alkyl group, an optionally substituted C<sub>2-6</sub> alkenyl group, an optionally substituted C<sub>2-6</sub> alkynyl group, an optionally substituted C<sub>3-10</sub> cycloalkyl group, an optionally substituted C<sub>5-6</sub> cycloalkenyl group, an optionally substituted C<sub>6-10</sub> aryl group, an optionally substituted C<sub>7-14</sub> aralkyl group, an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl
group, an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl C₁₋₄ alkyl group or an optionally substituted 5-membered or 6-membered saturated heterocyclic group (when A is -(CH₂)ₘN(R⁴)⁻, -(CH₂)ₙOCON(R⁴)⁻, -(CH₂)ₚCON(R⁴)⁻, -(CH₂)ₚN(R⁴)CON(R⁴)⁻ or -(CH₂)ₚSO₂N(R⁴)⁻, R⁴ and B may be bonded to each other to form a ring)), or two of R³ᵃ, R³ᵇ, R³ᶜ and R³ᵈ are hydrogen atoms, and the other two are bonded to each other to form a bridged ring together with the heteroring;

R⁴ is a hydrogen atom, an optionally substituted C₁₋₆ alkyl group, an optionally substituted C₃₋₆ cycloalkyl group, an optionally substituted C₆₋₁₀ aryl group, an optionally substituted C₇₋₁₄ aralkyl group or an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl group;

s is 0, 1 or 2 (when A is -(CH₂)ₘN(R⁴)⁻, s is 0 or 2, and when A is -(CH₂)ₚOCON(R⁴)⁻, s is 1 or 2); and

n is 0, 1 or 2, or a salt thereof (see WO 2008/136457).

(9) A compound represented by the formula

\[
\begin{align*}
R¹ & \quad R² & \quad R³ & \quad R⁴ & \quad R⁵ & \quad R⁶ & \quad R⁷ & \quad R⁸ & \quad R⁹ & \quad R¹₀ & \\
R¹₁ & \quad R¹₂ & \quad R¹₃ & \quad R¹₄ & & & & & & & \\
R²ˡ & \quad R²ʳ & \quad R³ˡ & \quad R³ʳ & \quad R⁴ʳ & \quad R⁵ʳ & \quad R⁶ʳ & \quad R⁷ʳ & \quad R⁸ʳ & \quad R⁹ʳ & \quad R¹₀ʳ & \\
\end{align*}
\]

[0029]

[0030]

wherein R¹ᵃ is a hydrogen atom, a halogen atom, a hydroxyl group, a formyl group, a carboxy group, a cyano group, an optionally substituted C₁₋₆ alkyl group, an optionally substituted C₂₋₆ alkenyl group, an optionally substituted C₂₋₆ alkynyl group, an optionally substituted C₃₋₆ cycloalkyl group, a C₁₋₆ alkylthio group, a C₁₋₆ alkylsulfonyl group, a C₁₋₆ alkoxy group optionally substituted by a halogen atom, a C₁₋₄ alkoxy or C₃₋₆ cycloalkyl, an optionally substituted C₃₋₆ cycloalkoxy group, an optionally substituted amino group, aminocarbonyl group, C₁₋₄
alkoxycarbonyl group, a C<sub>1-4</sub> alkylcarbonyl group, an optionally substituted C<sub>6-10</sub> aryl group, an optionally substituted C<sub>6-10</sub> aryloxy group or an optionally substituted C<sub>7-14</sub> aralkyloxy group;

R<sup>1b</sup> is a C<sub>1-6</sub> alkyl group substituted by mono-C<sub>1-6</sub> alkoxy carbonylamino, an optionally substituted C<sub>1-6</sub> alkylsulfinyl group, an optionally substituted C<sub>1-6</sub> alkylsulfonyl group, a substituted C<sub>1-6</sub> alkoxy group, an optionally substituted amino group, an optionally substituted aminocarbonyl group, an optionally substituted C<sub>1-4</sub> alkoxy carbonyl group or an optionally substituted C<sub>1-4</sub> alkylcarbonyl group (wherein the substituted C<sub>1-6</sub> alkoxy group is substituted by one group selected from the group consisting of hydroxy, C<sub>1-4</sub> alkoxy, C<sub>3-6</sub> cycloalkoxy, trifluoromethyl, trifluoromethoxy, difluoromethoxy, carboxy, mono-C<sub>1-6</sub> alkylcarbonylamino and mono-C<sub>1-6</sub> alkoxy carbonylamino),

R<sup>1c</sup> is a hydrogen atom, a halogen atom, a hydroxyl group, a formyl group, a carboxy group, a cyano group, an optionally substituted C<sub>1-6</sub> alkyl group, an optionally substituted C<sub>3-6</sub> cycloalkyl group, an optionally substituted C<sub>5-6</sub> cycloalkenyl group, an optionally substituted 5-membered or 6-membered saturated heterocyclic group, an optionally substituted C<sub>1-6</sub> alkylthio group, an optionally substituted C<sub>1-6</sub> alkylsulfinyl group, an optionally substituted C<sub>1-6</sub> alkylsulfonyl group, an optionally substituted C<sub>6-10</sub> arythio group, an optionally substituted C<sub>6-10</sub> arylsulfinyl group, an optionally substituted C<sub>6-10</sub> arylsulfonyl group, an optionally substituted C<sub>1-6</sub> alkoxy group, an optionally substituted C<sub>3-6</sub> cycloalkyroxy group, an optionally substituted C<sub>6-10</sub> aryloxy group, an optionally substituted C<sub>7-14</sub> aralkyloxy group, an optionally substituted amino group, an optionally substituted aminocarbonyl group, an optionally substituted C<sub>1-4</sub> alkoxy carbonyl group, an optionally substituted C<sub>3-6</sub> cycloalkyloxy carbonyl group, an optionally substituted C<sub>1-4</sub> alkylcarbonyl group, an optionally substituted C<sub>3-6</sub> cycloalkylcarbonyl group, an optionally substituted C<sub>6-10</sub>
arylcarbonyl group, an optionally substituted C₇₋₁₄ aralkyl group or an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroarylcarbonyl group, or R₁ᵃ is a hydrogen atom; R₁ᵇ and R₁ᶜ in combination form a fused ring together with the hetero ring, which contains at least one hetero atom;

R² is a hydrogen atom, an optionally substituted C₁₋₆ alkyl group, an optionally substituted C₂₋₆ alkenyl group, an optionally substituted C₂₋₆ alkynyl group, an optionally substituted C₃₋₁₀ cycloalkyl group, an optionally substituted C₅₋₆ cycloalkenyl group, an optionally substituted C₆₋₁₀ aryl group, an optionally substituted C₇₋₁₄ aralkyl group or an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl group (when R₁ᵃ is a C₁₋₆ alkoxy group substituted by a halogen atom, R² is not a hydrogen atom);

R₃ᵃ, R₃ᵇ, R₃ᶜ and R₃ᵈ are the same or different and each independently is a halogen atom, a cyano group or a group: -A-B (wherein A is a single bond, -(CH₂)₂O-, -(CH₂)₂N(R⁴) -, -(CH₂)₂SO₂-, -(CH₂)₂CO -, -(CH₂)₂COO -, -(CH₂)₂N(R⁴)CO -, -(CH₂)₂N(R⁴)SO₂-, -(CH₂)₂N(R⁴)COO -, -(CH₂)₂OCON(R⁴) -, -(CH₂)₂O-CO -, -(CH₂)₂CON(R⁴) -, -(CH₂)₂N(R⁴)CON(R⁴) - or -(CH₂)₂SO₂N(R⁴) -, B is a hydrogen atom, an optionally substituted C₁₋₆ alkyl group, an optionally substituted C₂₋₆ alkenyl group, an optionally substituted C₃₋₁₀ cycloalkyl group, an optionally substituted C₅₋₆ cycloalkenyl group, an optionally substituted C₆₋₁₀ aryl group, an optionally substituted C₇₋₁₄ aralkyl group, an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl group, an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl C₁₋₄ alkyl group or an optionally substituted saturated heterocyclic group (when A is -(CH₂)₂N(R⁴) -, -(CH₂)₂OCON(R⁴) -, -(CH₂)₂CON(R⁴) -, -(CH₂)₂N(R⁴)CON(R⁴) - or -(CH₂)₂SO₂N(R⁴) -, R⁴ and B may be bonded to each other to form a ring), or two of R₃ᵃ, R₃ᵇ, R₃ᶜ and R₃ᵈ are hydrogen atoms, and the other two are bonded to each other to
form a bridged ring together with the hetero ring; R^4 is a hydrogen atom, optionally substituted C_{1-6} alkyl group, an optionally substituted C_{3-10} cycloalkyl group, an optionally substituted C_{6-10} aryl group, an optionally substituted C_{7-14} aralkyl group or an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl group; s is 0, 1 or 2 (when A is -(CH_2)_sN(R^4)-, s is 0 or 2, and when A is -(CH_2)_sCON(R^4)-, s is 1 or 2); and n is 0, 1 or 2, or a salt thereof (see WO2008/093737).

(10) A compound represented by the formula

\[ \text{[0031]} \]

\[ \text{[0032]} \]

wherein R1 is hydrogen, unsubstituted or substituted alkyl!, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocyclyl or unsubstituted or substituted cycloalkyl;

R2 is unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted cycloalkyl, or acyl;

R3 is hydrogen, unsubstituted or substituted aryl or unsubstituted or substituted alkyl;

R4 is unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted cycloalkyl, or acyl;

or R3 and R4 may form together a 3 to 7 membered nitrogen containing saturated hydrocarbon ring which can be
unsubstituted or substituted;
R6 is hydrogen, halo, unsubstituted alkyl or unsubstituted alkoxy;
R7 and R8 are independently of each other hydrogen or halo; and
T is methylene or carbonyl; or a salt thereof (see WO2007/077005).

(11) A compound represented by the formula

![Chemical Structure][1]

[0034]
wherein R1 is hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocyclyl or unsubstituted or substituted cycloalkyl;
R2 is unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted cycloalkyl, or acyl;
R3 is hydrogen, unsubstituted or substituted aryl or unsubstituted or substituted alkyl,
R4 is unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted cycloalkyl, or acyl;
or R3 and R4 may form together a 3 to 7 membered nitrogen containing saturated hydrocarbon ring which can be unsubstituted or substituted; and
T is methylene or carbonyl; or a salt thereof (see
A compound represented by the formula

\[
\text{(12)} \quad \text{wherein}
\]

ing A is a 5- or 6-membered aromatic heterocycle optionally having substituent(s);

U, V and W are each independently C or N, provided that when any one of U, V and W is N, then the others should be C;

R_a and R_b are each independently a cyclic group optionally having substituent(s), a C_{1-10} alkyl group optionally having substituent(s), a C_{2-10} alkenyl group optionally having substituent(s), or a C_{2-10} alkynyl group optionally having substituent(s);

X is a bond, or a spacer having 1 to 6 atoms in the main chain;

Y is a spacer having 1 to 6 atoms in the main chain;

R_c is a hydrocarbon group optionally containing heteroatom(s) as the constituting atom(s), which optionally has substituent(s);

m and n are each independently 1 or 2; and

ring B optionally further has substituent(s), or a salt thereof (see WO2007/094513).

On the other hand, as heterocyclic compounds, the following compounds have been reported.

(13) In WO2007/112227, for example, a compound having the following formula is reported as a CCR4 inhibitor.
(14) In WO2006/101780, for example, a compound having the following formula is reported as a kinesin inhibitor.

(15) In WO2005/047251, for example, a compound having the following formula is reported as a melanocortin receptor agonist.

(16) In WO2005/019206, for example, a compound having the following formula is reported as a kinesin inhibitor.
(17) In WO2005/018547, for example, a compound having the following formula is reported as a kinesin inhibitor.

(18) In WO2004/037171, for example, a compound having the following formula is reported as a kinesin inhibitor.
(19) In WO2003/079973, for example, a compound having the following formula is reported as a kinesin inhibitor.

\[ \text{[0050]} \]

\[
\begin{array}{c}
\text{F} \\
\text{N} \\
\text{Me}
\end{array}
\]

\[
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{NH}
\end{array}
\]

\[
\begin{array}{c}
\text{Ph} \\
\text{(CH2)3-NH2}
\end{array}
\]

(20) In WO2003/037274, for example, a compound having the following formula is reported as a Na\(^+\) channel inhibitor.

\[ \text{[0052]} \]

\[
\begin{array}{c}
\text{Me} \\
\text{O}
\end{array}
\]

\[
\begin{array}{c}
\text{n-Pr}
\end{array}
\]

\[
\begin{array}{c}
\text{Cl}
\end{array}
\]

(21) In WO97/09308, for example, a compound having the following formula is reported as a NPY receptor antagonist.

\[ \text{[0054]} \]

\[
\begin{array}{c}
\text{CH3}
\end{array}
\]

(22) In WO2003/000677, for example, a compound having the following formula is reported as an ORL-1 receptor ligand.

\[ \text{[0056]} \]
However, these reports do not describe a renin inhibitory activity.

5 CITATION LIST

Patent Literature

patent document 1: WO2009/14217
patent document 2: WO2009/05002
patent document 3: WO2009/001915
patent document 4: WO2008/153182
patent document 5: WO2008/153135
patent document 6: WO2008/139941
patent document 7: WO2008/136457
patent document 8: WO2009/051112
patent document 9: WO2008/093737
patent document 10: WO2007/077005
patent document 11: WO2007/006534
patent document 12: WO2007/094513
patent document 14: WO2006/101780
patent document 15: WO2005/047251
patent document 16: WO2005/019206
patent document 17: WO2005/018547
patent document 18: WO2004/037171
patent document 19: WO2003/079973
patent document 20: WO2003/037274
patent document 21: WO97/09308

Non Patent Literature


SUMMARY OF THE INVENTION

[0058]

There is a demand on the development of a compound having a superior renin inhibitory activity, which is useful as a medicament (e.g., agent for the prophylaxis or treatment of hypertension, various organ damages attributable to hypertension, and the like) and a novel renin inhibitor.

[0059]

The present inventors have conducted various studies, and as a result, first succeeded in the creation of novel compounds represented by the following formulas (I) and (II), and a salt thereof, and found that the compound and a salt thereof unexpectedly have a superior renin inhibitory activity, and are useful as medicaments such as renin inhibitor and the like, which resulted in the completion of the present invention.

[0059A]

Various embodiments of the claimed invention relate to a compound represented by the formula (I):
wherein R¹ is a C₁₋₆ alkyl group; R² is (1) a C₁₋₆ alkyl group optionally having 1 to 3 substituents selected from (a) a hydroxy group, (b) a halogen atom, (c) a C₁₋₆ alkoxy group, (d) a C₁₋₆ alkylcarbonyloxy group, (e) an aromatic heterocyclic group optionally having 1 to 3 halogen atoms, (f) a C₃₋₁₀ cycloalkyl group, and (g) a cyclic amino group optionally having an oxo group, (2) a 3- to 10-membered heterocyclic group optionally having 1 to 3 substituents selected from a C₁₋₆ alkyl group and an oxo group, (3) a carboxy group, (4) a C₁₋₆ alkoxy-carbonyl group optionally having 1 to 3 substituents selected from a nonaromatic heterocyclic group optionally having 1 to 3 substituents selected from a C₁₋₆ alkyl group and oxo group, (5) a C₁₋₆ alkyl-carbonyl group, or (6) a group represented by the formula: -CO-NR’R” wherein R’ and R” are each a hydrogen atom, or R’ and R” form, together with the nitrogen atom bonded thereto, a nitrogen-containing heterocycle optionally having 1 to 3 substituents selected from halogen atoms; and X is (1) a hydrogen atom; (2) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from (a) a halogen atom, (b) a hydroxy group, (c) a C₁₋₆ alkoxy group optionally having a C₁₋₆ alkoxy group or a halogen atom, (d) a C₁₋₆ alkylthio group, (e) an aryl group, (f) an aryloxy group optionally having a C₁₋₆ alkoxy group or a halogen atom, and (g) a heteroaryl group; or (3) a C₃₋₁₀ cycloalkyl group, or a salt thereof.
Various embodiments of the claimed invention relate to a compound represented by the formula (II):

\[
\begin{align*}
\text{II}
\end{align*}
\]

wherein \( R^1 \) is a C\(_{1-6}\) alkyl group; \( R^3 \) is a C\(_{1-6}\) alkoxy group optionally substituted by a C\(_{1-6}\) alkoxy group or a halogen atom, a C\(_{1-6}\) alkylthio group, a C\(_{3-10}\) cycloalkyl group optionally substituted by a C\(_{1-6}\) alkyl group, an aryl group or a heteroaryl group optionally substituted by a C\(_{1-6}\) alkyl group; \( X^1 \) is a C\(_{1-6}\) alkylene group; and the group represented by

\[
\begin{align*}
\text{(III)}
\end{align*}
\]

is a group represented by

\[
\begin{align*}
\text{(IV)}
\end{align*}
\]

wherein \( R^4 \) is (1) a hydrogen atom, (2) a cyano (nitrile) group, (3) a C\(_{1-6}\) alkyl group optionally having 1 to 3 substituents selected from (a) a hydroxy group, (b) a C\(_{1-6}\) alkoxy group, (c) a C\(_{1-6}\) alkyl-
carbonyloxy group, (d) an aromatic heterocyclic group optionally having 1 to 3 halogen atoms, (e) a C₃₋₁₀ cycloalkyl group, and (f) a cyclic amino group optionally having an oxo group, (4) a 3- to 10-membered heterocyclic group optionally having 1 to 3 substituents selected from a C₁₋₆ alkyl group and an oxo group, (5) a carboxy group, (6) a C₁₋₆ alkoxy-carbonyl group optionally having 1 to 3 substituents selected from a nonaromatic heterocyclic group optionally having 1 to 3 substituents selected from a C₁₋₆ alkyl group and oxo group or (7) a group represented by the formula: \(-\text{CO-} \text{NR}^R \text{R}''\)

wherein \(\text{R}^R\) and \(\text{R}''\) are each a hydrogen atom, or \(\text{R}^R\) and \(\text{R}''\) form, together with the nitrogen atom bonded thereto, a nitrogen-containing heterocycle optionally having 1 to 3 substituents selected from halogen atom(s), or a salt thereof.

[0059C]

Various embodiments of the claimed invention relate to a compound, wherein the compound is \(\text{N-[(3S,5R)-5-carbamoylpiperidin-3-yl]-1-(4-methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide or a salt thereof.}\)

[0059D]

Various embodiments of the claimed invention relate to a compound, wherein the compound is \(\text{N-[(3S,5R)-5-[1-hydroxyethyl]piperidin-3-yl]-1-(4-methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide or a salt thereof.}\)

[0059E]

Various embodiments of the claimed invention relate to a compound, wherein the compound is \(\text{1-(4-Methoxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonylpiperidin-3-yl)\text{-1H-benzimidazole-2-carboxamide or a salt thereof.}\}

[0059F]

Various embodiments of the claimed invention relate to a compound, wherein the compound is \(\text{1-(4-Hydroxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonylpiperidin-3-yl)\text{-1H-benzimidazole-2-carboxamide or a salt thereof.}\}

[0059F]
1H-benzimidazole-2-carboxamide or a salt thereof.

[0059G]

Various embodiments of the claimed invention relate to a compound, wherein the compound is 1-(4-Methoxybutyl)-N-[[3S,5R]-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-N-propyl-1H-benzimidazole-2-carboxamide or a salt thereof.

[0059H]

Various embodiments of the claimed invention relate to a pharmaceutical composition comprising the compound as described above and a pharmaceutically acceptable carrier.

[0059I]

Various embodiments of the claimed invention relate to use of the compound as described above for the prophylaxis or treatment of a circulatory disease in a mammal.

[0059J]

Various embodiments of the claimed invention relate to use of the compound as described above for the prophylaxis or treatment of hypertension and/or various organ damages attributable to hypertension in a mammal.

[0059K]

Various embodiments of the claimed invention relate to use of the compound as described above for the production of a prophylactic or therapeutic agent for a circulatory disease.

[0059L]

Various embodiments of the claimed invention relate to use of the compound as described above for the production of a prophylactic or therapeutic agent for hypertension and/or various organ damages attributable to hypertension.

[0059M]

Various embodiments of the claimed invention relate to use of the compound as described above for inhibiting renin activity.
[0060]

The present invention relates to [1] a compound represented by the formula (I):

[0061]
[0062]

wherein

R\(^1\) is a hydrogen atom, an alkyl group optionally having substituent(s), an alkenyl group optionally having substituent(s) or a cycloalkyl group optionally having substituent(s);

R\(^2\) is a halogen atom, a hydroxy group, a cyano (nitrile) group, an amino group optionally having substituent(s), a mercapto group optionally having a substituent (the mercapto group is optionally oxidized), an alkyl group optionally having substituent(s) other than a substituted amino group, an alkoxy group optionally having substituent(s), a 3- to 10-membered cyclic hydrocarbon group optionally having substituent(s), a 3- to 10-membered heterocyclic group optionally having substituent(s) or an acyl group (wherein when the acyl group is \(-\text{CONR'}R''\), then R' and R" are both hydrogen atoms or form, together with the nitrogen atom bonded thereto, a nitrogen-containing heterocycle optionally having substituent(s));

X is absent, or a hydrogen atom, an alkyl group optionally substituted by group(s) other than a heterospiro ring optionally having substituent(s) or a cycloalkyl group optionally having substituent(s); and

ring A is a heterocycle optionally having substituent(s), which is other than

[0063]
[0064] wherein ring C is a heterocycle optionally having substituent(s), ring D is a benzene ring optionally having substituent(s), \( R'' \) is a substituted alkyl group or a substituted alkoxy group, \( R''' \) is a substituent, and X is as defined above), or a salt thereof;

[2] a compound represented by the formula (II):

\[
\begin{align*}
\text{wherein} \\
R^1 \text{ is a hydrogen atom, an alkyl group optionally having substituent(s), an alkenyl group optionally having}
\end{align*}
\]
substituent(s) or a cycloalkyl group optionally having substituent(s);

$R^3$ is an alkyl group optionally substituted by group(s) other than a heterospiro ring optionally having substituent(s), an alkenyl group optionally having substituent(s), a cycloalkyl group optionally having substituent(s), an alkylthio group optionally having substituent(s), an alkylsulfinyl group optionally having substituent(s), an alkylsulfonyl group optionally having substituent(s), an alkoxy group optionally having substituent(s), an aryl group optionally having substituent(s) or a heteroaryl group optionally having substituent(s);

$X^1$ is a C$_{1-6}$ alkylene group optionally substituted by group(s) other than a heterospiro ring optionally having substituent(s);

ring $A^1$ is a fused heterocycle optionally having substituent(s);

ring $B$ is a 5- to 7-membered nitrogen-containing heterocycle optionally having substituent(s); and

$n$ is 0, 1 or 2,
or a salt thereof;

[3] a compound represented by the formula (II):

\[ \text{[0065]} \]

\[ \text{(II)} \]

\[ \text{[0066]} \]

wherein

$R^1$ is a hydrogen atom, an alkyl group optionally having
substituent(s), an alkenyl group optionally having 
substituent(s) or a cycloalkyl group optionally having 
substituent(s); 
R³ is an alkyl group optionally substituted by group(s) other 
than a heterospiro ring optionally having substituent(s), an 
alkenyl group optionally having substituent(s), a cycloalkyl 
group optionally having substituent(s), an alkylthio group 
optionally having substituent(s), an alkylsulfinyl group 
optionally having substituent(s), an alkylsulfonyl group 
optionally having substituent(s), an alkoxy group optionally 
having substituent(s), an aryl group optionally having 
substituent(s) or a heteroaryl group optionally having 
substituent(s); 
X¹ is a C₁₋₆ alkylene group optionally substituted by group(s) 
other than a heterospiro ring optionally having 
substituent(s); 
ring A¹ is a fused heterocycle optionally having 
substituent(s); 
ring B is a 5- to 7-membered nitrogen-containing heterocycle 
optionally having substituent(s); and 
n is 0, 1 or 2, provided that ring A¹ is other than 
[0067]
[0068]

wherein ring C is a heterocycle optionally having substituent(s), ring D is a benzene ring optionally having substituent(s), R\(^{''}\) is a substituted alkyl group or a substituted alkoxy group, R\(^{'''}\) is a substituent, and other symbols are as defined above, or a salt thereof;

[4] a compound represented by the formula (II):

[0069]
[0070]

wherein

R\(^1\) is a hydrogen atom, an alkyl group optionally having substituent(s), an alkenyl group optionally having substituent(s) or a cycloalkyl group optionally having substituent(s);

R\(^3\) is an alkyl group optionally substituted by group(s) other than a heterospiro ring optionally having substituent(s), an alkenyl group optionally having substituent(s), a cycloalkyl group optionally having substituent(s), an alkylthio group optionally having substituent(s), an alkylsulfinyl group optionally having substituent(s), an alkylsulfonyl group optionally having substituent(s), an alkoxy group optionally having substituent(s), an aryl group optionally having substituent(s) or a heteroaryl group optionally having substituent(s);

X\(^1\) is a C\(_{1-6}\) alkylene group optionally substituted by group(s) other than a heterospiro ring optionally having substituent(s);

ring A\(^1\) is a fused heterocycle optionally having substituent(s);

ring B is a 5- to 7-membered nitrogen-containing heterocycle optionally substituted by substituent(s) selected from a halogen atom, a hydroxy group, a cyano (nitrile) group, an amino group optionally having substituent(s), a mercapto group optionally having a substituent (the mercapto group is
optionally oxidized), an alkyl group optionally having substituent(s) other than a substituted amino group, an alkoxy group optionally having substituent(s), a 3- to 10-membered cyclic hydrocarbon group optionally having substituent(s), a 3- to 10-membered heterocyclic group optionally having substituent(s), and an acyl group (wherein when the acyl group is -CONR'R", then R' and R" are both hydrogen atoms or form, together with the nitrogen atom bonded thereto, a nitrogen-containing heterocycle optionally having substituent(s)); and

n is 0, 1 or 2,
or a salt thereof;

[5] a compound represented by the formula (II):

\[
\begin{array}{c}
\text{A}^1 \\
\text{X}^1 \text{R}^3 \\
\text{R}^1 \\
\text{N} \\
\text{R}^2 \\
\text{B} \\
\text{R}^3 \\
\text{N} \text{H} \\
\end{array}
\]

(II)

\[
\begin{array}{c}
R^1 \text{ is a hydrogen atom, an alkyl group optionally having substituent(s), an alkenyl group optionally having substituent(s) or a cycloalkyl group optionally having substituent(s);} \\
R^2 \text{ is an alkyl group optionally substituted by group(s) other than a heterospiro ring optionally having substituent(s), an alkenyl group optionally having substituent(s), a cycloalkyl group optionally having substituent(s), an alkylthio group optionally having substituent(s), an alkylsulfinyl group optionally having substituent(s), an alkylsulfonyl group optionally having substituent(s), an alkoxy group optionally having substituent(s), an aryl group optionally having substituent(s), an aryloxy group optionally having substituent(s), a heterocyclic group optionally having substituent(s), and a salt thereof};
\end{array}
\]
substituent(s) or a heteroaryl group optionally having substituent(s);
X<sup>1</sup> is a C<sub>1-6</sub> alkylene group optionally substituted by group(s) other than a hetero.spiro ring optionally having substituent(s);
ring A<sup>1</sup> is a fused heterocycle optionally having substituent(s);
ring B is a 5- to 7-membered nitrogen-containing heterocycle optionally substituted by substituent(s) selected from a halogen atom, a hydroxy group, a cyano (nitrile) group, an amino group optionally having substituent(s), a mercapto group optionally having a substituent (the mercapto group is optionally oxidized), an alkyl group optionally having substituent(s) other than a substituted amino group, an alkoxy group optionally having substituent(s), a 3- to 10-membered cyclic hydrocarbon group optionally having substituent(s), a 3- to 10-membered heterocyclic group optionally having substituent(s), and an acyl group (wherein when the acyl group is -CONR'<R'', then R' and R'' are both hydrogen atoms or form, together with the nitrogen atom bonded thereto, a nitrogen-containing heterocycle optionally having substituent(s)); and n is 0, 1 or 2, provided ring A<sup>1</sup> is other than
[0074]
wherein ring C is a heterocycle optionally having substituent(s), ring D is a benzene ring optionally having substituent(s), R'' is a substituted alkyl group or a substituted alkoxy group, R''' is a substituent, and other symbols are as defined above, or a salt thereof;
[6] the compound of any of the above-mentioned [1] to [5], wherein ring A and ring A₁ are each a ring represented by the formula

[0075]
wherein
\(R^a\) and \(R^b\) are each independently a hydrogen atom, a halogen atom, an alkyl group optionally having substituent(s), an alkoxy group optionally having substituent(s) or an acyl group;
\(R^c\) is a hydrogen atom, a halogen atom, \(=O, =S\), an alkyl group optionally having substituent(s), an alkoxy group optionally having substituent(s) or an acyl group;
\(Y^1\) and \(Y^2\) are each independently \(\text{CH or N}\); and
\(Z\) is \(\text{CH}_2, \text{NH, O or S}\);

[7] the compound of any of the above-mentioned [1] to [5], wherein ring A and ring \(A^2\) are each a ring represented by the formula

[0077]

[0078]

wherein
\(R^a\) and \(R^b\) are each a hydrogen atom;
\(R^c\) is a hydrogen atom, a halogen atom, \(=O, =S\), an alkyl group optionally having substituent(s), an alkoxy group optionally having substituent(s) or an acyl group;
\(Y^1\) and \(Y^2\) are each independently \(\text{CH or N}\); and
\(Z\) is \(\text{CH}_2, \text{NH, O or S}\);

[8] the compound of any of the above-mentioned [1] to [5], wherein ring A or ring \(A^2\) is a ring represented by the formula

[0079]
[0080]
wherein Y¹, Y², Rª and Rª are as defined in the above-mentioned [7];

[0081]

[0082]
wherein ring A or ring A¹ is a ring represented by the formula

[0083]

[0084]

[0084]
wherein Rª is a hydrogen atom, a halogen atom, a hydroxy group, a cyano (nitrile) group, an amino group optionally having substituent(s), a mercapto group optionally having a substituent (the mercapto group is optionally oxidized), an alkyl group optionally having substituent(s) other than a substituted amino group, an alkoxy group optionally having substituent(s), a 3- to 10-membered cyclic hydrocarbon group
optionally having substituent(s), a 3- to 10-membered heterocyclic group optionally having substituent(s) or an acyl group (wherein when the acyl group is \( \text{CONR}^\prime R^\prime \), then \( R^\prime \) and \( R^\prime \) are both hydrogen atoms or form, together with the nitrogen atom bonded thereto, a nitrogen-containing heterocycle optionally having substituent(s));

[11] the compound of any of the above-mentioned [2] to [5], wherein ring B is a ring represented by the formula

\[
\text{[0085]}
\]

\[
\text{[0086]}
\]

wherein \( R^4 \) is

(1) a hydrogen atom,

(2) a cyano (nitrile) group,

(3) a \( C_{1-6} \) alkyl group optionally having 1 to 3 substituents selected from

(a) a hydroxy group,

(b) a \( C_{1-6} \) alkoxy group,

(c) a \( C_{1-6} \) alkyl-carbonyloxy group,

(d) an aromatic heterocyclic group optionally having 1 to 3 halogen atoms,

(e) a \( C_{3-10} \) cycloalkyl group, and

(f) a cyclic amino group optionally having an oxo group,

(4) a 3- to 10-membered heterocyclic group optionally having 1 to 3 substituents selected from a \( C_{1-6} \) alkyl group and an oxo group,

(5) a carboxy group,

(6) a \( C_{1-6} \) alkoxy-carbonyl group optionally having 1 to 3 substituents selected from a nonaromatic heterocyclic group optionally having 1 to 3 substituents selected from a \( C_{1-6} \) alkyl group and an oxo group or

(7) a group represented by the formula: \(-\text{CO-NR}^\prime R^\prime\)
wherein R' and R" are each a hydrogen atom, or R' and R" form, together with the nitrogen atom bonded thereto, a nitrogen-containing heterocycle optionally having 1 to 3 substituents selected from halogen atom(s);

[12] the compound of any of the above-mentioned [2] to [5], wherein ring B is a ring represented by

![Chemical Structure]

[0087]

wherein R^4 is

1. a cyano (nitrile) group,
2. a C_{1-6} alkyl group optionally having 1 to 3 substituents selected from
   a. a hydroxy group,
   b. a C_{1-6} alkoxy group,
   c. a C_{1-6} alkyl-carbonyloxy group,
   d. an aromatic heterocyclic group optionally having 1 to 3 halogen atoms,
   e. a C_{3-10} cycloalkyl group, and
   f. a cyclic amino group optionally having an oxo group,
3. a 3- to 10-membered heterocyclic group optionally having 1 to 3 substituents selected from a C_{1-6} alkyl group and an oxo group,
4. a carboxy group,
5. a C_{1-6} alkoxy-carbonyl group optionally having 1 to 3 substituents selected from a nonaromatic heterocyclic group optionally having 1 to 3 substituents selected from a C_{1-6} alkyl group and an oxo group or
6. a group represented by the formula: \(-\text{CO-NR}^R \text{R}^"\) wherein R' and R" are each a hydrogen atom, or R' and R" form, together with the nitrogen atom bonded thereto, a nitrogen-containing heterocycle optionally having 1 to 3
substituents selected from halogen atom(s);
wherein ring B is a ring represented by

\[
\text{HN} - \text{R}^4
\]

[0090]

wherein \( R^4 \) is \(-\text{CO-NR}^2\text{R}^2\) wherein \( R^1 \) and \( R^2 \) are each a hydrogen atom, or \( R^1 \) and \( R^2 \) form, together with the nitrogen atom bonded thereto, a nitrogen-containing heterocycle optionally having 1 to 3 substituents selected from halogen atom(s);
[14] the compound of any of the above-mentioned [1] to [5],
wherein \( R^2 \) is a \( \text{C}_1-\text{C}_6 \) alkyl group optionally having substituent(s);
[15] the compound of the above-mentioned [1], wherein \( R^2 \) is an acyl group (wherein when the acyl group is \(-\text{CONR}^2\text{R}^2\), then \( R^1 \) and \( R^2 \) are both hydrogen atoms or form, together with the nitrogen atom bonded thereto, a nitrogen-containing heterocycle optionally having substituent(s));
[16] the compound of the above-mentioned [1], wherein \( X \) is a \( \text{C}_1-\text{C}_6 \) alkyl group optionally substituted by a \( \text{C}_1-\text{C}_6 \) alkoxy group;
[17] the compound of any of the above-mentioned [2] to [5],
wherein \( X^1 \) is a \( \text{C}_1-\text{C}_6 \) alkenylene group optionally substituted by group(s) other than a heterospiro ring optionally having substituent(s) and an oxo group;
[18] the compound of any of the above-mentioned [2] to [5],
wherein \( X^1 \) is a \( \text{C}_1-\text{C}_6 \) alkenylene group;
[19] the compound of any of the above-mentioned [2] to [5],
wherein \( R^3 \) is a \( \text{C}_1-\text{C}_6 \) alkoxy group optionally having substituent(s);
[20] the compound of the above-mentioned [1], wherein \( R^3 \) is a \( \text{C}_1-\text{C}_6 \) alkyl group optionally having substituent(s), \( R^2 \) is an acyl
group (wherein when the acyl group is \(-\text{CONR}'\text{R}''\), then \(\text{R}'\) and \(\text{R}''\) are both hydrogen atoms or form, together with the nitrogen atom bonded thereto, a nitrogen-containing heterocycle optionally having substituent(s)),

\[
\text{ring A is a ring represented by the formula}
\]

[0091]

\[
\text{wherein } Y^1, Y^2, R^a \text{ and } R^b \text{ are as defined in the above-mentioned [7], and}
\]

\(X \text{ is a C}_{1-6} \text{ alkyl group optionally substituted by a C}_{1-6} \text{ alkoxy group;}
\]

[21] the compound of any of the above-mentioned [2] to [5], wherein \(R^1\) is a C_{1-6} alkyl group optionally having substituent(s),

\(R^3\) is a C_{1-6} alkoxy group optionally having substituent(s),

\(\text{ring A}^1\) is a ring represented by the formula

[0093]

[0094]

\[
\text{wherein } Y^1, Y^2, R^a \text{ and } R^b \text{ are as defined in the above-mentioned [7],}
\]

\(X^1\) is a C_{1-6} alkylene group, and

\(\text{ring B}\) is a ring represented by the formula

[0095]
[0096] wherein R₄ is -CO-NR'R'' wherein R' and R'' are each a hydrogen atom, or R' and R'' form, together with the nitrogen atom bonded thereto, a nitrogen-containing heterocycle optionally having 1 to 3 substituents selected from halogen atom(s);

[22] N-{[3S,5R]-5-carbamoylpiperidin-3-yl}-1-(4-methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide or a salt thereof;

[23] N-{[3S,5R]-5-[1-hydroxyethyl]piperidin-5-yl}-1-(4-methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide or a salt thereof;

[24] 1-(4-methoxybutyl)-N-(2-methylpropyl)-N-{[3S,5R]-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide or a salt thereof;

[25] 1-(4-hydroxybutyl)-N-(2-methylpropyl)-N-{[3S,5R]-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide or a salt thereof;

[26] 1-(2-fluorophenyl)-5-(4-methoxybutyl)-N-(2-methylpropyl)-N-{[3S,5R]-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-1,2,3-triazole-4-carboxamide or a salt thereof;

[27] 1-(4-methoxybutyl)-N-{[3S,5R]-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-N-propyl-1H-benzimidazole-2-carboxamide or a salt thereof;

[28] a prodrug of the compound of any of the above-mentioned [1] to [5];

[29] a medicament comprising the compound of any of the above-mentioned [1] to [5], or a prodrug thereof as an active ingredient;

[30] the medicament of the above-mentioned [29], which is a renin inhibitor;

[31] the medicament of the above-mentioned [29], which is a
prophylactic or therapeutic agent of a circulatory disease;
[32] the medicament of the above-mentioned [29], which is a
prophylactic or therapeutic agent of hypertension and/or
various organ damages attributable to hypertension;
[33] a method for the prophylaxis or treatment of a
circulatory disease in a mammal comprising administering the
compound of any of the above-mentioned [1] to [5] or a prodrug
thereof to the mammal;
[34] a method for the prophylaxis or treatment of hypertension
and/or various organ damages attributable to hypertension in a
mammal comprising administering the compound of any of the
above-mentioned [1] to [5] or a prodrug thereof to the mammal;
[35] use of the compound of any of the above-mentioned [1] to
[5] or a prodrug thereof for the production of a prophylactic
or therapeutic agent for a circulatory disease;
[36] use of the compound of any of the above-mentioned [1] to
[5] or a prodrug thereof for the production of a prophylactic
or therapeutic agent for hypertension and/or various organ
damages attributable to hypertension, and the like.

[0097]

Compound (I) has a superior renin inhibitory activity,
and thus it is useful as an agent for the prophylaxis or
treatment of hypertension, various organ damages attributable
to hypertension, and the like.

DETAILED DESCRIPTION OF THE INVENTION

[0098]

Examples of the "halogen atom" in the present
specification include fluorine, chlorine, bromine and iodine.

Examples of the "C_1-4 alkylenedioxy group" in the present
specification include methylenedioxy, ethylenedioxy,
trimethylenedioxy and the like.

[0099]

Examples of the "alkyl group" in the present
specification include methyl, ethyl, propyl, isopropyl, butyl,
isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl,
1-ethylpropyl, hexyl, isoheptyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl and the like. Among these, a C_{1-6} alkyl group is preferable.

Examples of the “alkenyl group” in the present specification include ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-buteny1, 2-buteny1, 3-buteny1, 3-methyl-2-buteny1, 1-penteny1, 2-penteny1, 3-penteny1, 4-penteny1, 4-methyl-3-penteny1, 1-hexeny1, 3-hexeny1, 5-hexeny1 and the like. Among these, a C_{2-6} alkenyl group is preferable.

Examples of the “alkynyl group” in the present specification include ethyny1, 1-propyny1, 2-propyny1, 1-butyny1, 2-butyny1, 3-butyny1, 1-penty1, 2-penty1, 3-pentyny1, 4-pentyny1, 1-hexyny1, 2-hexyny1, 3-hexyny1, 4-hexyny1, 5-hexyny1, 1-hepty1, 1-octyny1 and the like. Among these, a C_{2-6} alkynyl group is preferable.

Examples of the “cycloalkyl group” in the present specification include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohepty1, cyclooctyl, bicyclo[2.2.1]hepty1, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl, bicyclo[4.3.1]decyl, adamantyl and the like. Among these, a C_{3-10} cycloalkyl group is preferable.

Examples of the “alkythio group” in the present specification include methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio, pentylthio, isopenty1, neopenty1, 1-ethy1propylthio, hexylthio, isoheptylthio, 1,1-dimethylbutylthio, 2,2-dimethylbutylthio, 3,3-dimethylbutylthio, 2-ethylbutylthio and the like. Among these, a C_{1-6} alky1thio group is preferable.
Examples of the “alkylsulfinyl group” in the present specification include methylsulfinyl, ethylsulfinyl, propylsulfinyl, isopropylsulfinyl, butylsulfinyl, isobutylsulfinyl, sec-butylsulfinyl, tert-butylsulfinyl, pentylsulfinyl, isopentylsulfinyl, neopen tylsulfinyl, 1-ethylpropylsulfinyl, hexylsulfinyl, isohexylsulfinyl, 1,1-dimethylbutylsulfinyl, 2,2-dimethylbutylsulfinyl, 3,3-dimethylbutylsulfinyl, 2-ethylbutylsulfinyl and the like. Among these, a C\textsubscript{1-6} alkylsulfinyl group is preferable.

Examples of the “alkylsulfonyl group” in the present specification include methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, isobutylsulfonyl, sec-butylsulfonyl, tert-butylsulfonyl, pentylsulfonyl, isopenty lsulfonyl, neopenty lsulfonyl, 1-ethylpropylsulfonyl, hexylsulfonyl, isohexylsulfonyl, 1,1-dimethylbutylsulfonyl, 2,2-dimethylbutylsulfonyl, 3,3-dimethylbutylsulfonyl, 2-ethylbutylsulfonyl and the like. Among these, a C\textsubscript{1-6} alkylsulfonyl group is preferable.

Examples of the “alkoxy group” in the present specification include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, isopentyloxy, neopen tyloxy, 1-ethylpropelyoxy, hexyloxy, isohexyloxy, 1,1-dimethylbutyloxy, 2,2-dimethylbutyloxy, 3,3-dimethylbutyloxy, 2-ethylbutyloxy and the like. Among these, a C\textsubscript{1-6} alkoxy group is preferable.

Examples of the “C\textsubscript{1-6} alkoxy-carbonyl group” in the present specification include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl and the like.

Examples of the “C\textsubscript{1-6} alkyl-carbonyl group” in the present specification include acetyl, propanoyl, butanoyl, isobutanoyl, pentanoyl, isopentanoyl, hexanoyl and the like.

The “optionally halogenated” in the present specification
means being optionally substituted by 1 to 5, preferably 1 to 3, halogen atoms.

[0108]
Examples of the “C₁₋₆ alkylene group” in the present specification include methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, -CH(CH₃)₂⁻, -C(CH₃)₂⁻, -CH(CH₂CH₃)₂⁻, -C(CH₂CH₃)₂⁻, -CH(CH₃)₂⁻CH₂⁻, -CH₂(C(CH₃)₂)₂⁻, -CH(CH₃)₂⁻CH₂⁻, -CH₂-C(CH₃)₂⁻, -CH₂(CH(CH₃)₂)₂⁻, -CH₂-C(CH₃)₂⁻CH₂⁻, -C(CH₃)₂⁻CH₂⁻, -C(CH₃)₂⁻CH₂⁻, -CH₂-C(CH₃)₂⁻CH₂⁻, -C(CH₃)₂⁻ and the like.

[0109]
Examples of the “hydrocarbon group” of the “hydrocarbon group optionally having substituent(s)” in the present specification include alkyl group, alkenyl group, alkynyl group, alkylidene group, cycloalkyl group, cycloalkenyl group, cycloalkadienyl group, aryl group, aralkyl group, arylalkenyl group, cycloalkylalkyl group and the like. Preferably, C₁₋₁₀ alkyl group, C₂₋₁₀ alkenyl group, C₂₋₁₀ alkynyl group, C₁₋₃ alkylidene group, C₃₋₁₀ cycloalkyl group, C₃₋₁₀ cycloalkenyl group, C₄₋₁₀ cycloalkadienyl group, C₆₋₁₄ aryl group, C₇₋₁₆ aralkyl group, C₈₋₁₃ arylalkenyl group, C₃₋₁₀ cycloalkyl-C₁₋₆ alkyl group and the like. The above-mentioned C₃₋₁₀ cycloalkyl group, C₃₋₁₀ cycloalkenyl group and C₄₋₁₀ cycloalkadienyl group may be each condensed with a benzene ring.

[0110]
Examples of the “C₁₋₁₀ alkyl group” in the present specification include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, heptyl, octyl, nonyl, decyl and the like. Among these, a C₁₋₆ alkyl group is preferable.

[0111]
Examples of the “C₂₋₁₀ alkenyl group” in the present specification include ethenyl, 1-propenyl, 2-propenyl, 2-
methyl-1-propenyl, 1-buteny1, 2-buteny1, 3-buteny1, 3-methyl-2-buteny1, 1-penteny1, 2-penteny1, 3-penteny1, 4-penteny1, 4-methyl-3-penteny1, 1-hexeny1, 3-hexeny1, 5-hexeny1, 1-heptyny1, 1-octeny1 and the like. Among these, a C_{2-6} alkenyl group is preferable.

[0112] Examples of the “C_{2-10} alkynyl group” in the present specification include ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-penty1, 2-penty1, 3-penty1, 4-penty1, 1-hexyny1, 2-hexyny1, 3-hexyny1, 4-hexyny1, 5-hexyny1, 1-heptyny1, 1-octeny1 and the like. Among these, a C_{2-6} alkynyl group is preferable.

Examples of the “C_{1-3} alkylidene group” in the present specification include methylidene, ethylidene, propylidene, isopropylidene and the like.

[0113] Examples of the “C_{3-10} cycloalkyl group” in the present specification include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohepty1, cyclooctyl, bicyclo[2.2.1]hepty1, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nony1, bicyclo[3.3.1]nony1, bicyclo[4.2.1]nony1, bicyclo[4.3.1]decyl, adamantyl and the like. Among these, a C_{3-6} cycloalkyl group is preferable. The above-mentioned C_{3-10} cycloalkyl may be condensed with a benzene ring, and examples of the fused group include indany1, tetrahydronaphthyl, fluoreny1 and the like.

[0114] Examples of the “C_{3-10} cycloalkenyl group” in the present specification include 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl, 3-cyclohexen-1-yl and the like. The above-mentioned C_{3-10} cycloalkenyl may be condensed with a benzene ring, and examples of the fused group include indeny1 and the like.

[0115] Examples of the “C_{4-10} cycloalkadienyl group” in the present specification include 2,4-cyclopentadien-1-yl, 2,4-
cyclohexadien-1-yl, 2,5-cyclohexadien-1-yl and the like. The above-mentioned C<sub>4-10</sub> cycloalkadienyl may be condensed with a benzene ring.

[0116]

Examples of the "C<sub>6-14</sub> aryl group" in the present specification include phenyl, 1-naphthyl, 2-naphthyl, biphenylyl, 2-anthryl and the like. Among these, a C<sub>6-10</sub> aryl group is preferable, and phenyl is more preferable. The above-mentioned C<sub>6-14</sub> aryl may be condensed with C<sub>3-10</sub> cycloalkane (examples of the C<sub>3-10</sub> cycloalkane include a ring corresponding to the above-mentioned C<sub>3-10</sub> cycloalkyl group), and examples of the fused group include tetrahydronaphthyl, indanyl and the like.

Examples of the "C<sub>7-16</sub> aralkyl group" in the present specification include benzyl, phenethyl, naphthylmethyl, biphenylylmethyl and the like.

Examples of the "C<sub>8-13</sub> arylalkenyl group" in the present specification include styryl and the like.

Examples of the "C<sub>3-10</sub> cycloalkyl-C<sub>1-6</sub> alkyl group" in the present specification include cyclopropylmethyl, cyclohexylmethyl and the like.

[0117]

The "hydrocarbon group" of the "hydrocarbon group optionally having substituent(s)" optionally has substituent(s) (e.g., 1 to 5, preferably 1 to 3 substituents) at substitutable position(s). When the number of the substituents is two or more, respective substituents may be the same or different.

[0118]

Examples of the "substituent" of the "hydrocarbon group optionally having substituent(s)" include the following substituents (hereinafter to be referred to as substituent group A).

(1) a halogen atom;
(2) a nitro group;
(3) a cyano (nitrile) group;
(4) a hydroxy group;
(5) an alkoxy group optionally having substituent(s);
(6) an amino group optionally having substituent(s);
(7) =O (oxo group);
(8) =S (thioxO group);
(9) a mercapto group optionally having a substituent (the mercapto group is optionally oxidized);
(10) a C1-4 alkylthio group;
(11) an alkyl group optionally having substituent(s);
(12) a C7-16 aralkyl group;
(13) an acyl group;
(14) a 3- to 10-membered cyclic hydrocarbon group optionally having substituent(s);
(15) a 3- to 10-membered heterocyclic group optionally having substituent(s) and the like.

Examples of the “3- to 10-membered cyclic hydrocarbon group” of the “3- to 10-membered cyclic hydrocarbon group optionally having substituent(s)” for substituent group A include C3-10 cycloalkyl group, C3-10 cycloalkenyl group, C4-10 cycloalkadienyl group, C6-10 aryl group and the like. Examples of the C3-10 cycloalkyl group, C3-10 cycloalkenyl group, C4-10 cycloalkadienyl group and C6-10 aryl group include those similar to the C3-10 cycloalkyl group, C3-10 cycloalkenyl group, C4-10 cycloalkadienyl group and C6-10 aryl group exemplified as the “hydrocarbon group” of the “hydrocarbon group optionally having substituent(s)”.

Examples of the “3- to 10-membered heterocyclic group” of the “3- to 10-membered heterocyclic group optionally having substituent(s)” for substituent group A include a 3- to 10-membered ring from the “heterocyclic group” of the “heterocyclic group optionally having substituent(s)” to be mentioned later.
Examples of the "substituent" of the "C_{1-6} alkyl group optionally having substituent(s)" and "C_{1-6} alkoxy group optionally having substituent(s)", "3- to 10-membered cyclic hydrocarbon group optionally having substituent(s)" and "3- to 10-membered heterocyclic group optionally having substituent(s)" for substituent group A include 1 to 5, preferably 1 to 3 selected from the following substituents (hereinafter to be referred to as substituent group B). When the number of the substituents is two or more, the respective substituents may be the same or different.

(1) a halogen atom;
(2) a nitro group;
(3) a cyano (nitrile) group;
(4) a hydroxy group;
(5) a C_{1-6} alkoxy group optionally having 1 to 3 halogen atoms;
(6) an amino group;
(7) a mono- or di-C_{1-6} alkylamino group;
(8) a C_{7-16} aralkylamino group;
(9) a C_{1-6} alkoxy-carbonylamino group;
(10) a C_{1-6} alkyl-carbonylamino group;
(11) a C_{1-6} alkyl-carbonyloxy group;
(12) a C_{1-6} alkyl-carbonyl group;
(13) a carboxy group;
(14) a C_{1-6} alkoxy-carbonyl group;
(15) a carbamoyl group;
(16) a mono- or di-C_{1-6} alkylcarbamoyl group;
(17) =O (oxo group);
(18) =S (thioxo group);
(19) a mercapto group;
(20) a C_{1-6} alkylthio group;
(21) a C_{1-6} alkylsulfinyl group;
(22) a C_{1-6} alkylsulfonyl group;
(23) a C_{1-4} alkylenedioxy group;
(24) a C₁₋₆ alkyl group optionally having 1 to 3 substituents selected from
   (a) a halogen atom,
   (b) a hydroxy group,
   (c) a C₁₋₆ alkoxy group,
   (d) a C₆₋₁₄ aryl group,
   (e) an amino group,
   (f) a mono- or di-C₁₋₆ alkylamino group,
   (g) a C₇₋₁₆ aralkylamino group, and
   (h) a C₁₋₆ alkoxy-carbonylamino group;
(25) an aryl group optionally having 1 to 3 halogen atoms;
(26) an aromatic heterocyclic group (e.g., pyridyl, pyrazolyl, triazolyl) optionally having 1 to 3 halogen atoms;
(27) a nonaromatic heterocyclic group (e.g., dioxolyl)
   optionally having 1 to 3 substituents selected from a C₁₋₆ alkyl group and an oxo group;
(28) a C₇₋₁₆ aralkyl group;
(29) a C₃₋₁₀ cycloalkyl group;
(30) a cyclic amino group (e.g., pyrrolidinyl, piperidino, morpholino, thiomorpholino, piperazinyl, imidazolidin-1-yl, pyrazolidin-1-yl etc.) optionally having an oxo group and the like.

[0123]

Examples of the "substituent" of the "amino group optionally having substituent(s)" for substituent group A include 1 or 2 selected from substituent group B. When the number of the substituents is two, the respective substituents may be the same or different.

Examples of the "substituent" of the "mercapto group optionally having a substituent" for substituent group A include substituent group B. The mercapto group may be oxidized by 1 or 2 oxygens.

[0124]

Examples of the "heterocyclic group" of the "heterocyclic group optionally having substituent(s)" in the present
specification include an aromatic heterocyclic group and a nonaromatic heterocyclic group.

Examples of the "aromatic heterocyclic group" include a 4- to 10-membered (preferably 5- or 6-membered) monocyclic aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atoms, 1 to 4 heteroatoms selected from an oxygen atom, a sulfur atom and a nitrogen atom, and a fused aromatic heterocyclic group. Examples of the fused aromatic heterocyclic group include a group derived from a fused ring wherein a ring corresponding to such 4- to 10-membered monocyclic aromatic heterocyclic group, and 1 or 2 rings selected from a 5- or 6-membered aromatic heterocycle containing 1 or 2 nitrogen atoms, a 5-membered aromatic heterocycle containing one sulfur atom and a benzene ring are condensed, and the like.

[0125]

Examples of the "aromatic heterocyclic group" include 4- to 7-membered (preferably 5- or 6-membered) monocyclic aromatic heterocyclic groups such as furyl (e.g., 2-furyl, 3-furyl), thiienyl (e.g., 2-thiienyl, 3-thiienyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl), pyrazinyl (e.g., 3-pyrazinyl, 4-pyrazinyl), pyrazinyl (e.g., 2-pyrazinyl), pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), imidazolyl (e.g., 1-imidazolyl, 2-imidazolyl, 3-imidazolyl, 5-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), isothiazolyl (e.g., 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl, 5-oxazolyl), isoxazolyl (e.g., 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), oxadiazolyl (e.g., 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl), thiadiazolyl (e.g., 1,2,4-thiadiazol-5-yl, 1,3,4-thiadiazol-2-yl), triazolyl (e.g., 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-4-yl), tetrazolyl (e.g., tetrazol-1-yl,
tetrazol-5-yl), triazinyl (e.g., 1,3,5-triazin-2-yl, 1,3,5-triazin-4-yl, 1,2,3-triazin-4-yl, 1,2,4-triazin-3-yl) and the like;
fused aromatic heterocyclic groups such as quinolyl (e.g., 2-quinolyl, 3-quinolyl, 4-quinolyl, 6-quinolyl), isoquinolyl
(e.g., 3-isoquinolyl), quinazolyl (e.g., 2-quinazolyl, 4-quinazolyl), quinoxalyl (e.g., 2-quinoxalyl, 6-quinoxalyl),
benzofuranyl (e.g., 2-benzofuranyl, 3-benzofuranyl),
benzothienyl (e.g., 2-benzothienyl, 3-benzothienyl),
benzoxazolyl (e.g., 2-benzoxazolyl), benzisoxazolyl (e.g., 7-benzisoxazolyl), benzothiazolyl (e.g., 2-benzothiazolyl),
benzimidazolyl (e.g., benzimidazol-1-yl, benzimidazol-2-yl, benzimidazol-5-yl), benzotriazolyl (e.g., 1H-1,2,3-benzotriazol-5-yl), indolyl (e.g., indol-1-yl, indol-2-yl, indol-3-yl, indol-5-yl), indazolyl (e.g., 1H-indazol-3-yl),
pyrrolopyrazinyl (e.g., 1H-pyrrolo[2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-b]pyrazin-6-yl), imidazopyridyl (e.g., 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, 2H-imidazo[1,2-a]pyridin-3-yl), imidazopyrazinyl (e.g., 1H-imidazo[4,5-b]pyrazin-2-yl), pyrazolopyridyl (e.g., 1H-pyrazolo[4,3-c]pyridin-3-yl), pyrazolothienyl (e.g., 2H-pyrazolo[3,4-b]thiophen-2-yl), pyrazolotriazinyl (e.g., pyrazolo[5,1-c][1,2,4]triazin-3-yl) and the like;
and the like.

[0126]
Examples of the “non-aromatic heterocyclic group” include a 3- to 10-membered (preferably 5- or 6-membered) monocyclic non-aromatic heterocyclic group containing, as a ring-
constituting atom besides carbon atoms, 1 to 4 heteroatoms
selected from an oxygen atom, a sulfur atom and a nitrogen atom, and a fused non-aromatic heterocyclic group. Examples of the fused non-aromatic heterocyclic group include a group derived from a fused ring wherein a ring corresponding to such 3- to 10-membered monocyclic non-aromatic heterocyclic group,
and 1 or 2 rings selected from a 5- or 6-membered heterocycle.
containing 1 or 2 nitrogen atoms, a 5-membered heterocycle containing one sulfur atom and a benzene ring are condensed, and the like.

Examples of the “non-aromatic heterocyclic group” include 4- to 7-membered (preferably 5- or 6-membered) monocyclic non-aromatic heterocyclic groups such as pyrrolidinyl (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl), piperidinyl (e.g., piperidino, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl), morpholinyl (e.g., morpholino), thiomorpholinyl (e.g., thiomorpholino), piperazinyl (e.g., 1-piperazinyl, 2-piperazinyl, 3-piperazinyl), hexamethyleniminyln (e.g., hexamethylenimin-1-yl), oxazolidinyl (e.g., oxazolidin-2-yl), thiazolidinyl (e.g., thiazolidin-2-yl), imidazolidinyl (e.g., imidazolidin-2-yl, imidazolidin-3-yl), oxazolinyl (e.g., oxazolin-2-yl), thiazolinyl (e.g., thiazolin-2-yl), imidazolinyl (e.g., imidazolin-2-yl, imidazolin-3-yl), dioxolyl (e.g., 1,3-dioxol-4-yl), dioxolanyl (e.g., 1,3-dioxolan-4-yl), dihydrooxadiazolyl (e.g., 4,5-dihydro-1,2,4-oxadiazol-3-yl), 2-thioxo-1,3-oxazolidin-5-yl, pyranyl (e.g., 4-pyranyl), tetrahydropyranyl (e.g., 2-tetrahydropyranyl, 3-tetrahydropyranyl, 4-tetrahydropyranyl), thiopyranyl (e.g., 4-thiopyranyl), tetrahydrothiopyranyl (e.g., 2-tetrahydrothiopyranyl, 3-tetrahydrothiopyranyl, 4-tetrahydrothiopyranyl), 1-oxidotetrahydrothiopyranyl (e.g., 1-oxidotetrahydrothiopyranyl-4-yl), 1,1-dioxidotetrahydrothiopyranyl (e.g., 1,1-dioxidotetrahydrothiopyranyl-4-yl), tetrahydrofuranyl (e.g., tetrahydrofuran-3-yl, tetrahydrofuran-2-yl), pyrazolidinyl (e.g., pyrazolidin-1-yl, pyrazolidin-3-yl), pyrazolinyl (e.g., pyrazolin-1-yl), tetrahydroprimidinyl (e.g., tetrahydroprimidin-1-yl), hexahydroprimidinyl (e.g., hexahydroprimidin-1-yl), dihydrotriazolyl (e.g., 2,3-dihydro-1H-1,2,3-triazol-1-yl), tetrahydrotriazolyl (e.g., 2,3,4,5-tetrahydro-1H-1,2,3-triazol-1-yl) and the like; fused non-aromatic heterocyclic groups such as dihydroindolyl
(e.g., 2,3-dihydro-1H-indol-1-yl), dihydroisoindolyl (e.g.,
1,3-dihydro-2H-isindol-2-yl), dihydrobenzofuranyl (e.g., 2,3-
dihydrobenzofuran-5-yl), dihydrobenzodioxinyl (e.g., 2,3-
dihydro-1,4-benzodioxinyl), dihydrobenzodioxepinyl (e.g., 3,4-
dihydro-2H-1,5-benzodioxepinyl), tetrahydrobenzofuranyl (e.g.,
4,5,6,7-tetrahydrobenzofuran-3-yl), chromenyl (e.g., 4H-
chromen-2-yl, 2H-chromen-3-yl), dihydroquinolinyl (e.g., 1,2-
dihydroquinolin-4-yl), tetrahydroquinolinyl (e.g., 1,2,3,4-
tetrahydroquinolin-4-yl), dihydroisoquinolinyl (e.g., 1,2-
dihydroisoquinolin-4-yl), tetrahydroisoquinolinyl (e.g.,
1,2,3,4-tetrahydroisoquinolin-4-yl), dihydropthalazinyl (e.g.,
1,4-dihydropthalazin-4-yl) and the like;
and the like.

[0127]

The above-mentioned "heterocyclic group" optionally has
substituent(s) (e.g., 1 to 5, preferably 1 to 3 substituents)
at substitutable position(s). When the number of the
substituents is two or more, the respective substituents may
be the same or different.

Examples of the "substituent" of the "heterocyclic group
optionally having substituents" include the groups exemplified
as the aforementioned substituent group A and the like.

[0128]

Examples of the "acyl group" in the present specification
include groups represented by the formulas: -COR\(^A\), -CO-OR\(^A\),
-SO\(_2\)R\(^A\), -SOR\(^A\), -CO-NR'R", -CS-NR'R" wherein R\(^A\) is a hydrogen atom,
a hydroxy group, a hydrocarbon group optionally having
substituent(s), an amino group optionally having
substituent(s) or a heterocyclic group optionally having
substituent(s). R' and R" are each a hydrogen atom, a
hydrocarbon group optionally having substituent(s) or a
heterocyclic group optionally having substituent(s), or R' and
R" form, together with the nitrogen atom bonded thereto, a
nitrogen-containing heterocycle optionally having
substituent(s), and the like.
Examples of the “hydrocarbon group” of the “hydrocarbon group optionally having substituent(s)” for R\textsuperscript{A}, R’ or R” include those similar to the “hydrocarbon group” of the aforementioned “hydrocarbon group optionally having substituent(s)”.

Examples of the “heterocyclic group” of the “heterocyclic group optionally having substituent(s)” for R\textsuperscript{A}, R’ or R” include those similar to the “heterocyclic group” of the aforementioned “heterocyclic group optionally having substituent(s)”.

Examples of the “amino group optionally having substituent(s)” for R\textsuperscript{A} include those similar to the “amino group optionally having substituent(s)” of the aforementioned substituent group A.

Examples of the substituent of the “hydrocarbon group optionally having substituent(s)” and “heterocyclic group optionally having substituent(s)” for R\textsuperscript{A}, R’ or R” include 1 to 5, preferably 1 to 3, selected from the aforementioned substituent group A. When the number of the substituents is two or more, the respective substituents may be the same or different.

Examples of the “nitrogen-containing heterocycle” of the “nitrogen-containing heterocycle optionally having substituent(s)” formed by R’ and R” together with the nitrogen atom bonded thereto include a 4- to 7-membered nonaromatic nitrogen-containing heterocycle containing, as a ring-constituting atom besides carbon atom, one nitrogen atom, and optionally further containing 1 or 2 hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom. The nonaromatic nitrogen-containing heterocycle may be condensed with a benzene ring.

Examples of the nitrogen-containing heterocycle include
azetidine, pyrrolidine, imidazolidine, pyrazolidine, piperidine, homopiperidine, piperazine, homopiperazine, morpholine, homomorpholine, thiomorpholine, thiohomomorpholine, dihydrobenzoxazine (e.g., 3,4-dihydro-2H-1,4-benzoxazine), 1,2,3,4-tetrahydroquinoline, 7-aza-bicyclo[2.2.1]heptane and the like.

The "nitrogen-containing heterocycle" optionally has (preferably 1 to 3, more preferably 1 or 2) substituent(s) at substitutable position(s). Examples of the substituent include substituent group B and the like. When the number of the substituents is two or more, the respective substituents may be the same or different.

[0132]

Preferable examples of the "acyl" include

(1) a formyl group;
(2) a carboxy group;
(3) a C₁₋₆ alkyl-carbonyl group;
(4) a C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl)

optionally having 1 to 3 substituents selected from the substituent group B;

(5) a group represented by the formula: \(-\text{CO-\text{NR'\text{R''}}}\)
wherein R' and R'' are each a hydrogen atom, a hydrocarbon group optionally having 1 to 3 substituents selected from the aforementioned substituent group B or a heterocyclic group optionally having 1 to 3 substituents selected from the aforementioned substituent group B, or R' and R'' optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing heterocycle optionally having 1 to 3 substituents selected from the aforementioned substituent group B, and the like.

[0133]

Examples of the "aryl group" in the present specification include C₆₋₁₄ aryl such as phenyl, 1-naphthyl, 2-naphthyl, biphenyl, 2-anthryl and the like. Among these, C₆₋₁₀ aryl is
preferable and phenyl is more preferable. The above-mentioned
aryl may be condensed with C_{3-10} cycloalkane (examples of the C_{3-}
10 cycloalkane include a ring corresponding to the above-
mentioned C_{3-10} cycloalkyl), and examples of the fused group
include tetrahydronaphthyl, indanyl and the like.

[0134]
Examples of the “heteroaryl group” in the present
specification include a monocyclic aromatic heterocyclic group
and a fused aromatic heterocyclic group from the “heterocyclic
group” of the aforementioned “heterocycle optionally having
substituent(s)”.

[0135]
Examples of the “heterocycle” in the present
specification include monocyclic heterocycle and fused
heterocycle.

Examples of the “monocyclic heterocycle” include
monocyclic aromatic heterocycle and monocyclic non-aromatic
heterocycle.

[0136]
Examples of the “monocyclic aromatic heterocycle” include
a 4- to 10-membered (preferably 5- or 6-membered) monocyclic
aromatic heterocycle containing, as a ring-constituting atom
besides carbon atoms, 1 to 4 heteroatoms selected from an
oxygen atom, a sulfur atom and a nitrogen atom.

Examples of the “monocyclic aromatic heterocycle” include
a 4- to 7-membered (preferably 5- or 6-membered) monocyclic
aromatic heterocycle such as furan, thiophene, pyridine,
pyrimidine, pyridazine, pyrazine, pyrrole, imidazole, pyrazole,
thiazole, isothiazole, oxazole, isoxazole, oxadiazolyl (e.g.,
1,2,4-oxadiazole, 1,3,4-oxadiazole), thiazole (e.g., 1,2,4-
30 thiazole, 1,3,4-thiazole), triazole (e.g., 1,2,4-
triazole, 1,2,3-triazole), tetrazole, triazine (e.g., 1,3,5-
triazine, 1,2,3-triazine, 1,2,4-triazine) and the like.

[0137]
Examples of the “monocyclic non-aromatic heterocycle”
include a 3- to 10-membered (preferably 5- or 6-membered) monocyclic non-aromatic heterocycle containing, as a ring-
constituting atom besides carbon atoms, 1 to 4 heteroatoms
selected from an oxygen atom, a sulfur atom and a nitrogen
atom.

Examples of the "monocyclic non-aromatic heterocycle"
include a 4- to 7-membered (preferably 5- or 6-membered)
monocyclic non-aromatic heterocycle such as pyrrolidine,
piperidine, morpholine, thiomorpholine, piperazine,
hexamethylenimine, oxazolidine, thiazolidine, imidazolidine,
oxazoline, thiazoline, imidazoline, dioxole, dioxolane,
dihydrooxadiazole (e.g., 4,5-dihydro-1,2,4-oxadiazole), 2-
thiooxo-1,3-oxazolidine, pyran, tetrahydropyrany, thiopyran,
tetrahydrothiopyran, 1-oxidetetrahydrothiopyran, 1,1-
dioxidetetrahydrothiopyran, tetrahydrofuran, pyrazolidine,
pyrazoline, tetrahydropyrimidine, dihydrotriazole,
tetrahydrotriazole (e.g., 2,3,4,5-tetrahydro-1H-1,2,3-
triazole) and the like.

[0138]

Examples of the "fused heterocycle" include fused
aromatic heterocycle and fused non-aromatic heterocycle.

Examples of the "fused aromatic heterocycle" include a
ring wherein a 4- to 7-membered (preferably 5- or 6-membered)
monocyclic aromatic heterocycle containing, as a ring-
constituting atom besides carbon atoms, 1 to 4 heteroatoms
selected from an oxygen atom, a sulfur atom and a nitrogen
atom, and 1 or 2 rings selected from a 5- or 6-membered
aromatic heterocycle containing 1 or 2 nitrogen atoms, a 5-
membered aromatic heterocycle containing one sulfur atom and a
benzene ring are condensed and the like.

[0139]

Examples of the "fused aromatic heterocycle" include
quinoline, isoquinoline, quinazoline, quinoxaline, benzofuran,
benzothiophene, benzoazole, benzisoxazole, benzothiazole,
benzimidazole, benzotriazole, indole, indazole,
pyrrolopyrazine (e.g., 1H-pyrrolo[2,3-b]pyrazine),
imidazopyridine (e.g., 3H-imidazo[4,5-b]pyridine, 1H-
imidazo[5,4-b]pyridine, 1H-imidazo[4,5-c]pyridine,
imidazo[1,2-a]pyridine), imidazopyrazine (e.g., 1H-
imidazo[4,5-b]pyrazine, imidazo[1,2-a]pyrazine),
imidazopyrimidine (e.g., imidazo[1,2-a]pyrimidine,
imidazo[1,2-c]pyrimidine), imidazopyridazine (e.g.,
imidazo[1,2-b]pyridazine), pyrazolopyridine (e.g., 1H-
pyrazolo[4,3-c]pyridine), thienopyrrole (e.g., 4H-thieno[3,2-
b]pyrrole), pyrazolothiophene (e.g., 2H-pyrazolo[3,4-
b]thiophene), pyrazolotriazine (e.g., pyrazolo[5,1-
c][1,2,4]triazine), pyrazolopyridine (e.g., 1H-pyrrolo[1,2-
b]pyridine), 1,4-dihydropyrrolo[3,2-b]pyrrole, 4H-furo[3,2-
b]pyrrole, 4H-thieno[3,2-b]pyrrole, 1H-furo[2,3-d]imidazole,
1H-thieno[2,3-d]imidazole and the like.

[0140]

Examples of the “fused non-aromatic heterocycle” include
a ring wherein a 4- to 7-membered (preferably 5- or 6-
membered) monocyclic non-aromatic heterocycle containing, as a
ring-constituting atom besides carbon atoms, 1 to 4
heteroatoms selected from an oxygen atom, a sulfur atom and a
nitrogen atom, and 1 or 2 rings selected from a 5- or 6-
membered aromatic heterocycle containing 1 or 2 nitrogen atoms,
a 5-membered aromatic heterocycle containing one sulfur atom
and a benzene aromatic ring are condensed, and the like.

Examples of the “fused non-aromatic heterocycle” include
dihydroindole (e.g., 1,2-dihydroindole), tetrahydroindole
(e.g., 4,5,6,7-tetrahydro-1H-indole), dihydroisoindole,
tetrahydroisoindole (e.g., 4,5,6,7-tetrahydroisoindole),
dihydrobenzofuran, dihydrobenzodioxine (e.g., 2,3-dihydro-1,4-
benzodioxine), dihydrobenzodioxepine (e.g., 3,4-dihydro-2H-
1,5-benzodioxepine), tetrahydrobenzimidazole (e.g., 4,5,6,7-
tetrahydro-1H-benzimidazole), tetrahydrobenzofuran (e.g.,
4,5,6,7-tetrahydrobenzofuran), chromene (e.g., 4H-chromene,
2H-chromene), dihydroquinoline (e.g., 1,2-dihydroquinoline),
tetrahydroquinoline (e.g., 1,2,3,4-tetrahydroquinoline),
dihydroisoquinoline (e.g., 1,2-dihydroisoquinoline),
tetrahydroisoquinoline (e.g., 1,2,3,4-tetrahydroisoquinoline),
dihydropthalazine (e.g., 1,4-dihydropthalazine), 1,4-
dihydrocyclopenta[b]pyrrole, 1,4-dihydrocyclopentaimidazole,
1,4-dihydropyrrolo[2,3-d]imidazole and the like.

[0141]

Examples of the “5- to 7-membered nitrogen-containing
heterocycle” in the present specification include pyrrolidine,
piperidine and homopiperidine.

[0142]

Each symbol in the formulas (I) and (II) is defined in
detail in the following.

R

In the formulas (I) and (II), R is a hydrogen atom, an
alkyl group optionally having substituent(s), an alkenyl group
optionally having substituent(s) or a cycloalkyl group
optionally having substituent(s).

Examples of the substituent of the “alkyl group
optionally having substituent(s)”, “alkenyl group optionally
having substituent(s)” and “cycloalkyl group optionally having
substituent(s)” for R include 1 to 5, preferably 1 to 3
selected from the aforementioned substituent group A. When the
number of the substituents is two or more, the respective
substituents may be the same or different.

R is preferably a hydrogen atom or a C alkyl group
optionally having substituent(s), more preferably a C alkyl
group (e.g., methyl group, ethyl group, propyl group,
isopropyl group, isobutyl group etc.) optionally having 1 to 3
substituents selected from halogen atom(s), a cyano group, a
hydroxy group, a C cycloalkyl (e.g., cyclopropyl) and the
like, and still more preferably, a C alkyl group
(particularly, isobutyl).

[0143]

R

64
In the formula (I), $R^2$ is a halogen atom, a hydroxy group, a cyano (nitrile) group, an amino group optionally having substituent(s), a mercapto group optionally having a substituent (the mercapto group is optionally oxidized), an alkyl group optionally having substituent(s) other than a substituted amino group, an alkoxy group optionally having substituent(s), a 3- to 10-membered cyclic hydrocarbon group optionally having substituent(s), a 3- to 10-membered heterocyclic group optionally having substituent(s), or an acyl group (wherein when the acyl group is $-\text{CONR}^1\text{R}^2$, then $\text{R}^1$ and $\text{R}^2$ are both hydrogen atoms or form, together with the nitrogen atom bonded thereto, a nitrogen-containing heterocycle optionally having substituent(s)).

[0144]

The "amino group" of the "amino group optionally having substituent(s)" for $R^2$ optionally has 1 or 2 substituents at substitutable position(s). When the number of the substituents is two, the respective substituents may be the same or different. Examples of the substituent include the aforementioned substituent group B.

[0145]

The "mercapto group" of the "mercapto group optionally having a substituent" for $R^2$ optionally has a substituent and optionally oxidized by 1 or 2 oxygens. Examples of the substituent include the aforementioned substituent group B.

[0146]

The "alkyl group" of the "alkyl group optionally having substituent(s) other than a substituted amino group" for $R^2$ optionally has (for example, 1 to 5, preferably 1 to 3) substituent(s) other than a substituted amino group at substitutable position(s). When the number of the substituents is two or more, the respective substituents may be the same or different. Examples of the substituent include substituent group B (except mono- or di-$C_{1-6}$ alkylamino group, $C_7-C_{16}$ aralkylamino group, $C_{1-6}$ alkoxy-carbonylamino group and $C_{1-6}$
alkyl-carbonylamino group). Examples of the "substituent" of the "substituted amino group" include unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocyclyl or unsubstituted or substituted cycloalkyl or acyl (e.g., C_1-6 cycloalkyl group or C_1-6 alkyl group substituted by heterocycle) and the like.

[0147]

The "alkoxy group" of the "alkoxy group optionally having substituent(s)" for R^2 optionally has (for example, 1 to 5, preferably 1 to 3) substituent(s). When the number of the substituents is two or more, the respective substituents may be the same or different. Examples of the substituent include the aforementioned substituent group B.

[0148]

The "cyclic hydrocarbon group" of the "3- to 10-membered cyclic hydrocarbon group optionally having substituent(s)" and the "heterocyclic group" of the "3- to 10-membered heterocyclic group optionally having substituent(s)" for R^2 optionally has (for example, 1 to 5, preferably 1 to 3) substituent(s). When the number of the substituents is two or more, the respective substituents may be the same or different. Examples of the substituent include the aforementioned substituent group B.

[0149]

Examples of the "cyclic hydrocarbon group" of the "3- to 10-membered cyclic hydrocarbon group optionally having substituent(s)" for R^2 include those similar to the "3- to 10-membered cyclic hydrocarbon group" of the "3- to 10-membered cyclic hydrocarbon group optionally having substituent(s)" of the aforementioned substituent group A.

[0150]

Examples of the "heterocyclic group" of the "3- to 10-membered heterocyclic group optionally having substituent(s)"
for $R^2$ include those similar to the "heterocyclic group" of the "3- to 10-membered heterocyclic group optionally having substituent(s)" of the aforementioned substituent group A.

[0151]

When the "acyl group" for $R^2$ is $-\text{CO-NR}^\prime R^\prime$, $R^\prime$ and $R^\prime$ are both hydrogen atoms or form, together with the nitrogen atom bonded thereto, a nitrogen-containing heterocycle optionally having substituent(s). Examples of the nitrogen-containing heterocycle include those mentioned above, and morpholine is particularly preferable.

Examples of the substituent of the "nitrogen-containing heterocycle optionally having substituent(s)" formed by $R^\prime$ and $R^\prime$ together with the nitrogen atom bonded thereto include 1 to 5, preferably 1 to 3, selected from the aforementioned substituent group B. When the number of the above-mentioned substituents is two or more, the respective substituents may be the same or different.

[0152]

$R^2$ is preferably a C$_{1-6}$ alkyl group (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl) optionally having substituent(s) other than a substituted amino group, a 3- to 10-membered heterocyclic group optionally having substituent(s) or an acyl group (wherein when the acyl group is $-\text{CONR}^\prime R^\prime$, $R^\prime$ and $R^\prime$ are both hydrogen atoms or form, together with the nitrogen atom bonded thereto, a nitrogen-containing heterocycle (e.g., morpholine) optionally having substituent(s)), more preferably

(1) a C$_{1-6}$ alkyl group (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl) optionally having 1 to 3 substituents

selected from

(a) a hydroxy group,
(b) a halogen atom (e.g., fluorine atom),
(c) a C$_{1-6}$ alkoxy group (e.g., methoxy, ethoxy),
(d) a C$_{1-6}$ alkyl-carbonyloxy group (e.g., acetyloxy),
(e) an aromatic heterocyclic group (e.g., pyridyl) optionally
having 1 to 3 halogen atoms,
(f) a C1-10 cycloalkyl group (e.g., cyclopropyl), and
(g) a cyclic amino group (e.g., pyrrolidinyl, piperidino, morpholino, thiomorpholino, piperazinyl, imidazolidin-1-yl, pyrazolidin-1-yl etc.) optionally having an oxo group,
(2) a 3- to 10-membered heterocyclic group (1,2,4-triazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, 4,5-dihydro-1,2,4-oxadiazolyl, tetrazolyl, tetrahydropyrimidinyl, oxazolyl, piperidinyl, pyrrolidinyl, hexahydropyrimidinyl) optionally having 1 to 3 substituents selected from a C1-6 alkyl group and an oxo group,
(3) a carboxy group,
(4) a C1-6 alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl)
optionally having 1 to 3 substituents selected from a nonaromatic heterocyclic group (e.g., dioxolyl) optionally having 1 to 3 substituents selected from a C1-6 alkyl group (e.g., methyl) and oxo group,
(5) a C1-6 alkyl-carbonyl group (e.g., acetyl), or
(6) the formula: -CO-NR'R"

wherein R' and R" are each a hydrogen atom, or R' and R" form, together with the nitrogen atom bonded thereto, a nitrogen-containing heterocycle (e.g., azetidine, morpholine, pyrrolidine, piperidine, 7-aza-bicyclo[2.2.1]heptane, homomorpholine, dihydrobenzoxazin (e.g., 3,4-dihydro-2H-1,4-benzoxazin)) optionally having 1 to 3 substituents selected from halogen atom(s) (e.g., fluorine atom).

[0153]

R3

In the formula (II), R3 is an alkyl group optionally substituted by group(s) other than a heterospiro ring optionally having substituent(s), an alkenyl group optionally having substituent(s), a cycloalkyl group optionally having substituent(s), an alkylthio group optionally having substituent(s), an alkylsulfinyl group optionally having
substituent(s), an alkylsulfonyl group optionally having substituent(s), an alkoxy group optionally having substituent(s), an aryl group optionally having substituent(s) or a heteroaryl group optionally having substituent(s).

[0154]

Examples of the "heterospiro ring" of the "alkyl group optionally substituted by group(s) other than a heterospiro ring optionally having substituent(s)" for $R^3$ include a spiro ring formed from a 4- to 7-membered (preferably 5- or 6-membered) monocyclic non-aromatic heterocycle containing, as a ring constituting atom besides carbon atom, 1 to 4 hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom and a C$_3$-10 cycloalkane (as the C$_3$-10 cycloalkane, a ring corresponding to the above-mentioned C$_3$-10 cycloalkyl can be mentioned, which is optionally condensed with a benzene ring), a spiro ring formed from the monocyclic non-aromatic heterocycles, and the like.

[0155]

Examples of the "heterospiro ring" include a spiro ring formed from a 4- to 7-membered (preferably 5- or 6-membered) monocyclic non-aromatic heterocycle such as pyrrolidine, piperidine, morpholine, thiomorpholine, piperazine, hexamethyleneimine, oxazolidine, thiazolidine, imidazolidine, oxazoline, thiazoline, imidazoline, dioxole (e.g., 1,3-dioxole), dioxolane (e.g., 1,3-dioxolane), dihydrooxadiazole (e.g., 4,5-dihydro-1,2,4-oxadiazole), 2-thioxo-1,3-oxazolidine, pyran, tetrahydropyran, thiopyran, tetrahydrothiopyran, 1-oxidetetrahydrothiopyran, 1,1-dioxidetetrahydrothiopyran, tetrahydrofuran, pyrazolidine, pyrazoline, tetrahydropyrimidine, dihydrotriazole (e.g., 2,3-dihydro-1H-1,2,3-triazole), tetrahydrotriazole (e.g., 2,3,4,5-tetrahydro-1H-1,2,3-triazole) and the like, and a C$_3$-10 cycloalkane such as cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane and the like or a fused ring (e.g., indane, tetrahydronaphthalene, fluorene etc.) formed from the
C₃₋₁₀ cycloalkane and benzene ring; or a spiro ring formed from
the monocyclic non-aromatic heterocycles, a spiro ring formed
from pyrrolidine, piperidine, morpholine, thiomorpholine,
piperazine and the like and, cyclopropane, cyclobutane,
cyclopentane, cyclohexane, indane, tetrahydronaphthalene and
the like is preferable.

As the "heterospiro ring", spiro[indane-1,4'-piperidine]
and the like can be specifically mentioned.

As the substituent of the "heterospiro ring", 1 to 5,
preferably 1 to 3, selected from the aforementioned
substituent group A can be mentioned. When the number of the
substituents is two or more, the respective substituents may
be the same or different.

[0156]

The "alkyl group" of the "alkyl group optionally
substituted by group(s) other than a heterospiro ring
optionally having substituent(s)" for R³ optionally has (for
example, 1 to 5, preferably 1 to 3) substituent(s) other than
the "heterospiro ring optionally having substituent(s)" at
substitutable position(s). When the number of the substituents
is two or more, the respective substituents may be the same or
different. Examples of the substituent include the
aforementioned substituent group A.

[0157]

Examples of the substituent of the "alkenyl group
optionally having substituent(s)", "cycloalkyl group
optionally having substituent(s)", "alkylthio group optionally
having substituent(s)", "alkylsulfinyl group optionally having
substituent(s)", "alkylsulfonyl group optionally having
substituent(s)", "alkoxy group optionally having
substituent(s)", "aryl group optionally having substituent(s)"
and "heteroary1 group optionally having substituent(s)" for R³
include 1 to 5, preferably 1 to 3, selected from the
aforementioned substituent group A. When the number of the
substituents is two or more, the respective substituents may
be the same or different.

[0158]

R³ is preferably a C₁-₆ alkoxy group (e.g., methoxy, ethoxy) optionally having substituent(s), a C₁-₆ alkylthio group (e.g., methylthio) optionally having substituent(s), a C₃-₁₀ cycloalkyl group (e.g., cyclopropyl) optionally having substituent(s), an aryl (e.g., phenyl) group optionally having substituent(s), or a heteroaryl group (e.g., thienyl) optionally having substituent(s), more preferably, a C₁-₆ alkoxy group (e.g., methoxy, ethoxy) optionally substituted by a C₁-₆ alkoxy group (e.g., methoxy, ethoxy) or a halogen atom (e.g., fluorine atom), a C₁-₆ alkylthio group (e.g., methylthio), a C₃-₁₀ cycloalkyl group (e.g., cyclopropyl) optionally substituted by a C₁-₆ alkyl group (e.g., methyl), an aryl group (e.g., phenyl) or a heteroaryl group (e.g., thienyl, thiazolyl, pyridyl, pyrazolyl, imidazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl) optionally substituted by a C₁₋₆ alkyl group (e.g., methyl), more preferably, a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy) optionally having substituent(s).

[0159]

X

In the formula (I), X is absent or a hydrogen atom, an alkyl group optionally substituted by group(s) other than a heterospiro ring optionally having substituent(s) or a cycloalkyl group optionally having substituent(s).

Examples of the "heterospiro ring optionally having substituent(s)" of the "alkyl group optionally substituted by group(s) other than a heterospiro ring optionally having substituent(s)" for X include those similar to the "heterospiro ring optionally having substituent(s)" of the aforementioned "C₁₋₆ alkyl group optionally substituted by group(s) other than a heterospiro ring optionally having substituent(s)" for R³.

The "alkyl group" of the "alkyl group optionally substituted by group(s) other than a heterospiro ring
optionally having substituent(s)" for X optionally has (for example, 1 to 5, preferably 1 to 3) substituent(s) other than the heterospiro ring optionally having substituent(s) at substitutable position(s). When the number of the substituents is two or more, the respective substituents may be the same or different. Examples of the substituent include a halogen atom, a hydroxy group, an alkenyl group optionally having substituent(s), an alkynyl group optionally having substituent(s), a cycloalkyl group optionally having substituent(s), a cycloalkyloxy group optionally having substituent(s), an alkylthio group optionally having substituent(s), an alkylsulfinyl group optionally having substituent(s), an alkylsulfonyl group optionally having substituent(s), an alkoxy group optionally having substituent(s), an aryl group optionally having substituent(s), a heteroaryl group optionally having substituent(s), an aryloxy group optionally having substituent(s), and an acyl group.

[0160] Examples of the substituent of the "alkenyl group optionally having substituent(s)", "alkynyl group optionally having substituent(s)", "cycloalkyl group optionally having substituent(s)", "cycloalkyloxy group optionally having substituent(s)", "alkylthio group optionally having substituent(s)", "alkylsulfinyl group optionally having substituent(s)", "alkylsulfonyl group optionally having substituent(s)", "alkoxy group optionally having substituent(s)", "aryl group optionally having substituent(s)", "heteroaryl group optionally having substituent(s)" and "aryloxy group optionally having substituent(s)" exemplified as the "substituent" of the "alkyl group optionally substituted by group(s) other than a heterospiro ring optionally having substituent(s)" for X include 1 to 5, preferably 1 to 3, selected from the aforementioned substituent group A. When the number of the substituents is
two or more, the respective substituents may be the same or
different.

[0161]
Examples of the substituent of the "cycloalkyl group
optionally having substituent(s)" for X include 1 to 5,
preferably 1 to 3, selected from the aforementioned
substituent group A. When the number of the substituents is
two or more, the respective substituents may be the same or
different.

[0162]
X is preferably
(1) a hydrogen atom;
(2) a C₁-₆ alkyl group (e.g., methyl, ethyl, propyl, isopropyl,
butyl, hexyl) optionally substituted by 1 to 3 substituents
selected from
(a) a halogen atom (e.g., fluorine atom),
(b) a hydroxy group,
(c) a C₁-₆ alkoxy group (e.g., methoxy, ethoxy) optionally
having a C₁-₆ alkoxy group (e.g., methoxy) or a halogen atom
(e.g., fluorine atom),
(d) a C₁-₆ alkylthio group (e.g., methylthio),
(e) an aryl group (e.g., phenyl),
(f) a aryloxy group (e.g., phenyloxy) optionally having a C₁-₆
alkoxy group (e.g., methoxy) or a halogen atom (e.g., fluorine
atom), and
(g) a heteroaryl group (e.g., thiényl, thiazolyl); or
(3) a C₃-₁₀ cycloalkyl group (e.g., cyclopropyl), more
preferably, a C₁-₆ alkyl group (e.g., methyl, ethyl, propyl,
isopropyl, butyl) optionally substituted by a C₁-₆ alkoxy group
(e.g., methoxy, ethoxy).

[0163]
X¹
In the formula (II), X¹ is a C₁-₆ alkyene group
optionally substituted by group(s) other than a heterospiro
ring optionally having substituent(s).
Examples of the "heterospiro ring optionally having substituent(s)" of the "C1-6 alkyylene group optionally substituted by group(s) other than a heterospiro ring optionally having substituent(s)" for X₁ optionally has (for example, 1 to 5, preferably 1 to 3) substituent(s) other than a heterospiro ring optionally having substituent(s) at substitutable position(s). When the number of the substituents is two or more, the respective substituents may be the same or different. Examples of the substituent include the aforementioned substituent group A.

X₁ is preferably a "C1-6 alkylene group optionally substituted by group(s) other than a heterospiro ring optionally having substituent(s)" and an oxo group", more preferably, a C1-6 alkylene group (e.g., methylene, ethylene, trimethylene, tetramethylene).

[0164]

Ring A and ring A₁

In the formula (I), ring A is a heterocycle optionally having substituent(s), and in the formula (II), ring A₁ is a fused heterocycle optionally having substituent(s). However, ring A is not
[0166] wherein -X is as defined above, ring C is a heterocycle optionally having substituent(s), ring D is a benzene ring optionally having substituent(s), R'' is a substituted alkyl group or a substituted alkoxy group and R''' is a substituent, and ring A^1 is not

[0167]
[0168] wherein ring C is a heterocycle optionally having substituent(s), ring D is a benzene ring optionally having substituent(s), R'' is a substituted alkyl group or a substituted alkoxy group, R''' is a substituent, and other symbols are as defined above.

[0169] More preferably, the "heterocycle" of the "heterocycle optionally having substituent(s)" for ring A and the "fused heterocycle" of the "fused heterocycle optionally having substituent(s)" for ring A^1 are not the following rings.

[0170]
[0171] wherein

5 $R^{1a}$ is an optionally substituted C$_{1-6}$ alkyl group, a C$_{3-6}$ cycloalkoxy group substituted by C$_{1-4}$ alkoxy, an optionally substituted C$_{2-6}$ alkenyl group, an optionally substituted C$_{2-6}$ alkenyloxy group, an optionally substituted C$_{3-6}$ alkynyl group, an optionally substituted C$_{3-6}$ alkynyloxy group, an optionally substituted C$_{1-6}$ alkylsulfinyl group, an optionally substituted C$_{1-6}$ alkylsulfonyl group, an optionally substituted C$_{1-6}$ alkoxy group, an optionally substituted amino group, an optionally substituted aminocarbonyl group, an optionally substituted C$_{1-4}$ alkoxy carbonyl group or an optionally substituted C$_{1-4}$ alkyl carbonyl group;

10 $R^{1b}$ and $R^{1e}$ are the same or different and each independently is a hydrogen atom, a cyano group, an optionally substituted C$_{1-6}$ alkyl group, an optionally substituted C$_{1-6}$ alkoxy group, an optionally substituted C$_{2-6}$ alkenyl group, C$_{1-6}$ alkylsulfonyl group, or a halogen atom;

15 $R^{1c}$ and $R^{1d}$ are the same or different and each independently is a hydrogen atom, a halogen atom, a hydroxyl group, a formyl group, a carboxy group, a cyano group, an optionally substituted C$_{1-6}$ alkyl group, an optionally substituted C$_{2-6}$ alkenyl group, an optionally substituted C$_{3-10}$ cycloalkyl group, an optionally substituted C$_{2-6}$ alkynyl group, an optionally substituted C$_{1-4}$ alkoxy group, an optionally substituted C$_{1-4}$ alkylsulfonyl group, an optionally substituted C$_{1-4}$ alkoxy carbonyl group or an optionally substituted C$_{1-4}$ alkyl carbonyl group;
substituted C₅₋₆ cycloalkenyl group, an optionally substituted C₆₋₁₀ aryl group, an optionally substituted C₇₋₁₄ aralkyl group, an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl group, an optionally substituted 5-membered or 6-membered saturated heterocyclic group, an optionally substituted C₁₋₆ alkylthio group, an optionally substituted C₁₋₆ alkyisulfanyl group, an optionally substituted C₁₋₆ alkylsulfonyl group, an optionally substituted C₆₋₁₀ arlythio group, an optionally substituted C₆₋₁₀ arylsulfonyl group, an optionally substituted C₁₋₆ arloxy group, an optionally substituted C₁₋₆ alkoxycarbonyl group, an optionally substituted C₃₋₆ alkynyloxy group, an optionally substituted C₃₋₁₀ cycloalkynyloxy group, an optionally substituted C₆₋₁₀ aryloxy group, an optionally substituted C₇₋₁₄ aralkyloxy group, an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl group, an optionally substituted amino group, an optionally substituted aminocarbonyl group, an optionally substituted aminosulfonyl group, an optionally substituted C₁₋₄ alkoxycarbonyl group, an optionally substituted C₃₋₁₀ cycloalkoxycarbonyl group, an optionally substituted C₁₋₄ alkylcarbonyl group, an optionally substituted C₃₋₁₀ cycloalkylcarbonyl group, an optionally substituted C₆₋₁₀ arylcarbonyl group or an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroarylcarbonyl group; R²⁻ is a hydrogen atom, a halogen atom, a cyano group, an optionally substituted C₃₋₆ cycloalkyl group, an optionally substituted C₂₋₆ alkenyl group, an optionally substituted C₂₋₆ alkenyloxy group, an optionally substituted C₃₋₆ alkynyl group, an optionally substituted C₃₋₆ alkynyl group, an optionally substituted C₃₋₁₀ cycloalkyloxy group, an optionally substituted C₁₋₆ alkoxy group or an optionally substituted C₁₋₆ alkyl group; R₁⁰⁻ is a hydrogen atom, a halogen atom, a hydroxyl group, a formyl group, a carboxy group, a cyano group, an optionally substituted C₁₋₆ alkyl group, an optionally substituted C₂₋₆ alkenyl group, an optionally substituted C₂₋₆ alkenyl group, an optionally substituted C₆₋₁₀ cycloalkyloxy group, an optionally substituted C₁₋₆ alkoxy group or an optionally substituted C₁₋₆ alkyl group;
optionally substituted C₃₋₆ cycloalkyl group, a C₁₋₆ alkylthio group, C₁₋₆ alkylsulfonyl group, a C₁₋₆ alkoxy group optionally substituted by a halogen atom, C₁₋₄ alkoxy or C₃₋₆ cycloalkyl, an optionally substituted C₃₋₆ cycloalkoxy group, an optionally substituted amino group, an aminocarbonyl group, a C₁₋₄ alkoxy carbonyl group, a C₁₋₄ alkylcarbonyl group, an optionally substituted C₆₋₁₀ aryl group, an optionally substituted C₆₋₁₀ aryloxy group or an optionally substituted C₇₋₁₄ aralkyloxy group;

or R¹₉ is a hydrogen atom; R¹b' and R¹c' in combination form a fused ring with a benzene ring, which contains at least one hetero atom.

[0172]

[0173]

wherein R¹a is an optionally substituted C₁₋₆ alkyl group, an optionally substituted C₂₋₆ alkenyl group, an optionally substituted C₂₋₆ alkynyl group, an optionally substituted C₃₋₁₀ cycloalkyl group, an optionally substituted C₅₋₆ cycloalkenyl group or an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl-C₁₋₄ alkyl group; R¹b, R¹c, R¹d and R¹e are the same or different and each independently is a hydrogen atom, a halogen atom, a hydroxyl group, a formyl group, a carboxyl group, a cyano group, an optionally substituted C₁₋₆ alkyl group, an optionally substituted C₂₋₆ alkenyl group, an optionally substituted C₂₋₆ alkynyl group, an optionally substituted C₃₋₁₀ cycloalkyl group, an optionally substituted C₅₋₆ cycloalkenyl group, an optionally substituted C₆₋₁₀ aryl group, an optionally substituted C₇₋₁₄ aralkyl group, an optionally substituted 5-membered to 10-
membered monocyclic or polycyclic heteroaryl group, an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl C$_{1-4}$ alkyl group, an optionally substituted saturated heterocyclic group, an optionally
substituted C$_{1-6}$ alkylthio group, an optionally substituted C$_{1-6}$ alkylsulfinyl group, an optionally substituted C$_{1-6}$ alkylsulfonyl group, an optionally substituted C$_{6-10}$ arylthio group, an optionally substituted C$_{6-10}$ arylsulfinyl group, an optionally substituted C$_{6-10}$ arylsulfonyl group, an optionally
substituted C$_{1-6}$ alkoxy group, an optionally substituted C$_{3-6}$ alkynyloxy group, an optionally substituted C$_{3-6}$ cycloalkyloxy group, an optionally substituted C$_{6-10}$ aryloxy group, an optionally substituted C$_{7-14}$ aralkyloxy group, an optionally
substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryloxy group, an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl C$_{1-4}$ alkoxy group, an optionally substituted amino group, an optionally substituted aminocarboxyl group, an optionally substituted aminocarbonyloxy group, an optionally substituted
aminosulfonyl group, an optionally substituted C$_{1-6}$ alkoxy carbonyl group, an optionally substituted C$_{3-6}$ cycloalkyloxy carbonyl group, an optionally substituted C$_{1-4}$ alkyl carbonyl group, an optionally substituted C$_{3-6}$ cycloalkyl carbonyl group, an optionally substituted C$_{6-10}$ ary carbonyl group or an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl carbonyl group; $R^{1f}$ is a hydrogen atom, a halogen atom, a hydroxyl group, a cyano group, an optionally substituted C$_{1-6}$ alkyl group, an optionally substituted C$_{2-6}$ alkenyl group, an optionally
substituted C$_{2-6}$ alkynyl group, an optionally substituted C$_{3-10}$ cycloalkyl group, an optionally substituted C$_{5-6}$ cycloalkenyl group, an optionally substituted C$_{6-10}$ aryl group, an optionally substituted C$_{7-14}$ aralkyl group, an optionally substituted 5-
membered to 10-membered monocyclic or polycyclic heteroaryl group, an optionally substituted 5-membered to 10-membered
monocyclic or polycyclic heteroaryl C_{1-4} alkyl group, an optionally substituted saturated heterocyclic group, an optionally substituted C_{1-6} alkylthio group, an optionally substituted C_{1-6} alkylsulfinyl group, an optionally substituted C_{1-6} alkylsulfonyl group, an optionally substituted C_{1-6} alkoxy group, an optionally substituted C_{3-6} alkynyloxy group, an optionally substituted C_{3-6} cycloalkyloxy group, an optionally substituted C_{6-10} aryloxy group, an optionally substituted C_{7-14} aralkyloxy group, an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl C_{1-4} alkoxy group, an optionally substituted amino group, an optionally substituted aminocarbonyl group, an optionally substituted aminosulfonyl group, an optionally substituted C_{1-4} alkoxy carbonyl group, an optionally substituted C_{3-6} cycloalkyloxy carbonyl group, an optionally substituted C_{1-4} alkyl carbonyl group, an optionally substituted C_{3-6} cycloalkyl carbonyl group, an optionally substituted C_{6-10} aryl carbonyl group or an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl carbonyl group.

![Chemical Structure Image]

[0174]

wherein R^{1a} is an optionally substituted C_{1-6} alkyl group, an optionally substituted C_{2-10} alkenyl group, an optionally substituted C_{2-6} alkynyl group, an optionally substituted C_{3-6} cycloalkyl group, an optionally substituted C_{5-6} cycloalkenyl group, an optionally substituted C_{1-6} alkyl sulfinyl group, an optionally substituted C_{1-6} alkyl sulfonyl group, an optionally substituted aminocarbonyl group, an optionally substituted C_{1-4}
alkoxycarbonyl group or an optionally substituted \( C_{1-4} \)
aldehydylcarbonyl group;
\( R^{1b} \) and \( R^{1e} \) are the same or different and each independently is
a hydrogen atom, a halogen atom, a cyano group, an optionally
substituted \( C_{1-6} \) alkyl group, an optionally substituted \( C_{1-6} \)
alkoxy group, an optionally substituted \( C_{3-6} \) cycloalkyloxy group
or an optionally substituted aminocarbonyl group;
\( R^{1c} \) and \( R^{1d} \) are the same or different and each independently is
a hydrogen atom, a halogen atom, a hydroxyl group, a formyl
group, a carboxy group, a cyano group, an optionally
substituted \( C_{1-6} \) alkyl group, an optionally substituted \( C_{2-6} \)
alkenyl group, an optionally substituted \( C_{2-6} \) alkynyl group, an
optionally substituted \( C_{3-10} \) cycloalkyl group, an optionally
substituted \( C_{5-6} \) cycloalkenyl group, an optionally substituted
\( C_{6-10} \) aryl group, an optionally substituted \( C_{7-14} \) aralkyl group,
an optionally substituted 5-membered to 10-membered monocyclic
or polycyclic heteroaryl group, an optionally substituted 5-
membered to 10-membered monocyclic or polycyclic heteroaryl \( C_{1-4} \)
alkyl group, an optionally substituted saturated heterocyclic
group, an optionally substituted \( C_{1-6} \) alkylthio group, an
optionally substituted \( C_{1-6} \) alkylsulfinyl group, an optionally
substituted \( C_{1-6} \) alkylsulfonyl group, an optionally substituted
\( C_{6-10} \) arylthio group, an optionally substituted \( C_{6-10} \)
arylthio group, an optionally substituted \( C_{6-10} \) arylsulfinyl group, an optionally substituted \( C_{6-10} \) arylsulfonyl
group, an optionally substituted \( C_{1-6} \) alkoxy group, an
optionally substituted \( C_{3-6} \) alknyloxy group, an optionally
substituted \( C_{3-10} \) cycloalkyloxy group, an optionally substituted
\( C_{6-10} \) aryloxy group, an optionally substituted \( C_{7-14} \) aralkyloxy
group, an optionally substituted 5-membered to 10-membered
monocyclic or polycyclic heteroaryloxy group, an optionally
substituted 5-membered to 10-membered monocyclic or polycyclic
heteroaryl \( C_{1-4} \) alkyloxy group, an optionally substituted amino
group, an optionally substituted aminocarbonyl group, an
optionally substituted aminosulfonyl group, an optionally
substituted \( C_{1-4} \) alkoxy carbonyl group, an optionally substituted
C₃₋₆ cycloalkyl oxycarbonyl group, an optionally substituted C₁₋₄ alkyl carbonyl group, an optionally substituted C₃₋₆ cycloalkyl carbonyl group, an optionally substituted C₆₋₁₀ aryl carbonyl group or an optionally substituted 5-membered to 10-membered monocyclic or polycyclic heteroaryl carbonyl group; Rⱼ is a hydrogen atom, a halogen atom, a cyano group, an optionally substituted C₁₋₆ alkyl group, an optionally substituted C₁₋₆ alkoxy group, an optionally substituted C₃₋₁₀ cycloalkyl group, an optionally substituted C₂₋₆ alkenyl group, an optionally substituted C₂₋₆ alkenyloxy group, an optionally substituted C₃₋₆ alkynyl group, an optionally substituted C₃₋₆ alkynoxy group or an optionally substituted C₃₋₁₀ cycloalkyloxy group.

[0176]

Examples of the substituent of the "heterocycle optionally having substituent(s)" for ring A and the "fused heterocycle optionally having substituent(s)" for ring A¹ include 1 to 5, preferably 1 to 3, selected from the aforementioned substituent group A. When the number of the substituents is two or more, the respective substituents may be the same or different.

Ring A is preferably a monocyclic heterocycle such as pyrimidine, pyrrole, imidazole, pyrazole or triazole (1,2,3-triazole, 1,2,4-triazole) and the like; or a fused heterocycle such as indole, benzimidazole, 1H-pyrrolo[1,2-b]pyridine, 3H-imidazo[4,5-b]pyridine, imidazo[1,2-a]pyridine, 5,6,7,8-tetrahydroimidazo[1,2-a]pyridine, 4,5,6,7-tetrahydro-1H-indole, 4,5,6,7-tetrahydro-1H-benzimidazole, 1,4-dihydrocyclopent[a]pyrrole, 1,4-dihydropyrrolo[3,2-b]pyrrole, 4H-furo[3,2-b]pyrrole, 4H-thieno[3,2-b]pyrrole, 1,4-dihydrocyclopentaimidazole, 1,4-dihydro[2,3-d]imidazole, 1H-furo[2,3-d]imidazole or 1H-thieno[2,3-d]imidazole, imidazo[1,2-a]pyrimidine, imidazo[1,2-a]pyrazine, imidazo[1,2-c]pyrimidine, imidazo[1,2-b]pyridazine, benzofuran, benzo thiophene, benzothiazole, quinoline,
isoquinoline and the like, each of which optionally has 1 to 5, preferably 1 to 3, substituent(s) selected from substituent group A.

Preferable ring A\(^1\) is a fused heterocycle selected from ring A.

Each of ring A and ring A\(^1\) is more preferably a ring represented by any of the formulas

\[ \begin{align*}
&\text{[0177]} \\
&\text{[0178]} \\
&\text{[0179]} \\
&\text{[0180]} \\
&\text{[0181]} 
\end{align*} \]

wherein \( R^a \) and \( R^b \) are each independently a hydrogen atom, a halogen atom (e.g., fluorine atom, chlorine atom), an alkyl group optionally having substituent(s), an alkoxy group (e.g., methoxy) optionally having substituent(s), or an acyl group (e.g., \( C_{1-6} \) alkoxy-carbonyl) (particularly preferably a hydrogen atom);

\( R^c \) is a hydrogen atom, a halogen atom (e.g., fluorine atom, chlorine atom), =O, =S, an alkyl group optionally having substituent(s), an alkoxy (e.g., methoxy) group optionally having substituent(s), or an acyl group (e.g., \( C_{1-6} \) alkoxy-carbonyl);

\( Y^1 \) and \( Y^2 \) are each independently CH or N; and

\( Z \) is CH\(_2\), NH, O or S, more preferably a ring represented by
wherein $Y^1$, $Y^2$, $R^a$, and $R^b$ are as defined above.

[0182]

Examples of the substituent of the "alkyl group optionally having substituent(s)" and "alkoxy group optionally having substituent(s)" for $R^a$, $R^b$ or $R^c$ include 1 to 5, preferably 1 to 3, selected from the aforementioned substituent group B. When the number of the substituents is two or more, the respective substituents may be the same or different.

Each of ring A and ring $A^1$ is more preferably a ring represented by any of the formulas

[0183]

\[
\begin{array}{c}
\begin{array}{c}
\text{R}^a \quad \text{R}^b \\
\text{Y}^1 \\
\text{Z} \\
\text{R}^c
\end{array}
\end{array}
\]

and

[0184]

wherein $R^a$ and $R^b$ are each independently a hydrogen atom, a halogen atom (e.g., fluorine atom, chlorine atom), a C$_1$-6 alkoxy group (e.g., methoxy), or a C$_1$-6 alkoxy-carbonyl group (e.g., methoxycarbonyl) (particularly preferably a hydrogen atom); $R^c$ is a hydrogen atom or =O;

$Y^1$ and $Y^2$ are each independently CH or N; and

$Z$ is S, more preferably, a ring represented by

[0185]

\[
\begin{array}{c}
\begin{array}{c}
\text{R}^a \\
\text{Y}^1 \\
\text{Z} \\
\text{R}^b
\end{array}
\end{array}
\]

[0186]

wherein $R^a$ and $R^b$ are each independently a hydrogen atom, a halogen atom (e.g., fluorine atom, chlorine atom), a C$_1$-6 alkoxy group (e.g., methoxy), or a C$_1$-6 alkoxy-carbonyl group (e.g.,
methoxycarbonyl) (particularly preferably a hydrogen atom); and

$Y^1$ and $Y^2$ are each independently CH or N, more preferably,

\[ \text{[0187]} \]

[Diagram]

\[ \text{[0188]} \]

Ring B

In the formula (II), ring B is a 5- to 7-membered nitrogen-containing heterocycle optionally having

\[ \text{[0189]} \]

substituent(s), $n$ is 0, 1 or 2 and NH constituting ring B is unsubstituted.

\[ \text{[0190]} \]

\[ \text{[0191]} \]

Examples of the substituent of the “5- to 7-membered nitrogen-containing heterocycle optionally having

\[ \text{[0192]} \]

substituent(s)” for ring B include 1 to 5, preferably 1 to 3, selected from the aforementioned substituent group A or two substituents bonded to the carbon atoms adjacent to ring B may be bonded to form C$_{3-10}$ cycloalkane (e.g., cyclopentane, cyclohexane) to be condensed with ring B. When the number of the substituents is two or more, the respective substituents may be the same or different.

Ring B is preferably a 6-membered ($n=1$) nitrogen-containing heterocycle optionally having 1 to 5, preferably 1 to 3, substituents selected from substituent group A, more preferably, the formula
more preferably, a ring represented by the formula

\[ \text{[0192]} \]

\[ \text{HN} \]

\[ \text{R}^4 \]

\[ \text{[0193]} \]

wherein \( R^4 \) is

- a hydrogen atom,
- a halogen atom,
- a hydroxy group,
- a cyano (nitrile) group,

an amino group optionally having substituent(s),

- a mercapto group optionally having a substituent (the mercapto group is optionally oxidized)

- an alkyl group optionally having substituent(s) other than a substituted amino group,

- an alkoxy group optionally having substituent(s),

- a 3- to 10-membered cyclic hydrocarbon group optionally having substituent(s),

- a 3- to 10-membered heterocyclic group optionally having substituent(s) or

an acyl group (wherein when the acyl group is \(-\text{CONR}'\text{R}''\), then \( R' \) and \( R'' \) are both hydrogen atoms or form, together with the nitrogen atom bonded thereto, a nitrogen-containing heterocycle optionally having substituent(s)).

\[ \text{[0194]} \]

The "alkyl group" of the "alkyl group optionally having substituent(s) other than a substituted amino group" for \( R^4 \) optionally has (for example, 1 to 5, preferably 1 to 3) substituent(s) other than the substituted amino group at substitutable position(s). When the number of the substituents is two or more, the respective substituents may be the same or different. Examples of the substituent include substituent group B (except mono- or di-C\(_{1-6}\) alkylamino group, C\(_{7-16}\)
aralkylamino group, C₁₋₆ alkoxy-carbonylamino group and C₁₋₆ alkyl-carbonylamino group). Examples of the “substituent” of the “substituted amino group” include unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocyclyl or unsubstituted or substituted cycloalkyl or acyl (e.g., C₁₋₆ alkyl group substituted by C₁₋₆ cycloalkyl group or heterocycle) and the like.

10 [0195]

Examples of the substituent of the “alkoxy group optionally having substituent(s)”,” 3- to 10-membered cyclic hydrocarbon group optionally having substituent(s)” and “3- to 10-membered heterocyclic group optionally having substituent(s)” for R⁴ include 1 to 5, preferably 1 to 3, selected from the aforementioned substituent group B. When the number of the substituents is two or more, the respective substituents may be the same or different.

Examples of the “substituent” of the “amino group optionally having substituent(s)” for R⁴ include 1 or 2 selected from the aforementioned substituent group B. When the number of the substituents is two, the respective substituents may be the same or different.

Examples of the “substituent” of the “mercapto group optionally having a substituent” for R⁴ include the aforementioned substituent group B. The mercapto group may be oxidized by 1 or 2 oxygens.

Examples of the substituent of the “nitrogen-containing heterocycle optionally having substituent(s)” formed by R’ and R” together with the nitrogen atom include 1 to 5, preferably 1 to 3, selected from the aforementioned substituent group B. When the number of the above-mentioned substituents is two or more, the respective substituents may be the same or different.

Ring B is more preferably a ring represented by the

35 formula
[0196]

HN

[0197]

wherein \( R^4 \) is

5 a hydrogen atom,

5 a halogen atom,

5 a hydroxy group,

5 a cyano (nitrile) group,

an amino group optionally having 1 or 2 substituents selected from the substituent group B,

a mercapto group optionally having a substituent selected from the substituent group B (the mercapto group is optionally oxidized),

a \( C_{1-6} \) alkyl group optionally having 1 or 2 substituents selected from the substituent group B,

5 a \( C_{1-6} \) alkoxy group optionally having a substituent selected from the substituent group B,

5 a 3- to 10-membered cyclic hydrocarbon group optionally having 1 to 3 substituents selected from the substituent group B,

5 a 3- to 10-membered heterocyclic group optionally having 1 to 3 substituents selected from the substituent group B,

a carboxy group,

a \( C_{1-6} \) alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl)

optionally having 1 to 3 substituents selected from the substituent group B, or

a group represented by the formula: \(-\text{CONR}'\text{R}''\)

wherein \( R' \) and \( R'' \) are each a hydrogen atom, or \( R' \) and \( R'' \) form, together with the nitrogen atom bonded thereto, a nitrogen-containing heterocycle optionally having 1 to 3 substituents selected from the aforementioned substituent group B.

Ring B is more preferably a ring represented by
wherein $R^4$ is

5  (1) a hydrogen atom,
      (2) a cyano (nitrile) group,
      (3) a C$_{1-6}$ alkyl group (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl) optionally having 1 to 3 substituents selected from
     (a) a hydroxy group,
     (b) a C$_{1-6}$ alkoxy group (e.g., methoxy, ethoxy),
     (c) a C$_{1-6}$ alkyl-carbonyloxy group (e.g., acetyloxy),
     (d) an aromatic heterocyclic group (e.g., pyridyl, pyrazolyl, triazolyl) optionally having 1 to 3 halogen atoms,
     (e) a C$_{3-10}$ cycloalkyl group (e.g., cyclopropyl), and
     (f) a cyclic amino group (e.g., pyrrolidinyl, piperidino, morpholino, thiomorpholino, piperazinyl, imidazolidin-1-yl, pyrazolidin-1-yl etc.) optionally having an oxo group,
     (4) a 3- to 10-membered heterocyclic group (1,2,4-triazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, 4,5-dihydro-1,2,4-oxadiazolyl, tetrazolyl, tetrahydropyrimidinyl, oxazolyl, piperidiny1, pyrrolidinyl, hexahydropyrimidinyl) optionally having 1 to 3 substituents selected from a C$_{1-6}$ alkyl group and an oxo group,
    (5) a carboxy group,
    (6) a C$_{1-6}$ alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl) optionally having 1 to 3 substituents selected from a nonaromatic heterocyclic group (e.g., dioxolyl) optionally having 1 to 3 substituents selected from a C$_{1-6}$ alkyl group (e.g., methyl) and oxo group, or
    (7) a group represented by the formula: $-\text{CO-NR'R}$
wherein R′ and R″ are each a hydrogen atom, or form, together with the nitrogen atom bonded thereto, a nitrogen-containing heterocycle (e.g., azetidine, morpholine, pyrrolidine, piperidine, 7-aza-bicyclo[2.2.1]heptane, homomorpholine, dihydrobenzoxazine (e.g., 3,4-dihydro-2H-1,4-benzoxazine)) optionally having 1 to 3 substituents selected from halogen atom(s) (e.g., fluorine atom).

Preferable examples of compound (I) include the following.

[Compound I-1]

A compound represented by the formula (I) wherein ring A is a ring represented by

\[
\begin{align*}
\text{R}^a & \quad \text{R}^b \\
\text{Y} & \quad \text{N}
\end{align*}
\]

[0202]

wherein R^a and R^b are each independently a hydrogen atom, a halogen atom, an alkyl group optionally having substituent(s), an alkoxy group optionally having substituent(s) or an acyl group (particularly preferably a hydrogen atom); Y^1 and Y^2 are each independently CH or N;

R^1 is a C_{1-6} alkyl group optionally having substituent(s),
R^2 is a C_{1-6} alkyl group (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl) optionally having substituent(s) other than a substituted amino group or an acyl group (wherein when the acyl group is -CONR′R″, then R′ and R″ are both hydrogen atoms or form, together with the nitrogen atom bonded thereto, a nitrogen-containing heterocycle (e.g., morpholine) optionally having substituent(s)), and
X is a C_{1-6} alkyl group optionally substituted by an alkoxy group (e.g., methoxy, ethoxy), or a salt thereof.

[0203]
Here, examples of the substituent of the "C<sub>1-6</sub> alkyl group optionally having substituent(s)" for R<sup>a</sup> include 1 to 5, preferably 1 to 3, selected from the aforementioned substituent group A.

Examples of the substituent of the "C<sub>1-6</sub> alkyl group optionally having substituent(s)" and "C<sub>1-6</sub> alkoxy group optionally having substituent(s)" for R<sup>a</sup> or R<sup>b</sup> include 1 to 5, preferably 1 to 3, selected from the aforementioned substituent group B.

Examples of the substituent of the "C<sub>1-6</sub> alkyl group optionally having substituent(s)" other than a substituted amino group" for R<sup>2</sup> include 1 to 5, preferably 1 to 3, selected from the aforementioned substituent group B. When the number of the above-mentioned substituents is two or more, the respective substituents may be the same or different.

[0204]

[Compound I-2]

A compound represented by the formula (II) wherein ring A<sup>1</sup> is a ring represented by

![Diagram]

[0205]

wherein R<sup>a</sup> and R<sup>b</sup> are each independently a hydrogen atom, a halogen atom, an alkyl group optionally having substituent(s), an alkoxy group optionally having substituent(s), or an acyl
group (particularly preferably a hydrogen atom); 
Y1 and Y2 are each independently CH or N,
ring B is a ring represented by

\[ \text{[0207]} \]

\[ \text{[0208]} \]

wherein R4 is
a hydrogen atom,
a halogen atom,
a hydroxy group,
a cyano (nitrile) group,
an amino group optionally having substituent(s),
an mercapto group optionally having a substituent (the mercapto group is optionally oxidized),
an alkyl group optionally having substituent(s),
an alkoxy group optionally having substituent(s),
a 3- to 10-membered cyclic hydrocarbon group optionally having substituent(s),
a 3- to 10-membered heterocyclic group optionally having substituent(s), or
an acyl group,
R1 is a C1-6 alkyl group optionally having substituent(s),
R3 is a C1-6 alkoxy group optionally having substituent(s), and
X1 is a C1-6 alkylene group, or a salt thereof.

\[ \text{[0209]} \]

Here, examples of the substituent of the "C1-6 alkyl group optionally having substituent(s)" for R1 and the "C1-6 alkoxy group optionally having substituent(s)" for R3 include 1 to 5, preferably 1 to 3, selected from the aforementioned substituent group A.

Examples of the substituent of the "C1-6 alkyl group optionally having substituent(s)" and "C1-6 alkoxy group
optionally having substituent(s)" for \( R^a \) or \( R^b \) include 1 to 5, preferably 1 to 3, selected from the aforementioned substituent group B.

Examples of the substituent of the “C\(_{1-6}\) alkyl group optionally having substituent(s)”, “C\(_{1-6}\) alkoxy group optionally having substituent(s)”, “3- to 10-membered cyclic hydrocarbon group optionally having substituent(s)” and “3- to 10-membered heterocyclic group optionally having substituent(s)” for \( R^4 \) include 1 to 5, preferably 1 to 3, selected from the aforementioned substituent group B. When the number of the above-mentioned substituents is two or more, the respective substituents may be the same or different.

Examples of the “substituent” of the “amino group optionally having substituent(s)” for \( R^4 \) include 1 or 2 selected from the aforementioned substituent group B. When the number of the above-mentioned substituents is two, the respective substituents may be the same or different.

Examples of the “substituent” of the “mercapto group optionally having a substituent” for \( R^4 \) include the aforementioned substituent group B. The mercapto group may be oxidized by 1 or 2 oxygens.

[0210]
[Compound I-3]

A compound represented by the formula (II) wherein ring \( A^2 \) is a ring represented by

![Diagram](image)

[0212]

wherein \( R^a \) and \( R^b \) are each independently a hydrogen atom, a halogen atom, an alkyl group optionally having substituent(s), an alkoxy group optionally having substituent(s) or an acyl
group (particularly preferably a hydrogen atom); 
Y¹ and Y² are each independently CH or N,
ring B is a ring represented by

[0213]

\[
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{R}^4 \\
\end{array}
\]

[0214]
wherein \( R^4 \) is
a hydrogen atom,
a halogen atom,
a hydroxy group,
a cyano (nitrile) group,
an amino group optionally having substituent(s),
an mercapto group optionally having a substituent (the mercapto group is optionally oxidized),
an alkyl group optionally having substituent(s) other than a substituted amino group,
an alkoxy group optionally having substituent(s),
a 3- to 10-membered cyclic hydrocarbon group optionally having substituent(s),
a 3- to 10-membered heterocyclic group optionally having substituent(s), or
an acyl group (wherein when the acyl group is \(-\text{CONR}' R''\), then \( R' \) and \( R'' \) are both hydrogen atoms or form, together with the nitrogen atom bonded thereto, a nitrogen-containing heterocycle optionally having substituent(s)),
\( R^1 \) is a C₁₋₆ alkyl group optionally having substituent(s),
\( R^3 \) is a C₁₋₆ alkoxy group optionally having substituent(s), and
\( X^1 \) is a C₁₋₆ alkylene group, or a salt thereof.

[0215]
Here, Examples of the substituent of the "C₁₋₆ alkyl group optionally having substituent(s)" for \( R^1 \) and the "C₁₋₆ alkoxy group optionally having substituent(s)" for \( R^3 \) include 1 to 5,
preferably 1 to 3, selected from the aforementioned substituent group A.

Examples of the substituent of the "C_{1-6} alkyl group optionally having substituent(s)" and "C_{1-6} alkoxy group optionally having substituent(s)" for R^6 or R^p include 1 to 5, preferably 1 to 3, selected from the aforementioned substituent group B.

Examples of the substituent of the "C_{1-6} alkyl group optionally having substituent(s)" other than a substituted amino group", "C_{1-6} alkoxy group optionally having substituent(s)"", "3- to 10-membered cyclic hydrocarbon group optionally having substituent(s)" and "3- to 10-membered heterocyclic group optionally having substituent(s)" for R^4 include 1 to 5, preferably 1 to 3, selected from the aforementioned substituent group B.

Examples of the substituent of the "nitrogen-containing heterocycle optionally having substituent(s)" formed by R' and R" together with the nitrogen atom bonded thereto include 1 to 5, preferably 1 to 3, selected from the aforementioned substituent group B. When the number of the above-mentioned substituents is two or more, the respective substituents may be the same or different.

Examples of the "substituent" of the "amino group optionally having substituent(s)" for R^4 include 1 or 2 selected from the aforementioned substituent group B. When the number of the above-mentioned substituents is two, the respective substituents may be the same or different.

Examples of the "substituent" of the "mercapto group optionally having a substituent" for R^4 include the aforementioned substituent group B. The mercapto group may be oxidized by 1 or 2 oxygens.

[0216]
[Compound I-4]

A compound represented by the formula (II) wherein ring A^1 is a ring represented by any one of
wherein \( R^a \) and \( R^b \) are each independently a hydrogen atom, a halogen atom (e.g., fluorine atom, chlorine atom), a C\(_{1-6}\) alkoxy group (e.g., methoxy), or C\(_{1-6}\) alkoxy-carbonyl group (e.g., methoxycarbonyl) (particularly preferably a hydrogen atom); \( R^c \) is a hydrogen atom, or =O; \( Y^1 \) and \( Y^2 \) are each independently CH or N; \( Z \) is S, ring B is a ring represented by

wherein \( R^d \) is

1. a hydrogen atom,
2. a cyano (nitrile) group,
3. a C\(_{1-6}\) alkyl group (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl) optionally having 1 to 3 substituents selected from
   a. a hydroxy group,
   b. a C\(_{1-6}\) alkoxy group (e.g., methoxy, ethoxy),
   c. a C\(_{1-6}\) alkyl-carbonyloxy group (e.g., acetyloxy),
   d. an aromatic heterocyclic group (e.g., pyridyl, pyrazolyl, triazolyl) optionally having 1 to 3 halogen atoms,
   e. a C\(_{3-10}\) cycloalkyl group (e.g., cyclopropyl), and
   f. a cyclic amino group (e.g., pyrrolidinyl, piperidino, morpholino, thiomorpholino, piperazinyl, imidazolidin-1-yl,
pyrazolidin-1-yl etc.) optionally having an oxo group,
(4) a 3- to 10-membered heterocyclic group (1,2,4-triazolyl,
1,3,4-oxadiazoxy, 1,2,4-oxadiazoxy, 4,5-dihydro-1,2,4-
oxadiazoxy, tetrazolyl, tetrahydropyrimidinyl, oxazolyl,
piperidinyl, pyrrolidinyl, hexahydropyrimidinyl) optionally
having 1 to 3 substituents selected from a C₁₋₆ alkyl group and
an oxo group,
(5) a carboxy group,
(6) a C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl,
ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl)
optionally having 1 to 3 substituents selected from a
nonaromatic heterocyclic group (e.g., dioxolyl) optionally
having 1 to 3 substituents selected from a C₁₋₆ alkyl group
(e.g., methyl) and oxo group or
(7) a group represented by the formula: –CO–NR′R″
wherein R′ and R″ are each a hydrogen atom, or
R′ and R″ form, together with the nitrogen atom bonded thereto,
a nitrogen-containing heterocycle (e.g., azetidine, morpholine,
pyrrolidine, piperidine, 7-aza-bicyclo[2.2.1]heptane,
homomorphyline, dihydrobenzoxazin (e.g., 3,4-dihydro-2H-1,4-
benzoxazin)) optionally having 1 to 3 substituents selected
from halogen atom(s) (e.g., fluorine atom),
R³ is a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy) optionally
substituted by a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy) or a
halogen atom (e.g., fluorine atom), a C₁₋₆ alkylthio group (e.g.,
methylthio), a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl)
optionally substituted by a C₁₋₆ alkyl group (e.g., methyl), an
aryl group (e.g., phenyl) or a heteroaryl group (e.g., thiienyl,
thiazolyl, pyridyl, pyrazolyl, imidazolyl, 1,3,4-oxadiazoxy,
1,2,4-oxadiazoxy) optionally substituted by a C₁₋₆ alkyl group
(e.g., methyl), and
X¹ is a C₁₋₆ alkylene group (e.g., methylene, ethylene,
trimethylene, tetramethylene), or a salt thereof.

[0221]

[Compound I-5]
A compound represented by the formula (I) wherein ring A is a pyrimidine optionally having substituent(s), a pyrrole optionally having substituent(s), an imidazole optionally having substituent(s), a pyrazole optionally having substituent(s) or a triazole (e.g., 1,2,3-triazole, 1,2,4-triazole) optionally having substituent(s), R² is

(1) a C₁₋₆ alkyl group (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl) optionally having 1 to 3 substituents selected from

(a) a hydroxy group,
(b) a halogen atom (e.g., fluorine atom),
(c) a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy),
(d) a C₁₋₆ alkyl-carbonyloxy group (e.g., acetyloxy),
(e) an aromatic heterocyclic group (e.g., pyridyl) optionally having 1 to 3 halogen atoms,
(f) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl), and
(g) a cyclic amino group (e.g., pyrrolidinyl, piperidino, morpholino, thiomorpholino, piperazinyl, imidazolidin-1-yl, pyrazolidin-1-yl etc.) optionally having an oxo group,

(2) a 3- to 10-membered heterocyclic group (1,2,4-triazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, 4,5-dihydro-1,2,4-oxadiazolyl, tetrazolyl, tetrahydropyrimidinyl, oxazolyl, piperidinyl, pyrrolidinyl, hexahydropyrimidinyl) optionally having 1 to 3 substituents selected from a C₁₋₆ alkyl group and an oxo group,

(3) a carboxy group,
(4) a C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl) optionally having 1 to 3 substituents selected from a nonaromatic heterocyclic group (e.g., dioxolyl) optionally having 1 to 3 substituents selected from a C₁₋₆ alkyl group (e.g., methyl) and oxo group,

(5) a C₁₋₆ alkyl-carbonyl group (e.g., acetyl), or

(6) a group represented by the formula: -CO-NR’R"
wherein $R'$ and $R''$ are each a hydrogen atom, or
$R'$ and $R''$ form, together with the nitrogen atom bonded thereto,
a nitrogen-containing heterocycle (e.g., azetidine, morpholine,
pyrrolidine, piperidine, 7-aza-bicyclo[2.2.1]heptane,
homomorpholine, dihydrobenzoazin (e.g., 3,4-dihydro-2H-1,4-
benzoazin)) optionally having 1 to 3 substituents selected
from halogen atom(s) (e.g., fluorine atom),
$R^1$ is a C$_{1-6}$ alkyl group (e.g., isobutyl), and
X is
(1) a hydrogen atom;
(2) a C$_{1-6}$ alkyl group (e.g., methyl, ethyl, propyl, isopropyl,
butyl, hexyl) optionally substituted by 1 to 3 substituents
selected from
(a) a halogen atom (e.g., fluorine atom),
(b) a hydroxy group,
(c) a C$_{1-6}$ alkoxy group (e.g., methoxy, ethoxy) optionally
having a C$_{1-6}$ alkoxy group (e.g., methoxy) or a halogen atom
(e.g., fluorine atom),
(d) a C$_{1-6}$ alkylthio group (e.g., methylthio),
(e) an aryl group (e.g., phenyl),
(f) an aryloxy group (e.g., phenoxy) optionally having a C$_{1-6}$
alkoxy group (e.g., methoxy) or a halogen atom (e.g., fluorine
atom), and
(g) a heteroaryl group (e.g., thienyl, thiazolyl); or
(3) a C$_{3-10}$ cycloalkyl group (e.g., cyclopropyl),
or a salt thereof.

[0222]
Here, examples of the substituent of the "pyrimidine" of
"pyrimidine optionally having substituent(s)", "pyrrole" of
"pyrrole optionally having substituent(s)", "imidazole" of
"imidazole optionally having substituent(s)", "pyrazole" of
"pyrazole optionally having substituent(s)" and "triazole" of
"triazole optionally having substituent(s)" for ring A include
1 to 3 selected from the aforementioned substituent group A.
A compound represented by the formula (I) wherein
R\textsuperscript{1} is a C\textsubscript{1-6} alkyl group optionally having substituent(s);
R\textsuperscript{2} is an acyl group (wherein when the acyl group is -CONR'\textsuperscript{''},
then R' and R'' are both hydrogen atoms or form, together with
the nitrogen atom bonded thereto, a nitrogen-containing
heterocycle optionally having substituent(s));
ring A is a ring represented by the formula

![Chemical Structure](image)

wherein R\textsuperscript{a} and R\textsuperscript{b} are each a hydrogen atom; and Y\textsuperscript{1} and Y\textsuperscript{2} are
each independently CH or N, and
X is a C\textsubscript{1-6} alkyl group optionally substituted by a C\textsubscript{1-6} alkoxy
group, or a salt thereof.

A compound represented by the formula (II) wherein
R\textsuperscript{1} is a C\textsubscript{1-6} alkyl group optionally having substituent(s),
R\textsuperscript{2} is a C\textsubscript{1-6} alkoxy group optionally having substituent(s),
ring A\textsuperscript{1} is a ring represented by the formula

![Chemical Structure](image)

wherein R\textsuperscript{a} and R\textsuperscript{b} are each a hydrogen atom; and Y\textsuperscript{1} and Y\textsuperscript{2} are
each independently CH or N,
X\textsuperscript{1} is a C\textsubscript{1-6} alkylene group, and
ring B is

[0228]

wherein \( R^4 \) is \(-\text{CO-}NR'R'' \) wherein \( R' \) and \( R'' \) are each a hydrogen atom, or \( R' \) and \( R'' \) form, together with the nitrogen atom bonded thereto, a nitrogen-containing heterocycle optionally having 1 to 3 substituents selected from halogen atom(s), or a salt thereof.

[0229]

Examples of the salts of compound (I) and compound (II) include metal salts, ammonium salts, salts with organic bases, salts with inorganic acids, salts with organic acids, salts with basic or acidic amino acids, and the like.

Preferable examples of the metal salt include alkali metal salts such as sodium salt, potassium salt and the like; alkaline earth metal salts such as calcium salt, magnesium salt, barium salt and the like; aluminum salt and the like.

Preferable examples of the salt with organic base include a salt with trimethylamine, triethylamine, pyridine, picoline, 2,6-lutidine, ethanolamine, diethanolamine, triethanolamine, cyclohexylamine, dicyclohexylamine, N,N-dibenzylethylenediamine or the like.

Preferable examples of the salt with inorganic acid include a salt with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid or the like.

Preferable examples of the salt with organic acid include a salt with formic acid, acetic acid, trifluoroacetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid or the like.
Preferable examples of the salt with basic amino acid include a salt with arginine, lysine, ornithine or the like. Preferable examples of the salt with acidic amino acid include a salt with aspartic acid, glutamic acid or the like.

Of these, a pharmaceutically acceptable salt is preferable. When the compound has an acidic functional group, examples thereof include inorganic salts such as alkali metal salts (e.g., sodium salt, potassium salt, etc.), alkaline earth metal salts (e.g., calcium salt, magnesium salt, barium salt, etc.) and the like, ammonium salts, and the like. When the compound has a basic functional group, examples thereof include salts with inorganic acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like, and salts with organic acids such as acetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid and the like.

[0230]

The production methods of compound (I) and compound (II) are shown in the following.

Compound (I) compound (II) are obtained by, for example, methods shown in the following reaction schemes or a method analogous thereto, or the like.

Each of compounds (II)-(XXXXI) shown in the reaction schemes may form a salt. Examples of the salt include salts similar to the salts of compound (I) and compound (II).

The compound obtained in each step can also be used for the next reaction directly as the reaction mixture or as a crude product. In addition, it can also be isolated from the reaction mixture according to a conventional method, and can be isolated and purified by a known method such as phase transfer, concentration, solvent extraction, fractional distillation, pH conversion, crystallization, recrystallization, chromatography and the like.

[0231]
The reaction schemes thereof are shown in the following.

Each symbol of the compounds in the schemes is as defined above. R is a C1-4 alkyl group, E is a carboxyl group, an alkali metal salt of carboxyl group, a chlorocarbonyl group, an acid anhydride, a trichloromethyl group, a trichloromethylcarbonyl group or an ester group, Q is a hydrogen atom or an alkali metal atom, W is a hydrogen atom or any substituent, V is a hydrogen atom, an alkyl group or an alkali metal atom, LG is a leaving group (e.g., chloro group, bromo group, iodo group, methanesulfonate group etc.) or a hydroxyl group, and PG is an N-protecting group (e.g., benzyl group, tert-butoxycarbonyl group, benzyloxy carbonyl group etc.).

[0232]

(Reaction 1)

[0233]

\[
\begin{align*}
\text{A} & \ x^1 R^3 & \text{condensation} & \xrightarrow{\text{deprotection}} \\
\text{B} & \ x^1 R^3 & \text{(IV)} & \text{(V)} & \text{(II)} \\
\text{A} & \ x^1 R^3 & \text{(III)} & \text{(V)} & \text{(II)}
\end{align*}
\]

[0234]

Compound (V) can be produced by a condensation reaction of compound (III) and compound (IV).

Compound (III) can be produced according to a method known per se, for example, the method described in Bioorganic and Medicinal Chemistry (Bioorg. Med. Chem.), 2001, vol. 9, page 1045-1057 and the like, or a method analogous thereto.

Compound (IV) may be a commercially available product, or can be produced according to a method known per se, for

When E is a carboxyl group, the condensation reaction is performed according to a conventional peptide synthesis technique, for example, an acid chloride method, an acid anhydride method, a mixed anhydride method, a method of using N,N'-dicyclohexylcarbodiimide (DCC), an active ester method, a method of using N,N'-carbonyldimidazole (CDI), a method of using diethyl cyanophosphosphate (DEPC), a method of using N-ethyl-N'(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC·HCl) and 1-hydroxybenzotriazole (HOBT), or the like. Compound (IV) is used in a proportion of about 1 to 2 mol, preferably about 1.0 to 1.1 mol, per 1 mol of compound (III). The reagent used in the above-mentioned method is used in a proportion of about 1 mol to large excess, preferably about 1.1 to 5 mol, per 1 mol of compound (III). The reaction temperature is generally -10 to 80°C, preferably 0 to 30°C.

When E is an alkali metal salt of a carboxyl group, the condensation reaction is advantageously performed according to a method using WSC·HCl and HOBT. Compound (IV) is used in an amount of about 1 to 2 mol, preferably about 1.0 to 1.1 mol, per 1 mol of compound (III). WSC·HCl is used in an amount of about 1 to 4 mol, preferably about 1.5 to 2.5 mol, per 1 mol of compound (III). HOBT is used in an amount of about 1 to 8 mol, preferably about 2.5 to 5.0 mol, per 1 mol of compound (III). The reaction temperature is generally -10 to 100°C, preferably 40 to 70°C.

In both cases, the condensation reaction is preferably performed in a solvent. Examples of the usable solvent include halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like, ethers such as diethyl ether, tetrahydrofuran, dioxane and the like, amides such as N,N-dimethylformamide, N,N-dimethylacetamide.
and the like, dimethyl sulfoxide, pyridine, acetonitrile and a mixed solvent thereof.

While the reaction time varies depending on the reagent or solvent to be used, it is generally 30 min to 3 days, preferably 30 min to 15 hr.

Compound (V) can also be produced by further carrying out the above-mentioned reaction in combination with one or more of known hydrolysis reaction, acylation reaction, alkylation reaction, amination reaction, oxidation-reduction reaction, cyclization reaction, carbon chain extension reaction, substituent exchange reaction and the like, as desired.

Compound (II) can be produced by removing the N-protecting group FG of compound (V). In addition, in each of the aforementioned reactions, when the starting compound has an amino group, a carboxyl group or a hydroxy group as a substituent, a protecting group generally used in peptide chemistry and the like may be introduced into these groups. By removing the protecting group as necessary after the reaction, the objective compound can be obtained. Introduction or removal of these protective groups may be carried out according to a method known per se, for example, the method disclosed in Theodora W. Greene and Peter G. M. Wuts, "Protective Groups in Organic Synthesis, 3rd Ed.", Wiley-Interscience (1999), or the like.

Examples of the amino-protecting group include formyl group; C_{1-6} alkyl-carbonyl group, phenylcarbonyl group, C_{1-6} alkoxy-carbonyl group, allyloxy carbonyl (Alloc) group, phenyloxycarbonyl group, fluorenlymethyloxycarbonyl (Fmoc) group, C_{7-10} aralkyl-carbonyl group (e.g., benzylcarbonyl etc.), C_{7-10} aralkyloxy-carbonyl group (e.g., benzlyoxycarbonyl (Cbz) etc.), C_{7-10} aralkyl group (e.g., benzyl etc.), trityl group, phthaloyl group, dithiasuccinyl group, N,N-dimethylaminomethylene group, each of which optionally has substituent(s) and the like. Examples of the substituent...
include phenyl group, halogen atom, C_{1-6} alkyl-carbonyl group, C_{1-6} alkoxy group (e.g., methoxy, ethoxy, trifluoromethoxy etc.) optionally substituted by halogen atom, nitro group and the like, and the number of the substituents is 1 to 3.

Examples of the protecting group for carboxyl group include C_{1-6} alkyl group, allyl group, benzyl group, phenyl group, trityl group, trialkylsilyl group, each of which optionally has substituent(s), and the like. Examples of the substituent include halogen atom, a formyl group, C_{1-6} alkyl-carbonyl group, C_{1-6} alkoxy group (e.g., methoxy, ethoxy, trifluoromethoxy etc.) optionally substituted by halogen atom, nitro group and the like, and the number of the substituents is 1 to 3.

Examples of the protecting group for hydroxy group include C_{1-6} alkyl group, C_{7-20} aralkyl group (e.g., benzyl, trityl etc.), a formyl group, C_{1-6} alkyl-carbonyl group, benzoyl group, C_{7-10} aralkyl-carbonyl group (e.g., benzylcarbonyl etc.), 2-tetrahydropyranyl group, tetrahydrofuranyl group, trialkylsilyl group (e.g., trimethylsilyl, tert-butyldimethylsilyl, diisopropylethylsilyl etc.), each of which optionally has substituent(s), and the like. Examples of the substituent include halogen atom, C_{1-6} alkyl group, phenyl group, C_{7-10} aralkyl group (e.g., benzyl etc.), C_{1-6} alkoxy group, nitro group and the like, and the number of the substituents is 1 to 4.

When compound (II) is obtained as a free compound, it can be converted to an object salt by a method known per se or a method analogous thereto, and when it is obtained as a salt, it can be converted to a free form or other object salt by a method known per se or a method analogous thereto.

[0236]
(Reaction 2)

[0237]
[0238]

Compound (VII) can be produced by a reaction of compound (VI) with compound (IV).

Compound (VI) may be a commercially available product, or can be produced according to a method known per se, for example, the method described in Journal of Organic Chemistry (J. Org. Chem.), 2002, vol. 67, page 9276-9287 and the like, or a method analogous thereto.

The condensation reaction of compound (VI) and compound (IV) can be performed under the conditions of the method used for the aforementioned production of compound (V).

Compound (V) can be produced from compound (VII).

The reaction from compound (VII) to compound (V) can be performed according to a method known per se, for example, the method described in Bioorganic and Medicinal Chemistry Letters (Bioorg. Med. Chem. Lett.), 2000, vol. 10, page 957-961 or Journal of Medicinal Chemistry (J. Med. Chem.), 1996, vol. 39, page 2856-2859 and the like, or a method analogous thereto.

Compound (V) can also be produced by further performing the above-mentioned reaction in combination with one or more of known hydrolysis, acylation reaction, alkylation reaction, amination reaction, oxidation reduction reaction, cyclization reaction, carbon chain extension reaction, substituent exchange reaction and the like, as desired.

[0239]
(Reaction 3)

[0240]

This method is used for the production of compound (II) wherein ring A is a fused imidazole ring.

Compound (VIII) can be produced from compound (IV).

Compound (VIII) can be produced using compound (IV) and according to a known method, for example, the method described in Tetrahedron, 1993, vol. 49, page 4015-4034 and the like, or a method analogous thereto.


Compound (X) can be produced from compound (VIII) and compound (IX) according to a known method, for example, the method described in Journal of Chemical Society Perkin transaction 2 (J. Chem. Soc. Perkin Trans. 2), 2001, page

When LG is a substitutable leaving group, compound (XI) may be a commercially available product, or can be produced according to a method known per se, for example, the method described in WO2005003122 and the like, or a method analogous thereto.

When LG is a hydroxyl group, compound (XI) may be a commercially available product, or can be produced according to a method known per se, for example, the method described in WO2005003122 and the like, or a method analogous thereto.

Compound (XII) can be produced from compound (X) and compound (XI) according to a known method, for example, the method described in EP1479676 or Bioorganic and Medicinal Chemistry Letters (Bioorg. Med. Chem. Lett.), 2006, vol. 16, page 4638-4640 or Bioorganic and Medicinal Chemistry Letters (Bioorg. Med. Chem. Lett.), 1997, vol. 7, page 2819-2824, and the like, or a method analogous thereto.

Compound (XII) can also be produced by further performing the above-mentioned reaction in combination with one or more of known hydrolysis, acylation reaction, alkylation reaction, amination reaction, oxidation reduction reaction, cyclization reaction, carbon chain extension reaction, substituent exchange reaction and the like, as desired.

Compound (II) can be produced by removing N-protecting group PG from compound (XII). In each of the above-mentioned reactions, when the starting compound has an amino group, a carboxyl group or a hydroxyl group as a substituent, these groups may be protected with a protecting group generally used in peptide chemistry and the like. In this case, the object compound can be obtained by removing the protecting group as necessary after the reaction. These protecting groups can be introduced or removed according to a method known per se, for example, the method described in Theodora W. Greene and Peter

When compound (II) is obtained as a free compound, it can be converted to an object salt by a method known per se or a method analogous thereto, and when it is obtained as a salt, it can be converted to a free form or other object salt by a method known per se or a method analogous thereto.

(Reaction 4)

[0242]

Compound (XII) can also be produced from compound (VIII) and compound (XIII).

[0244]

Compound (XIII) may be a commercially available product, or can be produced according to a method known per se, for example, the method described in Heterocycles (Heterocycles), 1998, vol. 48, page 1347-1364 and the like, or a method analogous thereto.

The reaction to produce compound (XII) from compound (VIII) and compound (XIII) can be performed under the conditions employed for the production of compound (X).

Compound (XII) can also be produced by further performing the above-mentioned reaction in combination with one or more of known hydrolysis, acylation reaction, alkylation reaction, amination reaction, oxidation reduction reaction, cyclization reaction, carbon chain extension reaction, substituent exchange reaction and the like, as desired.
Compound (XIV) can be produced using compound (IX) and according to a known method, for example, the method described in Journal of Medicinal Chemistry (J. Med. Chem.), 2005, vol. 48, page 8289-8298 and the like or a method analogous thereto.

Compound (X) can be produced from compound (XIV) and compound (IV) according to a known method, for example, the method described in Journal of Medicinal Chemistry (J. Med. Chem.), 2005, vol. 48, page 8289-8298 page and the like or a method analogous thereto.

Compound (X) can also be produced by performing the above-mentioned reaction in combination with one or more of known hydrolysis, acylation reaction, alkylation reaction, amination reaction, oxidation reduction reaction, cyclization reaction, carbon chain extension reaction, substituent exchange reaction and the like, as desired.
Compound (XV) can be produced using compound (XIII) and according to a known method, for example, the method described in Journal of Medicinal Chemistry (J. Med. Chem.), 2005, vol. 48, page 8289-8298 and the like or a method analogous thereto.

Compound (XII) can be produced from compound (XV) and compound (IV) according to a known method, for example, the method described in Journal of Medicinal Chemistry (J. Med. Chem.), 2005, vol. 48, page 8289-8298 and the like or a method analogous thereto.

Compound (XII) can also be produced by further performing the above-mentioned reaction in combination with one or more of known hydrolysis, acylation reaction, alkylation reaction, amination reaction, oxidation reduction reaction, cyclization reaction, carbon chain extension reaction, substituent exchange reaction and the like, as desired.

(Reaction 7)
[0253]

Compound (XV) may be a commercially available product, or can be produced according to a method known per se, for example, the method described in Heterocycles (Heterocycles), 2006, vol. 67, page 769-775 and the like, or a method analogous thereto.

Compound (X) can be produced from compound (XV) and compound (IV) according to a known method, for example, the method described in Bioorganic and Medicinal Chemistry Letters (Bioorg. Med. Chem. Lett.), 1997, vol. 7, page 1863-1868, and the like, or a method analogous thereto.

Compound (X) can also be produced by performing the above-mentioned reaction in combination with one or more of known hydrolysis, acylation reaction, alkylation reaction, amination reaction, oxidation reduction reaction, cyclization reaction, carbon chain extension reaction, substituent exchange reaction and the like, as desired.

[0254]
(Reaction 8)

[0255]

[0256]

Compound (XVI) may be a commercially available product, or can be produced according to a method known per se, for example, the method described in Journal of Organic Chemistry (J. Org. Chem.), 2002, vol. 69, page 2626-2629 and the like, or a method analogous thereto.

Compound (XVII) can be produced from compound (XVI) and compound (XI) according to a known method, for example, the

Compound (XVIII) can be produced by subjecting compound (XVII) to known hydrolysis, for example, alkali hydrolysis or acid hydrolysis.

Compound (XII) can be produced from compound (XVIII) and compound (IV) according to a known method, for example, the method described in Bioorganic and Medicinal Chemistry Letters (Bioorg. Med. Chem. Lett.), 1997, vol. 7, page 1863-1868, and the like or a method analogous thereto.

Compound (XII) can also be produced by further performing the above-mentioned reaction in combination with one or more of known hydrolysis, acylation reaction, alkylation reaction, amination reaction, oxidation reduction reaction, cyclization reaction, carbon chain extension reaction, substituent exchange reaction and the like, as desired.

(Reaction 9)

[0257]

[0258]

[0259]

This method is used for the production of a compound
wherein compound (IV) is a structure shown by compound (XXIV).

Compound (XIX) can be produced according to a method known per se, for example, US6018046 etc. or a method analogous thereto.

Compounds (XX), (XXI) and (XXII) can be each produced by subjecting compound (XIX) to a known reduction reaction, for example, a hydrogenation reaction in the presence of a metal catalyst and the like, and then introducing a PG group (a protecting group) by known reactions.


The hydrogenation reaction is more advantageously performed under acidic conditions. Preferable examples of the acid for this step include mineral acids such as mineral acid, hydrochloric acid and the like, organic acids such as acetic acid and the like, and the like. The amount of the acid to be used is about 1 mol to large excess per 1 mol of compound (XIX).

As the metal catalyst used for the hydrogenation reaction, for example, rhodium carbon, platinum oxide, palladium carbon, rhodium-platinum oxide alloy and the like are preferable. The amount of the catalyst to be used is about 0.01 g to 1 g, preferably about 0.05 g to 0.3 g, per 1 g of compound (XIX).

The hydrogenation reaction is advantageously performed using a solvent inert to the reaction. The solvent is not particularly limited as long as the reaction proceeds, for example, organic acid such as acetic acid and the like, mineral acid such as hydrochloric acid and the like, alcohols such as methanol, ethanol, propanol and the like, hydrocarbons
such as benzene, toluene, cyclohexane, hexane and the like, ethers such as diethyl ether, tetrahydrofuran, dioxane and the like, esters such as ethyl acetate and the like, highly-polar solvent such as N,N-dimethylformamide or N-methylpyrrolidone and the like or a mixed solvent thereof and the like are preferable.

While the reaction time varies depending on the reagents and solvents to be used, it is generally 30 min to 60 hr, preferably 30 min to 30 hr.

The reaction temperature is generally 0 to 150°C, preferably 20 to 70°C.

After the reduction reaction, the reaction mixture is neutralized by adding an inorganic base (e.g., sodium hydroxide, potassium carbonate etc.), an organic base (e.g., triethylamine etc.) and the like and concentrated or, the reaction mixture is directly concentrated and the concentrate is neutralized by adding an inorganic base (e.g., sodium hydroxide, potassium carbonate etc.), an organic base (e.g., triethylamine etc.) and the like, and the protecting group (PG group) is introduced thereinto to give compounds (XX), (XXI) and (XXII). The protecting group (PG group) can be introduced according to a method known per se, for example, the method described in Theodora W. Greene and Peter G. M. Wuts, "Protective Groups in Organic Synthesis, 3rd Ed.", Wiley-Interscience (1999), and the like.

Compounds (XX), (XXI) and (XXII) can be isolated from the mixture of compounds (XX), (XXI) and (XXII), respectively, by a known purification method, for example, silica gel column chromatography, recrystallization, high-pressure liquid chromatography and the like.

Compound (XXI) can also be produced according to a method known per se, for example, the method described in WO97/18813 and the like, or a method analogous thereto.

Compound (XXIII) can be produced by a rearrangement reaction (e.g., Curtius rearrangement and the like) of
compound (XXI) or compound (XXII).

Compound (XXIII) can be produced according to a method known *per se*, for example, the method described in US5817678 and the like, or a method analogous thereto.

Compound (XXIV) can be produced by a reaction to introduce substituent $R^1$ into the amino group of compound (XXIII) (e.g., reductive alkylation).

Compound (XXIV) can be produced according to a known method, for example, Bioorganic and Medicinal Chemistry Letters (Bioorg. Med. Chem. Lett.), 2005, vol. 15, page 833-838 or a method analogous thereto.

[0260]
(Reaction 10)

[0261]

This method is used for the production of a compound wherein compound (IV) is a structure shown by compound (XXVIII).

Compound (XXV) can be separated from compound (XXI), which is a mixture of compounds (XXV) and (XXVI), by a known purification method, for example, diastereomer salt method, optically active column chromatography and the like.

Compound (XXV) can also be produced according to a method known *per se*, for example, the method described in Tetrahedron Letters, 2003, vol. 44, page 1611-1614 and the like, or a
method analogous thereto.

Compound (XXVII) can be produced by a rearrangement reaction (e.g., Curtius rearrangement and the like) of compound (XXV).

Compound (XXVII) can be produced according to a known method, for example, the method described in Tetrahedron Letters, 2003, vol. 44, page 1611-1614 and the like, or a method analogous thereto.

Compound (XXVIII) can be produced by a reaction to introduce substituent R into the amino group of compound (XXVII) (e.g., reductive alkylation).

Compound (XXVIII) can be produced according to a known method, for example, Bioorganic and Medicinal Chemistry Letters (Bioorg. Med. Chem. Lett.), 2005, vol. 15, page 833-838 or a method analogous thereto.

[0263]
(Reaction 11)

[0264]

[0265]

Compound (XXIX) can also be produced according to a method known per se, for example, the method described in Tetrahedron Letters, 2003, vol. 44, page 1611-1614 and the like, or a method analogous thereto.

Compound (XXV) can be produced by a known asymmetric esterification reaction and using compound (XXIX).

Compound (XXV) can also be produced according to a known method, for example, the method described in Journal of American Chemical Society (J. Am. Chem. Soc.), 2000, vol. 122, page 9542-9543 and the like or a method analogous thereto.
Compound (XXXI) can be produced by a condensation reaction of compound (XXIX) and compound (XXX).


Compound (XXX) may be a commercially available product, or can be produced according to a method known per se, for example, the method described in Bioorganic and Medicinal Chemistry Letters (Bioorg. Med. Chem. Lett.), 2005, vol. 15, page 833-838 or EP1757582 and the like, the method described for the synthesis of compound (XXVIII), or a method analogous thereto.

When E is a carboxyl group, the condensation reaction is performed by a general method of peptide synthesis, for example, acid chloride method, acid anhydride method, mixed acid anhydride method, a method using N,N'-dicyclohexylcarbodiimide (DCC), activity ester method, a
method using N,N'-carbonyldiimidazole (CDI), a method using diethyl cyanophosphate (DEPC), a method using N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC·HCl) and 1-hydroxybenzotriazole (HOBr) and the like. Compound (XXX) is used in a proportion of about 1 to 2 mol, preferably about 1.0 to 1.1 mol, per 1 mol of compound (XXIX). The reagent used in the above-mentioned method is used in a proportion of about 1 mol to large excess, preferably about 1.1 to 5 mol, per 1 mol of compound (XXIX). The reaction temperature is generally -10 to 80°C, preferably 0 to 30°C.

When E is an alkali metal salt of a carboxyl group, the condensation reaction is advantageously performed by a method using WSC·HCl and HOBr. Compound (XXX) is used in a proportion of about 1 to 2 mol, preferably about 1.0 to 1.1 mol, per 1 mol of compound (XXIX). WSC·HCl is used in a proportion of about 1 to 4 mol, preferably about 1.5 to 2.5 mol, per 1 mol of compound (XXIX). HOBr is used in a proportion of about 1 to 8 mol, preferably about 2.5 to 5.0 mol, per 1 mol of compound (XXIX). The reaction temperature is generally -10 to 100°C, preferably 40 to 70°C.

In any case, the condensation reaction is preferably performed in a solvent, and examples of the solvent include halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like, ethers such as diethyl ether, tetrahydrofuran, dioxane and the like, amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like, dimethyl sulfoxide, pyridine, acetonitrile and a mixed solvent thereof.

While the reaction time varies depending on the reagents and solvents to be used, it is generally 30 min to 3 days, preferably 30 min to 15 hr.

Compound (XXXI) can also be produced by further performing the above-mentioned reaction in combination with one or more of known hydrolysis, acylation reaction, alkylation reaction, amination reaction, oxidation reduction
reaction, cyclization reaction, carbon chain extension reaction, substituent exchange reaction and the like, as desired.

[0268]

Compound (I) can be produced by removing N-protecting group PG from compound (XXXI). In each of the above-mentioned reactions, when the starting compound has an amino group, a carboxyl group or a hydroxyl group as a substituent, these groups may be protected with a protecting group generally used in peptide chemistry and the like. In this case, the object compound can be obtained by removing the protecting group as necessary after the reaction. These protecting groups can be introduced or removed according to a method known per se, for example, the method described in Theodora W. Greene and Peter G. M. Wuts, "Protective Groups in Organic Synthesis, 3rd Ed.", Wiley-Interscience (1999) and the like, or a method analogous thereto. As the amino-protecting group, for example, a formyl group; C_{1-6} alkyl-carbonyl group, phenylcarbonyl group, C_{1-6} alkoxy-carbonyl group, allyloxy carbonyl (Alloc) group, phenyloxycarbonyl group, fluorenylmethyloxycarbonyl (Fmoc) group, C_{7-10} aralkyl-carbonyl group (e.g., benzyloxy carbonyl and the like), C_{7-10} aralkylloxycarbonyl group (e.g., benzyloxy carbonyl (Cbz) and the like), C_{7-10} aralkyl group (e.g., benzyl and the like), trityl group, phthaloyl group, dithiasuccinoyl group, N,N-dimethylaminomethylene group, each optionally having substituent(s), and the like can be mentioned. As the substituent(s), for example, phenyl group, a halogen atom, C_{1-6} alkyl-carbonyl group, C_{1-6} alkoxy group optionally substituted by halogen atom(s) (e.g., methoxy, ethoxy, trifluoromethoxy and the like), nitro group and the like can be used. The number of the substituents is 1 to 3.

As the carboxyl-protecting group, for example, C_{1-6} alkyl group, allyl group, benzyl group, phenyl group, trityl group, trialkylsilyl group, each optionally having substituent(s),
and the like can be mentioned. As the substituent(s), for example, a halogen atom, a formyl group, C_{1-6} alkyl-carbonyl group, C_{1-6} alkoxy group optionally substituted by halogen atom(s) (e.g., methoxy, ethoxy, trifluoromethoxy and the like), nitro group and the like can be used. The number of the substituents is 1 to 3.

As the hydroxy-protecting group, for example, C_{1-6} alkyl group, C_{7-20} aralkyl group (e.g., benzyl, trityl and the like), a formyl group, C_{1-6} alkyl-carbonyl group, benzoyl group, C_{7-10} aralkyl-carbonyl group (e.g., benzylcarbonyl and the like), 2-tetrahydropyranyl group, tetrahydrofuranyl group, trialkylsilyl group (e.g., trimethylsilyl, tert-butyldimethylsilyl, diisopropylethylsilyl and the like), each optionally having substituent(s), and the like can be mentioned. As the substituent(s), for example, a halogen atom, C_{1-6} alkyl group, phenyl group, C_{7-10} aralkyl group (e.g., benzyl and the like), C_{1-6} alkoxy group, nitro group and the like can be used. The number of the substituents is 1 to 4.

When compound (I) is obtained as a free compound, it can be converted to the object salt according to a method known per se or a method analogous thereto, and when it is obtained as a salt, it can be converted to a free compound or other object salt according to a method known per se or a method analogous thereto.

(Reaction 13)

[0269]

[0270]

[0271]
Compound (XXXII) can be produced by reacting compound (VI) with compound (XXX).

Compound (VI) may be a commercially available product, or can be produced according to a method known per se, for example, the method described in Journal of Organic Chemistry (J. Org. Chem.), 2002, vol. 67, page 9276-9287 and the like, or a method analogous thereto.

The condensation reaction of compound (VI) and compound (XXX) can be performed under the conditions employed for the production of the aforementioned compound (V).

Compound (XXXI) can be produced from compound (XXXII).

The reaction from compound (XXXII) to compound (XXXI) can be performed according to a method known per se, for example, the method described in Bioorganic and Medicinal Chemistry Letters (Bioorg. Med. Chem. Lett.), 2000, vol. 10, page 957-961 or Journal of Medicinal Chemistry (J. Med. Chem.), 1996, vol. 39, page 2856-2859 and the like or a method analogous thereto.

Compound (XXXI) can also be produced by performing the above-mentioned reaction in combination with one or more of known hydrolysis, acylation reaction, alkylation reaction, amination reaction, oxidation reduction reaction, cyclization reaction, carbon chain extension reaction, substituent exchange reaction and the like, as desired.

[0272]
(Reaction 14)

[0273]
This method can be used for the production of compound (I) wherein ring A is a fused imidazole ring.

Compound (XXXIII) can be produced from compound (XXX).

Compound (XXXIII) can be produced using compound (XXX) and according to a known method, for example, the method described in Tetrahedron (Tetrahedron), 1993, vol. 49, page 4015-4034 and the like or a method analogous thereto.


Compound (XXXIV) can be produced from compound (XXXIII) and compound (IX) according to a known method, for example, the method described in Journal of Chemical Society Perkin transaction 2 (J. Chem. Soc. Perkin Trans. 2), 2001, page

Compound (XXXIV) can also be produced by further performing the above-mentioned reaction in combination with one or more of known hydrolysis, acylation reaction, alkylation reaction, amination reaction, oxidation reduction reaction, cyclization reaction, carbon chain extension reaction, substituent exchange reaction and the like, as desired.

When LG is a substitutable leaving group, compound (XXXV) may be a commercially available product, or can be produced according to a method known per se, for example, the method described in WO2005003122 and the like, or a method analogous thereto.

When LG is a hydroxyl group, compound (XXXV) may be a commercially available product, or can be produced according to a method known per se, for example, the method described in WO2005003122 and the like, or a method analogous thereto. Compound (XXXVI) can be produced from compound (XXXIV) and compound (XXXV) according to a known method, for example, the method described in EP1479676 or Bioorganic and Medicinal Chemistry Letters (Bioorg. Med. Chem. Lett.), 2006, vol. 16, page 4638-4640 or Bioorganic and Medicinal Chemistry Letters (Bioorg. Med. Chem. Lett.), 1997, vol. 7, page 2819-2824, and the like or a method analogous thereto.

Compound (XXXVI) can also be produced by further performing the above-mentioned reaction in combination with one or more of known hydrolysis, acylation reaction, alkylation reaction, amination reaction, oxidation reduction reaction, cyclization reaction, carbon chain extension reaction, substituent exchange reaction and the like, as desired.

Compound (I) can be produced by removing N-protecting group PG from compound (XXXVI). In each of the above-mentioned
reactions, when the starting compound has an amino group, a carboxyl group or a hydroxyl group as a substituent, these groups may be protected with a protecting group generally used in peptide chemistry and the like. In this case, the object compound can be obtained by removing the protecting group as necessary after the reaction. These protecting groups can be introduced or removed according to a method known per se, for example, a method analogous to the method described in Theodora W. Greene and Peter G. M. Wuts, "Protective Groups in Organic Synthesis, 3rd Ed.", Wiley-Interscience (1999) and the like.

When X of compound (I) is a hydrogen atom, the compound can be produced by removing N-protecting group PG from compound (XXXIV). In each of the above-mentioned reactions, when the starting compound has an amino group, a carboxyl group or a hydroxyl group as a substituent, these groups may be protected with a protecting group generally used in peptide chemistry and the like. In this case, the object compound can be obtained by removing the protecting group as necessary after the reaction. These protecting groups can be introduced or removed according to a method known per se, for example, a method analogous to the method described in Theodora W. Greene and Peter G. M. Wuts, "Protective Groups in Organic Synthesis, 3rd Ed.", Wiley-Interscience (1999) and the like.

When compound (I) is obtained as a free compound, it can be converted to an object salt by a method known per se or a method analogous thereto, and when it is obtained as a salt, it can be converted to a free form or other object salt by a method known per se or a method analogous thereto.

[0275]
(Reaction 15)
[0276]
Compound (XXXVI) can also be produced from compound (XXXIII) and compound (XXXVII).

Compound (XXXVII) may be a commercially available product, or can be produced according to a method known per se, for example, the method described in Heterocycles (Heterocycles), 1998, vol. 48, page 1347-1364 and the like, or a method analogous thereto.

The reaction to produce compound (XXXVI) from compound (XXXIII) and compound (XXXVII) can be performed under the conditions employed for the production of compound (XXXIV).

Compound (XXXVI) can also be produced by further performing the above-mentioned reaction in combination with one or more of known hydrolysis, acylation reaction, alkylation reaction, amination reaction, oxidation reduction reaction, cyclization reaction, carbon chain extension reaction, substituent exchange reaction and the like, as desired.

[0278] (Reaction 16)

[0279]
Compound (XXXIV) can be produced from compound (XIV) and compound (XXX) according to a known method, for example, the method described in Journal of Medicinal Chemistry (J. Med. Chem.), 2005, vol. 48, page 8289-8298 and the like or a method analogous thereto.

Compound (XXXIV) can also be produced by further performing the above-mentioned reaction in combination with one or more of known hydrolysis, acylation reaction, alkylation reaction, amination reaction, oxidation reduction reaction, cyclization reaction, carbon chain extension reaction, substituent exchange reaction and the like, as desired.

(Reactions 17, 18)

Compound (XXXIX) can be produced using compound (XXXVIII)
and according to a known method, for example, the method described in Journal of Medicinal Chemistry (J. Med. Chem.), 2005, vol. 48, page 8289-8298 and the like or a method analogous thereto.

Compound (XXXVI) can be produced from compound (XXXIX) and compound (XXX) according to a known method, for example, the method described in Journal of Medicinal Chemistry (J. Med. Chem.), 2005, vol. 48, page 8289-8298 and the like or a method analogous thereto.

Compound (XXXVI) can also be produced by further performing the above-mentioned reaction in combination with one or more of known hydrolysis, acylation reaction, alkylation reaction, amination reaction, oxidation reduction reaction, cyclization reaction, carbon chain extension reaction, substituent exchange reaction and the like, as desired.

[0284]
(Reaction 18)

[0285]

[0286]

Compound (XV) may be a commercially available product, or can be produced according to a method known per se, for example, the method described in Heterocycles, 2006, vol. 67, page 769-775 and the like, or a method analogous thereto.

Compound (XXXIV) can be produced from compound (XV) and compound (XXX) according to a known method, for example, the method described in Bioorganic and Medicinal Chemistry Letters

Compound (XXXIV) can also be produced by further performing the above-mentioned reaction in combination with one or more of known hydrolysis, acylation reaction, alkylation reaction, amination reaction, oxidation reduction reaction, cyclization reaction, carbon chain extension reaction, substituent exchange reaction and the like, as desired.

[0287]
(Reaction 19)

[0288]

[0289]

Compound (XVI) may be a commercially available product, or can be produced according to a method known per se, for example, the method described in Journal of Organic Chemistry (J. Org. Chem.), 2004, vol. 69, page 2626-2629 and the like, or a method analogous thereto.

Compound (XXXX) can be produced from compound (XVI) and compound (XXXV) according to a known method, for example, the method described in EP1479676 or Bioorganic and Medicinal Chemistry Letters (Bioorg. Med. Chem. Lett.), 2006, vol. 16, page 4638-4640 or Bioorganic and Medicinal Chemistry Letters (Bioorg. Med. Chem. Lett.), 1997, vol. 7, page 2819-2824, and the like or a method analogous thereto.

Compound (XXXXI) can be produced by a known hydrolysis, for example, alkali hydrolysis or acid hydrolysis.

Compound (XXXVI) can be produced from compound (XXXXI)
and compound (XXX) according to a known method, for example, the method described in Bioorganic and Medicinal Chemistry Letters (Bioorg. Med. Chem. Lett.), 1997, vol. 7, page 1863-1868, and the like or a method analogous thereto. Compound (XXXVI) can also be produced by further performing the above-mentioned reaction in combination with one or more of known hydrolysis, acylation reaction, alkylation reaction, amination reaction, oxidation reduction reaction, cyclization reaction, carbon chain extension reaction, substituent exchange reaction and the like, as desired.

[0290]

Compound (I) and compound (II) may be used as prodrugs. A prodrug of compound (I) or compound (II) means a compound which is converted to compound (I) or compound (II) with a reaction due to an enzyme, an gastric acid, etc. under the physiological condition in the living body, that is a compound which is converted to compound (I) or compound (II) with oxidation, reduction, hydrolysis, etc. according to an enzyme; a compound which is converted to compound (I) or compound (II) by hydrolysis etc. due to gastric acid, etc.

Examples of a prodrug of compound (I) or compound (II) include a compound wherein an amino group of compound (I) or compound (II) is acylated, alkylated or phosphorylated (e.g., compound wherein amino group of compound (I) or compound (II) is eicosanoylated, alanylated, pentyaminocarbonylated, (5-methyl-2-oxo-1,3-dioxolen-4-yl) methoxycarbonylated, tetrahydrofuranylated, pyrrolidylmethylated, pivaloyloxyethylated or tert-butylated, and the like); a compound wherein a hydroxy group of compound (I) or compound (II) is acylated, alkylated, phosphorylated or borated (e.g., a compound wherein a hydroxy group of compound (I) or compound (II) is acetylated, palmitoylated, propanoylated, pivaloylated, succinylated, fumarylated, alanylated or dimethylaminomethylcarbonylated, and the like); a compound
wherein a carboxyl group of compound (I) or compound (II) is esterified or amidated (e.g., a compound wherein a carboxyl group of compound (I) or compound (II) is ethyl esterified, phenyl esterified, carboxymethyl esterified, dimethylaminomethyl esterified, pivaloyloxyethyl esterified, ethoxycarbonyloxyethyl esterified, phthalidyl esterified, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl esterified, cyclohexyloxycarbonylethyl esterified or methylamidated, and the like) and the like. These compounds can be produced from compound (I) by a method known per se.

A prodrug of compound (I) and compound (II) may also be one which is converted into compound (I) or compound (II) under a physiological condition, such as those described in IYAKUHIN no KAIHATSU (Development of Pharmaceuticals), Vol.7, Design of Molecules, p.163-198, Published by HIROKAWA SHOTEN (1990).

When compound (I) and compound (II) has an isomer such as optical isomer, stereoisomer, positional isomer, rotational isomer and the like, any isomers and a mixture thereof are encompassed in compound (I) or compound (II). For example, when compound (I) or compound (II) has an optical isomer, an optical isomer resolved from a racemate is also encompassed in compound (I) and compound (II). Such isomer can be obtained as a single product by a synthesis method, a separation method (e.g., concentration, solvent extraction, column chromatography, recrystallization etc.), optical resolution method (e.g., fractional recrystallization, chiral column method, diastereomer method etc.) and the like known per se.

Compound (I) and compound (II) may be a crystal, and both a single crystal and crystal mixtures are encompassed in compound (I) and compound (II). Crystals can be produced by crystallization according to crystallization methods known per se.

Compound (I) and compound (II) may be a solvate (e.g.,
hydrate etc.) or a non-solvate (e.g., non-hydrate etc.), both of which are encompassed in compound (I) and compound (II).

A compound labeled with an isotope (e.g., $^3$H, $^{14}$C, $^{35}$S, $^{125}$I and the like) and the like is also encompassed in compound (I) and compound (II).

Deuterium-converted compound wherein $^3$H has been converted to $^2$H(D) are also encompassed in the compound (I) and compound (II).

[0292]

Compound (I) or compound (II) or its prodrug, or salts thereof (hereinafter, sometimes to be abbreviated to as a compound of the present invention) exhibit superior renin inhibitory activity. They have low toxicity (e.g., acute toxicity, chronic toxicity, genetic toxicity, reproductive toxicity, cardiac toxicity, drug interaction, carcinogenicity, etc.) and high water-solubility, and are excellent in the aspects of stability, pharmacokinetics (absorbability, distribution, metabolism, excretion, etc.) and efficacy, thus being useful as medicine.

[0293]

The compound of the present invention acts as a renin inhibitory drug in mammals (e.g., mouse, rat, hamster, rabbit, cat, dog, cattle, sheep, monkey, human, etc.), and is useful as a drug inhibiting the RA system by inhibiting the biosynthesis of AII, and is useful as an agent for the prophylaxis or treatment of various diseases caused by the RA system.

Examples of such diseases include hypertension (e.g., essential hypertension, renal vascular hypertension, renoparenchymal hypertension, primary aldosteronism, Cushing's syndrome etc.), blood pressure circadian rhythm abnormality, heart diseases (e.g., cardiac hypertrophy, acute heart failure, chronic heart failure including congestive heart failure, failure of expansion, cardiac myopathy, angina pectoris, myocarditis, atrial fibrillation, arrhythmia, tachycardia,
cardiac infarction etc.), cerebrovascular disorders (e.g., asymptomatic cerebrovascular disorder, transient cerebral ischemia, cerebrovascular dementia, hypertensive encephalopathy, cerebral infarction etc.), cerebral edema, cerebral circulatory disorder, recurrence and sequel of cerebrovascular disorders (e.g., neurotic symptom, psychic symptom, subjective symptom, disorder in daily living activities etc.), ischemic peripheral circulation disorder, myocardial ischemia, venous insufficiency, progression of cardiac insufficiency after myocardial infarction, renal diseases (e.g., nephritis, glomerulonephritis, glomerulosclerosis, renal failure, nephrotic syndrome, thrombotic vasculopathy, complication of dialysis, organ damage including nephropathy by radiation irradiation etc.), arteriosclerosis including atherosclerosis (e.g., aneurysm, coronary arteriosclerosis, cerebral arteriosclerosis, peripheral arteriosclerosis etc.), vascular hypertrophy, vascular hypertrophy or obliteration and organ damages after intervention (e.g., percutaneous transluminal coronary angioplasty, stenting, coronary angioscopy, intravascular ultrasound, douse thrombolytic therapy etc.), vascular re-obliteration and restenosis after bypass, polycythemia, hypertension, organ damage and vascular hypertrophy after transplantation, rejection after transplantation, ocular diseases (e.g., glaucoma, ocular hypertension etc.), thrombosis, multiple organ disorder, endothelial dysfunction, hypertensive tinnitus, other cardiovascular diseases (e.g., deep vein thrombosis, obstructive peripheral circulatory disorder, arteriosclerosis obliterans, thromboangiitis obliterans, ischemic cerebral circulatory disorder, Raynaud’s disease, Berger disease etc.), metabolic and/or nutritional disorders (e.g., diabetes, impaired glucose tolerance, insulin resistance, hyperinsulinemia, diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, obesity, hyperlipidemia, hypercholesterolemia, hyperuricacidemia, hyperkalemia,
hypernatremia etc.), metabolic syndrome, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), nerve degeneration diseases (e.g., Alzheimer's disease, Parkinson's disease, Creutzfeldt-Jakob disease, multiple sclerosis, amyotrophic lateral sclerosis, AIDS encephalopathy etc.), central nervous system disorders (e.g., damages such as cerebral hemorrhage and cerebral infarction, and sequela and complication thereof, head injury, spinal injury, cerebral edema, sensory malfunction, sensory functional disorder, autonomic nervous system disorder, autonomic nervous system malfunction etc.), dementia, migraine, defects of memory, disorder of consciousness, amnesia, anxiety symptom, catatonic symptom, discomfort mental state, sleep disorder, agrypnia, psychopathies (e.g., depression, epilepsy, alcoholism etc.), inflammatory diseases (e.g., arthritis such as rheumatoid arthritis, osteoarthritis, rheumatoid myelitis, periostitis etc.; inflammation after operation or injury; remission of swelling; pharyngitis; cystitis; pneumonia; atopic dermatitis; inflammatory intestinal diseases such as Crohn's disease, ulcerative colitis etc.; meningitis; inflammatory ocular disease; inflammatory pulmonary disease such as pneumonia, pulmonary silicosis, pulmonary sarcoidosis, pulmonary tuberculosis etc.), allergic diseases (e.g., allergic rhinitis, conjunctivitis, gastrointestinal allergy, pollinosis, anaphylaxis etc.), chronic obstructive pulmonary disease, interstitial pneumonia, pneumocytis carinii pneumonia, collagen diseases (e.g., systemic lupus erythematoses, scleroderma, polyarteritis etc.), hepatic diseases (e.g., hepatitis including chronic hepatitis, hepatic cirrhosis etc.), portal hypertension, digestive system disorders (e.g., gastritis, gastric ulcer, gastric cancer, gastric disorder after operation, dyspepsia, esophageal ulcer, pancreatitis, colon polyp, cholelithiasis, hemorrhoidal disease, varices ruptures of esophagus and stomach etc.), blood and/or myelopoietic diseases (e.g., erythrocytosis, vascular purpura,
autoimmune hemolytic anemia, disseminated intravascular coagulation syndrome, multiple myelopathy etc.), bone diseases (e.g., fracture, refracture, osteoporosis, osteomalacia, bone Paget's disease, sclerosing myelitis, rheumatoid arthritis, joint tissue dysfunction and the like caused by osteoarthritis of the knee and diseases similar to these), solid tumor, tumors (e.g., malignant melanoma, malignant lymphoma, cancer of digestive organs (e.g., stomach, intestine etc.) etc.), cancer and cachexia following cancer, metastasis cancer, endocrinopathy (e.g., Addison's disease, pheochromocytoma etc.), urinary organ and/or male genital diseases (e.g., cystitis, prostatic hypertrophy, prostatic cancer, sex infectious disease etc.), female disorders (e.g., climacteric disorder, gestosis, endometriosis, hysteromyoma, ovarian disease, breast disease, sex infectious disease etc.), disease relating to environment and occupational factors (e.g., radiation hazard, hazard by ultraviolet, infrared or laser beam, altitude sickness etc.), respiratory diseases (e.g., cold syndrome, pneumonia, asthma, pulmonary hypertension, pulmonary thrombosis and pulmonary embolism etc.), infectious diseases (e.g., viral infectious diseases with cytomegalovirus, influenza virus, herpes virus etc., rickettsiosis, bacterial infectious disease etc.), toxemias (e.g., sepsis, septic shock, endotoxin shock, Gram-negative sepsis, toxic shock syndrome etc.), otolaryngological diseases (e.g., Meniere's syndrome, tinnitus, dysgeusia, vertigo, disequilibrium, dysphagia etc.), skin diseases (e.g., keloid, Hemangioma, psoriasis etc.), eye disease (e.g., cataract, glaucoma etc.), intradialytic hypotension, myasthenia gravis, systemic diseases such as chronic fatigue syndrome and the like.

[0294]

The compound of the present invention can be used in combination with an existing hypertension therapeutic drug such as an ACE inhibitor (captopril, enalapril maleate, alacepril, delapril hydrochloride, imidapril hydrochloride,
quinapril hydrochloride, cilazapril, temocapril hydrochloride, trandolapril, benazepril hydrochloride, perindopril, lisinopril, etc.), ARB (losartan potassium, candesartan cilexetil, valsartan, TAK-536, TAK-491, TAK-591, irbesartan, telmisartan, eprosartan, olmesartan medoxomil, etc.), an aldosterone receptor antagonist (spironolactone, eplerenone, etc.), a Ca-ion channel inhibitor (verapamil hydrochloride, diltiazem hydrochloride, nifedipine, amlodipine besilate, azelnidipine, aranidipine, efondipine hydrochloride, cilnidipine, nicardipine hydrochloride, nisoldipine, nitrendipine, nilvadipine, barnidipine hydrochloride, felodipine, benidipine hydrochloride, manidipine hydrochloride, etc.), a diuretic (trichlormethiazide, hydrochlorothiazide, benzylhydrochlorothiazide, indapamide, triamterine, meticrone, mefruside, furosemide, triamterene, chlorthalidone etc.), a β-blocker (propranolol hydrochloride, atenolol, metoprolol tartrate, bisoprolol fumarate, etc.), an α,β-blocker (carvedilol, etc.), and the like.

[0295]
Moreover, the compound of the present invention can be also used in combination with an antithrombotic drug such as heparin sodium, heparin calcium, warfarin calcium (Warfarin), a blood coagulation factor Xa inhibitor, drug having a function of balance correction in the coagulation-fibrinolysis system, an oral thrombin inhibitor (aragatroban, dabigatran, etc.), a thrombolytic drug (tPA, urokinase, etc.), an antiplatelet drug [aspirin, sulfinpyrazone (Anturane), dipyridamol (Persantine), ticlopidine hydrochloride (Panaldine), clopidogrel, cilostazol (Pletal), GPIIb/IIIa antagonist (abciximab, tirofiban, etc.)], and the like. Also, the compound can be used in combination with a lipid lowering drug or a cholesterol lowering drug. Examples thereof include a squalene synthase inhibitor (lapaquistat acetate etc.), fibrates (clofibrate, benzafibrate, gemfibrozil, etc.), nicotinic acid, its derivatives and analogs (acicimox,
probucol, etc.), a bile acid binding resin (cholestryramine, colestipol, etc.), an omega-3 polyunsaturated fatty acid (EPA (eicosapentaenoic acid), DHA (docosahexaenoic acid), or a mixture thereof etc.), a compound inhibiting cholesterol absorption (sitosterol, neomycin, etc.), and a squalene epoxidase inhibitor (NB-598 and its analogs, etc.). Furthermore, other possible combination components are an oxidosqualene-lanosterol cyclase, for example, a decalin derivative, an azadecalin derivative, an indane derivative and the like. Combination with a HMG-CoA reductase (3-hydroxy-3-methylglutaryl coenzyme A reductase) inhibitor (atorvastatin calcium hydrate, pravastatin sodium, simvastatin, itavastatin, lovastatin, fluvastatin, etc.) is also possible.

[0296]

The compound of the present invention can also be used in combination with a therapeutic drug for diabetes or a therapeutic drug for diabetic complications. For example, the compound of the present invention can be used in combination with an insulin preparation, an insulin sensitivity improving drug [pioglitazone hydrochloride, rosiglitazone, etc.], an α-glucosidase inhibitor [voglibose, acarbose, miglitol, emiglitate etc.], biguanide [phenformin, metformin, buformine etc.], insulin secretagogue [tolbutamide, glibenclamide, gliclazide, nateglinide, mitiglinide, glimepiride etc.], a dipeptidylpeptidase IV inhibitor [Alogliptin benzoate, Vidagliptin (LAF237), P32/98, Saxagliptin (BMS-477118) etc.], glucose sensitivity insulin secretagogue (TAK-875 etc.), GPR40 agonist, GK activator, SGLT inhibitor (dapagliflozin, remogliflozin etc.), Kinedak, Penfill, Humulin, Euglucon, Glimicron, Daonil, Novolin, Monotard, Glucobay, Dimelin, Rastinon, Bacilcon, Deamelin S, Iszilin family, or the like.

[0297]

In addition, the compound can be also used together with other pharmaceutical components, including a bone disease medicine, a myocardial protective drug, a coronary artery
disease medicine, a chronic cardiac failure medicine, a hypothyroidism medicine, a nephrotic syndrome medicine, a chronic renal failure medicine, a gynecological disease medicine, an infection medicine, or the like.

The administration mode may be exemplified by (1) administration of a single preparation obtained by simultaneously formulating the compound of the present invention and the combination drug, (2) simultaneous administration through the same administration route of two preparations obtained by separately formulating the compound of the present invention and the combination drug, (3) administration with a time interval through the same administration route of two preparations obtained by separately formulating the compound of the present invention and the combination drug, (4) simultaneous administration through different administration routes of two preparations obtained by separately formulating the compound of the present invention and the combination drug, (5) administration with a time interval through different administration routes of two preparations obtained by separately formulating the compound of the present invention and the combination drug (e.g., administration in order of the compound of the present invention and then the combination drug, or administration in the reverse order), or the like. The amount of the combination drug to be administered can be appropriately selected with reference to the clinically used dosage. The mixing ratio of the compound of the present invention and the combination drug can be appropriately selected in accordance with the subject of administration, administration route, disease to be treated, symptoms, combination, and the like.

The compound of the present invention can be also used in combination with, for example, gene therapy involving VEGF, TNFα or the like, or therapeutic methods involving various antibody medicines or the like.
The compound of the present invention can be safely administered individually, or according to ordinary methods (e.g., methods described in the Japanese Pharmacopeia, etc.), as a pharmaceutical composition mixed with pharmaceutically acceptable carriers, for example, a tablet (including a sugar-coated tablet and a film-coated tablet), a film, a powder, a granule, a capsule, a liquid, an emulsion, a suspension, an injectable preparation, a suppository, a sustained release preparation, a patch and the like, either orally or parenterally (e.g., topical, rectal, intravenous administration, etc.).

The dosage form of the aforementioned pharmaceutical preparation may be exemplified by oral preparations such as a tablet (including a sublingual tablet and a buccal disintegration tablet), a film (including a buccal disintegration film), a capsule (including a soft capsule and a microcapsule), a granule, a powder, a troche, a syrup, an emulsion, a suspension and the like; and parenteral preparations such as an injectable preparation (e.g., a subcutaneous injectable preparation, an intravenous injectable preparation, intramuscular injectable preparation, intraperitoneal injectable preparation, a drip infusion), external preparation (e.g., a percutaneous preparation, an ointment), a suppository (e.g., a rectal suppository, a vaginal suppository), a pellet, a transnasal preparation, a transpulmonary preparation (inhalant), an eye drop and the like.

These preparations may be controlled release preparations such as a rapid release preparation, a sustained release preparation and the like (e.g., a sustained release microcapsule).

The content of the compound of the present invention in the pharmaceutical composition is about 0.01 to 100% by weight of the entire composition.
The amount of administration of the compound of the present invention may vary depending on the subject of administration, administration route, subject disease or the like; however, in the case of administering orally to an adult as a hypertension medicine, the amount of administration is about 0.0005 to 2 mg/kg of body weight, preferably about 0.001 to 1 mg/kg of body weight, and more preferably about 0.001 to 0.5 mg/kg of body weight, in terms of compound (I) or (II), the active ingredient, possibly once to several times a day.

[0300]

The aforementioned pharmaceutically acceptable carrier may be exemplified by various organic or inorganic carrier materials that are conventionally used as preparation materials, for example, excipient, gliding agent, binding agent and disintegrant for solid preparations; or solvent, solution aid, suspending agent, isotonic agent, buffering agent, soothing agent and the like for liquid preparations. Further, if necessary, additives such as preservative, antioxidant, colorant, sweetening agent, adsorbing agent, wetting agent and the like can be also used.

Examples of the excipient include lactose, white sugar, D-mannitol, starch, corn starch, crystalline cellulose, light anhydrous silicic acid and the like.

Examples of the gliding agent include magnesium stearate, calcium stearate, talc, colloidal silica and the like.

Examples of the binding agent include crystalline cellulose, white sugar, D-mannitol, dextrin, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, starch, sucrose, gelatin, methylcellulose, carboxymethylcellulose sodium and the like.

Examples of the disintegrant include starch, carboxymethylcellulose, carboxymethylcellulose calcium, carboxymethylstarch sodium, L-hydroxypropylcellulose and the like.

Examples of the solvent include water for injection,
alcohol, propylene glycol, Macrogol, sesame oil, corn oil, olive oil and the like.

Examples of the solubilizing agent include polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate and the like.

Examples of the suspending agent include surfactants such as stearyl triethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzetonium chloride, glycerin monostearate and the like; hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose sodium, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and the like; and the like.

Examples of the isotonic agent include glucose, D-sorbitol, sodium chloride, glycerin, D-mannitol and the like.

Examples of the buffering agent include buffer solutions such as phosphates, acetates, carbonates, citrates and the like.

Examples of the soothing agent include benzyl alcohol and the like.

Examples of the preservative include parahydroxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid and the like.

Examples of the antioxidant include sulfites, ascorbic acid, α-tocopherol and the like.

Examples of the colorant include water-soluble Food coal tar dyes (e.g., Food dyes such as Food Red No. 2 and No. 3, Food Yellow No. 4 and No. 5, Food Blue No. 1 and No. 2, and the like), water-insoluble lake dyes (e.g., aluminum salts of the aforementioned water-soluble Food coal tar dyes), natural dyes (e.g., β-carotene, chlorophyll, red iron oxide) and the like.

Examples of the sweetening agent include saccharin sodium, dipotassium glycyrrhizinate, aspartame, stevia and the like.
EXAM PLES

[0301]

The present invention is explained in detail in the following by referring to Reference Examples, Examples,
Preparation Examples and Experimental Examples, which are not to be construed as limitative. Of the synthesis starting materials used in Reference Examples and Examples, synthesis methods of known compounds are omitted.

“Room temperature” in the following Reference Examples and Examples represents a temperature of about 10°C to about 35°C, and “%” represents weight% unless otherwise stated. Provided that, yield represents mol/mol%.

1H-NMR spectra were measured with a Varian MERCURY 300 (300 MHz) spectrometer or a BRUKER ADVANCE 300 spectrometer (300 MHz) using tetramethylsilane as an internal standard. All of the δ values are represented in ppm.

LC/MS spectra were measured under the following conditions (condition 1 or 2).
Condition 1: Equipment: Agilent 1100 HPLC (Gilson 215 autosampler)/Waters ZQ, or Waters 2795/ZQ
Column: CapcellPak C18UG120 (1.5 mmID x 35 mmL, S-3 μm), manufactured by Shiseido Co., Ltd.
solvent: SOLUTION A (0.05 % trifluoroacetic acid-containing water), SOLUTION B (0.04 % trifluoroacetic acid-containing water)
gradient cycle: 0.00 min (A/B=90/10), 2.00 min (A/B=5/95), 2.75 min (A/B=5/95), 2.76 min (A/B=90/10), 3.45 min (A/B=90/10)
flow rate: 0.5 ml/min
detection: UV (220 nm)
Mass spectrum: electrospray method (ESI)
condition 2: Measurement instrument: LC-MS system, Waters Corporation
HPLC part: HP1100, Agilent Technologies, Inc.
MS part: Micromass ZMD
HPLC conditions

Column: CAPCELL PAK C18UG120, S-3 μm, 1.5 × 35 mm
(Shiseido Co., Ltd.)
Solvent: Solution A; 0.05% trifluoroacetic acid-containing water, Solution B; 0.04% trifluoroacetic acid-containing acetonitrile

Gradient cycle: 0.00 min (Solution A/Solution B=90/10), 2.00 min (Solution A/Solution B=5/95), 2.75 min (Solution A/Solution B=5/95), 2.76 min (Solution A/Solution B=90/10),
3.60 min (Solution A/Solution B=90/10)

Injection volume: 2 μL, Flow rate: 0.5 mL/min,
Detection method: UV 220 nm

MS conditions
Ionization method: ESI

For reversed-phase preparative HPLC, Gilson Inc. UniPoint System equipped with YMC CombiPrep ODS-A (20 mmID × 50 mmL, S-5 μm) column was used, and elution was performed using 0.1 % trifluoroacetic acid-containing acetonitrile-water (10:90 - 100:0) at flow rate of 25 mL/min. Alternatively, the reversed-phase preparative HPLC was performed under the following conditions.

Equipment: Gilson Inc., High Throughput Purification System
Column: YMC Combi Prep Hydro Sphere S-5 μm, 19×50 mm
Solvent: Solution A; 0.1% trifluoroacetic acid-containing water, Solution B; 0.1% trifluoroacetic acid-containing acetonitrile

Gradient cycle: 0.00 min (Solution A/Solution B=95/5), 1.00 min (Solution A/Solution B=95/5), 5.20 min (Solution A/Solution B=5/95), 6.40 min (Solution A/Solution B=5/95),
6.50 min (Solution A/Solution B=95/5), 6.60 min (Solution A/Solution B=95/5)
Flow rate: 20 mL/min, Detection method: UV 220 nm
The microwave reactor used was Discover of CEM.

Other symbols used in the present text indicate the following.

DMF: N,N-dimethylformamide, DMA: N,N-dimethylacetamide, DMSO: dimethyl sulfoxide, THF: tetrahydrofuran.
HOBt: 1-hydroxybenzotriazole monohydrate, WSC·HCl: 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride.
TFA: trifluoroacetic acid.

MSA: methanesulfonic acid, DIEA: N-ethyldiisopropylamine, M: mole concentration.

Reference Example 1

dimethyl pyridine-3,5-dicarboxylate

Pyridine-3,5-dicarboxylic acid (25.5 g) was suspended in methanol (184 ml), and thionyl chloride (33.8 ml) was added dropwise at room temperature. The reaction mixture was stirred with heating under reflux for 3 hr, and the mixture was allowed to cool to room temperature and concentrated under reduced pressure. The residue was diluted with water, and the mixture was extracted with ethyl acetate. The aqueous layer was neutralized with 5M aqueous sodium hydroxide solution, and extracted with ethyl acetate. The extract was washed successively with saturated aqueous sodium hydrogen carbonate solution and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give the object product (27.9 g) as a powder.
$^1$H-NMR (CDCl$_3$) $\delta$ 4.00 (6H, s), 8.88 (1H, t), 9.37 (2H, d)

[0305]

Reference Example 2

(3RS,5SR)-1-(tert-butoxycarbonyl)-5-(methoxycarbonyl)piperidine-3-carboxylic acid and (3RS,5RS)-1-(tert-butoxycarbonyl)-5-(methoxycarbonyl)piperidine-3-carboxylic acid and 1-tert-butyl 3,5-dimethyl piperidine-1,3,5-tricarboxylate

[0306]

Dimethyl pyridine-3,5-dicarboxylate (15 g) was dissolved in methanol (150 ml), and 6M hydrochloric acid (19 ml) and rhodium-carbon (1.5 g) were added. The reaction mixture was stirred under hydrogen pressurization (5 atm) at 50°C for 25 hr. The mixture was allowed to cool to room temperature, the rhodium catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethanol (100 ml), and triethylamine (16 ml) and di-tert-butyl bicarbonate (18.5 g) were successively added under ice-cooling. The reaction mixture was stirred at room temperature for 15 hr, and concentrated under reduced pressure. The residue was dissolved in 0.5M hydrochloric acid and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and fractions eluted with hexane-ethyl acetate (7:1 - 1:4) were obtained. A less polar fraction was concentrated under reduced pressure to give 1-tert-butyl 3,5-dimethyl piperidine-1,3,5-tricarboxylate (15.2 g). A highly-polar fraction was
concentrated under reduced pressure, and the residue was diluted with ethyl acetate. The precipitate was collected by filtration and washed with ethyl acetate to give (3RS,5SR)-1-(tert-butoxycarbonyl)-5-(methoxycarbonyl)piperidine-3-carboxylic acid (2.1 g) as a powder. The filtrate was concentrated under reduced pressure to give a mixture (4.2 g) of (3RS,5SR)-1-(tert-butoxycarbonyl)-5-(methoxycarbonyl)piperidine-3-carboxylic acid and (3RS,5RS)-1-(tert-butoxycarbonyl)-5-(methoxycarbonyl)piperidine-3-carboxylic acid.

(3RS,5SR)-1-(tert-butoxycarbonyl)-5-(methoxycarbonyl)piperidine-3-carboxylic acid

$^1$H-NMR (CDCl$_3$) $\delta$ 1.47 (9H, s), 1.72 (1H, d), 2.41-2.63 (3H, m), 2.72 (2H, br s), 3.71 (3H, s), 4.38 (2H, d)

mixture of (3RS,5SR)-1-(tert-butoxycarbonyl)-5-(methoxycarbonyl)piperidine-3-carboxylic acid and (3RS,5RS)-1-(tert-butoxycarbonyl)-5-(methoxycarbonyl)piperidine-3-carboxylic acid

$^1$H-NMR (CDCl$_3$) $\delta$ 1.44-1.47 (9H, m), 1.60-1.82 (1H, m), 2.10 (1H, br s), 2.38-2.61 (3H, m), 2.72 (2H, br s), 3.71 (3H, s), 4.38 (2H, br s)

1-tert-butyl 3,5-dimethyl piperidine-1,3,5-tricarboxylate

$^1$H-NMR (CDCl$_3$) $\delta$ 1.45-1.49 (9H, m), 1.63-1.76 (1H, m), 2.07 (1H, br s), 2.38-2.55 (2H, m), 2.61-2.89 (2H, m), 3.70 (6H, s), 4.35 (2H, br s)

Reference Example 3

(3S,5R)-1-(tert-butoxycarbonyl)-5-(methoxycarbonyl)piperidine-3-carboxylic acid

[0308]

[0309]

[0310]
A mixture of (3RS,5SR)-1-(tert-butoxycarbonyl)-5-(methoxycarbonyl)piperidine-3-carboxylic acid (6.16 g), (R)-(+)-1-phenylethylamine (2.60 g) and ethanol (24 ml) was dissolved by heating to 70°C, and recrystallized. The precipitated crystals were collected by filtration, dissolved in ethanol (7 ml) again and recrystallized. The precipitated crystals were collected by filtration, the obtained crystals were suspended in water, acidified by adding saturated aqueous potassium hydrogen sulfate solution, and the mixture was extracted 3 times with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give the object product (915 mg) as a powder.

specific optical rotation [α]_20D: -6.2° (after drying, 20.12 mg, methanol, 2 ml, 100 mm)

^1H-NMR (DMSO-d_6) δ 1.39 (9H, s), 1.52 (1H, q), 2.18-2.54 (3H, m), 2.55-2.78 (2H, m), 3.63 (3H, s), 4.03-4.23 (2H, m), 12.51 (1H, br s)

[0311]

Reference Example 4
(3R,5S)-1-(tert-butoxycarbonyl)piperidine-3,5-dicarboxylic acid

[0312]

![Chemical Structure](image)

Dimethyl pyridine-3,5-dicarboxylate (62.8 g) was dissolved in acetic acid (300 mL), 5% rhodium-carbon (6 g) was added and the mixture was stirred under hydrogen pressurization (5 atm) at 50°C for 20 hr. The reaction mixture was allowed to cool to room temperature, the rhodium catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residue was dissolved in methanol (300
mL), and triethylamine (180 mL) and di-tert-butyl bicarbonate (105 g) were successively added under ice-cooling. The reaction mixture was stirred at room temperature for 15 hr, and concentrated under reduced pressure. The residue was dissolved in water, and the mixture was adjusted to pH 3 with 6M hydrochloric acid and extracted with ethyl acetate. The ethyl acetate extraction layer was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in methanol (300 mL), and 8N aqueous sodium hydroxide solution (161 mL) was added dropwise at room temperature. The reaction mixture was stirred at room temperature for 20 hr, and methanol was evaporated under reduced pressure. The concentrate was diluted with saturated aqueous sodium hydrogen carbonate solution (100 ml) and washed twice with diethyl ether. The basic aqueous layer was acidified (pH 3) with 6M hydrochloric acid. The precipitated powder was collected by filtration, washed with water and air-dried to give the object product (80.5 g) as a powder.

1H-NMR (DMSO-d$_6$) δ 1.34-1.43 (9H, m), 1.48 (1H, m), 2.15-2.42 (3H, m), 2.59-2.72 (2H, m), 4.13 (2H, d)

[0314]
Reference Example 5
(3S,5R)-1-(tert-butoxycarbonyl)-5-(methoxycarbonyl)piperidine-3-carboxylic acid

[0315]

![Chemical Structure](image)

[0316]
(3R,5S)-1-(tert-Butoxycarbonyl)piperidine-3,5-dicarboxylic acid (113 g) was suspended in acetic anhydride (1000 ml), and the mixture was heated under reflux for 3 hr
and concentrated under reduced pressure. Toluene (100 ml) was added to the residue and the mixture was concentrated under reduced pressure. Toluene (100 ml) was added again and the mixture was concentrated under reduced pressure. A similar reaction was repeated twice to give a residue (209 g). The obtained residue (51 g) and quinidine (71 g) were dissolved in THF (900 ml), and the mixture was cooled to -40°C. A solution of methanol (81 ml) in THF (100 ml) was added dropwise over 30 min, and the mixture was stirred at the same temperature for 6 hr. THF (about 700 ml) was evaporated under reduced pressure, ethyl acetate was added and the mixture was washed with 2N hydrochloric acid. The aqueous layer was extracted with ethyl acetate, and the organic layers were combined, washed successively with 2N hydrochloric acid and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was concentrated under reduced pressure. A similar reaction was repeated 3 times and the obtained residue (216 g) was suspended in ethanol (835 ml). (R)-(+)−1-Phenylethylamine (91 g) was added and dissolved by heating the mixture to 70°C. The hot ethanol solution was quickly filtered, and the filtrate was stood still at room temperature for 12 hr. The precipitated colorless crystals were collected by filtration, washed successively with ethyl acetate-hexane and hexane, and air dried. The obtained solid was suspended in water, saturated aqueous potassium hydrogen sulfate solution was added and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated to dryness to give the object product (148 g) as a solid.

$^1$H-NMR (DMSO-d$_6$) δ 1.39 (9H, s), 1.52 (1H, q), 2.18-2.54 (3H, m), 2.55-2.78 (2H, m), 3.63 (3H, s), 4.03-4.23 (2H, m), 12.51 (1H, br s)

[0317]
Reference Example 6

1-tert-butyl 3-methyl (3R,5S)-5-aminopiperidine-1,3-
dicarboxylate

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\text{[0318]}
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\text{[0319]}
\]

(3S,5R)-1-(tert-Butoxycarbonyl)-5-(methoxycarbonyl)piperidine-3-carboxylic acid (2.83 g) was suspended in toluene (36 ml), diphenylphosphoryl azide (2.60 ml) and triethylamine (1.70 ml) were added, and the mixture was stirred at 100°C for 1 hr. The reaction mixture was cooled to room temperature, benzyl alcohol (1.53 ml) and triethylamine (7.00 ml) were added and the mixture was stirred at 80°C for 3 hr. The reaction mixture was concentrated, the residue was dissolved in ethyl acetate, and the solution was washed with water, 0.5M hydrochloric acid, and saturated brine in this order, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (1:3 - 3:1) was concentrated under reduced pressure. The obtained residue was dissolved in methanol (60 ml), 10% palladium carbon (50% in water) (150 mg) was added and the mixture was stirred under a hydrogen pressurization (5 atom) at ambient temperature for 5 hr. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give the object product (1.83 g) as an oil.

\[\text{^1H-NMR (CDCl}_{3}\] \delta 1.22-1.43 (4H, m), 1.46 (9H, s), 2.27-2.79 (4H, m), 3.70 (3H, s), 4.13 (2H, br s) \]

[0320]

In the same manner as in the method shown in Reference Example 6, the following compound (Reference Example 7) was obtained.
Reference Example 7

1-tert-butyl 3-methyl 5-aminopiperidine-1,3-dicarboxylate

\[
\begin{array}{c}
\text{NH}_2 \\
\text{O} \\
\text{N} \\
\text{O} \\
\end{array} \\
\text{O} \\
\]

\[\text{[0323]}\]

\[\text{^1H-NMR} \ (\text{CDCl}_3) \ \delta \ 1.19-1.41 \ (3\text{H, m}), \ 1.46-1.50 \ (9\text{H, m}), \ 1.82-2.78 \ (4\text{H, m}), \ 3.49 \ (1\text{H, m}), \ 3.64-3.73 \ (3\text{H, m}), \ 4.15 \ (2\text{H, br s})\]

Reference Example 8

1-tert-butyl 3-methyl (3R,5S)-5-[(2-methylpropyl)amino]piperidine-1,3-dicarboxylate

\[
\begin{array}{c}
\text{NH} \\
\text{O} \\
\text{N} \\
\text{O} \\
\end{array} \\
\text{O} \\
\]

\[\text{[0325]}\]

1-tert-Butyl 3-methyl (3R,5S)-5-aminopiperidine-1,3-dicarboxylate (1.83 g), isobutyraldehyde (0.78 ml) and acetic acid (0.49 ml) were dissolved in methanol (50 ml), and the mixture was stirred at room temperature for 30 min. Sodium triacetoxyborohydride (3.80 g) was added to the reaction mixture, and the mixture was stirred at room temperature for 7 hr. The reaction mixture was concentrated under reduced pressure, the concentrate was basified with aqueous sodium bicarbonate, and extracted with ethyl acetate. The extract was washed with water and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (1:1) - ethyl acetate 100% - ethyl acetate-
methanol (9:1) was concentrated under reduced pressure to give the object product (1.42 g) as an oil.

\(^1\)H-NMR (CDCl\(_3\)) \(\delta\) 0.90 (6H, d), 1.22-1.38 (3H, m), 1.46 (9H, s), 1.69 (1H, dt), 2.23-2.39 (2H, m), 2.44-2.59 (1H, m), 2.47 (2H, d), 2.74 (1H, br s), 3.69 (3H, s), 4.18-4.34 (2H, m)

[0327]

In the same manner as in the method shown in Reference Example 8, the following compound (Reference Example 9) was obtained.

[0328]

Reference Example 9
1-tert-butyl 3-methyl 5-[(2-methylpropyl)amino]piperidine-1,3-dicarboxylate

[0329]

\[\begin{array}{c}
\text{NH} \\
\text{O} \\
\text{O} \\
\text{N}
\end{array}\]

[0330]

\(^1\)H-NMR (CDCl\(_3\)) \(\delta\) 0.93-1.09 (2H, m), 1.02 (4H, d), 1.45 (9H, d), 2.05 (3H, s), 2.65-2.79 (2H, m), 2.83-2.98 (1H, m), 3.25 (1H, dd), 3.49 (2H, s), 3.58-3.75 (3H, m), 3.94 (1H, d)

[0331]

Reference Example 10
ethyl 1-(4-methoxybutyl)-7-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylate

[0332]

[0333]

A solution of ethyl 7-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (207 mg), 4-methoxybutyl methanesulfonate (273 mg) and cesium carbonate (652 mg) in N,N-dimethylacetamide (10 ml)
was stirred at 60°C for 15 hr. After cooling to room
temperature, the reaction mixture was diluted with water and
extracted with ethyl acetate (10 ml×2). The extract was washed
with saturated brine, and dried over anhydrous magnesium
sulfate. The solvent was evaporated under reduced pressure.
The residue was subjected to silica gel column chromatography,
and a fraction eluted with ethyl acetate-hexane (5:95 – 3:7)
was concentrated under reduced pressure to give the object
product (250 mg).

MS (ESI+, m/e) 294 (M+1)

[0334]
Reference Example 11
1-(4-methoxybutyl)-7-oxo-4,5,6,7-tetrahydro-1H-indole-2-
carboxylic acid

[0335]

\[
\text{Ethyl 1-(4-methoxybutyl)-7-oxo-4,5,6,7-tetrahydro-1H-
indole-2-carboxylate (250 mg) and lithium hydroxide}
\]
monohydrate (54 mg) were dissolved in ethanol (4 ml) and water
(2 ml), and the mixture was stirred at 60°C for 3 hr. The
solvent was concentrated under reduced pressure, and the
residue was neutralized with 1N hydrochloric acid, extracted
with ethyl acetate (10 ml×2), and dried over anhydrous
magnesium sulfate. The solvent was evaporated under reduced
pressure. The residue was subjected to silica gel column
chromatography, and a fraction eluted with ethyl acetate-
hexane (5:95 – 3:7) was concentrated under reduced pressure to
give the object product (215 mg).

MS (ESI+, m/e) 266 (M+1)

[0337]
Reference Example 12
4-methoxybutyl 1-(4-methoxybutyl)-4,5,6,7-tetrahydro-1H-indole-2-carboxylate

[0338]

A solution of 4,5,6,7-tetrahydro-1H-indole-2-carboxylic acid (280 mg), 4-methoxybutyl methanesulfonate (775 mg) and cesium carbonate (2.77 g) in N,N-dimethylacetamide (25 ml) was stirred at 65°C for 15 hr. After cooling to room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate (20 ml×2). The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (5:95 - 3:7) was concentrated under reduced pressure to give the object product (375 mg).

MS (ESI+, m/e) 338 (M+1)

[0340]

In the same manner as in Reference Example 11, the following compound (Reference Example 13) was obtained.

[0341]
Reference Example 13
1-(4-methoxybutyl)-4,5,6,7-tetrahydro-1H-indole-2-carboxylic acid

[0342]

[0343]
MS (ESI+, m/e) 252 (M+1)
Reference Example 14
1-(4-methoxybutyl)-1H-indole-2-carboxylic acid

Methyl 1H-indole-2-carboxylate (0.67 g), cesium carbonate (1.9 g) and 4-methoxybutyl methanesulfonate (0.70 g) were suspended in DMA (20 ml), and the suspension was stirred at 60°C for 4 hr. The reaction mixture was concentrated under reduced pressure, the residue was diluted with water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained residue was subjected to silica gel chromatography, and a fraction eluted with ethyl acetate-hexane (0:10 - 4:6) was concentrated under reduced pressure. The obtained residue was dissolved in methanol (10 ml), 4N aqueous sodium hydroxide solution (5 ml) was added, and the mixture was heated at 80°C for 2 hr. The mixture was allowed to cool to room temperature, acidified with 1N aqueous hydrochloric acid and extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the object product (0.77 g).

$^1$H-NMR (DMSO-d$_6$) δ 1.32 -1.53 (2H, m), 1.63-1.79 (2H, m), 3.18 (3H, s), 3.28 (2H, t), 4.59 (2H, t), 7.11 (1H, s), 7.23 (1H, d), 7.32 (1H, s), 7.58 (1H, dd), 7.67 (1H, d)
MS (ESI+, m/e) 248 (M+1)

Reference Example 15
tert-butyl (3S,5R)-3-[[1-(4-methoxybutyl)-1H-indol-2-
[0347]

1-(4-Methoxybutyl)-1H-indole-2-carboxylic acid (210 mg), tert-butyl (3S,5R)-3-[(2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (270 mg) and N,N-diisopropylethylamine (560 μl) were dissolved in 1,2-dichloroethane (10 ml), chloro-N,N,N′,N′-tetramethylformamidinium hexafluorophosphate (360 mg) was added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated, and the residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (0:10 - 10:0) was concentrated under reduced pressure to give the object product (83 mg).

MS (ESI+, m/e) 599 (M+1)

[0349]
Reference Example 16
methyl 2-[(tert-butoxycarbonyl)(4-methoxybutyl)amino]-3-nitrobenzoate

[0350]

[0351]
Methyl 2-[(tert-butoxycarbonyl)amino]-3-nitrobenzoate (3.0 g), 4-methoxybutyl methanesulfonate (2.0 g) and potassium carbonate (2.1 g) were dissolved in DMF (30 ml), and the mixture was stirred at 60°C overnight. The reaction mixture was concentrated, aqueous potassium carbonate solution was added, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (0:10-8:2) was concentrated under reduced pressure to give the object product (2.9 g).

\[^1H-NMR\ (CDCl_3) \delta 1.28-1.34\ (9H, m), 1.47-1.61\ (6H, m), 3.28\ (3H, s), 3.30-3.40\ (2H, m), 3.90-3.95\ (3H, m), 7.49\ (IH, s), 7.91-8.02\ (IH, m), 8.04-8.16\ (IH, m)\]

Reference Example 17

methyl 1-[(4-methoxybutyl)-2-[(trichloromethyl)]-1H-benzimidazole-7-carboxylate

[0353]

Methyl 2-[(tert-butoxycarbonyl)(4-methoxybutyl)amino]-3-nitrobenzoate (2.9 g) was dissolved in methanol (30 ml), palladium-carbon (5%, 500 mg) was added, and the mixture was stirred for 3 hr under a hydrogen atmosphere. The reaction mixture was filtered through celite\textsuperscript{TM}, and the filtrate was concentrated under reduced pressure. The residue (1.8 g) was dissolved in acetic acid (40 ml), methyl 2,2,2-trichloroethanimidate (0.88 ml) was added, and the mixture was stirred at 50°C for 6 hr. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The
extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give the object product (2.6 g).

\[ ^1H\text{-NMR (CDCl}_3\text{)} \delta 1.71 \text{ (4H, br s), 3.31 (3H, s), 3.37 (2H, t), 4.00 (3H, s), 4.91 (1H, dd), 4.92 (1H, d), 7.36 (1H, t), 7.83 (1H, dd), 8.06 (1H, dd) \]

[0355]
Reference Example 18
methyl 3-[(2-methoxyethoxy)methyl]imidazo[1,2-a]pyridine-2-carboxylate

[0356]

[0357]
To a solution of methyl 3-(hydroxymethyl)imidazo[1,2-a]pyridine-2-carboxylate (0.30 g) in DMF (5 ml) was added sodium hydride (60 mg) under ice-cooling. The mixture was stirred at room temperature for 30 min, 2-methoxyethyl bromide (220 mg) was added under ice-cooling, and the mixture was stirred at 60°C for 3 hr. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with aqueous potassium carbonate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was subjected to silica gel chromatography, and a fraction eluted with ethyl acetate-hexane (0:10 - 10:0) was concentrated under reduced pressure to give the object product (0.16 g).

\[ ^1H\text{ NMR (CDCl}_3\text{)} \delta 3.42 \text{ (3H, s), 3.48-3.57 (2H, m), 3.65 (2H, dd), 3.95-4.00 (3H, m), 5.31 (2H, d), 6.88 (1H, dd), 7.26 (1H, dd), 7.66 (1H, dt), 8.07-8.20 (1H, m) \]

MS (ESI+, m/e) 265 (M+1)
Reference Example 19
1-tert-butyl 3-methyl (3R,5S)-5-\{[(benzyloxy)carbonyl]amino\}piperidine-1,3-dicarboxylate

\[
\begin{align*}
\text{HN} & \quad \text{O} \\
\text{O} & \quad \text{NH} \\
\text{O} & \quad \text{N} \\
\text{O} & \quad \text{O}
\end{align*}
\]

Reference Example 20
(3S,5R)-1-(tert-Butoxycarbonyl)-5-\{(methoxycarbonyl)piperidine-3-carboxylic acid (2.83 g) was suspended in toluene (36 ml), diphenylphosphoryl azide (2.60 ml) and triethylamine (1.70 ml) were added and the mixture was stirred at 100°C for 1 hr. The reaction mixture was cooled to room temperature, benzyl alcohol (1.53 ml) and triethylamine (7.00 ml) were added and the mixture was stirred at 80°C for 3 hr. The reaction mixture was concentrated, the residue was dissolved in ethyl acetate, washed with water, 0.5M hydrochloric acid and saturated brine in this order, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (1:3 - 3:1) was concentrated under reduced pressure to give the object product (2.79 g) as an oil. MS (ESI+, m/e) 393 (M+1)

\[
(3R,5S)-5-\{[(benzyloxy)carbonyl]amino\}-1-(tert-butoxycarbonyl)piperidine-3-carboxylic acid
\]
[0363]

To a solution (700 ml) of 1-tert-butyl 3-methyl (3R,5S)-
5-\{[\(\text{benzyloxy}\)carbonyl]amino\}piperidine-1,3-dicarboxylate
(115 g) in methanol was added 1M aqueous sodium hydroxide
solution (350 ml) under ice-cooling, and the mixture was
stirred at room temperature for 12 hr. The reaction mixture
was concentrated under reduced pressure to about 1/3 volume,
and the residual aqueous solution was washed with ethyl
acetate-hexane (1:1, 600 ml). The aqueous layer was
neutralized with 1M hydrochloric acid and the mixture was
extracted with ethyl acetate. The extract was washed with
saturated brine, and dried over anhydrous magnesium sulfate.
The solvent was evaporated under reduced pressure to give the
object product (98.5 g).

\(^1H\text{-NMR (DMSO-}d_6\text{)} \delta: 1.33 (1H, br s), 1.40 (9H, s), 2.09 (1H, d),
2.36-2.52 (3H, m), 3.93-4.09 (2H, m), 5.03 (2H, s), 7.28-7.43
(5H, m), 12.52 (1H, br s).

[0364]
Reference Example 21
dert-butyl (3S,5R)-3-\{\(\text{benzyloxy}\)carbonyl]amino\}-5-
(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[0365]

[0366]
(3R,5S)-5-[(Benzylxoy)carbonyl]amino)-1-(tert-butoxycarbonyl)piperidine-3-carboxylic acid (49.2 g), morpholine (11.4 ml), 1H-benzotriazol-1-ol (10.0 g) and triethylamine (40 ml) were dissolved in DMF (250 ml), WSC·HCl (30.0 g) was added, and the mixture was stirred at room temperature for 4 days. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The extract was washed successively with saturated aqueous sodium hydrogen carbonate solution and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give the object product (62.9 g).

1H-NMR (CDCl₃) δ: 1.46 (9H, s), 1.69 (2H, br s), 2.04 (1H, s), 2.73 (2H, br s), 2.79-2.96 (1H, m), 3.52-3.65 (6H, m), 3.69 (2H, d), 3.67 (1H, br s), 4.04 (1H, d), 5.09 (2H, s), 5.40 (1H, br s), 7.25-7.41 (5H, m).

Reference Example 22
tert-butyl (3S,5R)-3-[(2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[0368]

[0369]
tert-Butyl (3S,5R)-3-[(benzylxoy)carbonyl]amino)-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (58 g) and palladium(II) hydroxide-carbon (5 g) were suspended in methanol (400 ml) and the mixture was stirred under a hydrogen atmosphere (1 atom) at room temperature for 16 hr. The palladium catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue and acetic acid (8.8 ml) were dissolved in methanol (400 ml), 2-methylpropanal (14.0 ml) was added, and the mixture was
stirred at room temperature for 1 hr. Sodium triacetoxynorbornyldride (40.4 g) was added to the reaction mixture, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated under reduced pressure, and the concentrate was basified with 3.5M aqueous potassium carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to basic silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (1:5) - ethyl acetate-hexane (1:1) was concentrated under reduced pressure to give the object product (33.3 g).

_1H-NMR (CDCl₃)_  δ: 0.90 (6H, d), 1.46 (9H, s), 1.54 (1H, d), 1.69 (1H, dt), 1.96-2.12 (2H, m), 2.23-2.37 (1H, m), 2.47 (3H, d), 2.66 (1H, d), 3.61 (1H, br s), 3.55 (2H, d), 3.69 (5H, ddd), 4.01-4.46 (2H, m).

[0370]
Reference Example 23

 tert-butyl (3S,5R)-3-[[1-(4-methoxybutyl)-7-oxo-4,5,6,7-tetrahydro-1H-indol-2-yl]carbonyl][2-methylpropyl]amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[0371]

[0372]
1-(4-Methoxybutyl)-7-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylic acid (210 mg), tert-butyl (3S,5R)-3-[[2-methylpropyl]amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-
carboxylate (292 mg) and N,N-diisopropylethylamine (550 μl) were dissolved in 1,2-dichloroethane (10 ml), chloro-
N,N,N',N'-tetramethylformamidinium hexafluorophosphate (244 mg) was added, and the mixture was stirred at room temperature
for 15 hr. The reaction mixture was diluted with saturated aqueous sodium hydrogen carbonate solution and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (10:90 - 100:0) was concentrated under reduced pressure to give the object product (245 mg).
MS (ESI+, m/e) 617 (M+1)

[0373]
In the same manner as in Reference Example 23, the following compound (Reference Example 24) was obtained.

[0374]
Reference Example 24
tert-butyl (3S,5R)-3-[[1-(4-methoxybutyl)-4,5,6,7-tetrahydro-
1H-indol-2-yl]carbonyl](2-methylpropyl)amino]-5-(morpholin-4-
ylcarbonyl)piperidine-1-carboxylate

[0375]

MS (ESI+, m/e) 603 (M+1)

Example 1
1-(4-methoxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-
tert-Butyl (3S,5R)-3-[[1-(4-methoxybutyl)-4,5,6,7-tetrahydro-1H-indol-2-yl]carbonyl](2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (100 mg) was dissolved in dichloromethane (0.5 ml), TFA (0.5 ml) was added, and the mixture was stirred at room temperature for 15 min. The solvent was evaporated under reduced pressure, and the residue was neutralized with saturated aqueous sodium hydrogen carbonate. The mixture was extracted with ethyl acetate (10 ml×2), and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dried under reduced pressure to give the object product (45 mg).

MS (ESI+, m/e) 503 (M+1)

Example 2

1-(4-methoxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-7-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxamide monohydrochloride
[0381]
tert-Butyl (3S,5R)-3-[[1-(4-methoxybutyl)-7-oxo-4,5,6,7-tetrahydro-1H-indol-2-yl]carbonyl](2-methylpropyl)amino]-5-
(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (100 mg) was
dissolved in ethyl acetate (1 ml), 4N hydrogen chloride-ethyl
acetate solution (1 ml) was added, and the mixture was stirred
at room temperature for 1 hr. The solvent was evaporated under
reduced pressure, and the residue was dried under reduced
pressure to give the object product (52 mg).
MS (ESI+, m/e) 517 (M+1)

[0382]
Example 3
1-(4-methoxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-
4-ylcarbonyl)piperidin-3-yl]-1H-indole-2-carboxamide
hydrochloride

[0383]

[0384]
tert-Butyl (3S,5R)-3-[[1-(4-methoxybutyl)-1H-indol-2-
yl]carbonyl](2-methylpropyl)amino]-5-(morpholin-4-
ylcarbonyl)piperidine-1-carboxylate (83.4 mg) was dissolved in
4N hydrogen chloride-ethyl acetate (3 ml), and the mixture was
stirred at room temperature for 1.5 hr. The reaction mixture was concentrated to give the object product (67 mg).
MS (ESI+, m/e) 499 (M+1)

[0385]

Example 4

3-{[(2-methoxyethoxy)methyl]-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]imidazo[1,2-a]pyridine-2-carboxamide dihydrochloride

[0386]

Methyl 3-{[(2-methoxyethoxy)methyl]imidazo[1,2-a]pyridine-2-carboxylate (160 mg) and lithium hydroxide (76 mg) were dissolved in water (10 ml) and methanol (2 ml), and the mixture was stirred at 70°C for 6 hr. The mixture was allowed to cool to room temperature, acidified with 1N aqueous hydrochloric acid and extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue, tert-butyl (3S,5R)-3-{[2-methylpropyl]amino}-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (130 mg) and N,N-diisopropylethylamine (340 μg) were dissolved in 1,2-dichloroethane (10 ml), chloro-N,N,N′,N′-tetramethylformamidinium hexafluorophosphate (220 mg) was added, and the mixture was stirred at room temperature for 3 hr. The reaction mixture was concentrated, diluted with aqueous calcium carbonate solution and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate.
The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (0:10 - 10:0) was concentrated under reduced pressure. The residue was dissolved in 4N hydrogen chloride-ethyl acetate (1 ml), and the mixture was stirred at room temperature for 1.5 hr. The reaction mixture was concentrated to give the object product (65 mg).

MS (ESI+, m/e) 502 (M+1)

Example 5

4-(4-methoxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-((morpholin-4-ylcarbonyl)piperidin-3-yl)]-4H-thieno[3,2-b]pyrrole-5-carboxamide

4H-Thieno[3,2-b]pyrrole-5-carboxylic acid (160 mg), tert-butyl (3S,5R)-3-[(2-methylpropyl)amino]-5-((morpholin-4-ylcarbonyl)piperidine-1-carboxylate (250 mg) and N,N-diisopropylethylamine (630 µl) were dissolved in 1,2-dichloroethane (10 ml), chloro-N,N,N′,N′-tetramethylformamidinium hexafluorophosphate (410 mg) was added, and the mixture was stirred at room temperature for 3 hr. The reaction mixture was concentrated, diluted with aqueous calcium carbonate solution and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (0:10 - 10:0) was
concentrated under reduced pressure. The residue was dissolved in DMA (10 ml), cesium carbonate (790 mg) and 4-methoxybutyl methanesulfonate (230 mg) were added, and the mixture was stirred at 70°C overnight. The reaction mixture was concentrated under reduced pressure, the residue was diluted with water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in TFA (1.0 ml), and the mixture was stirred at room temperature for 30 min and concentrated under reduced pressure. This was purified by HPLC, and the object fraction was concentrated, diluted with aqueous calcium carbonate solution and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give the object product (52 mg).

MS (ESI+, m/e) 505 (M+1)

Example 6

methyl 2-{(2-methylpropyl)[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]carbamoyl}-1-(4-methoxybutyl)-3H-benzimidazole-7-carboxylate dihydrochloride

[0392]

![Chemical Structure](image)

[0393]

Methyl 1-(4-methoxybutyl)-2-(trichloromethyl)-1H-benzimidazole-7-carboxylate (0.44 g) and tert-butyl (3S,5R)-3-[(2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-
1-carboxylate (0.3 g) were dissolved in acetonitrile (5.0 ml) and water (5.0 ml), potassium carbonate (2.4 g) was added, and the mixture was stirred at 60°C overnight. The reaction mixture was cooled to room temperature, and the mixture was extracted with ethyl acetate. The extract was washed successively with 10% aqueous citric acid solution, aqueous sodium bicarbonate and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (0:10→10:0) was concentrated under reduced pressure, and a fraction eluted with ethyl acetate was concentrated under reduced pressure. The residue was dissolved in 4N hydrochloric acid-ethyl acetate solution, and the mixture was stirred for 30 min. The reaction mixture was concentrated, purified by HPLC, and the object fraction was concentrated, diluted with aqueous calcium carbonate solution and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and converted to hydrochloride with 4N hydrochloric acid-ethyl acetate solution to give the object product (9.3 mg).

MS (ESI+, m/e) 558 (M+1)

Example 7
(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl (3R,5S)-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino)piperidine-3-carboxylate dihydrochloride

[0395]
(3R,5S)-1-(tert-Butoxycarbonyl)-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl]{2-
methylpropyl}amino]piperidine-3-carboxylic acid (0.3 g) and 4-(hydroxymethyl)-5-methyl-1,3-dioxol-2-one (0.09 g) were dissolved in DMA (3.0 ml), toluenesulfonyl chloride (0.13 g), DMAP (0.014 g) and potassium carbonate (0.1 g) were added with stirring under ice-cooling, and the mixture was stirred for 6 hr under ice-cooling, and further at room temperature overnight. The reaction mixture was neutralized with 1N aqueous hydrochloric acid and extracted with ethyl acetate. The extract was washed successively with aqueous sodium bicarbonate and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (0:10→1:1) was concentrated under reduced pressure, and a fraction eluted with ethyl acetate was concentrated under reduced pressure. The residue was dissolved in 2N hydrochloric acid-ethyl acetate solution, and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated to give the object product (186 mg).

MS (ESI+, m/e) 543 (M+1)

Example 8
methyl (3R,5S)-5-[[1-(4-methoxybutyl)-1H-indol-2-yl]carbonyl]{2-methylpropyl}amino]piperidine-3-carboxylate
[0399]

1-(4-Methoxybutyl)-1H-indole-2-carboxylic acid (247 mg), 1-tert-butyl 3-methyl (3R,5S)-5-[(2-methylpropyl)amino]piperidine-1,3-dicarboxylate (314 mg) and diisopropylethylamine (862 µl) were dissolved in methylene chloride (5 ml), chloro-Ν,N,N′,N′-tetramethylformamidinium hexafluorophosphate (337 mg) was added, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (3:7) was concentrated under reduced pressure to give 1-tert-butyl 3-methyl (3R,5S)-5-[[1-(4-methoxybutyl)-1H-indol-2-yl]carbonyl]2-methylpropylamino)piperidine-1,3-dicarboxylate (40 mg) as an oil. The obtained 1-tert-butyl 3-methyl (3R,5S)-5-[[1-(4-methoxybutyl)-1H-indol-2-yl]carbonyl]2-methylpropylamino)piperidine-1,3-dicarboxylate (40 mg) was dissolved in methanol (2 ml), 4M hydrogen chloride-ethyl acetate (2 ml) was added, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was concentrated, and the residue was purified by reversed-phase preparative HPLC, and the object fraction was concentrated under reduced pressure. An aqueous sodium bicarbonate solution was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated to give the object product (13 mg).

MS (ESI+, m/e) 444 (M+1)

[0400]
Reference Example 25
methyl 1-(2-phenylethyl)-1H-indole-2-carboxylate

\[ \text{[0401]} \]

\[ \text{[0402]} \]
Methyl 1H-indole-2-carboxylate (526 mg) and (2-bromoethyl)benzene (1.11 g) were dissolved in DMA (15 ml), cesium carbonate (2.93 g) was added, and the mixture was stirred at 60°C for 15 hr. The reaction mixture was concentrated, and the residue was diluted with aqueous sodium bicarbonate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (3:7) was concentrated under reduced pressure to give the object product (318 mg) as an oil. MS (ESI+, m/e) 280 (M+1)

\[ \text{[0403]} \]
Reference Example 26
tert-butyl (3S,5R)-3-[(2-methylpropyl){[1-(2-phenylethyl)-1H-indol-2-yl]carbonyl}amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

\[ \text{[0404]} \]
Methyl 1-(2-phenylethyl)-1H-indole-2-carboxylate (318 mg) was dissolved in methanol (5 ml), 2M aqueous sodium hydroxide solution (1.14 ml) was added, and the mixture was stirred at room temperature for 17 hr. The aqueous layer was adjusted to pH 7 with 1M hydrochloric acid, saturated brine was added, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give 1-(2-phenylethyl)-1H-indole-2-carboxylic acid (300 mg).

The obtained 1-(2-phenylethyl)-1H-indole-2-carboxylic acid (300 mg), 1-tert-butyl 3-methyl (3R,5S)-5-[(2-methylpropyl)amino]piperidine-1,3-dicarboxylate (185 mg) and diisopropylethylamine (431 µl) were dissolved in methylene chloride (5 ml), chloro-N,N,N′,N′-tetramethylformamidinium hexafluorophosphate (168 mg) was added, and the mixture was stirred at room temperature for 15 hr. Aqueous sodium bicarbonate was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate was concentrated under reduced pressure to give the object product (83 mg).

MS (ESI+, m/e) 617 (M+1)

Example 9

N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1-(2-phenylethyl)-1H-indole-2-carboxamide hydrochloride

[0407]
[0408]

tert-Butyl (3S,5R)-3-[(2-methylpropyl){[1-(2-phenylethyl)-1H-indol-2-yl]carbonyl}amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (83 mg) was dissolved in 4M hydrogen chloride-ethyl acetate (2 ml), and the mixture was stirred at room temperature for 15 hr. The reaction mixture was concentrated to give the object product (75 mg).

MS (ESI+, m/e) 517 [M+1]

[0409]

Reference Example 27

N-(4-methoxybutyl)benzene-1,2-diamine

[0410]

[0411]

To a solution of phenylenediamine (10.8 g) and 4-methoxybutyl methanesulfonate (9.11 g) in acetonitrile (100 ml) was added potassium carbonate (20.7 g), and the mixture was stirred heated under reflux for 15 hr. Water was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (35:65) was concentrated under reduced pressure to give the object product (5.44 g).

$^1$H-NMR (CDCl$_3$) δ 1.67-1.82 (4H, m), 3.13 (2H, t), 3.24-3.39 (6H,
m), 3.38-3.50 (2H, m), 6.62-6.74 (3H, m), 6.81 (1H, m).
MS (ESI+, m/e) 195 (M+1)

[0412]
Reference Example 28

5 tert-butyl (3S,5R)-3-[[ethoxy(oxo)acetyl](2-
methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-
carboxylate

[0413]

To a solution of tert-butyl (3S,5R)-3-[(2-
methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-
carboxylate (9.24 g) and diisopropylethylamine (10.5 ml) in
DMA (100 ml) was added dropwise ethyl chloroglyoxylate (3.4
ml) at 0°C. The reaction mixture was stirred at room
temperature for 15 hr, and the reaction mixture was
concentrated. An aqueous sodium bicarbonate solution was added
to the residue, and the mixture was extracted with ethyl
acetate. The extract was washed with saturated brine, and
dried over anhydrous magnesium sulfate. The solvent was
evaporated under reduced pressure. The residue was subjected
to silica gel column chromatography, and a fraction eluted
with ethyl acetate was concentrated under reduced pressure to
give the object product (10.3 g).

1H-NMR (CDCl₃) δ 0.84-1.00 (6H, m), 1.37 (3H, q), 1.42-1.53 (9H,
m), 1.80-2.19 (3H, m), 2.26-2.42 (1H, m), 2.59-2.96 (1H, m),
2.97-3.30 (3H, m), 3.37-3.92 (9H, m), 4.01-4.26 (2H, m), 4.26-
4.40 (2H, m).
MS (ESI+, m/e) 470 (M+1)

[0415]
Reference Example 29
{[(3S,5R)-1-(tert-butoxycarbonyl)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl] (2-methylpropyl)amino} (oxo)acetic acid

[0416]

To a solution of tert-butyl (3S,5R)-3-{{ethoxy(oxo)acetyl} (2-methylpropyl)amino}-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (10.3 g) in ethanol (40 ml) was added 2M aqueous sodium hydroxide solution (22 ml), and the mixture was stirred at room temperature for 6 hr. The reaction mixture was adjusted to pH 7 with 1M hydrochloric acid, and extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give the object product (10.3 g).

$^1$H-NMR (CDCl$_3$) δ 0.78-0.99 (6H, m), 1.37-1.52 (9H, m), 1.79-2.16 (3H, m), 2.38-3.86 (14H, m), 3.93-4.43 (2H, m).

MS (ESI+, m/e) 442 (M+1)

[0418]

Reference Example 30

tert-butyl (3S,5R)-3-{[(2-[(4-methoxybutyl)amino]phenyl)amino} (oxo)acetyl] (2-methylpropyl)amino}-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[0419]
[0420]

\[
\{(3S,5R)-1-\text{[tert-Butoxycarbonyl]-5-\{morpholin-4-ylcarbonyl\}piperidin-3-yl}(2\text{-methylpropyl}\text{amino})(\text{oxo})\text{acetic acid (10.3 g), HOBt (4.13 g) and WSC\text{\textcdot}HCl (6.28 g) were dissolved in DMF (50 ml), N-(4-methoxybutyl)benzene-1,2-diamine (4.67 g) and diisopropylethylamine (11.3 ml) were added, and the mixture was stirred at room temperature for 15 hr and at 60°C for 2 hr. The reaction mixture was concentrated, and the residue was diluted with aqueous sodium bicarbonate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate was concentrated under reduced pressure to give the object product (9.11 g).
\]

\[
\text{H-NMR (CDCl}_3\text{) δ 0.86-1.03 (6H, m), 1.37-1.53 (9H, m), 1.70 (4H, d), 1.86-2.26 (3H, m), 2.37-2.97 (3H, m), 3.09-3.22 (3H, m), 3.25-3.48 (6H, m), 3.48-3.98 (10H, m), 4.01-4.97 (2H, m), 6.70-6.84 (2H, m), 7.10-7.21 (1H, m), 7.35 (1H, dd), 8.47-8.80 (1H, m).}
\]

\[
\text{MS (ESI+), m/e 618 (M+1)}
\]

[0421]

Reference Example 31
tert-butyl (3S,5R)-3-\{[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl\}(2-methylpropyl)amino]-5-\{morpholin-4-ylcarbonyl\}piperidine-1-carboxylate and 1-(4-methoxybutyl)-N-(2-methylpropyl)-N-(3S,5R)-5-\{morpholin-4-}
ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide

[0422]

[0423]

tert-Butyl (3S,5R)-3-[[2-{[(4- methoxybutyl)amino]phenyl)amino}(oxo)acetyl}(2- methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (9.11 g) was dissolved in acetic acid (50 ml), and the mixture was stirred at 80°C for 15 hr. The reaction mixture was cooled to room temperature and concentrated under reduced pressure, the residue was diluted with aqueous sodium bicarbonate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to basic silica gel column chromatography, and a fraction eluted with ethyl acetate was concentrated under reduced pressure to give tert-butyl (3S,5R)-3-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl}(2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (5.85 g), and a fraction eluted with ethyl acetate-methanol (85:15) was concentrated under reduced pressure to give 1-(4-methoxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide (580 mg).

[0424]

tert-butyl (3S,5R)-3-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl}(2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

^H-NMR (CDCl3) δ 0.63-0.80 (2H, m), 0.89-1.07 (4H, m), 1.41-1.59 (9H, m), 1.59-1.80 (2H, m), 1.87-2.23 (4H, m), 2.30-2.98
(3H, m), 3.21-3.46 (6H, m), 3.49-3.91 (10H, m), 3.95-4.47 (5H, m), 7.18-7.51 (3H, m), 7.56-7.84 (1H, m).

MS (ESI+, m/e) 600 (M+1)

1-(4-methoxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide

1H-NMR (CDCl₃) δ 0.64-0.74 (2H, m), 0.95-1.07 (4H, m), 1.43-1.74 (3H, m), 1.84-2.41 (4H, m), 2.48-2.67 (1H, m), 2.67-3.01 (3H, m), 3.03-3.44 (8H, m), 3.47-3.78 (9H, m), 4.06-4.46 (3H, m), 7.28-7.47 (3H, m), 7.62-7.81 (1H, m).

MS (ESI+, m/e) 500 (M+1)

Example 10

1-(4-methoxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide dihydrochloride

[0426]

[0427]

tert-Butyl (3S,5R)-3-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl] (2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (5.85 g) was dissolved in methanol (20 ml), 4M hydrogen chloride-ethyl acetate (20 ml) was added, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was concentrated, and the residue was diluted with aqueous sodium bicarbonate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to basic silica gel column chromatography, and a fraction eluted with ethyl acetate-
methanol (9:1) was concentrated under reduced pressure to give 1-(4-methoxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide (4.40 g). The obtained 1-(4-methoxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide (2.20 g) was dissolved in ethyl acetate (20 ml), 4M hydrogen chloride-ethyl acetate (5 ml) and methanol (20 ml) were added, and the mixture was stirred at room temperature for 5 min. The reaction mixture was concentrated under reduced pressure to give the object product (2.52 g).

$^1$H-NMR (DMSO-d$_6$) δ 0.63-0.76 (2H, m), 0.85-1.00 (4H, m), 1.40-1.60 (2H, m), 1.68-1.89 (2H, m), 1.93-2.17 (2H, m), 2.20-2.44 (2H, m), 2.81-3.81 (20H, m), 4.19-4.39 (3H, m), 7.23-7.46 (2H, m), 7.57-7.81 (2H, m), 8.38-9.77 (2H, m).

MS (ESI+, m/e) 500 (M+1)

[0428]

Reference Example 32

5-fluoro-N-(4-methoxybutyl)-2-nitroaniline

[0429]

5-Fluoro-2-nitroaniline (1.0 g) was dissolved in THF (20 ml), sodium hydride (60% in oil, 384 mg) was added, and the mixture was stirred at room temperature for 30 min. 4-Methoxybutyl methanesulfonyl (1.28 g) was added, and the mixture was heated under reflux with stirring for 15 hr. The reaction mixture was cooled to room temperature and saturated brine was added, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted
with ethyl acetate-hexane (30:70) was concentrated under reduced pressure to give the object product (494 mg).

$^1$H-NMR (CDCl$_3$) 6 1.66-1.77 (2H, m), 1.78-1.89 (2H, m), 3.25-3.34 (2H, m), 3.36 (3H, s), 3.45 (2H, t), 6.36 (1H, ddd), 6.49 (1H, dd), 8.16-8.27 (2H, m).

MS (ESI+, m/e) 243 (M+1)

[0431]
Reference Example 33
4-fluoro-2-(4-methoxybutylamino)aniline

[0432]

[0433]
5-Fluoro-N-(4-methoxybutyl)-2-nitroaniline (494 mg) was dissolved in methanol (20 ml), 10% palladium carbon (50% in water, 100 mg) was added, and the mixture was stirred under a hydrogen stream at ambient temperature and normal pressure for 15 hr. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give the object product (451 mg) as an oil.

$^1$H-NMR (CDCl$_3$) 6 1.63 (2H, br s), 1.67-1.81 (4H, m), 3.08 (1H, br s), 3.10 (2H, t), 3.36 (3H, s), 3.39-3.47 (2H, m), 6.26-6.38 (2H, m), 6.61 (1H, dd).

MS (ESI+, m/e) 213 (M+1)

[0434]
Reference Example 34
tert-butyl (3S,5R)-3-[[[(4-fluoro-2-[[4-methoxybutyl]amino]phenyl]amino)(oxo)acetyl](2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[0435]
[(3S,5R)-1-(tert-Butoxycarbonyl)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl] (2-methylpropyl)amino) (oxo)acetic acid (221 mg), HOBt (95 mg) and WSC·HCl (144 mg) were dissolved in DMF (5 mL), 4-fluoro-2-(4-methoxybutylamino)aniline (106 mg) and diisopropylethylamine (97 µL) were added, and the mixture was stirred at room temperature for 15 hr and at 60°C for 2 hr. The reaction mixture was cooled to room temperature, and concentrated under reduced pressure. The residue was diluted with aqueous sodium bicarbonate and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate was concentrated under reduced pressure to give the object product (9.11 mg).

1H-NMR (CDCl3) δ 0.89-1.01 (6H, m), 1.39-1.53 (9H, m), 1.61-1.79 (4H, m), 1.88-2.19 (2H, m), 3.05-3.21 (4H, m), 3.30-3.37 (5H, m), 3.38-3.49 (3H, m), 3.48-3.79 (12H, m), 3.95-4.22 (1H, m), 6.35-6.48 (2H, m), 7.11-7.21 (1H, m), 8.52 (1H, s).

MS (ESI+, m/e) 636 (M+1)

Example 11
6-fluoro-1-(4-methoxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide dihydrochloride

[0438]
[0439]

tert-Butyl (3S,5R)-3-{{(4-fluoro-2-[(4-
methoxybutyl)amino]phenyl)amino}(oxo)acetyl}(2-
methylpropyl)amino)-5-(morpholin-4-ylcarbonyl)piperidine-1-
carboxylate (294 mg) was dissolved in acetic acid (5 ml), and
the mixture was stirred at 80°C for 3 days. The reaction
mixture was cooled to room temperature; 4M hydrogen chloride-
ethyl acetate (5 ml) was added to the reaction mixture, and
the mixture was stirred at room temperature for 2 hr. The
reaction mixture was concentrated, and the residue was diluted
with aqueous sodium bicarbonate, and extracted with ethyl
acetate. The extract was washed with saturated brine, and
dried over anhydrous sodium sulfate. The solvent was
evaporated under reduced pressure. The residue was subjected
to basic silica gel column chromatography, and a fraction
eluted with ethyl acetate-methanol (85:15) was concentrated
under reduced pressure. The residue was dissolved in ethyl
acetate, 4M hydrogen chloride-ethyl acetate (1 ml) was added,
and the mixture was concentrated again to give the object
product (113 mg).

$^1$H-NMR (DMSO-d$_6$) δ 0.64-0.79 (2H, m), 0.83-1.01 (4H, m), 1.37-
1.60 (2H, m), 1.66-1.89 (2H, m), 1.91-2.18 (2H, m), 2.15-2.44
(1H, m), 2.85-3.85 (20H, m), 4.30 (3H, t), 7.09-7.25 (1H, m),
7.57-7.79 (2H, m), 8.57 (1H, br s), 9.20-9.42 (1H, m), 9.46-
9.81 (1H, m).

MS (ESI+, m/e) 518 (M+1)

[0440]

Reference Example 35
6-fluoro-1-(4-methoxybutyl)-2-(trichloromethyl)-1H-benzimidazole

[0441]

4-Fluoro-2-(4-methoxybutylamino)aniline (4.28 g) was dissolved in acetic acid (100 ml), methyl 2,2,2-trichloroethanamidate (2.49 ml) was added dropwise, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated under reduced pressure, and the residue was azeotroped with toluene. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate was concentrated under reduced pressure to give the object product (6.53 g).

¹H-NMR (CDCl₃) δ 1.71-1.84 (2H, m), 2.00-2.14 (2H, m), 3.38 (3H, s), 3.48 (2H, t), 4.46-4.59 (2H, m), 7.03-7.16 (2H, m), 7.81 (1H, dd).

MS (ESI+, m/e) 339 (M+1)

[0443]

Reference Example 36

tert-butyl (3S,5R)-3-[(6-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl)carbonyl][2-methylpropyl]amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[0444]
[0445]
6-Fluoro-1-(4-methoxybutyl)-2-(trichloromethyl)-1H-benzimidazole (1.02 g) and tert-butyl (3S,5R)-3-[(2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (1.11 g) were dissolved in acetonitrile (50 ml) and water (25 ml), potassium carbonate (4.15 g) was added, and the mixture was stirred at 60°C for 17 hr. The reaction mixture was cooled to room temperature, and the mixture was extracted with ethyl acetate. The extract was washed successively with 10% aqueous citric acid solution, aqueous sodium bicarbonate and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate was concentrated under reduced pressure to give the product (595 mg).

1H-NMR (CDCl₃) δ 0.64-0.82 (3H, m), 0.89-1.05 (3H, m), 1.41-1.60 (9H, m), 1.59-1.78 (2H, m), 1.83-2.24 (3H, m), 2.28-2.99 (3H, m), 3.33 (17H, d), 3.96-4.43 (5H, m), 7.00-7.17 (2H, m), 7.49-7.75 (1H, m).

MS (ESI+, m/e) 618 (M+1)

[0446]
Example 12
6-fluoro-1-(4-methoxybutyl)-N-(2-methylpropyl)-N-[3S,5R]-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide dihydrochloride

[0447]

[0448]
tert-Butyl (3S,5R)-3-[[6-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate was dissolved in 4M hydrogen chloride-ethyl acetate (5 ml), and the mixture was stirred at room temperature for 4 hr. The reaction mixture was concentrated to give the object product (567 mg).

\[^1^H\text{-NMR (DMSO-d}6\text{)} \delta 0.64-0.79 (2H, m), 0.83-1.01 (4H, m), 1.37-1.60 (2H, m), 1.66-1.89 (2H, m), 1.91-2.18 (2H, m), 2.15-2.44 (1H, m), 2.85-3.85 (20H, m), 4.30 (3H, t), 7.09-7.25 (1H, m), 7.57-7.79 (2H, m), 8.57 (1H, br s), 9.20-9.42 (1H, m), 9.46-9.81 (1H, m).

MS (ESI+, m/e) 518 (M+1)

[0449]

Reference Example 37

1-tert-butyl 3-methyl (3R,5S)-5-[[6-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]piperidine-1,3-dicarboxylate and (3R,5S)-1-(tert-butoxycarbonyl)-5-[[6-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]piperidine-3-carboxylic acid

[0450]

[0451]

6-Fluoro-1-(4-methoxybutyl)-2-(trichloromethyl)-1H-benzimidazole (3.40 g) and 1-tert-butyl 3-methyl (3R,5S)-5-[[2-methylpropyl]amino]piperidine-1,3-dicarboxylate (3.14 g) were dissolved in acetonitrile (100 ml) and water (50 ml), cesium carbonate (32.6 g) was added, and the mixture was stirred at 60°C for 17 hr. The reaction mixture was cooled to room temperature, adjusted to pH 7 with 1M hydrochloric acid,
and extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (1:1) was concentrated under reduced pressure to give 1-tert-butyl 3-methyl (3R,5S)-5-[[6-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl] (2-methylpropyl)amino)piperidine-1,3-dicarboxylate (1.60 g), and a fraction eluted with ethyl acetate was concentrated under reduced pressure to give (3R,5S)-1-(tert-butoxycarbonyl)-5-[[6-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl] (2-methylpropyl)amino)piperidine-3-carboxylic acid (1.36 g).

[0452]

1-tert-butyl 3-methyl (3R,5S)-5-[[6-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl] (2-methylpropyl)amino)piperidine-1,3-dicarboxylate

$^1$H-NMR (CDCl$_3$) $\delta$ 0.70-0.82 (4H, m), 1.00 (2H, d), 1.29-1.36 (3H, m), 1.44-1.52 (6H, m), 1.58-1.72 (2H, m), 1.72-2.04 (3H, m), 2.12-2.37 (1H, m), 2.42-2.93 (3H, m), 3.28-3.80 (12H, m), 4.15-4.51 (4H, m), 7.00-7.14 (2H, m), 7.59-7.77 (1H, m).

MS (ESI+, m/e) 563 (M+1)

(3R,5S)-1-(tert-butoxycarbonyl)-5-[[6-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl] (2-methylpropyl)amino)piperidine-3-carboxylic acid

$^1$H-NMR (CDCl$_3$) $\delta$ 0.69-0.83 (4H, m), 0.95-1.07 (2H, m), 1.16-1.30 (3H, m), 1.42-1.55 (6H, m), 1.60-1.73 (3H, m), 1.75-2.10 (5H, m), 2.40-2.94 (2H, m), 3.29-3.68 (10H, m), 4.15-4.36 (2H, m), 7.02-7.18 (2H, m), 7.86-8.07 (1H, m).

MS (ESI+, m/e) 549 (M+1)

[0453]

Reference Example 38

(3R,5S)-1-(tert-butoxycarbonyl)-5-[[6-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl] (2-methylpropyl)amino)piperidine-3-carboxylic acid
1-tert-Butyl 3-methyl (3R,5S)-5-[(6-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl)carbonyl](2-methylpropyl)amino]piperidine-1,3-dicarboxylate (1.6 g) was dissolved in ethanol (100 ml), 2M aqueous sodium hydroxide solution (14.2 ml) was added, and the mixture was stirred at 50°C for 5 hr. The reaction mixture was cooled to room temperature, adjusted to pH 7 with 1M hydrochloric acid, and extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate was concentrated under reduced pressure to give the object product (1.55 g).

^1H-NMR (CDCl₃) δ 0.69-0.83 (4H, m), 0.95-1.07 (2H, m), 1.16-1.30 (3H, m), 1.42-1.55 (6H, m), 1.60-1.73 (3H, m), 1.75-2.10 (5H, m), 2.40-2.94 (2H, m), 3.29-3.68 (10H, m), 4.15-4.36 (2H, m), 7.02-7.18 (2H, m), 7.86-8.07 (1H, m).

MS (ESI+, m/e) 549 (M+1)

Reference Example 39

tert-butyl (3S,5R)-3-[(6-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl)carbonyl](2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[0457]
(3R,5S)-1-(tert-Butoxycarbonyl)-5-[[6-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-
5 methylpropyl)amino)piperidine-3-carboxylic acid (1.05 g), HOBt (361 mg) and WSC·HCl (549 mg) were dissolved in DMF (50 ml), morpholine (332 µl) and diisopropylethylamine (780 µl) were added, and the mixture was stirred at 60°C for 4 hr. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, and the residue was diluted with aqueous sodium bicarbonate. The mixture was extracted with ethyl acetate, and the extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate was concentrated under reduced pressure to give the object product (1.14 g).

$\text{H-NMR (CDCl}_3\) \delta 0.64-0.82 (3H, m), 0.89-1.05 (3H, m), 1.41-1.60 (9H, m), 1.59-1.78 (2H, m), 1.83-2.24 (3H, m), 2.28-2.99 (3H, m), 3.33 (17H, d), 3.96-4.43 (5H, m), 7.00-7.17 (2H, m), 7.49-7.75 (1H, m).

MS (ESI+, m/e) 618 (M+1)

[0459]

In the same manner as in Reference Example 32, the following compound (Reference Example 40) was obtained.

[0460]

Reference Example 40

4-fluoro-N-(4-methoxybutyl)-2-nitroaniline

[0461]
[0462]

$^1$H-NMR (CDCl$_3$) $\delta$ 1.66-1.89 (4H, m), 3.25-3.40 (5H, m), 3.44 (2H, t), 6.84 (1H, dd), 7.21-7.30 (1H, m), 7.84-8.05 (2H, m).

[0463]

In the same manner as in Reference Example 33, the following compound (Reference Example 41) was obtained.

[0464]

Reference Example 41

5-fluoro-2-(4-methoxybutylamino)aniline

[0465]

$^1$H-NMR (CDCl$_3$) $\delta$ 1.66-1.78 (4H, m), 3.12 (1H, br s), 3.04-3.11 (2H, m), 3.35 (3H, s), 3.39-3.46 (2H, m), 3.58 (2H, br s), 6.42-6.51 (2H, m), 6.53-6.60 (1H, m).

[0467]

In the same manner as in Reference Example 34, the following compound (Reference Example 42) was obtained.

[0468]

Reference Example 42

tert-butyl (3S,5R)-3-(((5-fluoro-2-[(4-methoxybutyl)amino]phenyl)amino)(oxo)acetyl)(2-methylpropyl)amino)-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[0469]
MS (ESI+, m/e) 636 (M+1)

In the same manner as in Example 11, the following compound (Example 13) was obtained.

Example 13
5-fluoro-1-(4-methoxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide dihydrochloride

MS (ESI+, m/e) 518 (M+1)

In the same manner as in Reference Example 35, the following compound (Reference Example 43) was obtained.

Reference Example 43
5-fluoro-1-(4-methoxybutyl)-2-(trichloromethyl)-1H-benzimidazole
MS (ESI+, m/e) 339 (M+1)

In the same manner as in Reference Example 37, the following compound (Reference Example 44) was obtained.

Reference Example 44
1-tert-butyl 3-methyl (3R,5S)-5-[[5-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino)piperidine-1,3-dicarboxylate

MS (ESI+, m/e) 563 (M+1)

In the same manner as in Reference Example 38, the following compound (Reference Example 45) was obtained.

Reference Example 45
(3R,5S)-1-(tert-butoxycarbonyl)-5-[[5-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino)piperidine-3-carboxylic acid
MS (ESI+, m/e) 549 (M+1)

Reference Example 46

5 tert-butyl (3S)-3-[(2-methylpropyl)amino]piperidine-1-carboxylate

10 tert-Butyl (3S)-3-aminopiperidine-1-carboxylate (5.0 g), isobutylaldehyde (2.66 ml) and acetic acid (1.72 ml) were dissolved in methanol (100 ml), and the mixture was stirred at room temperature for 10 min. Sodium triacetoxyborohydride (13.2 g) was added to the reaction mixture, and the mixture was stirred at room temperature for 30 min. The reaction mixture was basified with aqueous sodium bicarbonate, and extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. A part of the residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (35:65) was concentrated under reduced pressure to give the object product (3.04 g) as an oil.

$^1$H-NMR (CDCl$_3$) δ 0.79-1.15 (8H, m), 1.16-1.36 (1H, m), 1.36-1.56 (11H, m), 1.58-1.80 (2H, m), 1.80-2.00 (1H, m), 2.35-2.60
(3H, m), 2.74-2.99 (1H, m), 3.68-3.91 (1H, m).

MS (ESI+, m/e) 257 (M+1)

[0485]

Reference Example 47

tert-butyl (3S)-3-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino)piperidine-1-carboxylate

[0486]

1-(4-Methoxybutyl)-2-(trichloromethyl)-1H-benzimidazole (470 mg) and tert-butyl (3S)-3-[(2-methylpropyl)amino]piperidine-1-carboxylate (400 mg) were dissolved in acetonitrile (30 ml) and water (15 ml), potassium carbonate (2.02 g) was added, and the mixture was stirred at 80°C for 15 hr. The reaction mixture was cooled to room temperature and diluted with saturated brine. The mixture was extracted with ethyl acetate, and the extract was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (60:40) was concentrated under reduced pressure to give the object product (446 mg).

MS (ESI+, m/e) 487 (M+1)

[0488]

In the same manner as in Example 12, the following compound (Example 14) was obtained.

[0489]

Example 14

1-(4-methoxybutyl)-N-(2-methylpropyl)-N-[(3S)-piperidin-3-yl]-1H-benzimidazole-2-carboxamide dihydrochloride
MS (ESI+, m/e) 387 (M+1).

Reference Example 48
N-(4-methoxybutyl)-3-nitropyridin-2-amine

2-Chloro-3-nitropyridine (3.54 g) and 4-methoxybutan-1-amine·hydrochloride (3.12 g) were suspended in 2-propanol (100 ml), diisopropylethylamine (11.6 µl) was added and the mixture was heated under reflux with stirring for 4 days. The reaction mixture was cooled to room temperature, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (3:7) was concentrated under reduced pressure to give the object product (4.26 g).

\( ^1H-NMR \text{(CDCl}_3 \text{)} \delta 1.63-1.85 \ (4 \text{H, m}), 3.35 \ (3 \text{H, s}), 3.44 \ (2 \text{H, t}), 3.61-3.72 \ (2 \text{H, m}), 6.57-6.67 \ (1 \text{H, m}), 8.31 \ (1 \text{H, br s}), 8.36-8.51 \ (2 \text{H, m}). \)

In the same manner as in Reference Example 33, the following compound (Reference Example 49) was obtained.

Reference Example 49
2-(4-methoxybutylamino)-3-aminopyridine
[0497]

$^1$H-NMR (CDCl$_3$) $\delta$ 1.66-1.83 (4H, m), 3.36 (3H, s), 3.42-3.55 (4H, m), 3.69 (2H, br s), 5.05 (1H, br s), 6.52 (1H, dd), 6.85 (1H, dd), 7.67 (1H, dd).

[0498]

In the same manner as in Reference Example 35, the following compound (Reference Example 50) was obtained.

[0499]

Reference Example 50
3-(4-methoxybutyl)-2-(trichloromethyl)-3H-imidazo[4,5-b]pyridine

[0500]

[0501]

MS (ESI+, m/e) 322 (M+1)

In the same manner as in Reference Example 47, the following compound (Reference Example 51) was obtained.

[0502]

Reference Example 51

tert-butyl $(3S)-3-\{[3-(4$-$methoxybutyl)$-3H$-$imidazo[4,5$-$b]$-$pyridin$-$2$-$yl]carbonyl\}(2$-$methylpropyl)$amino$)piperidine$-1$-$carboxylate

[0503]
[0504]
MS (ESI+, m/e) 488 (M+1)

In the same manner as in Example 12, the following compound (Example 15) was obtained.

[0505]
Example 15
3-(4-methoxybutyl)-N-(2-methylpropyl)-N-[(3S)-piperidin-3-yl]-3H-imidazo[4,5-b]pyridine-2-carboxamide dihydrochloride

[0506]

[0507]
MS (ESI+, m/e) 388 (M+1)
Reference Example 52
1-(4-methoxybutyl)-4,5,6,7-tetrahydro-1H-benzimidazole

[0508]

[0509]
4,5,6,7-Tetrahydro-1H-benzimidazole (2.45 g) was dissolved in DMF (20 ml), sodium hydride (60% in oil, 880 mg) was added, and the mixture was stirred at room temperature for 30 min. 4-Methoxybutyl methanesulfonate (1.28 g) was added, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was concentrated under reduced pressure, water was added and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate was concentrated under reduced pressure to give the object product (2.90 g).
MS (ESI+, m/e) 209 (M+1)

[0510]
Reference Example 53
methyl 1-(4-methoxybutyl)-4,5,6,7-tetrahydro-1H-benzimidazole-2-carboxylate

[0511]

[0512]

1-(4-Methoxybutyl)-4,5,6,7-tetrahydro-1H-benzimidazole (625 mg) was dissolved in acetonitrile (5 ml), and the mixture was cooled to -15°C. Triethylamine (1.25 ml) and methyl chlorocarbonate (691 µl) were added dropwise. The reaction mixture was heated to room temperature and stirred for 12 hr. The reaction mixture was again cooled to -15°C, triethylamine (1.25 ml) and methyl chlorocarbonate (691 µl) were added dropwise, heated to room temperature and stirred for 12 hr.

This operation was further repeated 3 times, aqueous sodium bicarbonate was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to basic silica gel column chromatography, and a fraction eluted with ethyl acetate was concentrated under reduced pressure to give the object product (225 mg).

MS (ESI+, m/e) 267 (M+1)

[0513]
Reference Example 54
tert-butyl (3S,5R)-3-[[1-(4-methoxybutyl)-4,5,6,7-tetrahydro-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[0514]
Methyl 1-(4-methoxybutyl)-4,5,6,7-tetrahydro-1H-benzimidazole-2-carboxylate (225 mg) was dissolved in ethanol (10 ml) and water (5 ml), lithium hydroxide monohydrate (53 mg) was added, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was concentrated under reduced pressure, and the residue was azeotroped with toluene. The residue was dissolved in 1,2-dichloroethane, tert-butyl (3S,5R)-3-[(2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (314 mg), diisopropylethylamine (732 µl) and chloro-N,N,N',N'-tetramethylformamidinium hexafluorophosphate (168 mg) were added, and the mixture was stirred at room temperature for 15 hr. Aqueous sodium bicarbonate was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was subjected to basic silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (6:4) was concentrated under reduced pressure to give the object product (178 mg).

MS (ESI+, m/e) 604 (M+1)

In the same manner as in Example 12, the following compound (Example 16) was obtained.

Example 16
1-(4-methoxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-4,5,6,7-tetrahydro-1H-
benzimidazole-2-carboxamide dihydrochloride

\[ 0518 \]

\[
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{O} \\
\text{2HCl} \\
\text{N} \\
\text{N} \\
\text{O} \\
\end{array}
\]

\[ 0519 \]

MS (ESI+, m/e) 504 (M+1)

Reference Example 55
tert-butyl (3R,5S)-3-carbamoyl-5-[[5-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl] carbonyl](2-methylpropyl)amino]piperidine-1-carboxylate

\[ 0520 \]

\[
\begin{array}{c}
\text{F} \\
\text{N} \\
\text{N} \\
\text{O} \\
\text{O} \\
\text{N} \\
\text{O} \\
\text{NH}_2 \\
\end{array}
\]

\[ 0521 \]

(3R,5S)-1-(tert-Butyloxycarbonyl)-5-[[5-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl] carbonyl](2-methylpropyl)amino]piperidine-3-carboxylic acid (549 mg), 1H-1,2,3-benzotriazol-1-ol ammonium salt (304 mg) and WSC·HCl (288 mg) were dissolved in DMF (5 ml), diisopropylethylamine (517 µl) was added, and the mixture was stirred at 60°C for 3 hr. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, and the residue was diluted with aqueous sodium bicarbonate and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction
eluted with ethyl acetate was concentrated under reduced pressure to give the object product (1.14 g).

MS (ESI+, m/e) 548 (M+1)

[0522]

In the same manner as in Reference Example 55, the following compound (Reference Example 56) was obtained.

[0523]

Reference Example 56

tert-butyl (3R,5S)-3-carbamoyl-5-\{[6-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl\}(2-methylpropyl)amino)piperidine-1-carboxylate

[0524]

[0525]

MS (ESI+, m/e) 548 (M+1)

In the same manner as in Reference Example 39, the following compounds (Reference Examples 57-59) were obtained.

[0526]

Reference Example 57

tert-butyl (3S,5R)-3-\{[5-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl\}(2-methylpropyl)amino)-5-(pyrrolidin-1-ylcarbonyl)piperidine-1-carboxylate

[0527]

[0528]
MS (ESI+, m/e) 602 (M+1)

Reference Example 58
tert-butyl (3R,5S)-3-(azetidin-1-ylcarbonyl)-5-[[5-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-5 methylpropyl)amino]piperidine-1-carboxylate

[0529]

MS (ESI+, m/e) 558 (M+1)

Reference Example 59
tert-butyl (3S,5R)-3-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-(piperidin-1-ylcarbonyl)piperidine-1-carboxylate

[0531]

In the same manner as in Example 12, the following compounds (Examples 17-22) were obtained.

[0532]

MS (ESI+, m/e) 598 (M+1)

Example 17
(3R,5S)-5-[[6-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]piperidine-3-carboxylic acid dihydrochloride

[0533]

[0534]
MS (ESI+, m/e) 449 (M+1)

Example 18

5-fluoro-1-(4-methoxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(pyrrolidin-1-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide dihydrochloride

MS (ESI+, m/e) 502 (M+1)

Example 19

N-[(3S,5R)-5-carbamoylpiperidin-3-yl]-5-fluoro-1-(4-methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide dihydrochloride

MS (ESI+, m/e) 448 (M+1)

Example 20
N-[(3S,5R)-5-carbamoylpiperidin-3-yl]-6-fluoro-1-(4-methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide dihydrochloride

**[0540]**

**[0541]**
MS (ESI+, m/e) 448 (M+1)
Example 21
1-(4-methoxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(piperidin-1-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide dihydrochloride

**[0542]**

**[0543]**
MS (ESI+, m/e) 498 (M+1)
Example 22
5-fluoro-1-(4-methoxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(4H-1,2,4-triazol-3-yl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide dihydrochloride

**[0544]**
**[0545]**

MS (ESI+, m/e) 472 (M+1)

Example 23

N-[(3S,5R)-5-(azetidin-1-ylcarbonyl)piperidin-3-yl]-5-fluoro-1-(4-methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide

**[0546]**

**[0547]**

tert-Butyl (3R,5S)-3-(azetidin-1-ylcarbonyl)-5-[[[[5-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]piperidine-1-carboxylate (80 mg) was dissolved in trifluoroacetic acid (3 ml), and the mixture was stirred at room temperature for 1 hr. Aqueous sodium bicarbonate was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give the object product (42 mg).

MS (ESI+, m/e) 488 (M+1)

**[0548]**

Reference Example 60

tert-butyl (3S,5R)-3-[[[6-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-
(hydroxymethyl)piperidine-1-carboxylate

[0549]

To a solution of (3R,5S)-1-(tert-butoxycarbonyl)-5-[[6-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino)piperidine-3-carboxylic acid (274 mg) and 4-methylmorpholine (66 µl) in THF (5 ml) was added dropwise ethyl chlorocarbonate (57 µl) at 0°C, and the mixture was stirred at the same temperature for 1 hr. Sodium borohydride (57 mg) and methanol (1 ml) were added to the reaction mixture, and the mixture was stirred at 0°C for 1 hr. The reaction mixture was diluted with aqueous sodium bicarbonate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to basic silica gel column chromatography, and a fraction eluted with ethyl acetate was concentrated under reduced pressure to give the object product (182 mg).

MS (ESI+, m/e) 535 (M+1)

[0551]

Example 24

6-fluoro-N-[(3S,5R)-5-(hydroxymethyl)piperidin-3-yl]-1-(4-methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide dihydrochloride

[0552]
[0553]
tert-Butyl (3S,5R)-3-[[6-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-
5 (hydroxymethyl)piperidine-1-carboxylate (182 mg) was dissolved in 10-20% hydrogen chloride-methanol (5 ml), and the mixture was stirred at room temperature for 3 days. The reaction mixture was concentrated to give the object product (169 mg). MS (ESI+, m/e) 435 (M+1)

[0554]
Reference Example 61
2-(trichloromethyl)-1H-benzimidazole

[0555]

[0556]
O-Phenylenediamine (25 g) was dissolved in acetic acid (750 ml), and methyl 2,2,2-trichloroacetimidate (28.5 ml) was added dropwise over 15 min. After stirring at room temperature for 1 hr, the reaction mixture was concentrated to about 150 ml, and poured into water (1500 ml). The precipitated crystals were collected by filtration, washed with water (1000 ml) and suspended in toluene (500 ml). The solvent was evaporated under reduced pressure. The residue was again suspended in toluene (500 ml) and the solvent was evaporated under reduced pressure. The residue was dried under reduced pressure to give the object product (51.8 g).

^1H-NMR (CDCl₃) δ 7.31-7.45 (2H, m), 7.49-7.55 (1H, m), 7.89 (1H,
d), 9.74 (1H, br s)

[0557]

In the same manner as in Reference Example 61, the following compounds (Reference Examples 62-63) were obtained.

[0558]

Reference Example 62
5,6-difluoro-2-(trichloromethyl)-1H-benzimidazole

[0559]

\[
\begin{array}{c}
\text{F} \\
\text{N} \\
\text{NH} \\
\text{CCl}_3
\end{array}
\]

[0560]

\[1^1\text{H-NMR (CDCl}_3\text{)} \delta 7.10-7.83 (2H, m), 10.10 (1H, br s)\]

Reference Example 63
4-chloro-2-(trichloromethyl)-1H-benzimidazole

[0561]

\[
\begin{array}{c}
\text{Cl} \\
\text{N} \\
\text{NH} \\
\text{CCl}_3
\end{array}
\]

[0562]

\[1^1\text{H-NMR (CDCl}_3\text{)} \delta 7.14-7.51 (3H, m), 9.59-10.26 (1H, m)\]

Reference Example 64
1-tert-buty1 3-methyl (3R,5S)-5-[(1H-benzimidazol-2-ylcarbonyl)(2-methylpropyl)amino]piperidine-1,3-dicarboxylate

[0563]

\[
\begin{array}{c}
\text{N} \\
\text{NH}
\end{array}
\]

[0564]

2-(Trichloromethyl)-1H-benzimidazole (19 g) and 1-tert-buty1 3-methyl (3R,5S)-5-[(2-methylpropyl)amino]piperidine-
1,3-dicarboxylate (25 g) were dissolved in THF (1200 ml), sodium hydrogen carbonate (67 g) and water (600 ml) were added, and the mixture was stirred at room temperature for 1 hr and at 50°C for 1 hr. After evaporation of the solvent, the residue was extracted 3 times with ethyl acetate (700 ml). The extract was washed successively with 10%-aqueous citric acid solution (500 ml) and brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (1000 ml), subjected to basic silica gel column chromatography, and a fraction eluted with ethyl acetate was concentrated under reduced pressure to give the object product (30.6 g).

$^1$H-NMR (CDCl$_3$) δ 0.78-1.09 (6 H, m), 1.17-1.55 (9 H, m), 1.77-2.95 (5 H, m), 3.11-3.79 (6 H, m), 3.99-4.73 (4 H, m), 7.24-7.41 (2 H, m), 7.45-7.59 (1 H, m), 7.72-7.88 (1 H, m), 10.66-10.98 (1 H, m)

MS (ESI+, m/e) 459 (M+1)

Reference Example 65

tert-butyl (3S,5R)-3-[(5,6-difluoro-1H-benzimidazol-2-yl)carbonyl]-(2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

$$\text{F} \quad \text{F}$$
$$\text{N} \quad \text{N}$$
$$\text{F} \quad \text{F}$$

[0566]

To a solution of 5,6-difluoro-2-(trichloromethyl)-1H-benzimidazole (500 mg) and tert-butyl (3S,5R)-3-[(2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (680 mg) in THF (50 ml) were added sodium hydrogen carbonate (1.3 g) and water (20 ml), and the mixture was
stirred at room temperature for 1 hr and extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (1:1 - 1:0) was concentrated under reduced pressure to give the object product (710 mg).

MS (ESI+, m/e) 550 (M+1)

[0568]

In the same manner as in Reference Example 65, the following compounds (Reference Examples 66-68) were obtained.

[0569]

Reference Example 66
1-tert-butyl 3-methyl (3R,5S)-5-[[5,6-difluoro-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino)piperidine-1,3-dicarboxylate

[0570]

MS (ESI+, m/e) 495 (M+1)

Reference Example 67
1-tert-butyl 3-methyl (3R,5S)-5-{{4-chloro-1H-benzimidazol-2-yl}carbonyl}(2-methylpropyl)amino)piperidine-1,3-dicarboxylate

[0572]
1-tert-butyl 3-methyl 5-[(1H-benzimidazol-2-ylcarbonyl)(2-methylpropyl)amino]piperidine-1,3-dicarboxylate

1-tert-butyl 3-methyl (3R,5S)-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]piperidine-1,3-dicarboxylate

1-tert-Butyl 3-methyl (3R,5S)-5-[(1H-benzimidazol-2-ylcarbonyl)(2-methylpropyl)amino]piperidine-1,3-dicarboxylate (30 g) and 4-methoxybutyl methanesulfonate (12.5 g) were
dissolved in DMA (600 ml), cesium carbonate (32 g) was added, and the mixture was stirred at 70°C for 12 hr. The reaction mixture was poured into ice water (1000 ml), and the mixture was extracted twice with ethyl acetate (1000 ml). The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (1:4 - 1:1) was concentrated under reduced pressure to give the object product (28.7 g).

^1H-NMR (CDCl₃) δ 0.76 (4H, d), 1.01 (2H, d), 1.30-1.52 (9H, m), 1.58-2.07 (4H, m), 2.10-2.93 (4H, m), 3.27-3.75 (12H, m), 4.06-4.57 (5H, m), 7.26-7.48 (3H, m), 7.79 (1H, d)

MS (ESI+, m/e) 545 (M+1)

[0578]

In the same manner as in Reference Example 69, the following compounds (Reference Examples 70-72) were obtained.

[0579]

Reference Example 70

tert-butyl (3S,5R)-3-[[5,6-difluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[0580]

MS (ESI+, m/e) 636 (M+1)

Reference Example 71

1-tert-butyl 3-methyl (3R,5S)-5-[[5,6-difluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]piperidine-1,3-dicarboxylate

[0581]
[0582]

[0583]
MS (ESI+, m/e) 495 (M+1)

Reference Example 72
1-tert-butyl 3-methyl 5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino)piperidine-1,3-dicarboxylate

[0584]

[0585]
MS (ESI+, m/e) 545 (M+1)

Reference Example 73
1-tert-butyl 3-methyl (3R,5S)-5-[[7-chloro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino)piperidine-1,3-dicarboxylate and 1-tert-butyl 3-methyl (3R,5S)-5-[[4-chloro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino)piperidine-1,3-dicarboxylate

[0586]
[0587]

1-tert-Butyl 3-methyl (3R,5S)-5-{{(4-chloro-1H-benzimidazol-2-yl)carbonyl}(2-methylpropyl)amino)piperidine-1,3-dicarboxylate (1.7 g) and 4-methoxybutyl methanesulfonate (754 mg) were dissolved in DMA (50 ml), cesium carbonate (1.7 g) was added, and the mixture was stirred at 70°C for 12 hr. The reaction mixture was poured into ice water (100 ml), and the mixture was extracted twice with ethyl acetate (100 ml).

The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a less polar fraction eluted with ethyl acetate-hexane (1:4 - 1:1) was concentrated under reduced pressure to give 1-tert-butyl 3-methyl (3R,5S)-5-{{[7-chloro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl}(2-methylpropyl)amino)piperidine-1,3-dicarboxylate (200 mg).

MS (ESI+, m/e) 580 (M+1)

A highly-polar fraction was concentrated to give 1-tert-butyl 3-methyl (3R,5S)-5-{{[4-chloro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl}(2-methylpropyl)amino)piperidine-1,3-dicarboxylate (1.4 g).

MS (ESI+, m/e) 580 (M+1)

[0588]

Reference Example 74

(3R,5S)-1-(tert-butoxycarbonyl)-5-{{[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl}(2-methylpropyl)amino)piperidine-3-carboxylic acid

[0589]
1-tert-Butyl 3-methyl (3R,5S)-5-\{[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl\}(2-methylpropyl)amino)piperidine-1,3-dicarboxylate (15 g) was dissolved in methanol (150 ml), 4N-aqueous sodium hydroxide solution (250 ml) was added, and the mixture was stirred at 50°C for 1 hr. The solvent was evaporated under reduced pressure, and the residue was ice-cooled, neutralized with 2N hydrochloric acid, and extracted twice ethyl acetate (500 ml). The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was dried under reduced pressure to give the object product (15.0 g).

In the same manner as in Reference Example 74, the following compounds (Reference Examples 75-78) were obtained.

Reference Example 75
(3R,5S)-1-(tert-butoxycarbonyl)-5-\{[5,6-difluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl\}(2-methylpropyl)amino)piperidine-3-carboxylic acid
MS (ESI+, m/e) 567 (M+1)
Reference Example 76

(3R,5S)-1-(tert-butoxycarbonyl)-5-[[7-chloro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl]{2-methylpropyl)amino]piperidine-3-carboxylic acid

MS (ESI+, m/e) 565 (M+1)
Reference Example 77

(3R,5S)-1-(tert-butoxycarbonyl)-5-[[4-chloro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl]{2-methylpropyl)amino]piperidine-3-carboxylic acid

MS (ESI+, m/e) 565 (M+1)
Reference Example 78
1-(tert-butoxycarbonyl)-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino)piperidine-3-carboxylic acid

[0599]

MS (ESI+, m/e) 531 (M+1)
Reference Example 79
tert-butyl (3R,5S)-3-(hydroxymethyl)-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino)piperidine-1-carboxylate

[0601]

Sodium borohydride (4.45 g) was suspended in THF (25 ml)-ethanol (75 ml), and calcium chloride (6.5 g) was added. After stirring at 0°C for 1 hr, a solution of 1-tert-butyl 3-methyl (3R,5S)-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino)piperidine-1,3-dicarboxylate (4.0 g) in THF (50 ml) was added. After stirring at room temperature for 12 hr, ethyl acetate (150 ml) and water (50 ml) were slowly added in this order, and the mixture was filtered. The organic layer of the filtrate was partitioned, washed with brine, and dried over anhydrous sodium sulfate.

The solvent was evaporated under reduced pressure. The residue
was dried under reduced pressure to give the object product (1.8 g).

\[ ^{1}H\text{-NMR (CDCl}_3 \delta 0.77 (4H, d), 1.02 (2H, d), 1.31-1.51 (9H, m), 1.56-2.88 (9H, m), 3.24-3.73 (11H, m), 3.98-4.48 (5H, m), 7.28-7.53 (3H, m), 7.79 (1H, dd) } \]

MS (ESI+, m/e) 517 (M+1)

[0603]
Reference Example 80
tert-butyl (3R,5S)-3-carbamoyl-5-\{[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl\}(2-methylpropyl)amino]piperidine-1-carboxylate

[0604]

[0605]
A solution of (3R,5S)-1-(tert-butoxycarbonyl)-5-\{[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl\}(2-methylpropyl)amino]piperidine-3-carboxylic acid (540 mg), 1H-1,2,3-benzotriazol-1-ol ammonium salt (345 mg) and WSC·HCl (383 mg) in DMF (10 ml) was stirred at room temperature for 24 hr, and the mixture was poured into water and extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (1:9 - 1:0) was concentrated under reduced pressure to give the object product (270 mg).

\[ ^{1}H\text{-NMR (CDCl}_3 \delta 0.77 (3H, d) 0.93-1.07 (3H, m), 1.21-1.55 (9H, m), 1.55-3.01 (9H, m), 3.24-4.60 (12H, m), 5.45 (1H, d), 5.66-6.06 (1H, m), 7.23-7.52 (3H, m), 7.79 (1H, d) } \]

MS (ESI+, m/e) 430 (M+1)
In the same manner as in Reference Example 80, the following compound (Reference Example 81) was obtained.

Reference Example 81
tert-butyl (3R,5S)-3-carbamoyl-5-[[5,6-difluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino)piperidine-1-carboxylate

MS (ESI+, m/e) 566 (M+1)

Reference Example 82
tert-butyl (3S,5R)-3-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino)-5-(pyrrolidin-1-ylcarbonyl)piperidine-1-carboxylate

(3R,5S)-1-( tert-Butoxycarbonyl)-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino)piperidine-3-carboxylic acid (400 mg) and pyrrolidine (59 mg) were dissolved in DMF (10 ml), WSC·HCL (217 mg) and HOBt (150 mg) were added, and the mixture was stirred at 50°C for 12 hr. The reaction mixture was poured into 10%
aqueous sodium bicarbonate, and the mixture was extracted with ethyl acetate. The extracts were combined and washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (1:1 - 1:0) was concentrated under reduced pressure to give the object product (420 mg).

MS (ESI+, m/e) 584 (M+1)

In the same manner as in Reference Example 82, the following compounds (Reference Examples 83-91) were obtained.

Reference Example 83
tert-butyl (3RS,5RS)-3-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

MS (ESI+, m/e) 600 (M+1)

Reference Example 84
tert-butyl (3R,5S)-3-(azetidin-1-ylcarbonyl)-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino)piperidine-1-carboxylate
[0617]
MS (ESI+, m/e) 570 (M+1)
Reference Example 85
tert-butyl (3R,5S)-3-[(4,4-difluoropiperidin-1-yl)carbonyl]-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino)piperidine-1-carboxylate

[0618]

[0619]
MS (ESI+, m/e) 634 (M+1)
Reference Example 86
tert-butyl (3R,5S)-3-(7-azabicyclo[2.2.1]hepta-7-ylcarbonyl)-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino)piperidine-1-carboxylate

[0620]

[0621]
MS (ESI+, m/e) 610 (M+1)
Reference Example 87
tert-butyl (3S,5R)-3-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-(1,4-oxazepan-4-ylcarbonyl)piperidine-1-carboxylate

[0622]

[0623]
MS (ESI+, m/e) 614 (M+1)
Reference Example 88
tert-butyl (3R,5S)-3-(2,3-dihydro-4H-1,4-benzoxazin-4-ylcarbonyl)-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]piperidine-1-carboxylate

[0624]

[0625]
MS (ESI+, m/e) 648 (M+1)
Reference Example 89
tert-butyl (3R,5S)-3-(azetidin-1-ylcarbonyl)-5-[[5,6-difluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]piperidine-1-carboxylate

[0626]
MS (ESI+, m/e) 606 (M+1)
Reference Example 90

5 tert-butyl (3S,5R)-3-[[7-chloro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

MS (ESI+, m/e) 634 (M+1)
Reference Example 91

10 tert-butyl (3S,5R)-3-[[4-chloro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

MS (ESI+, m/e) 634 (M+1)
Reference Example 92
tert-butyl (3R,5S)-3-[(1-hydroxy-1-methylethyl)-5-{{[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl}(2-methylpropyl)amino]piperidine-1-carboxylate

[0632]

[0633]
A solution of 1-tert-butyl 3-methyl (3R,5S)-5-{{[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl}(2-methylpropyl)amino]piperidine-1,3-dicarboxylate (330 mg) in THF (5 ml) was cooled to -40°C, a solution (1 ml) of 3M-methyl magnesium bromide in ether was added and the mixture was stirred at room temperature for 1 hr. The reaction mixture was poured into saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (1:1 – 1:0) was concentrated under reduced pressure to give the object product (180 mg).

MS (ESI+, m/e) 545 (M+1)

[0634]
In the same manner as in Reference Example 92, the following compound (Reference Example 93) was obtained.

[0635]
Reference Example 93
tert-butyl (3S,5R)-3-{{[5,6-difluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl}(2-methylpropyl)amino]-5-(1-hydroxy-1-methylethyl)piperidine-1-carboxylate

[0636]
[0637]

MS (ESI+, m/e) 581 (M+1)

Reference Example 94

tert-butyl (3R,5S)-3-formyl-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino)piperidine-1-carboxylate

[0638]

[0639]

To a solution of tert-butyl (3R,5S)-3-(hydroxymethyl)-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino)piperidine-1-carboxylate (1.0 g) in acetonitrile (20 ml) was added 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one (0.98 g), and the mixture was stirred at room temperature for 3 hr. 10% Aqueous sodium thiosulfate solution was added to the reaction mixture, and the mixture was stirred for 30 min. After partitioning, the organic layer was washed with saturated aqueous sodium hydrogen carbonate and brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (1:1) was concentrated under reduced pressure to give the object product (1.0 g).
MS (ESI+, m/e) 515 (M+1)

[0640]
Reference Example 95
tert-butyl (3R,5S)-3-((1-hydroxyethyl)-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino)piperidine-1-carboxylate

[0641]

[0642]
To a solution of tert-butyl (3R,5S)-3-formyl-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino)piperidine-1-carboxylate (150 mg) in THF (10 ml) was added 3M-methyl magnesium bromide-ether solution (0.3 ml), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was poured into saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (1:1 - 1:0) was concentrated under reduced pressure to give the object product (100 mg).
MS (ESI+, m/e) 531 (M+1)

[0643]
In the same manner as in Reference Example 95, the following compound (Reference Example 96) was obtained.

[0644]
Reference Example 96
tert-butyl (3R,5S)-3-[cyclopropyl(hydroxy)methyl]-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-
methylpropyl)amino]piperidine-1-carboxylate

[0645]

[0646]

MS (ESI+, m/e) 557 (M+1)
Reference Example 97
tert-butyl (3R,5S)-3-[hydroxy(pyridin-2-yl)methyl]-5-[[1-(4-
methoxybutyl)-1H-benzimidazol-2-yl)carbonyl](2-
methylpropyl)amino)piperidine-1-carboxylate

[0647]

[0648]

To a solution of bromopyridine (0.058 ml) cooled to -78°C in THF (5 ml) was added 1.6M-butyllithium hexane solution (0.33 ml) and the mixture was stirred for 30 min. A solution of tert-butyl (3R,5S)-3-formyl-5-[[[1-(4-methoxybutyl)-1H-
benzimidazol-2-yl)carbonyl](2-methylpropyl)amino]piperidine-1-
carboxylate (257 mg) in THF (5 ml) was added and the mixture was stirred at -20°C for 2 hr. The reaction mixture was poured into saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography,
and a fraction eluted with ethyl acetate-hexane (1:1 - 1:0) was concentrated under reduced pressure to give the object product (100 mg). MS (ESI+, m/e) 594 (M+1)

5 [0649]

Reference Example 98
tert-butyl (3S,5R)-3-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl] (2-methylpropyl)amino]-5-(oxiran-2-yl)piperidine-1-carboxylate

[0650]

[0651]

Trimethylsulfoxonium iodide (240 mg) was dissolved in DMSO (5 ml), sodium hydride (60% in oil, 45 mg) was added, and the mixture was stirred at room temperature for 30 min. A solution of tert-butyl (3R,5S)-3-formyl-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl] (2-methylpropyl)amino]piperidine-1-carboxylate (450 mg) in DMSO (10 ml) was added and the mixture was stirred at room temperature for 30 min. The reaction mixture was poured into saturated aqueous ammonium chloride solution and the mixture was extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate was concentrated under reduced pressure to give the object product (230 mg). MS (ESI+, m/e) 529 (M+1)

[0652]

Reference Example 99
tert-butyl (3R,5S)-3-{1-hydroxy-2-methoxyethyl}-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]piperidine-1-carboxylate

[0653]

5

[0654]

tert-Butyl (3S,5R)-3-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-oxirane-2-ylpiperidine-1-carboxylate (200 mg) was dissolved in methanol (5 ml), 28% sodium methyleate-methanol solution was added, and the mixture was stirred at 70°C for 6 hr. The solvent was evaporated under reduced pressure, and the residue was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (1:1 - 1:0) was concentrated under reduced pressure to give the object product (157 mg).

MS (ESI+, m/e) 561(M+1)

[0655]

Reference Example 100
tert-butyl (3S,5R)-3-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-(5-methyl-1,3,4-oxadiazol-2-yl)piperidine-1-carboxylate

[0656]
Methyltetrazole (63 mg) and (3R,5S)-1-(tert-butoxycarbonyl)-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl]2-methylpropyl]amino)piperidine-3-carboxylic acid (265 mg) were dissolved in toluene (5 ml), DCC (155 mg) was added and the mixture was stirred at 100°C for 12 hr. The reaction mixture was diluted with ethyl acetate, filtered and the solvent of the mother liquor was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (1:1 - 1:0) was concentrated under reduced pressure to give the object product (100 mg).

MS (ESI+, m/e) 569 (M+1)

Example 25
N-[(3S,5R)-5-carbamoylpiperidin-3-yl]-1-(4-methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide dihydrochloride

Tert-Butyl (3R,5S)-3-carbamoyl-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino)piperidine-1-carboxylate (260 mg) was dissolved in ethyl acetate (3 ml), 4N hydrogen chloride-ethyl
acetate (5 ml) was added, and the mixture was stirred for 1 hr. The solvent was evaporated under reduced pressure to give the object product (220 mg).

$^1$H-NMR (DMSO-d$_6$) δ 0.61-0.79 (3H, m), 0.88-0.99 (3H, m), 1.45-
1.60 (2H, m), 1.74-1.88 (2H, m), 2.07-2.41 (2H, m), 2.70-3.01
(1H, m), 3.10-3.63 (9H, m), 4.21-4.41 (3H, m), 7.12 (1H, br s),
7.28-7.48 (2H, m), 7.53-7.84 (3H, m), 8.98 (2H, br s), 9.54-
9.95 (2H, m)

MS (ESI+, m/e) 430 (M+1)

[0661]

In the same manner as in Example 25, the following compounds (Examples 26-39) were obtained.

[0662]

Example 26

1-(4-methoxybutyl)-N-(2-methylpropyl)-N-[(3RS,5RS)-5-
(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-
carboxamide dihydrochloride

[0663]

[0664]

MS (ESI+, m/e) 500 (M+1)

Example 27

1-(4-methoxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-
(pyrrolidin-1-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-
carboxamide dihydrochloride

[0665]
[0666]
MS (ESI+, m/e) 484 (M+1)
Example 28
N-{(3S,5R)-5-[4,4-difluoropiperidin-1-yl) carbonyl]piperidin-3-yl}-1-(4-methoxybutyl)-N-[(2-methylpropyl)-1H-benzimidazole-2-carboxamide dihydrochloride

[0667]

[0668]
MS (ESI+, m/e) 534 (M+1)
Example 29
N-{(3S,5R)-5-[(7-azabicyclo[2.2.1]hept-7-yl)carbonyl]piperidin-3-yl}-1-(4-methoxybutyl)-N-[(2-methylpropyl)-1H-benzimidazole-2-carboxamide dihydrochloride

[0669]

[0670]
MS (ESI+, m/e) 510 (M+1)
Example 30
1-(4-methoxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-[(1,4-oxazepan-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide dihydrochloride

[0671]

[0672]
MS (ESI+, m/e) 514 (M+1)
Example 31
N-[(3S,5R)-5-(2,3-dihydro-4H-1,4-benzoxazin-4-ylcarbonyl)piperidin-3-yl]-1-(4-methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide dihydrochloride

[0673]

[0674]
MS (ESI+, m/e) 548 (M+1)
Example 32
methyl (3R,5S)-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino)piperidine-3-carboxylate dihydrochloride

[0675]
[0676]
MS (ESI+, m/e) 445 (M+1)
Example 33
(3R,5S)-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino)piperidine-3-carboxylic acid dihydrochloride

[0677]

[0678]
MS (ESI+, m/e) 431 (M+1)
Example 34
5,6-difluoro-1-(4-methoxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide dihydrochloride

[0679]

[0680]
MS (ESI+, m/e) 536 (M+1)
Example 35
N-[(3S,5R)-5-carbamoylpiperidin-3-yl]-5,6-difluoro-1-(4-methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamidine dihydrochloride

[0681]

![Chemical Structure](image)

[0682]

MS (ESI+, m/e) 466 (M+1)

Example 36

7-chloro-1-(4-methoxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide dihydrochloride

[0683]

![Chemical Structure](image)

[0684]

MS (ESI+, m/e) 534 (M+1)

Example 37

4-chloro-1-(4-methoxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide dihydrochloride

[0685]
[0686]
MS (ESI+, m/e) 534 (M+1)
Example 38
N-[(3S,5R)-5-(1-hydroxy-1-methylethyl)piperidin-3-yl]-1-(4-
methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-
carboxamide dihydrochloride

[0687]

[0688]

10 tert-Butyl (3R,5S)-3-(1-hydroxy-1-methylethyl)-5-[[1-(4-
methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-
methylpropyl)amino)piperidine-1-carboxylate (180 mg) was
dissolved in ethyl acetate (2 ml), 4N hydrogen chloride-ethyl
acetate (4 ml) was added, and the mixture was stirred for 1 hr.
The solvent was evaporated under reduced pressure to give the
object product (130 mg).

1H-NMR (DMSO-d6) δ 0.64-0.75 (2H, m), 0.86-0.98 (4H, m), 1.40-
1.58 (2H, m), 1.65-1.88 (2H, m), 1.88-2.36 (4H, m), 2.69-3.63
(3H, m), 3.79-3.95 (3H, m), 4.07-4.40 (5H, m), 4.99 (2H, br s),
7.22-7.44 (2H, m), 7.62-7.79 (2H, m), 8.41 (1H, br s), 8.67-
8.87 (1H, m), 9.14 (1H, br s)
MS (ESI+, m/e) 445 (M+1)

[0689]
Example 39
5,6-difluoro-N-[(3S,5R)-5-(1-hydroxy-1-methylethyl)piperidin-

3-yl]-1-(4-methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide dihydrochloride

[0690]

5

[0691]

MS (ESI+, m/e) 481 (M+1)
Example 40
N-[(3S,5R)-5-(hydroxymethyl)piperidin-3-yl]-1-(4-methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide dihydrochloride

[0692]

[0693]

To tert-butyl (3R,5S)-3-(hydroxymethyl)-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino)piperidine-1-carboxylate (150 mg) in THF (2 ml) was added TFA (5 ml) and the mixture was stirred at room temperature for 1 hr. The solvent was evaporated under reduced pressure, and the residue was subjected to reversed-phase preparative HPLC and the eluted fraction was concentrated under reduced pressure. The residual aqueous layer was neutralized with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate, 10 - 20% hydrogen chloride-methanol was added, and the solvent was evaporated under reduced pressure to give the object product (75 mg).
$^1$H-NMR (DMSO-$d_6$) $\delta$ 0.67-0.76 (3H, m), 0.90-0.99 (3H, m), 1.37-1.58 (2H, m), 1.63-1.88 (2H, m), 1.86-2.21 (2H, m), 2.50 (2H, dt), 3.02-4.92 (16H, m), 7.37 (2H, d), 7.63-7.84 (2H, m), 8.65 (1H, br s), 9.05-9.74 (1H, m)

MS (ESI+, m/e) 417 (M+1)

[0694]

In the same manner as in Example 40, the following compounds (Examples 41-44) were obtained.

[0695]

Example 41

1-((4-methoxybutyl)-N-[(3S,5R)-5-((5-methyl-1,3,4-oxadiazol-2-yl)piperidin-3-yl]-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide dihydrochloride

[0696]

[0697]

MS (ESI+, m/e) 469 (M+1)

Example 42

N-[(3S,5R)-5-(1-hydroxyethyl)piperidin-3-yl]-1-(4-methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide dihydrochloride

[0698]

[0699]

MS (ESI+, m/e) 431 (M+1)

Example 43
N-\{(3S,5R)-5-[cyclopropyl\,(hydroxy)methyl]\,piperidin-3-yl\}-1-(4-methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide dihydrochloride

[0700]

\[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{OH} \\
\end{array}
\]

5

[0701]

MS (ESI+, m/e) 457 (M+1)

Example 44

N-\{(3S,5R)-5-[hydroxy(pyridin-2-yl)methyl]\,piperidin-3-yl\}-1-(4-methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide trihydrochloride

[0702]

\[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{OH} \\
\end{array}
\]

15

[0703]

MS (ESI+, m/e) 494 (M+1)

Example 45

N-\{(3S,5R)-5-[azetidin-1-ylcarbonyl]\,piperidin-3-yl\}-1-(4-methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide

[0704]
[0705]

To tert-butyl (3R,5S)-3-[(azetidin-1-ylcarbonyl)-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]piperidine-1-carboxylate (230 mg) in 1,2-dichloroethane (3 mL) was added TFA (3 mL) and the mixture was stirred at room temperature for 1 hr. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate-water, and neutralized with saturated aqueous sodium hydrogen carbonate. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure to give the object product (100 mg).

MS (ESI+, m/e) 470 (M+1)

[0706]

Example 46

N-[(3S,5R)-5-[(azetidin-1-ylcarbonyl)piperidin-3-yl]-5,6-difluoro-1-(4-methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide 1/2 fumarate

[0707]

[0708]

To tert-butyl (3R,5S)-3-[(azetidin-1-ylcarbonyl)-5-[[[5,6-difluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]piperidine-1-carboxylate (270 mg) in 1,2-
dichloroethane (3 ml) was added TFA (5 ml) and the mixture was stirred at room temperature for 1 hr. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate-water, and neutralized with saturated aqueous sodium hydrogen carbonate. The organic layer was dried over anhydrous sodium sulfate, fumaric acid (23 mg) was added, and the solvent was evaporated under reduced pressure to give the object product (210 mg).

MS (ESI+, m/e) 506 (M+1)

**[0709]**
Example 47
{(3R,5S)-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]piperidin-3-yl}methyl acetate dihydrochloride

![Chemical structure image](image)

**[0710]**

**[0711]**

tert-Butyl (3R,5S)-3-(hydroxymethyl)-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]piperidine-1-carboxylate (200 mg) was dissolved in ethyl acetate (2 ml), 4N hydrogen chloride-ethyl acetate (5 ml) was added, and the mixture was stirred for 1 hr. The solvent was evaporated under reduced pressure to give the object product (200 mg).

MS (ESI+, m/e) 459 (M+1)

**[0712]**
Example 48
N-[(3S,5R)-5-(1-hydroxy-2-methoxyethyl)piperidin-3-yl]-1-(4-methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide dihydrochloride
[0713]

[0714]

tert-Butyl (5S)-3-(1-hydroxy-2-methoxyethyl)-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino)piperidine-1-carboxylate (150 mg) was dissolved in 10-20% hydrogen chloride methanol solution (10 ml), and the mixture was stirred at room temperature for 3 hr. The solvent was evaporated under reduced pressure to give the object product (140 mg).

MS (ESI+, m/e) 461 (M+1)

[0715]

Example 49

1-(4-methoxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-yl)carbonyl]piperidin-3-yl]-1H-benzimidazole-2-carboxamide methanesulfonate

[0716]

[0717]

tert-Butyl (3S,5R)-3-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-(morpholin-4-yl)carbonyl)piperidine-1-carboxylate (10.2 g) was dissolved in ethyl acetate (17 ml) and methanol (5 ml), 4N hydrogen chloride-ethyl acetate (34 ml) was added, and the mixture was stirred for 1 hr. The reaction mixture was poured
into 10%-aqueous sodium hydrogen carbonate solution (125 ml),
and the mixture was extracted with ethyl acetate. The extract
was washed with brine, and dried over anhydrous sodium sulfate.
The solvent was evaporated under reduced pressure. A part (7.8
g) of the residue (8.1 g) was dissolved in ethyl acetate (60
ml), and dissolved in methanesulfonic acid (1.5 g) by heating
(90°C). This was stood at room temperature for 4 days, and the
precipitated crystals were collected by filtration to give the
object product as crude crystals (7.3 g).

MS (ESI+, m/e) 500 (M+1)

Reference Example 101
2-fluoro-N-(4-methoxybutyl)-6-nitroaniline

To a solution of 1,2-difluoro-3-nitrobenzene (5.15 g) and
4-methoxybutan-1-amine hydrochloride (5.42 g) in acetonitrile
(100 ml) was added diisopropylethylamine (17 μl), and the
mixture was stirred at 60°C for 12 hr. 4-Methoxybutan-1-amine
hydrochloride (1.00 g) was further added, and the mixture was
stirred at 70°C for 5 hr. The reaction mixture was
concentrated under reduced pressure, saturated aqueous sodium
hydrogen carbonate was added, and the mixture was extracted
with ethyl acetate. The extract was dried over anhydrous
magnesium sulfate, and concentrated under reduced pressure.
The residue was subjected to silica gel column chromatography,
and a fraction eluted with hexane - ethyl acetate-hexane (3:7)
was concentrated under reduced pressure to give the object
product (7.70 g).

^1H-NMR (CDCl₃) δ 1.62-1.82 (4 H, m), 3.34 (3 H, s), 3.42 (2 H,
t), 3.61 (2 H, ddd), 6.56 (1 H, ddd), 7.17 (1 H, ddd), 7.85 (1
H, br s), 7.95 (1 H, dt)
Reference Example 102
3-fluoro-2-(4-methoxybutylamino)aniline

5

2-Fluoro-N-(4-methoxybutyl)-6-nitroaniline (3.54 g) was dissolved in methanol (50 ml), palladium-carbon (5%, 140 mg) was added, and the mixture was stirred for 3.5 hr under a hydrogen atmosphere. The reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure to give the object product (3.05 g).

$^1$H-NMR (CDCl$_3$) δ 1.49-1.76 (4 H, m), 2.89-3.12 (1 H, m), 2.98 (2 H, t), 3.34 (3 H, s), 3.40 (2 H, t), 3.91 (2 H, br s), 6.43-6.52 (2 H, m), 6.78 (1 H, td)

Reference Example 103
(3R,5S)-1-(tert-butoxycarbonyl)-5-[[7-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino)piperidine-3-carboxylic acid

3-Fluoro-2-(4-methoxybutylamino)aniline (3.05 g) was dissolved in acetic acid (80 ml), methyl 2,2,2-trichloroethanoimidate (1.92 ml) was added, and the mixture was stirred for 1.5 hr. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with diisopropyl ether, and washed with water. The organic layer
was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was immediately dissolved in acetonitrile-water (2:1, 225 ml), and 1-tert-butyl 3-methyl (3R,5S)-5-\{2-methylpropyl\}amino)piperidine-1,3-dicarboxylate (3.58 g) was added. Potassium carbonate (16 g) was added, and the mixture was stirred at 80°C for 19 hr. The reaction mixture was concentrated under reduced pressure, diluted with saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to silica gel chromatography, and a fraction eluted with ethyl acetate-hexane (5:95) - ethyl acetate - ethyl acetate-methanol (85:15) was concentrated under reduced pressure to give the object product (1.65 g).

MS (ESI+, m/e) 549 (M+1)

Reference Example 104

[0727]

tert-butyl (3S,5R)-3-\{[7-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl\}(2-methylpropyl)amino)-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[0728]

![Chemical structure](image)

[0729]

(3R,5S)-1-(tert-Butoxycarbonyl)-5-\{[7-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl\}(2-methylpropyl)amino)piperidine-3-carboxylic acid (207 mg), morpholine (87 µl), HOBt (40 mg) and triethylamine (210 µl) were dissolved in DMF (10 ml), WSC·HCl (180 mg) was added, and the mixture was stirred at 50°C for 1 hr. The reaction mixture
was concentrated under reduced pressure, diluted with saturated aqueous sodium hydrogen carbonate, and the mixture was extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (1:9) - ethyl acetate was concentrated under reduced pressure to give the object product (160 mg).

MS (ESI+, m/e) 618 (M+1)

Reference Example 105

tert-butyl (3R,5S)-3-carbamoyl-5-{{7-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl}carbonyl}(2-methylpropyl)amino)piperidine-1-carboxylate

(3R,5S)-1-[(tert-Butoxycarbonyl)-5-{{7-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl}carbonyl}(2-methylpropyl)amino)piperidine-3-carboxylic acid (360 mg), 1H-1,2,3-benzotriazol-1-ol ammonium salt (250 mg) and triethylamine (360 μl) were dissolved in DMF (10 ml), WSC·HCl (315 mg) was added, and the mixture was stirred at 50°C for 1 hr. The reaction mixture was concentrated under reduced pressure, diluted with saturated aqueous sodium hydrogen carbonate, and the mixture was extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (3:7) - ethyl acetate - ethyl
acetate-methanol (9:1) was concentrated under reduced pressure to give the object product (263 mg).

MS (ESI+, m/e) 548 (M+1)

Reference Example 106

tert-butyl (3S,5R)-3-{{7-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl}carbonyl}(2-methylpropyl)amino)-5-(4H-1,2,4-triazol-3-yl)piperidine-1-carboxylate

Reference Example 107

tert-Butyl (3R,5S)-3-carbamoyl-5-{{7-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl}carbonyl}(2-methylpropyl)amino)piperidine-1-carboxylate (115 mg) was dissolved in dimethylformamide dimethylacetal (5 ml), and the mixture was stirred at 100°C for 15 hr. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in acetic acid (7 ml). Hydrazine monohydrate (48 µl) was added and the mixture was stirred at 80°C for 3 hr. The reaction mixture was concentrated under reduced pressure, diluted with 0.5M aqueous sodium hydroxide solution, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate - ethyl acetate-methanol (9:1) was concentrated under reduced pressure to give the object product (130 mg).

MS (ESI+, m/e) 572 (M+1)
Reference Example 107
tert-butyl (3S,5R)-3-{{{7-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl}carbonyl}(2-methylpropyl)amino}-5-(pyrrolidin-1-yl)carbonyl)piperidine-1-carboxylate

[0737]

(3R,5S)-1-(tert-Butoxycarbonyl)-5-{{{7-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl}carbonyl}(2-methylpropyl)amino)piperidine-3-carboxylic acid (1.65 g), pyrrolidine (500 µl), HOBt (270 mg) and triethylamine (1.27 ml) were dissolved in DMF (50 ml), WSC·HCl (1.15 g) was added, and the mixture was stirred at 50°C for 1 hr. The reaction mixture was concentrated under reduced pressure, diluted with saturated aqueous sodium hydrogen carbonate, and the mixture was extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (5:95) - ethyl acetate - ethyl acetate-methanol (9:1) was concentrated under reduced pressure to give the object product (170 mg).
MS (ESI+, m/e) 602 (M+1)

[0739]
Example 50
7-fluoro-1-(4-methoxybutyl)-N-(2-methylpropyl)-N-{(3S,5R)-5-(morpholin-4-yl)carbonyl)piperidin-3-yl}-1H-benzimidazole-2-carboxamide dihydrochloride

[0740]
[0741]

tert-Butyl (3S,5R)-3-{{7-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl}carbonyl}(2-methylpropyl)amino)-5-
(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (160 mg) was
dissolved in 2M hydrogen chloride-ethyl acetate (3 ml), and
the mixture was stirred at room temperature for 10 hr. The
reaction mixture was concentrated under reduced pressure. The
residue was subjected to reversed-phase preparative HPLC, and
a fraction eluted with water-acetonitrile (9:1 - 6:4) was
collected, basified (pH 10) with saturated aqueous potassium
carbonate solution, and extracted with ethyl acetate. The
extract was dried over anhydrous magnesium sulfate, and
concentrated under reduced pressure. The residue was dissolved
in 1M hydrogen chloride-ethyl acetate (1 ml), and the reaction
mixture was concentrated under reduced pressure to give the
object product (104 mg).

MS (ESI+, m/e) 518 (M+1)

[0742]

In the same manner as in Example 50, the following
compounds (Examples 51-52) were obtained.

[0743]

Example 51

N-{{3S,5R}-5-carbamoylpiperidin-3-yl}-7-fluoro-1-(4-
methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-
carboxamide dihydrochloride

[0744]
[0745]
MS (ESI+, m/e) 448 (M+1)

[0746]
Example 52
7-fluoro-1-(4-methoxybutyl)-N-(2-methylpropyl)-N-\{(3S,5R)-5-(pyrrolidin-1-ylcarbonyl)piperidin-3-yl\}-1H-benzimidazole-2-carboxamide dihydrochloride

[0747]
MS (ESI+, m/e) 502 (M+1)

[0748]
Example 53
7-fluoro-1-(4-methoxybutyl)-N-(2-methylpropyl)-N-\{(3S,5R)-5-(4H-1,2,4-triazol-3-yl)piperidin-3-yl\}-1H-benzimidazole-2-carboxamide dihydrochloride

[0750]
tert-Butyl (3S,5R)-3-{{7-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl}carbonyl}(2-methylpropyl)amino)-5-(4H-1,2,4-triazol-3-yl)piperidine-1-carboxylate (130 mg) was dissolved in 2M hydrogen chloride-ethyl acetate (3 ml), and the mixture was stirred at room temperature for 12 hr. The reaction mixture was concentrated to give the object product (91 mg). MS (ESI+, m/e) 472 (M+1)

Reference Example 108

3-fluoro-N-(4-methoxybutyl)-2-nitroaniline

To a solution of 1,3-difluoro-2-nitrobenzene (3.00 g) and diisopropylethylamine (7 µl) in acetonitrile (30 ml) was added a solution of 4-methoxybutan-1-amine hydrochloride (2.51 g) in acetonitrile (10 ml), and the mixture was stirred at room temperature for 90 hr. The reaction mixture was concentrated under reduced pressure, and the residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (2:98 - 25:75) was concentrated under reduced pressure to give the object product (2.90 g). 1H-NMR (CDCl₃) δ 1.65-1.84 (4 H, m), 3.28 (2 H, ddd), 3.35 (3 H, s), 3.43 (2 H, t), 6.41 (1 H, ddd), 6.58 (1 H, d), 7.22-7.32 (2 H, m)

Reference Example 109

6-fluoro-2-(4-methoxybutylamino)aniline

3-Fluoro-N-(4-methoxybutyl)-2-nitroaniline (2.90 g) was dissolved in methanol (50 ml), palladium-carbon (5%, 230 mg)
was added, and the mixture was stirred for 3 hr under a hydrogen atmosphere. The reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure to give the object product (2.54 g).

\[ \delta \text{H-NMR (CDCl}_3) \delta 1.64-1.79 (4H, m), 3.14 (2H, t), 3.18-3.32 (2H, m), 3.35 (3H, s), 3.43 (2H, t), 3.53 (1H, br s), 6.42 (1H, d), 6.51 (1H, ddd), 6.73 (1H, td) \]

[0758]

Reference Example 110

1-tert-butyl 3-methyl (3R,5S)-5-({4-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl}carbonyl)(2-methylpropyl)amino)piperidine-1,3-dicarboxylate

[0759]

[0760]

6-Fluoro-2-(4-methoxybutylamino)aniline (2.54 g) was dissolved in acetic acid (90 ml), methyl 2,2,2-trichloroethanimidate (1.48 ml) was added, and the mixture was stirred for 1.5 hr. The reaction mixture was concentrated under reduced pressure, and the residue was suspended in toluene (50 ml) and concentrated under reduced pressure. This operation was repeated twice. The residue was immediately dissolved in acetonitrile-water (3:1, 200 ml), 1-tert-butyl 3-methyl (3R,5S)-5-((2-methylpropyl)amino)piperidine-1,3-dicarboxylate (3.70 g) was added, and potassium carbonate (16.5 g) was added and the mixture was stirred at 80°C for 19 hr. The reaction mixture was concentrated under reduced pressure, diluted with saturated aqueous ammonium chloride solution, and extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate, and concentrated under
reduced pressure. The residue was subjected to silica gel 
chromatography, and a fraction eluted with ethyl acetate-
hexane (5:95 - 1:1) was concentrated under reduced pressure to 
give the object product (195 mg).

MS (ESI+, m/e) 563(M+1)

[0761]

Reference Example 111
(3R,5S)-1-(tert-butoxycarbonyl)-5-{{4-fluoro-1-(4-
methoxybutyl)-1H-benzimidazol-2-yl}carbonyl}(2-
methylpropyl)amino)piperidine-3-carboxylic acid

[0762]

![Chemical Structure](attachment:chemical_structure.png)

[0763]

1-tert-Butyl 3-methyl (3R,5S)-5-{{4-fluoro-1-(4-
methoxybutyl)-1H-benzimidazol-2-yl}carbonyl}(2-
methylpropyl)amino)piperidine-1,3-dicarboxylate (195 mg) was 
dissolved in tetrahydrofuran-methanol (1:2, 15 ml), 2M aqueous 
sodium hydroxide solution (1 ml) was added, and the mixture 
was stirred at 45°C for 4 hr. The reaction mixture was 
concentrated under reduced pressure, neutralized with 
saturated aqueous ammonium chloride solution and extracted 
with ethyl acetate. The extract was dried over anhydrous 
magnesium sulfate, concentration under reduced pressure to 
give the object product (180 mg).

MS (ESI+, m/e) 549(M+1)

[0764]

In the same manner as in Reference Example 104, the 
following compound (Reference Example 112) was obtained.

[0765]

Reference Example 112
tert-butyl (3S,5R)-3-{{4-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl}carbonyl}(2-methylpropyl)amino)-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[0766]

MS (ESI+, m/e) 618 (M+1)

[0767]

Example 54

4-fluoro-1-(4-methoxybutyl)-N-(2-methylpropyl)-N-((3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl)-1H-benzimidazole-2-carboxamide dihydrochloride

[0769]

[0770]

tert-Butyl (3S,5R)-3-{{4-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl}carbonyl}(2-methylpropyl)amino)-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (75 mg) was dissolved in 3M hydrogen chloride-ethyl acetate (2 ml), and the mixture was stirred at room temperature for 30 min and concentrated to give the object product (67 mg).

MS (ESI+, m/e) 518 (M+1)

[0771]

Reference Example 113

tert-butyl (3-methoxy-2-nitrophenyl)carbamate
3-Methoxy-2-nitrobenzoic acid (10.25 g) was suspended in toluene (200 ml), and triethylamine (8.65 ml) and diphenylphosphoryl azide (13.4 ml) were added dropwise at room temperature. The mixture was stirred at 90°C for 1.5 hr, triethylamine (29 ml) and 2-methylpropan-2-ol (15 ml) were added, and the mixture was further stirred at 90°C for 2 hr. The reaction mixture was concentrated under reduced pressure, diluted with ethyl acetate, 0.5M hydrochloric acid (200 ml) was added, and the mixture was filtered through celite. The organic layer of the filtrate was collected, washed with saturated aqueous sodium hydrogen carbonate, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to silica gel chromatography, and a fraction eluted with ethyl acetate-hexane (5:95 - 1:1) was concentrated under reduced pressure to give the object product (10.18 g).

\[
{^1}H-NMR \ (CDCl_3) \delta \ 1.50 \ (8 \ H, \ s), \ 3.90 \ (3 \ H, \ s), \ 6.71 \ (1 \ H, \ d), \ 7.39 \ (2 \ H, \ t), \ 7.55 \ (1 \ H, \ br \ s), \ 7.77 \ (1 \ H, \ d)
\]

Reference Example 114
tert-buty1 (4-methoxybutyl)(3-methoxy-2-nitrophenyl)carbamate

tert-Butyl (3-methoxy-2-nitrophenyl)carbamate (3.00 g) and 4-methoxybutyl methanesulfonate (3.06 g) were dissolved in dimethylformamide (40 ml), cesium carbonate (7.30 g) was added,
and the mixture was stirred at 65°C for 4 hr. The reaction mixture was concentrated under reduced pressure, diluted with water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel chromatography, and a fraction eluted with ethyl acetate-hexane (5:95 - 7:3) was concentrated under reduced pressure to give the object product (2.11 g).

$^1$H-NMR (CDCl$_3$) δ 1.36 (9 H, br s), 1.47-1.71 (6 H, m), 3.30 (3 H, s), 3.37 (2 H, t), 3.91 (3 H, s), 6.86 (1 H, d), 6.98 (1 H, d), 7.40 (1 H, t)

[0777]
Reference Example 115

3-methoxy-N-(4-methoxybutyl)-2-nitroaniline

[0778]

[0779]

tert-Butyl (4-methoxybutyl)-(3-methoxy-2-nitrophenyl)carbamate (2.11 g) was dissolved in ethyl acetate (30 ml), 4M hydrogen chloride-ethyl acetate (15 ml) was added, and the mixture was stirred for 12 hr. The reaction mixture was concentrated under reduced pressure, diluted with saturated aqueous sodium hydrogen carbonate, and the mixture was extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate, concentration under reduced pressure to give the object product (1.50 g).

$^1$H-NMR (CDCl$_3$) δ 1.60-1.80 (4 H, m), 3.21 (2 H, ddd), 3.34 (3 H, s), 3.41 (2 H, t), 3.87 (3 H, s), 6.17 (1 H, br s), 6.25 (1 H, d), 6.37 (1 H, d), 7.22 (1 H, t)

[0780]
Reference Example 116

6-methoxy-2-(4-methoxybutylamino)aniline

[0781]
3-Methoxy-N-(4-methoxybutyl)-2-nitroaniline (230 mg) was dissolved in methanol (30 ml), palladium-carbon (5%, 90 mg) was added, and the mixture was stirred for 2 hr under a hydrogen atmosphere. The reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure to give the object product (210 mg).

$^1$H-NMR (CDCl$_3$) $\delta$ 1.67-1.78 (4 H, m), 3.10-3.20 (2 H, m), 3.31-3.47 (5 H, m), 3.35 (3 H, s), 3.84 (3 H, s), 6.37 (1 H, dd), 6.40 (1 H, dd), 6.77 (1 H, t)

Reference Example 117
tert-butyl (3S,5R)-3-{{(2-methoxy-6-{(4-methoxybutyl)amino}phenyl)amino}(oxo)acetyl}{2-methylpropyl)amino}-5-{(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

6-Methoxy-2-(4-methoxybutylamino)aniline (210 mg), {{(3S,5R)-1-(tert-butoxycarbonyl)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl}(2-methylpropyl)amino}(oxo)acetic acid (308 mg), HOBT (97 mg) and triethylamine (370 µl) were dissolved in 1,2-dichloroethane (15 ml), WSC·HCl (430 mg) was added, and the mixture was stirred at 60ºC for 2 hr. The reaction mixture was concentrated under reduced pressure, diluted with saturated aqueous sodium hydrogen carbonate, and the mixture was extracted with ethyl acetate. The extract was
dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (2:8) - ethyl acetate was concentrated under reduced pressure to give the object product (240 mg).

MS (ESI+, m/e) 648 (M+1)

[0786]

In the same manner as in Reference Example 103, the following compound (Reference Example 118) was obtained.

[0787]

Reference Example 118

(3R,5S)-1-(tert-butoxycarbonyl)-5-\{[4-methoxy-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl\}(2-methylpropyl)amino\}piperidine-3-carboxylic acid

[0788]

[0789]

MS (ESI+, m/e) 561 (M+1)

[0790]

In the same manner as in Reference Example 105, the following compound (Reference Example 119) was obtained.

[0791]

Reference Example 119

tert-butyl (3R,5S)-3-carbamoyl-5-\{[4-methoxy-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl\}(2-methylpropyl)amino\}piperidine-1-carboxylate

[0792]
In the same manner as in Reference Example 106, the following compound (Reference Example 120) was obtained.

Reference Example 120

**tert-butyl (3S,5R)-3-{{4-methoxy-1-(4-methoxybutyl)-1H-benzimidazol-2-yl}carbonyl}(2-methylpropyl)amino}-5-(4H-1,2,4-triazol-3-yl)piperidine-1-carboxylate**

In the same manner as in Reference Example 107, the following compound (Reference Example 121) was obtained.

Reference Example 121

**tert-butyl (3S,5R)-3-{{4-methoxy-1-(4-methoxybutyl)-1H-benzimidazol-2-yl}carbonyl}(2-methylpropyl)amino}-5-(pyrrolidin-1-ylcarbonyl)piperidine-1-carboxylate**
Reference Example 122

tert-butyl (3S,5R)-3-{{{4-methoxy-1-(4-methoxybutyl)-1H-benzimidazol-2-yl}carbonyl}(2-methylpropyl)amino}-5-(piperidin-1-yl)carbonyl)piperidine-1-carboxylate

(3R,5S)-1-(tert-Butoxycarbonyl)-5-{{{4-methoxy-1-(4-methoxybutyl)-1H-benzimidazol-2-yl}carbonyl}(2-methylpropyl)amino)piperidine-3-carboxylic acid (205 mg), piperidine (69 μl), HOBt (40 mg) and triethylamine (140 μl) were dissolved in DMF (10 ml), WSC·HCl (134 mg) was added, and the mixture was stirred at 50°C for 1 hr. The reaction mixture was concentrated under reduced pressure, diluted with saturated aqueous sodium hydrogen carbonate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (1:9) - ethyl acetate was concentrated under reduced pressure to give the
object product (65 mg).
MS (ESI+, m/e) 628 (M+1)

[0805]
Example 55

4-methoxy-1-{(4-methoxybutyl)-N-(2-methylpropyl)-N-\{(3S, 5R)-5-
(morpholin-4-ylcarbonyl)piperidin-3-yl\}-1H-benzimidazole-2-
carboxamide dihydrochloride

[0806]

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{N} & \quad \text{O} \\
\text{HN} & \quad \text{K2HCl}
\end{align*}
\]

[0807]

tert-Butyl (3S,5R)-3-\{{\{(2-methoxy-6-{(4-
methoxybutyl)amino}phenyl)amino\}(oxo)acetyl\}(2-
methylpropyl)amino\}-5-(morpholin-4-ylcarbonyl)piperidine-1-
carboxylate (240 mg) was dissolved in acetic acid (5 ml), and

the mixture was stirred at 80°C for 14 hr. The reaction
mixture was concentrated under reduced pressure, the residue
was dissolved in 2M hydrogen chloride-ethyl acetate (3 ml),
and the mixture was stirred at room temperature for 2 hr and
concentrated under reduced pressure. The residue was subjected
to reversed-phase preparative HPLC, and a fraction eluted with
water-acetonitrile (9:1 - 6:4) was collected, basified (pH 10)
with saturated aqueous potassium carbonate solution, and
extracted with ethyl acetate. The extract was dried over
anhydrous magnesium sulfate, and concentrated under reduced
pressure. The residue was dissolved in 0.7M hydrogen chloride-
ethyl acetate (1.2 ml), and the mixture was concentrated under
reduced pressure to give the object product (79 mg).
MS (ESI+, m/e) 530 (M+1)

[0808]

In the same manner as in Example 50 or Example 53, the
following compounds (Examples 56-59) were obtained.

[0809]
Example 56
N-[(3S,5R)-5-carbamoylpiperidin-3-yl]-4-methoxy-1-(4-
5 methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-
carboxamide dihydrochloride

[0810]

[0811]
10 MS (ESI+, m/e) 460 (M+1)

[0812]
Example 57
4-methoxy-1-[(4-methoxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-
(4H-1,2,4-triazol-3-yl)piperidin-3-yl]-1H-benzimidazole-2-
carboxamide dihydrochloride

[0813]

[0814]
MS (ESI+, m/e) 484 (M+1)

[0815]
Example 58
4-methoxy-1-[(4-methoxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-
(pyrrolidin-1-ylcarbonylpiperidin-3-yl)-1H-benzimidazole-2-
carboxamide dihydrochloride

[0816]
[0817]
MS (ESI+, m/e) 514 (M+1)

[0818]
Example 59
4-methoxy-1-(4-methoxybutyl)-N-(2-methylpropyl)-N-{(3S,5R)-5-(piperidin-1-ylcarbonyl)piperidin-3-yl}-1H-benzimidazole-2-carboxamide dihydrochloride

[0819]

[0820]
MS (ESI+, m/e) 528 (M+1)

[0821]
Reference Example 123

[0822]

[0823]
5-Methoxy-2-nitrobenzoic acid (10.30 g) was suspended in toluene (200 ml), triethylamine (9 ml) and diphenylphosphoryl azide (14 ml) were added dropwise at room temperature, and the
mixture was stirred at 95°C for 1.5 hr. Triethylamine (29 ml) and 2-methylpropan-2-ol (15 ml) were added, and the mixture was further stirred at 95°C for 3 hr. The reaction mixture was concentrated under reduced pressure, and diluted with ethyl acetate. 0.5M Hydrochloric acid (200 ml) was added, and the mixture was filtered through celite. The organic layer of the filtrate was collected, washed with saturated aqueous sodium hydrogen carbonate, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to silica gel chromatography, and a fraction eluted with ethyl acetate-hexane (5:95 - 1:1) was concentrated under reduced pressure to give the object product (13.28 g).

$^1$H-NMR (CDCl$_3$) δ 1.55 (9 H, s), 3.92 (3 H, s), 6.58 (1 H, dd), 8.16 (1 H, s), 8.18 (1 H, d), 10.10 (1 H, br s)

[0824]

In the same manner as in Reference Example 114, the following compound (Reference Example 124) was obtained.

[0825]
Reference Example 124
tert-butyl (4-methoxybutyl)(5-methoxy-2-nitrophenyl) carbamate

[0826]

$^1$H-NMR (CDCl$_3$) δ 1.25-1.54 (9 H, m), 1.54-1.81 (4 H, m), 3.30 (3 H, s), 3.34-3.44 (2 H, m), 3.56-3.79 (2 H, m), 3.89 (3 H, s), 6.72-6.89 (2 H, m), 7.96-8.09 (1 H, m)

[0828]

In the same manner as in Reference Example 115, the following compound (Reference Example 125) was obtained.

[0829]
Reference Example 125
5-methoxy-N-(4-methoxybutyl)-2-nitroaniline

\[ \text{[0830]} \]

\[
\text{[0831]} \]

\[^1\text{H-NMR (CDCl}_3\text{) } \delta 1.68-1.88 \text{ (4 H, m)}, 3.27-3.35 \text{ (2 H, m), 3.35 (3 H, s), 3.45 (2 H, t), 3.87 (3 H, s), 6.15 (1 H, d), 6.23 (1 H, dd), 8.14 (1 H, d), 8.32 (1 H, br s)} \]

\[ \text{[0832]} \]

In the same manner as in Reference Example 116, the following compound (Reference Example 126) was obtained.

\[ \text{[0833]} \]

Reference Example 126

4-methoxy-2-(4-methoxybutylamino)aniline

\[ \text{[0834]} \]

\[ \text{[0835]} \]

\[^1\text{H-NMR (CDCl}_3\text{) } \delta 1.65-1.81 \text{ (4 H, m), 2.99 (2 H, br s), 3.06-3.16 (2 H, m), 3.35 (3 H, s), 3.38-3.47 (2 H, m), 3.75 (3 H, s), 3.70 (1 H, br s), 6.17 (1 H, dd), 6.25 (1 H, d), 6.64 (1 H, d)} \]

Reference Example 127

6-methoxy-1-(4-methoxybutyl)-2-(trichloromethyl)-1H-benzimidazole

\[ \text{[0836]} \]

\[ \text{[0837]} \]

4-Methoxy-2-(4-methoxybutylamino)aniline (2.50 g) was dissolved in acetic acid (30 ml), methyl 2,2,2-
trichloroethanimidate (1.62 ml) was added, and the mixture was stirred for 1.5 hr. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with diisopropyl ether, and washed with water. The organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give the object product (1.75 g).

MS (ESI+, m/e) 351 (M+1)

[0838]

Reference Example 128

tert-butyl (3S,5R)-3-{{6-methoxy-1-(4-methoxybutyl)-1H-benzimidazol-2-yl} carbonyl}(2-methylpropyl)amino}-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[0839]

[0840]

6-Methoxy-1-(4-methoxybutyl)-2-(trichloromethyl)-1H-benzimidazole (330 mg) was dissolved in acetonitrile-water (2:1, 50 ml), and tert-butyl (3S,5R)-3-{(2-methylpropyl)amino}-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (350 mg) was added. Potassium carbonate (1.3 g) was added, and the mixture was stirred at 80°C for 5 hr. The reaction mixture was concentrated under reduced pressure, acidified (pH 3) with 6M hydrochloric acid, and the mixture was extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to silica gel chromatography, and a fraction eluted with ethyl acetate–hexane (3:7) - ethyl acetate was concentrated under reduced pressure. The residue was further subjected to reversed-phase preparative HPLC, and a fraction eluted with water-
acetonitrile (9:1 - 6:4) was collected, basified (pH 10) with saturated aqueous potassium carbonate solution, and extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give the object product (82 mg).

MS (ESI+, m/e) 630 (M+1)

Reference Example 129

(3R,5S)-1-(tert-butoxycarbonyl)-5-{{6-methoxy-1-(4-
10 methoxybutyl)-1H-benzimidazol-2-yl}carbonyl}(2-
methylpropyl)amino)piperidine-3-carboxylic acid

[0842]

[0843]

6-Methoxy-1-(4-methoxybutyl)-2-(trichloromethyl)-1H-
benzimidazole (1.42 g) was dissolved in acetonitrile-water
(2:1, 150 ml), 1-tert-butyl 3-methyl (3R,5S)-5-{{2-
methylpropyl}amino)piperidine-1,3-dicarboxylate (1.02 g) was
added, potassium carbonate (5.5 g) was added and the mixture
was stirred at 80°C for 19 hr. The reaction mixture was
concentrated under reduced pressure, acidified (pH3) with 6M
hydrochloric acid, and extracted with ethyl acetate. The
extract was dried over anhydrous magnesium sulfate, and
concentrated under reduced pressure. The residue was subjected
to silica gel chromatography, and a fraction eluted with ethyl
acetate-hexane (5:95) - ethyl acetate - ethyl acetate-methanol
(85:15) was concentrated under reduced pressure. The residue
was subjected to reversed-phase preparative HPLC, and a
fraction eluted with water-acetonitrile (9:1 - 6:4) was
collected, basified (pH 10) with saturated aqueous potassium carbonate solution, and extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give the object product (460 mg).

MS (ESI+, m/e) 561 (M+1)

[0844]

In the same manner as in Reference Example 105, the following compound (Reference Example 130) was obtained.

[0845]
Reference Example 130
tert-butyl (3R,5S)-3-carbamoyl-5-\{\{6-methoxy-1-(4-methoxybutyl)-1H-benzimidazol-2-yl\}carbonyl\}(2-methylpropyl)amino)piperidine-1-carboxylate

[0846]

MS (ESI+, m/e) 560 (M+1)

[0847]

In the same manner as in Reference Example 107, the following compound (Reference Example 131) was obtained.

[0848]

Reference Example 131
tert-butyl (3S,5R)-3-\{\{6-methoxy-1-(4-methoxybutyl)-1H-benzimidazol-2-yl\}carbonyl\}(2-methylpropyl)amino)-5-(pyrroloidin-1-ylcarbonyl)piperidine-1-carboxylate

[0850]
MS (ESI+, m/e) 614 (M+1)

Example 60

6-methoxy-1-(4-methoxybutyl)-N-(2-methylpropyl)-N-{(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl}-1H-benzimidazole-2-carboxamide dihydrochloride

MS (ESI+, m/e) 530 (M+1)

In the same manner as in Example 60, the following compounds (Examples 61-62) were obtained.
N-((3S,5R)-5-carbamoylpiperidin-3-yl)-6-methoxy-1-(4-methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide dihydrochloride

[0857]

[0858]
MS (ESI+, m/e) 460 (M+1)
Example 62
6-methoxy-1-(4-methoxybutyl)-N-(2-methylpropyl)-N-{(3S,5R)-5-(pyrrolidin-1-ylcarbonyl)piperidin-3-yl}-1H-benzimidazole-2-carboxamide dihydrochloride

[0859]

[0860]
MS (ESI+, m/e) 514 (M+1)
Reference Example 132
tert-butyl (3S,5R)-3-({1H-benzimidazol-2-ylcarbonyl}(2-methylpropyl)amino)-5-{(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[0861]
2-(Trichloromethyl)-1H-benzimidazole (2.00 g) and tert-butyl (3S,5R)-3-{(2-methylpropyl)amino}-5-(morpholin-4-yl)carbonylpiperidine-1-carboxylate (2.84 g) were dissolved in tetrahydrofuran-water (3:2,150 ml), sodium hydrogen carbonate (6.45 g) was added and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, diluted with water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The precipitated white solid was collected by filtration, washed with ethyl acetate-hexane (1:1) and dried to give the object product (3.03 g).

$^{1}$H-NMR (CDCl$_3$) δ 0.86-1.01 (6H, m), 1.30-1.50 (9H, m), 1.89-2.64 (3H, m), 2.68-3.08 (2H, m), 3.22-4.01 (10H, m), 4.07-4.44 (3H, m), 5.53-6.12 (1H, m), 7.27-7.42 (2H, m), 7.52 (1H, t), 7.61-7.86 (1H, m), 10.15-10.52 (1H, m)

MS (ESI+, m/e) 514 (M+1)

[0863]
Reference Example 133
tert-butyl (3S,5R)-3-{(2-methylpropyl){1-(2-phenylethyl)-1H-benzimidazol-2-yl}carbonyl}amino)-5-(morpholin-4-yl)carbonylpiperidine-1-carboxylate

[0864]
[0865]

tert-Butyl (3S,5R)-3-{(1H-benzimidazol-2-ylcarbonyl)(2-methylpropyl)amino}-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (147 mg) was dissolved in dimethylformamide (12 ml), (2-bromoethyl)benzene (58 µl) and cesium carbonate (200 mg) were added and the mixture was stirred at 65°C for 3 hr. (2-Bromoethyl)benzene (58 µl) was added, and the mixture was further stirred for 2 hr. The reaction mixture was concentrated under reduced pressure, diluted with water, and extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to silica gel chromatography, and a fraction eluted with ethyl acetate-hexane (1:9) - ethyl acetate was concentrated under reduced pressure to give the object product (164 mg).

MS (ESI+, m/e) 618 (M+1)

[0866]

Reference Example 134

2-(thiophen-2-yl)ethyl methanesulfonate

[0867]

[0868]

2-(Thiophen-2-yl)ethanol (1.05 g) was dissolved in tetrahydrofuran (25 ml), triethylamine (1.63 ml) and methanesulfonyl chloride (725 µl) were added and the mixture was stirred for 20 min. Saturated aqueous sodium hydrogen
carbonate (50 ml) was added to the reaction mixture, and the mixture was extracted with diisopropyl ether. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give the object product (1.62 g).

$^1$H-NMR (CDCl$_3$) δ 2.93 (3 H, s), 3.28 (2 H, ddd), 4.42 (2 H, t), 6.90–6.93 (1 H, m), 6.96 (1 H, dd), 7.20 (1 H, dd)

Reference Example 135

tert-butyl (3S,5R)-3-(((2-methylpropyl){1-(2-(thiophen-2-yl)ethyl)-1H-benzimidazol-2-yl}carbonyl)amino)-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[0870]

[0871]

tert-Butyl (3S,5R)-3-(((1H-benzimidazol-2-ylcarbonyl)(2-methylpropyl)amino)-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (150 mg) was dissolved in dimethylformamide (10 ml), 2-(thiophen-2-yl)ethyl methanesulfonate (90 mg) and cesium carbonate (190 mg) were added and the mixture was stirred at 65°C for 30 min. 2-Thiophen-2-ylethyl methanesulfonate (90 mg) was added, and the mixture was further stirred for 1 hr. The reaction mixture was concentrated under reduced pressure, diluted with water, and extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to silica gel chromatography, and a fraction eluted with ethyl acetate-hexane (1:9) - ethyl acetate was concentrated under
reduced pressure to give the object product (156 mg).
MS (ESI+, m/e) 624 (M+1)

[0872]

In the same manner as in Example 60, the following
5 compounds (Examples 63–64) were obtained.

[0873]
Example 63
N-(2-methylpropyl)-N-{(3S,5R)-5-(morpholin-4-
ylcarbonyl)piperidin-3-yl}-1-(2-phenylethyl)-1H-benzimidazole-
10 2-carboxamide dihydrochloride

[0874]

[0875]
15 MS (ESI+, m/e) 518 (M+1)

[0876]
Example 64
N-(2-methylpropyl)-N-{(3S,5R)-5-(morpholin-4-
ylcarbonyl)piperidin-3-yl}-1-(2-(thiophen-2-yl)ethyl)-1H-
20 benzimidazole-2-carboxamide dihydrochloride

[0877]

[0878]
25 MS (ESI+, m/e) 524 (M+1)
In the same manner as in the method shown in Reference Example 106, the compound described in the following Reference Example 136 was obtained.

Reference Example 136

tert-butyl (3S,5R)-3-\{(1-(4-methoxybutyl)-1H-benzimidazol-2-yl)carbonyl\}(2-methylpropyl)amino)-5-(4H-1,2,4-triazol-3-yl)piperidine-1-carboxylate

MS (ESI+, m/e) 454 (M+1)

Reference Example 137

tert-butyl (3R,5S)-3-cyano-5-\{(1-(4-methoxybutyl)-1H-benzimidazol-2-yl)carbonyl\}(2-methylpropyl)amino)piperidine-1-carboxylate

tert-Butyl (3R,5S)-3-carbamoyl-5-\{(1-(4-methoxybutyl)-1H-benzimidazol-2-yl)carbonyl\}(2-
methylpropyl)amino)piperidine-1-carboxylate (1.01 g) was dissolved in pyridine (10 ml), trifluoroacetic anhydride (570 μl) was added at 0°C, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated under reduced pressure, and diluted with ethyl acetate. 1M Hydrochloric acid was added, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to silica gel chromatography, and a fraction eluted with ethyl acetate-hexane (5:95) - ethyl acetate was concentrated under reduced pressure to give the object product (1.01 g).

MS (ESI+, m/e) 512 (M+1)

[0886]

Reference Example 138
tert-butyl (3S,5R)-3-{{1-(4-methoxybutyl)-1H-benzimidazol-2-yl}carbonyl}(2-methylpropyl)amino)-5-(1,2,4-oxadiazol-3-yl)piperidine-1-carboxylate

[0887]

[0888]

Hydroxylamine hydrochloride (383 mg) was dissolved in dimethyl sulfoxide (10 ml), and the mixture was stirred at 40°C for 30 min. Sodium hydrogen carbonate (463 mg) was added, and the mixture was stirred at 50°C for 1 hr. A solution of tert-butyl (3R,5S)-3-cyano-5-{{1-(4-methoxybutyl)-1H-benzimidazol-2-yl}carbonyl}(2-methylpropyl)amino)piperidine-1-carboxylate (282 mg) in dimethyl sulfoxide (10 ml) was further added, and the mixture was stirred at 90°C for 3 hr. The reaction mixture
was allowed to cool to room temperature, diluted with water, and extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in trimethyl orthoformate (5 ml) and the mixture was stirred at 100°C for 4 hr. The reaction mixture was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography, and a fraction eluted with ethyl acetate-hexane (5:95 - 3:7) was concentrated under reduced pressure to give the object product (230 mg).

MS (ESI+, m/e) 555 (M+1)

[0889]

Reference Example 139
tert-butyl (3S, 5R)-3-{{(1-(4-methoxybutyl)-1H-benzimidazol-2-yl)carbonyl}(2-methylpropyl)amino}-5-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)piperidine-1-carboxylate

[0890]

Hydroxylamine hydrochloride (418 mg) was dissolved in dimethyl sulfoxide (10 ml), and the mixture was stirred at 40°C for 30 min. Sodium hydrogen carbonate (506 mg) was added, and the mixture was stirred at 50°C for 1 hr. A solution of tert-butyl (3R,5S)-3-cyano-5-{{1-(4-methoxybutyl)-1H-benzimidazol-2-yl)carbonyl}(2-methylpropyl)amino)piperidine-1-carboxylate (308 mg) in dimethyl sulfoxide (10 ml) was further added, and the mixture was stirred at 90°C for 3 hr. The reaction mixture was allowed to cool to room temperature, diluted with water, and the mixture was extracted with ethyl acetate. The extract
was dried over anhydrous magnesium sulfate, concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (15 ml). 1,1'-Carbonylbis(1H-imidazole) (490 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (450 µl) were added and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with ethyl acetate. The mixture was washed with 0.5M hydrochloric acid and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to silica gel chromatography, and a fraction eluted with ethyl acetate-hexane (5:95) - ethyl acetate was concentrated under reduced pressure to give the object product (256 mg).

MS (ESI+, m/e) 571 (M+1)

[0892]
Reference Example 140
tert-butyl (3S,5R)-3-\{\{1-(4-methoxybutyl)-1H-benzimidazol-2-yl\}carbonyl\}(2-methylpropyl)amino)-5-(1H-tetrazol-5-yl)piperidine-1-carboxylate

[0893]

\[
\text{\includegraphics[width=0.5\textwidth]{image}}
\]

[0894]
tert-Butyl (3R,5S)-3-cyano-5-\{\{1-(4-methoxybutyl)-1H-benzimidazol-2-yl\}carbonyl\}(2-methylpropyl)amino)piperidine-1-carboxylate (320 mg) was dissolved in tetrahydrofuran (20 ml), azido(trimethyl)silane (1.5 ml) and dibutyl(oxo)stannane (100 mg) were added, and the mixture was heated under reflux with stirring for 43 hr. The reaction mixture was concentrated under reduced pressure, and the residue was subjected to
silica gel chromatography, and a fraction eluted with ethyl acetate - ethyl acetate-methanol (8:2) was concentrated under reduced pressure to give the object product (304 mg). MS (ESI+, m/e) 555 (M+1)

[0895]
In the same manner as in Example 60, the following compounds (Examples 65-68) were obtained.

[0896]
Example 65

1-(4-methoxybutyl)-N-(2-methylpropyl)-N-{(3S,5R)-5-(4H-1,2,4-triazol-3-yl)piperidin-3-yl}-1H-benzimidazole-2-carboxamide dihydrochloride

[0897]

[0898]
MS (ESI+, m/e) 454 (M+1)
Example 66
N-{(3S,5R)-5-cyanopiperidin-3-yl}-1-(4-methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide dihydrochloride

[0899]

[0900]
MS (ESI+, m/e) 412 (M+1)
Example 67
1-(4-methoxybutyl)-N-(2-methylpropyl)-N-{(3S,5R)-5-(1,2,4-oxadiazol-3-yl)piperidin-3-yl}-1H-benzimidazole-2-carboxamide dihydrochloride

[0902]
MS (ESI+, m/e) 455 (M+1)

[0903]
Example 68
1-(4-methoxybutyl)-N-(2-methylpropyl)-N-{(3S,5R)-5-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)piperidin-3-yl}-1H-benzimidazole-2-carboxamide dihydrochloride

[0904]
MS (ESI+, m/e) 471 (M+1)

[0905]
Example 69
1-(4-methoxybutyl)-N-(2-methylpropyl)-N-{(3S,5R)-5-(1H-tetrazol-5-yl)piperidin-3-yl}-1H-benzimidazole-2-carboxamide dihydrochloride

[0907]
tert-Butyl (3S,5R)-3-{{1-[(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl}(2-methylpropyl)amino}-5-(1H-tetrazol-5-yl)piperidine-1-carboxylate (304 mg) was dissolved in 2M hydrogen chloride-ethyl acetate (2 ml), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated, and ethyl acetate-diisopropyl ether was added. The precipitate was collected by filtration, and washed with ethyl acetate-diisopropyl ether to give the object product (219 mg).

MS (ESI+, m/e) 455 (M+1)

In the same manner as in Reference Example 106, the following compound (Reference Example 141) was obtained.

Reference Example 141

tert-butyl (3S,5R)-3-{{5-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl}(2-methylpropyl)amino}-5-(4H-1,2,4-triazol-3-yl)piperidine-1-carboxylate

[0912]
MS (ESI+, m/e) 572 (M+1)

Reference Example 142

tert-butyl (3S,5R)-3-[(benzyloxy)carbonyl](2-methylpropyl)amino]-5-(hydroxymethyl)piperidine-1-carboxylate

[0913]

[0914]

Powder calcium chloride (0.49 g) was suspended in ethanol (10 ml), sodium borohydride (0.34 g) was added while cooling to 0°C, and the mixture was stirred at 0°C for 30 min. A solution (10 ml) of 1-tert-butyl 3-methyl (3R,5S)-5-[(benzyloxy)carbonyl](2-methylpropyl)amino)piperidine-1,3-dicarboxylate (1.00 g) in THF was added to the reaction suspension, and the mixture was stirred at 0°C for 8 hr. 5% Aqueous sodium hydrogen sulfate solution was added to the reaction mixture for neutralization and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give the object product (0.88 g) as an oil.

$^1$H-NMR (CDCl$_3$) δ 0.90 (6H, d), 1.22-1.38 (3H, m), 1.46 (9H, s), 1.69 (1H, dt), 2.23-2.39 (2H, m), 2.44-2.59 (1H, m), 2.47 (2H, d), 2.74 (1H, br s), 3.69 (3H, s), 4.18-4.34 (2H, m)

[0915]

Reference Example 143
tert-butyl (3S,5S)-3-[(2-methylpropyl)amino]-5-[(2-oxopyrrololidin-1-yl)methyl]piperidine-1-carboxylate

[0916]
To a solution of tert-butyl (3S,5R)-3-
{(benzyloxy)carbonyl}(2-methylpropyl)amino)-5-
(hydroxymethyl)piperidine-1-carboxylate (0.47 g) in THF (15
ml) were added phthalimide (0.40 g), diisopropyl
azodicarboxylate (1.59 g) and triphenylphosphine (0.66 g) at
room temperature, and the mixture was stirred at room
temperature for 15 hr. The reaction mixture was concentrated
under reduced pressure, the residue was diluted with water,
and the mixture was extracted with ethyl acetate. The extract
was washed with saturated brine, dried over anhydrous sodium
sulfate, and concentrated under reduced pressure. The obtained
residue was subjected to silica gel chromatography, and a
fraction eluted with ethyl acetate-hexane (1:9 - 1:2) was
concentrated under reduced pressure. The obtained residue was
dissolved in ethanol (10 ml), hydrazine hydrate (95 µl) was
added, and the mixture was heated under reflux for 3 hr. The
mixture was allowed to cool to room temperature, the
precipitate was filtered off, and the filtrate was
concentrated under reduced pressure. The residue was dissolved
in THF (5 ml), diisopropylethylamine (0.29 µl) and 4-
bromobutyryl chloride (0.16 ml) were added at 0°C, and the
mixture was stirred at 0°C for 1 hr. The reaction mixture was
diluted with water, and extracted with ethyl acetate. The
extract was washed with saturated brine, dried over anhydrous
sodium sulfate, and concentrated under reduced pressure. The
residue was dissolved in THF (10 ml), potassium tert-butoxide
(0.38 g) was added at 0°C, and the mixture was stirred at 0°C
for 1 hr. The reaction mixture was concentrated under reduced
pressure, and the residue was diluted with water, and the
mixture was extracted with ethyl acetate. The extract was
washed with saturated brine, dried over anhydrous sodium
sulfate, and concentrated under reduced pressure. The obtained
residue was subjected to silica gel chromatography, and a
fraction eluted with ethyl acetate-hexane (1:3 - 1:0) was
concentrated under reduced pressure. The residue was dissolved in ethanol (10 ml), and 10% palladium-carbon (50% in water: 50 mg) was added. The reaction mixture was stirred under a hydrogen (normal pressure) at room temperature for 15 hr. The palladium catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give the object product (0.30 g).

\[ \text{H-NMR (CDCl}_3\text{) } \delta 0.90 (6H, d), 1.45 (11H, s), 1.68 (1H, dt), 2.04 (2H, qd), 1.77-2.10 (2H, m), 2.21-2.54 (6H, m), 3.18 (2H, br s), 3.40 (2H, ddd), 4.02 (1H, br s), 4.26 (1H, br s) \]

[0918]

In the same manner as in Reference Example 64, the following compound (Reference Example 144) was obtained.

[0919]

Reference Example 144
tert-butyl (3S,5S)-3-[(1H-benzimidazol-2-ylcarbonyl)(2-methylpropyl)amino]-5-[(2-oxopyrrolidin-1-yl)methyl]piperidine-1-carboxylate

[0920]

[0921]

MS (ESI+, m/e) 498 (M+1)

In the same manner as in Reference Example 69, the following compound (Reference Example 145) was obtained.

[0922]

Reference Example 145
tert-butyl (3S,5S)-3-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-[(2-oxopyrrolidin-1-yl)methyl]piperidine-1-carboxylate
[0924]

MS (ESI+, m/e) 584 (M+1)

In the same manner as in Example 60, the following compound (Example 70) was obtained.

[0925]

Example 70

1-(4-methoxybutyl)-N-(2-methylpropyl)-N\{3S,5R)-\{(2-oxopyrrolidin-1-yl)methyl\}piperidin-3-yl\}-1H-benzimidazole-2-carboxamide dihydrochloride

[0926]

MS (ESI+, m/e) 484 (M+1)

Reference Example 146
tert-butyl \{3S,5R)-\{\{1-(4-methoxybutyl)-1H-benzimidazol-2-yl\}carbonyl\}(2-methylpropyl)amino\}-5-\{morpholin-4-ylcarbonyl\}piperidine-1-carboxylate

[0928]
A solution of tert-butyl (3S,5R)-3-[(1H-benzimidazol-2-ylcarbonyl)(2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (200 mg), 4-methoxybutyl methanesulfonate (107 mg) and cesium carbonate (254 mg) in N,N-dimethylacetamide (5 ml) was stirred at 60°C for 15 hr. After cooling to room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate (10 ml×2). The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (5:95 - 3:7) was concentrated under reduced pressure to give the object product (190 mg).
[0932]

1-tert-Butyl 3,5-dimethyl piperidine-1,3,5-tricarboxylate (75 g) was dissolved in methanol (375 ml), and 2M aqueous sodium hydroxide solution (125 ml) was added dropwise at room temperature. The reaction mixture was stirred at room temperature for 14 hr, and methanol was evaporated under reduced pressure. The concentrate was diluted with saturated aqueous sodium hydrogen carbonate solution (100 ml) and washed twice with ethyl acetate. The basic aqueous layer was acidified (pH 2) with 6M hydrochloric acid, and the mixture was extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure to give the object product (71 g).

$^{1}$H-NMR (CDCl$_3$) δ 1.33-1.50 (9H, m), 1.60-1.82 (1H, m), 1.96-2.22 (1H, m), 2.41-2.58 (2H, m), 2.62-2.91 (2H, m), 3.34-3.91 (1H, m), 3.71 (3H, s), 4.37 (1H, br s), 7.55-8.47 (1H, m)

[0933]
Example 71

1-[(4-methoxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide

[0934]

[0935]

tert-Butyl (3S,5R)-3-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (5.85 g) was dissolved in methanol (20 ml), 4M hydrogen chloride-ethyl acetate (20 ml) was added, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was concentrated,
the residue was diluted with aqueous sodium bicarbonate, and, the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure.

The residue was subjected to basic silica gel column chromatography, and a fraction eluted with ethyl acetate-methanol (9:1) was concentrated under reduced pressure to give the object product (4.40 g).

MS (ESI+, m/e) 500 (M+1)

[0936]
Example 72
1-(4-methoxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide methanesulfonate

[0937]

[0938]

Crude crystals (163 g) of 1-(4-methoxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide methanesulfonate were dissolved in 2-butanone (1600 ml) with heating (65°C), and heptane (1600 ml) was added dropwise while keeping at 60°C or above. The seed crystal was added, and the mixture was stirred at 50 - 55°C for 1 hr and at room temperature for 12 hr and filtered. The crystals were washed with a small amount of 2-butanone-heptane (mixing ratio 1:2), and dried under reduced pressure to give the object product (155.6 g).

$^1$H-NMR (DMSO-d$_6$) δ 0.68-0.74 (2H, m), 0.89-0.99 (4H, m), 1.42-1.60 (2H, m), 1.70-1.87 (2H, m), 1.95-2.17 (2H, m), 2.15-2.39
(4H, m), 2.80-3.85 (20H, m), 4.15-4.40 (3H, m), 7.25-7.43 (2H, m), 7.62-7.75 (2H, m), 8.30 (1H, br s), 9.09 (1H, br s)

MS (ESI+, m/e) 500 (M+1)

melting point: 137-138°C

[0939]
Reference Example 149
tert-butyl (3S,5R)-3-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl] (2-methylpropyl)amino]-5-
methoxy(methyl) carbamoyl] piperidine-1-carboxylate

[0940]

[0941]
(3R,5S)-1-(tert-Butoxycarbonyl)-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl] (2-
methylpropyl)amino] piperidine-3-carboxylic acid (7.5 g), WSC-HCl (4.06 g) and HOBT (3.25 g) were dissolved in DMF (50 ml),
N-methoxymethylamine hydrochloride (1.38 g) and triethylamine (7.88 ml) were added and the mixture was stirred at room

20 temperature for 15 hr. The reaction mixture was diluted with water, and the mixture was extracted with ethyl acetate. The
extract was washed with water and brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under
reduced pressure. The residue was subjected to silica gel

column chromatography, and a fraction eluted with ethyl
acetate-hexane (1:4 - 9:1) was concentrated under reduced
pressure to give the object product (4.76 g).

1H-NMR (CDCl3) δ 0.73 (3 H, d), 1.01 (3 H, dd), 1.30 (4 H, s),
1.48 (5 H, s), 1.67 (2 H, dt), 1.91-2.03 (2 H, m), 2.20 (1 H, t), 2.41 (1 H, q), 2.60 - 3.13 (5 H, m), 3.15 - 3.24 (3 H, m),
30

291
3.32 (3 H, d), 3.34 – 3.47 (3 H, m), 3.67 – 3.81 (3 H, m), 3.92 – 4.47 (5 H, m), 7.27 – 7.40 (2 H, m), 7.41 – 7.53 (1 H, m), 7.72 (1 H, dd), 7.84 (1 H, d)
MS (ESI+, m/e) 574 (M+1)

[0942]
Reference Example 150
tert-butyl (3S,5R)-5-acetyl-3-\{[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl\}(2-methylpropyl)amino)piperidine-1-carboxylate

[0943]

[0944]
To a solution of tert-butyl (3S,5R)-3-\{[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl\}(2-methylpropyl)amino]-5-[methoxy(methyl)carbamoyl]piperidine-1-carboxylate (1.06 g) in THF (20 ml) was added 1M-methyl magnesium bromide-THF solution (9.24 ml), and the mixture was stirred at room temperature for 5 hr. The reaction mixture was poured into saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (1:9 – 3:2) was concentrated under reduced pressure to give the object product (0.59 g).

$^1$H-NMR (CDCl$_3$) δ 0.76 (3 H, d), 1.01 (3 H, d), 1.31 (4 H, s), 1.49 (5 H, s), 1.79 (2 H, br s), 2.00 (2 H, br s), 2.21 (3 H, s), 2.21 – 2.47 (2 H, m), 2.56 (1 H, br s), 2.74 (2 H, d),
3.22 - 3.37 (3 H, m), 3.42 (3 H, t), 3.78 (2 H, br s), 4.31 (5 H, d), 7.28 - 7.41 (2 H, m), 7.45 (1 H, d), 7.79 (1 H, d)
MS (ESI+, m/e) 529 (M+1)

[0945]

Reference Example 151
tert-butyl (3R,5S)-3-[(1-hydroxyethyl)-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]piperidine-1-carboxylate

[0946]

[0947]

To a solution of tert-butyl (3R,5S)-3-acetyl-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]piperidine-1-carboxylate (0.40 g) in ethanol (10 ml) was added sodium borohydride (29 mg), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with water. The mixture was acidified with 5% aqueous potassium hydrogen sulfate solution, and extracted with ethyl acetate. The extract was washed with water and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (1:9 - 3:1) was concentrated under reduced pressure to give the object product (0.40 g).

$^1$H-NMR (CDCl$_3$) δ 0.77 (4 H, dd), 1.02 (2 H, d), 1.16 - 1.27 (3 H, m), 1.33 (4 H, d), 1.48 (7 H, s), 1.83 (1 H, br s), 1.98 (2 H, d), 2.11 - 2.90 (3 H, m), 3.30 (1 H, d), 3.33 (3 H, s), 3.35 - 3.46 (3 H, m), 3.66 (4 H, br s), 4.17 - 4.48 (4 H, m),
7.28 - 7.40 (2 H, m), 7.40 - 7.48 (1 H, m), 7.79 (1 H, d)  
MS (ESI+, m/e) 531 (M+1)  

[0948]  
Reference Example 152  

tert-butyl (3S,5R)-3-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl][2-methylpropyl]amino]-5-propanoyl-piperidine-1-carboxylate  

[0949]  

[0950]  

To a solution of tert-butyl (3S,5R)-3-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl][2-methylpropyl]amino]-5-[methoxy(methyl)carbamoyl]piperidine-1-carboxylate (22.7 g) in THF (20 ml) was added 1M-ethylmagnesium bromide-THF solution (119 ml) at room temperature, and the mixture was stirred at room temperature for 5 hr. The reaction mixture was poured into saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (1:9 - 3:2) was concentrated under reduced pressure to give the object product (14.96 g).  
MS (ESI+, m/e) 543 (M+1)  

[0951]  
Reference Example 153  

tert-butyl (3R,5S)-3-(1-hydroxypropyl)-5-[[1-(4-
methoxybutyl)-1H-benzimidazol-2-yl]carbonyl)(2-
methylpropyl)amino]piperidine-1-carboxylate

[0952]

To a solution of tert-butyl (3S,5R)-3-[[1-(4-
methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-
methylpropyl)amino]-5-propanoyl-piperidine-1-carboxylate (2.60
g) in ethanol (30 ml) was added sodium borohydride (181 mg),
and the mixture was stirred at room temperature for 1 hr. The
reaction mixture was concentrated under reduced pressure, and
the residue was diluted with water, acidified with 5% aqueous
potassium hydrogen sulfate solution, and extracted with ethyl
acetate. The extract was washed with water and saturated brine,
and dried over anhydrous sodium sulfate. The solvent was
evaporated under reduced pressure. The residue was subjected
to silica gel column chromatography, and a fraction eluted
with ethyl acetate-hexane (1:9 - 1:1) was concentrated under
reduced pressure to give the object product (2.02 g).

1H-NMR (CDCl3) δ 0.76 (4 H, d), 0.91 - 1.08 (5 H, m), 1.33 (3 H, 
d), 1.48 (6 H, s), 1.55 (2 H, d), 1.64 - 1.90 (5 H, m), 1.91 -
2.03 (2 H, m), 2.10 - 2.42 (2 H, m), 2.59 (1 H, d), 3.31 (1 H, 
d), 3.33 (2 H, s), 3.42 (4 H, t), 3.65 (2 H, br s), 4.17 -
4.46 (4 H, m), 7.27 - 7.39 (2 H, m), 7.39 - 7.51 (1 H, m),
7.69 - 7.85 (1 H, m)
MS (ESI+, m/e) 545 (M+1)

[0954]
Example 73

N-[(3S,5R)-5-[(1R)-1-hydroxy-2-methoxyethyl]piperidin-3-yl]-1-
(4-methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide dihydrochloride (Example 73-1) and
N-{(3S,5R)-5-[(1S)-1-hydroxy-2-methoxyethyl]piperidin-3-yl}-1-(4-methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide dihydrochloride (Example 73-2)

[0955]

[0956]

10 tert-Butyl (3R,5S)-3-(1-hydroxy-2-methoxyethyl)-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl]{2-(methylpropyl)amino}piperidine-1-carboxylate (1.34 g) was optically resolved by normal phase chiral HPLC under the following conditions to give a first elution component (598 mg) and a second elution component (549 mg).

column: CHIRALPAK IC 50 mm ID×500 mmL
mobile phase: hexane-ethanol (700:300)
flow rate: 60 mL/min

temperature: 30°C
detection: UV (220 nm)

injection volume·concentration: 300 mg/load (5 mg/ml)

The obtained first elution component (495 mg) was dissolved in ethanol (1 ml), 12M hydrochloric acid (0.70 ml) was added and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in ethanol, and ethanol was evaporated under reduced pressure. This operation was repeated twice to give the object product (425 mg) of Example compound 73-1.
Example 73-1 spectrum data
$^1$H-NMR (CDCl$_3$) δ 0.71 (2 H, dd), 0.95 (4 H, dd), 1.38 - 1.63 (2 H, m), 1.66 - 1.86 (3 H, m), 1.86 - 2.04 (1 H, m), 2.12 (2 H, dd), 2.59 - 2.91 (1 H, m), 3.02 (1 H, d), 3.09 - 3.22 (4 H, m), 3.24 - 3.39 (9 H, m), 3.50 (2 H, br s), 3.62 (1 H, br s), 4.15 (2 H, br s), 4.21 - 4.39 (2 H, m), 7.15 - 7.53 (2 H, m), 7.55 - 7.87 (2 H, m), 8.33 - 9.18 (1 H, m), 9.43 (1 H, br s)
MS (ESI+, m/e) 461 (M+1)

The obtained second elution component (447 mg) was dissolved in ethanol (1 ml), 12M hydrochloric acid (0.70 ml) was added at room temperature and the mixture was stirred for 1 hr. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in ethanol, and ethanol was evaporated under reduced pressure. This operation was repeated twice to give the object product (365 mg) of Example compound 73-2.

Example 73-2 spectrum data
$^1$H-NMR (CDCl$_3$) δ 0.71 (2 H, dd), 0.81 - 1.12 (4 H, m), 1.31 - 1.61 (2 H, m), 1.62 - 1.98 (5 H, m), 1.98 - 2.23 (2 H, m), 2.57 - 2.87 (1 H, m), 3.14 (1 H, d), 3.18 - 3.23 (3 H, m), 3.23 - 3.39 (10 H, m), 3.39 - 3.63 (3 H, m), 4.23 - 4.38 (3 H, m), 7.16 - 7.51 (2 H, m), 7.55 - 7.86 (2 H, m), 8.29 - 9.11 (1 H, m), 9.38 (1 H, br s)
MS (ESI+, m/e) 461 (M+1)

Example 74
$N-\{(3S,5R)-5-[(1S)-1-hydroxyethyl]piperidin-3-yl\}-1-(4-methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide dihydrochloride (Example 74-1)

and
$N-\{(3S,5R)-5-[(1R)-1-hydroxyethyl]piperidin-3-yl\}-1-(4-methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-
carboxamide dihydrochloride (Example 74-2)

5 [0962]

tert-Butyl (3R,5S)-3-(1-hydroxyethyl)-5-{[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl}(2-methylpropyl)amino)piperidine-1-carboxylate (3.2 g) was optically resolved by normal phase chiral HPLC under the following conditions to give a first elution component (1.31 g) and a second elution component (1.22 g).

column: CHIRALPAK IC 50 mm ID×500 mmL
mobile phase: hexane-ethanol (900:100)
flow rate: 80 ml/min

temperature: 30℃
detection: UV (220 nm)

injection volume·concentration: 300 mg/load (5 mg/ml)

[0963]

The obtained first elution component (1.1 g) was dissolved in 10% hydrogen chloride containing methanol solution (40 ml), and the mixture was stirred at room temperature for 15 hr. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in ethanol, and ethanol was evaporated under reduced pressure. This operation was repeated twice to give the object product (0.90 g) of Example compound 74-1.

[0964]

Example 74-1 spectrum data

$^1$H-NMR (CDCl$_3$) δ 0.72 (3 H, dd), 0.84 – 1.18 (7 H, m), 1.45 – 1.66 (3 H, m), 1.67 – 1.98 (3 H, m), 2.00 – 2.19 (2 H, m),
2.54 - 2.81 (1 H, m), 2.92 - 3.23 (5 H, m), 3.25 - 3.40 (4 H, m), 3.40 - 3.70 (3 H, m), 4.07 - 4.47 (3 H, m), 7.23 - 7.51 (2 H, m), 7.54 - 7.91 (2 H, m), 8.56 - 9.55 (1 H, m), 9.86 (1 H, d)

MS (ESI+, m/e) 431 (M+1)

[0965]

The obtained second elution component (1.0 g) was dissolved in 10% hydrogen chloride containing methanol solution (40 ml) was stirred at room temperature for 15 hr. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in ethanol, and ethanol was evaporated under reduced pressure. This operation was repeated twice to give the object product (0.86 g) of Example compound 74-2.

[0966]

Example 74-2 spectrum data

$^1$H-NMR (CDCl₃) δ 0.71 (3 H, dd), 0.94 (3 H, d), 1.09 (3 H, dd), 1.27 - 1.64 (3 H, m), 1.70 (1 H, s), 1.74 - 2.00 (4 H, m), 2.00 - 2.29 (1 H, m), 2.54 - 2.76 (1 H, m), 3.11 (1 H, d), 3.20 (4 H, d), 3.24 - 3.62 (7 H, m), 4.32 (3 H, d), 7.16 - 7.54 (2 H, m), 7.72 (2 H, q), 8.27 - 9.22 (1 H, m), 9.36 - 9.56 (1 H, m)

MS (ESI+, m/e) 431 (M+1)

[0967]

Example 75

N-[(3S,5S)-5-{[(1S)-1-hydroxypropyl]piperidin-3-yl]-1-(4-methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide dihydrochloride (Example 75-1)

and

N-[(3S,5R)-5-[(1R)-1-hydroxypropyl]piperidin-3-yl]-1-(4-methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide dihydrochloride (Example 75-2)

[0968]
tert-Butyl (3R,5S)-3-(1-hydroxypropyl)-5-[(1-(4-methoxybutyl)-1H-benzimidazol-2-yl)carbonyl](2-
methylpropyl)amino)piperidine-1-carboxylate (2.11 g) was
optically resolved by normal phase chiral HPLC under the
following conditions to give a first elution component (1.26 g) and a second elution component (1.70 g).
column: CHIRALPAK IC 50 mm IDx500 mmL
mobile phase: hexane-ethanol (900:100)
flow rate: 80 ml/min
temperature: 30°C
detection: UV (220 nm)
injection volume-concentration: 300 mg/load (5 mg/ml)

The obtained first elution component (1.03 g) was
dissolved in ethanol (2 ml), 12M hydrochloric acid (1.5 ml)
was added and the mixture was stirred at room temperature for
1 hr. The reaction mixture was concentrated under reduced
pressure, the residue was dissolved in ethanol, and ethanol
was evaporated under reduced pressure. This operation was
repeated twice to give the object product (0.95 g) of Example
compound 75-1.

Example 75-1 spectrum data
$^1$H-NMR (CDCl$_3$) δ 0.71 (2 H, dd), 0.79 - 1.11 (7 H, m), 1.32 -
1.58 (4 H, m), 1.60 - 1.68 (1 H, m), 1.70 - 1.85 (3 H, m),
1.87 - 2.20 (2 H, m), 2.59 - 2.87 (1 H, m), 3.00 (1 H, d),
3.08 - 3.23 (4 H, m), 3.23 - 3.41 (6 H, m), 3.49 (1 H, d),
3.89 - 4.23 (2 H, m), 4.23 - 4.55 (2 H, m), 7.16 - 7.52 (2 H, m), 7.55 - 7.86 (2 H, m), 8.24 - 9.18 (1 H, m), 9.21 - 9.57 (1 H, m)

MS (ESI+, m/e) 445 (M+1)

[0972]
The obtained second elution component (0.85 g) was dissolved in ethanol (2 ml), 12M hydrochloric acid (1.5 ml) was added and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in ethanol, and ethanol was evaporated under reduced pressure. This operation was repeated twice to give the object product (0.78 g) of Example compound 75-2.

[0973]
Example 75-2 spectrum data

$^1$H-NMR (CDCl$_3$) $\delta$ 0.71 (2 H, dd), 0.78 - 1.01 (7 H, m), 1.26 - 1.66 (4 H, m), 1.66 - 1.86 (4 H, m), 1.93 (1 H, d), 2.02 - 2.23 (1 H, m), 2.53 - 2.84 (1 H, m), 3.03 - 3.24 (5 H, m), 3.31 (5 H, q), 3.37 - 3.56 (2 H, m), 4.16 (2 H, br s), 4.22 - 4.44 (2 H, m), 7.16 - 7.54 (2 H, m), 7.54 - 7.87 (2 H, m), 8.16 - 9.27 (1 H, m), 9.36 - 9.84 (1 H, m)

MS (ESI+, m/e) 445 (M+1)

[0974]
Example 76

N-[(3S,5R)-5-(1-hydroxypropyl)piperidin-3-yl]-1-(4-methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide dihydrochloride

[0975]
To a solution of tert-butyl (3R,5S)-3-(1-hydroxypropyl)-5-\{[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl\}(2-methylpropyl)amino)piperidine-1-carboxylate (200 mg) in ethanol (1 ml) was added 12M hydrochloric acid (0.30 ml), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in ethanol, and ethanol was evaporated under reduced pressure. This operation was repeated twice to give the object product (140 mg).

MS (ESI+, m/e) 445 (M+1)

Reference Example 154

tert-butyl (3S,5R)-3-\{[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl\}(2-methylpropyl)amino)-5-(1H-pyrazol-1-ylmethyl)piperidine-1-carboxylate

[0978]

\[ \begin{array}{c}
\text{N} \\
\text{N} \\
\text{N} \\
\text{O} \\
\text{O} \\
\end{array} \]

To a solution of tert-butyl (3R,5S)-3-(hydroxymethyl)-5-\{[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl\}(2-methylpropyl)amino)piperidine-1-carboxylate (517 mg) and triethylamine (0.21 ml) in ethyl acetate (20 ml) was added dropwise methanesulfonyl chloride (0.09 ml) at 0°C, and the mixture was stirred at 0°C for 1 hr. The reaction mixture was washed with water and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in DMF (5 ml), pyrazole (136 mg) and cesium carbonate (489 mg) were added and
the mixture was stirred at 90°C for 7 hr. The reaction mixture was cooled to room temperature, diluted with water and extracted with ethyl acetate. The extract was washed with water and brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (1:9 to 1:0) was concentrated under reduced pressure to give the object product (105 mg).

MS (ESI+, m/e) 567 (M+1)

[0980]

Reference Example 155
tert-butyl (3S,5R)-3-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-(1H-1,2,4-triazol-1-ylmethyl)piperidine-1-carboxylate

[0981]

A solution of tert-butyl (3R,5S)-3-(hydroxymethyl)-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino)piperidine-1-carboxylate (208 mg), 1,3,4-triazole (52 mg), triphenylphosphine (262 mg) and diisopropyl azodicarboxylate (40% toluene solution, 632 mg) in THF (5 ml) was stirred at 50°C for 15 hr. The reaction mixture was concentrated under reduced pressure, diluted with water and ethyl acetate, and the organic layer was separated. The organic layer was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl
acetate-hexane (1:5 - 1:0) and ethyl acetate-methanol (1:0 – 9:1) was concentrated under reduced pressure. The residue was subjected to basic silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (1:9 to 3:1) was concentrated under reduced pressure to give the object product (180 mg).

MS (ESI+, m/e) 568 (M+1)

[0983]

In the same manner as in Example 60, the following compounds (Examples 77-79) were obtained.

[0984]

Example 77

1-(4-methoxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(1H-pyrazol-1-ylmethyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide trihydrochloride

[0985]

[0986]

MS (ESI+, m/e) 467 (M+1)

Example 78

1-(4-methoxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(1H-1,2,4-triazol-1-ylmethyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide dihydrochloride

[0987]
[0988]
MS (ESI+, m/e) 468 (M+1)

Example 79
N-[(3S,5R)-5-acetylpiperidin-3-yl]-1-(4-methoxybutyl)-N-(2-
5 methylpropyl)-1H-benzimidazole-2-carboxamide dihydrochloride

[0989]

[0990]
10 MS (ESI+, m/e) 429 (M+1)

In the same manner as in Reference Example 149, the
following compound (Reference Example 156) was obtained.

[0991]
Reference Example 156

tert-butyl (3S,5R)-3-[[6-fluoro-1-(4-methoxybutyl)-1H-
benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-
[methoxy(methyl)carbamoyl]piperidine-1-carboxylate

[0992]

[0993]
MS (ESI+, m/e) 592 (M+1)

In the same manner as in Reference Example 150, the
following compound (Reference Example 157) was obtained.
Reference Example 157
tert-butyl (3R,5S)-3-acetyl-5-[[6-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]piperidine-1-carboxylate

[0995]

MS (ESI+, m/e) 547 (M+1)

In the same manner as in Reference Example 151, the following compound (Reference Example 158) was obtained.

Reference Example 158
tert-butyl (3S,5R)-3-[[6-fluoro-1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-(1-hydroxyethyl)piperidine-1-carboxylate

[0998]

MS (ESI+, m/e) 549 (M+1)

In the same manner as in Example 76, the following compound (Example 80) was obtained.

Example 80
6-fluoro-N-[(3S,5R)-5-(1-hydroxyethyl)piperidin-3-yl]-1-(4-methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide dihydrochloride

[1001]

[1002]

MS (ESI+, m/e) 449 (M+1)

In the same manner as in Reference Example 69, the following compounds (Reference Examples 159-160) were obtained.

[1003]

Reference Example 159

1-tert-butyl 3-methyl (3R,5S)-5-[(1-ethyl-1H-benzimidazol-2-yl)carbonyl](2-methylpropyl)amino)piperidine-1,3-dicarboxylate

[1004]

[1005]

MS (ESI+, m/e) 487 (M+1)

Reference Example 160

1-tert-butyl 3-methyl (3R,5S)-5-[[1-(cyclopropylmethyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino)piperidine-1,3-dicarboxylate

[1006]
In the same manner as in Reference Example 74, the following compounds (Reference Examples 161-162) were obtained.

Reference Example 161

(3R,5S)-1-(tert-butoxycarbonyl)-5-{{1-ethyl-1H-benzimidazol-2-yl}carbonyl}(2-methylpropyl)amino)piperidine-3-carboxylic acid

Reference Example 162

(3R,5S)-1-(tert-butoxycarbonyl)-5-{{1-(cyclopropylmethyl)-1H-benzimidazol-2-yl}carbonyl}(2-methylpropyl)amino)piperidine-3-carboxylic acid
[1012]
MS (ESI+, m/e) 499 (M+1)
Reference Example 163
tert-butyl (3S,5R)-3-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[1014]
(3R,5S)-1-(tert-Butoxycarbonyl)-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino)piperidine-3-carboxylic acid (10 g) and morpholine (1.6 g) were dissolved in DMF (100 ml), WSC·HCl (4.8 g) and HOBT (3.1 g) were added, and the mixture was stirred at 50°C for 12 hr. The reaction mixture was poured into 10% aqueous sodium bicarbonate, and the mixture was extracted with ethyl acetate. The extracts were combined, washed with brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (1:1 - 1:0) was concentrated under reduced pressure to give the object product (8.9 g).
1H-NMR (CDCl₃) δ 0.63-0.80 (2H, m), 0.89-1.07 (4H, m), 1.41-1.59 (9H, m), 1.59-1.80 (2H, m), 1.87-2.23 (4H, m), 2.30-2.98 (3H, m), 3.21-3.46 (6H, m), 3.49-3.91 (10H, m), 3.95-4.47 (5H, m), 7.18-7.51 (3H, m), 7.56-7.84 (1H, m).

MS (ESI+, m/e) 600 (M+1)

[1015]

In the same manner as in Reference Example 163, the following compounds (Reference Examples 164-165) were obtained.

[1016]

Reference Example 164
tert-butyl (3S,5R)-3-{{[1-(ethyl-1H-benzimidazol-2-yl)carbonyl](2-methylpropyl)amino}-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[1017]

[1018]

MS (ESI+, m/e) 542 (M+1)

Reference Example 165
tert-butyl (3S,5R)-3-{{[1-(cyclopropylmethyl)-1H-benzimidazol-2-yl]carbonyl}(2-methylpropyl)amino}-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[1019]
[1020]
MS (ESI+, m/e) 568 (M+1)  
In the same manner as in Example 60, the following compounds (Examples 81-82) were obtained.

[1021]
Example 81
1-ethyl-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylicarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide dihydrochloride

[1022]

[1023]
MS (ESI+, m/e) 442 (M+1)
Example 82
1-(cyclopropylmethyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylicarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide dihydrochloride

[1024]

[1025]
MS (ESI+, m/e) 468 (M+1)  
In the same manner as in Reference Example 79, the following compound (Reference Example 166) was obtained.
[1026]
Reference Example 166
tert-butyl (3S,5R)-3-\{[(1-ethyl-1H-benzimidazol-2-yl)carbonyl](2-methylpropyl)amino}-5-(hydroxymethyl)piperidine-1-carboxylate

[1027]

[1028]
10 MS (ESI+, m/e) 459 (M+1)

In the same manner as in Example 76, the following compound (Example 83) was obtained.

[1029]
Example 83
15 1-ethyl-N-[(3S,5R)-5-(hydroxymethyl)piperidin-3-yl]N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide dihydrochloride

[1030]

[1031]
20 MS (ESI+, m/e) 359 (M+1)

Reference Example 167
tert-butyl (3S,5R)-3-\{(1,3-benzothiazol-2-ylcarbonyl)(2-methylpropyl)amino\}-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[1032]
[1033]

1,3-Benzothiazole-2-carboxylic acid (29 mg), tert-butyl
5-(3S,5R)-3-[(2-methylpropyl)amino]-5-(morpholin-4-
ylcarbonyl)piperidine-1-carboxylate (50 mg) and N,N-
diisopropylethylamine (118 µl) were dissolved in acetonitrile
(3 ml), chloro-N,N,N',N'-tetramethylformamidinium
hexafluorophosphate (57 mg) was added at 0°C, and the mixture
was stirred at room temperature for 2 hr. The reaction mixture
was diluted with 10% aqueous sodium bicarbonate, and the
mixture was extracted with ethyl acetate. The extract was
washed with saturated brine, and dried over anhydrous sodium
sulfate. The solvent was evaporated under reduced pressure.
The residue was subjected to silica gel column chromatography,
and a fraction eluted with ethyl acetate-hexane (1:1 - 1:0)
was concentrated under reduced pressure to give the object
product (58 mg).
MS (ESI+, m/e) 531 (M+1)

[1034]

In the same manner as in Example 60, the following
compound (Example 84) was obtained.

[1035]
Example 84

N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-
ylcarbonyl)piperidin-3-yl]-1,3-benzothiazole-2-carboxamide
hydrochloride

[1036]
[1037]
MS (ESI+, m/e) 431 (M+1)

Example 85
1-(3-methoxypropyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-
(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-
carboxamide 1/2 sulfate

[1038]

[1039]

15 tert-Butyl (3S,5R)-3-[(1H-benzimidazol-2-ylcarbonyl)(2-
methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-
carboxylate (700 mg), 3-methoxypropan-1-ol (123 mg) and
triphenylphosphine (465 mg) were dissolved in THF (20 ml),
diisopropyl azodicarboxylate (40% toluene solution: 896 mg)
was added, and the mixture was stirred at room temperature for
60 hr. The reaction mixture was diluted with water, and the
mixture was extracted with ethyl acetate. The extract was
saturated aqueous sodium hydrogen carbonate and saturated
washed with brine, and dried over anhydrous sodium sulfate.
The solvent was evaporated under reduced pressure. The residue
was subjected to silica gel column chromatography, and a
fraction eluted with ethyl acetate-hexane (1:9 – 1:3) was
concentrated under reduced pressure. The obtained substance was dissolved in ethyl acetate (3 ml), 4M hydrogen chloride-ethyl acetate (3 ml) was added, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was basified with saturated aqueous sodium hydrogen carbonate, and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to basic silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (1:9 - 1:0) and ethyl acetate-methanol (93:7) was concentrated under reduced pressure. The obtained substance was dissolved in ethyl acetate (10 ml), sulfuric acid (42 mg) was added, and the solvent was evaporated under reduced pressure. The residue was dissolved in ethanol (10 ml), and the solvent was evaporated under reduced pressure. The residue was crystallized from ethyl acetate-methanol to give the object product (180 mg) as crystals.

\textbf{1H-NMR} (CDCl$_3$) $\delta$ 0.70 (2 H, d), 0.94 (4 H, dd), 1.69 - 2.28 (5 H, m), 2.60 - 2.85 (2 H, m), 2.85 - 3.15 (3 H, m), 3.15 - 3.25 (5 H, m), 3.41 - 3.74 (11 H, m), 3.86 - 4.20 (1 H, m), 4.20 - 4.52 (2 H, m), 7.18 - 7.48 (2 H, m), 7.53 - 7.84 (2 H, m)

MS (ESI+, m/e) 486 (M+1)

**Example 86**

1-((4-methoxybutyl))-N-(2-methylpropyl)-N-[(3R,5S)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide 1/2 sulfate

**Example 87**
[1042]

1-(4-Methoxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-y1carbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide (1 g) and sulfuric acid (0.055 ml) were dissolved in ethyl acetate (30 ml) and ethanol (1 ml) with heating (100°C), and stood while gradually cooling to room temperature. The precipitate was collected by filtration, and washed with ethyl acetate. The obtained crude crystals (0.37 g) were dissolved in ethyl acetate (3.75 ml) and ethanol (1.5 ml) with heating (70°C), and the seed crystal was added. The mixture was stood for 15 hr while gradually cooling to room temperature, and filtered. The crystals were washed with ethyl acetate, and dried under reduced pressure to give the object product (0.18 g) as crystals.

\[\text{H-NMR (DMSO-d6)} \delta 0.70 \text{ (2 H, d)}, 0.94 \text{ (4 H, dd)}, 1.30 - 1.61 \text{ (2 H, m)}, 1.78 \text{ (2 H, dd)}, 1.86 - 2.02 \text{ (1 H, m)}, 2.02 - 2.21 \text{ (1 H, m)}, 2.58 - 2.85 \text{ (2 H, m)}, 2.89 - 3.02 \text{ (1 H, m)}, 3.15 - 3.21 \text{ (3 H, m)}, 3.25 - 3.65 \text{ (17 H, m)}, 3.98 \text{ (1 H, br s)}, 4.19 - 4.53 \text{ (2 H, m)}, 7.23 - 7.56 \text{ (2 H, m)}, 7.62 - 8.00 \text{ (2 H, m)}\]

MS (ESI+, m/e) 500 (M+1)

[1043]

Reference Example 168
tert-butyl (3S,5R)-3-\{[1-(2-methoxy-2-oxoethyl)-1H-benzimidazol-2-ylcarbonyl](2-methylpropyl)amino]-5-(morpholin-4-y1carbonyl)piperidine-1-carboxylate

[1044]

[1045]

tert-Butyl (3S,5R)-3-{(1H-benzimidazol-2-ylcarbonyl)(2-
methylpropyl]amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (1.06 g) was dissolved in dimethylformamide (20 ml), methyl bromoacetate (390 μl) and cesium carbonate (2.02 g) were added and the mixture was stirred at 55°C for 1 hr. The reaction mixture was concentrated under reduced pressure, diluted with water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to silica gel chromatography, and a fraction eluted with ethyl acetate-hexane (1:9) - ethyl acetate was concentrated under reduced pressure to give the object product (1.19 g). MS (ESI+, m/e) 586 (M+1)

[1046]

Reference Example 169
tert-butyl (3S,5R)-3-[[1-(2-hydroxyethyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[1047]

Calcium chloride (650 mg) was suspended in ethanol (80 ml) and sodium borohydride (740 mg) was added at 0°C. After stirring at 0°C for 15 min, a solution of tert-butyl (3S,5R)-3-[[1-(2-methoxy-2-oxoethyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (1.15 g) in THF (80 ml) was added dropwise. After stirring at room temperature for 2 hr, the reaction mixture was diluted with 10% aqueous citric acid solution, and the
mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel chromatography, and a fraction eluted with ethyl acetate-hexane (1:9 - 1:0) - ethyl acetate-methanol (85:15) was concentrated under reduced pressure to give the object product (849 mg).

MS (ESI+, m/e) 558 (M+1)

[1049]

In the same manner as in the method shown in Example 60, the compound described in the following Example 87 was obtained.

[1050]

Example 87

methyl (2-((2-methylpropyl)[(3S,5R)-5-(morpholin-4-ylicarbonyl)piperidin-3-yl]carbamoyl]-1H-benzimidazol-1-yl)acetate dihydrochloride

[1051]

[1052]

MS (ESI+, m/e) 486 (M+1)

Example 88

1-(2-hydroxyethyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylicarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide dihydrochloride

[1053]
[1054]

tert-Butyl (3S,5R)-3-[[1-(2-hydroxyethyl)-1H-benzimidazol-2-yl]carbonyl] (2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (51 mg) was dissolved in 10% hydrogen chloride-methanol (4 ml), and the mixture was stirred at room temperature for 41 hr and concentrated to give the object product (44 mg).

MS (ESI+, m/e) 458 (M+1)

[1055]
Example 89
1-(2-cyclopropylethyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide dihydrochloride

[1056]

[1057]
To a solution of tert-butyl (3S,5R)-3-[(1H-benzimidazol-2-ylcarbonyl) (2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (257 mg), 2-cyclopropylethanol (86 mg) and triphenylphosphine (263 mg) in toluene (10 ml) was added diisopropyl azodicarboxylate (506 µl) at room temperature, and the mixture was stirred at the same
temperature for 17 hr. The reaction mixture was diluted with aqueous sodium bicarbonate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to basic silica gel column chromatography, and a fraction eluted with ethyl acetate was concentrated under reduced pressure to give tert-butyl (3S,5R)-3-[[1-(2-cyclopropylethyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate. The obtained tert-butyl (3S,5R)-3-[[1-(2-cyclopropylethyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate was dissolved in 4M hydrogen chloride-ethyl acetate (5 ml), and the mixture was stirred at room temperature for 3 hr. The reaction mixture was concentrated, and the residue was subjected to reversed-phase preparative HPLC and the eluted fraction was concentrated under reduced pressure. The residue was diluted with aqueous sodium bicarbonate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. 4M Hydrogen chloride-ethyl acetate (1 ml) was added and the mixture was stirred for 5 min. The solvent was evaporated under reduced pressure to give the object product (220 mg).

MS (ESI+, m/e) 482 (M+1)

[1058]
Reference Example 170
tert-butyl (3R,5S)-3-(1H-benzimidazol-2-yl)-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino)piperidine-1-carboxylate

[1059]
(3R,5S)-1-(tert-Butoxycarbonyl)-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]piperidine-3-carboxylic acid (265 mg), phenylenediamine (54 mg), 1H-benzotriazol-1-ol (95 mg) and N,N-diisopropylethylamine (259 µl) were dissolved in DMF (5 ml), WSC·HCl (144 mg) was added and the mixture was stirred at room temperature for 15 hr. The reaction mixture was diluted with aqueous sodium bicarbonate, and extracted with ethyl acetate. The extract was washed successively with water and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in acetic acid (5 ml), and the mixture was stirred at 80°C for 5 hr. The mixture was cooled to room temperature, and the reaction mixture was concentrated. To the residue was added aqueous sodium bicarbonate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate was concentrated under reduced pressure to give the object product (115 mg).

MS (ESI+, m/e) 603 (M+1)

In the same manner as in Example 12, the following compound (Example 90) was obtained.

Example 90
N-[(3S,5R)-5-(1H-benzimidazol-2-yl)piperidin-3-yl]-1-(4-methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide trihydrochloride

[1063]

MS (ESI+, m/e) 503 (M+1)
Reference Example 171

1-tert-butyl 3-methyl (3R,5S)-5-[(2-methylpropyl){[1-(2-phenylethyl)-1H-benzimidazol-2-yl]carbonyl}amino]piperidine-1,3-dicarboxylate

[1065]

[1066]

To a solution of 1-tert-butyl 3-methyl (3R,5S)-5-[(1H-benzimidazol-2-yl)carbonyl](2-methylpropyl)amino]piperidine-1,3-dicarboxylate (1.38 g) and (2-bromoethyl)benzene (810 μl) in N,N-dimethylacetamide (30 ml) was added cesium carbonate (2.93 g), and the mixture was stirred at 65°C for 15 hr. (2-Bromoethyl)benzene (810 μl) was added to the reaction mixture, and the mixture was further stirred at 65°C for 5 hr. The reaction mixture was cooled to room temperature, diluted with water and extracted with ethyl acetate. The extract was washed
with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (1:1) was concentrated under reduced pressure to give the object product (1.40 g).

MS (ESI+, m/e) 563 (M+1)

Reference Example 172

(3R,5S)-1-(tert-butoxycarbonyl)-5-[(2-methylpropyl)\{(1-(2-phenylethyl)-1H-benzimidazol-2-yl)carbonyl\}amino]piperidine-3-carboxylic acid

[1068]

\[\text{Structure diagram}\]

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[1069]

1-tert-Butyl 3-methyl (3R,5S)-5-[(2-methylpropyl)\{(1-(2-phenylethyl)-1H-benzimidazol-2-yl)carbonyl\}amino]piperidine-1,3-dicarboxylate (1.12 g) was dissolved in methanol, 2M aqueous sodium hydroxide solution (10 ml) was added dropwise at room temperature. The reaction mixture was stirred at 50°C for 3 hr. The reaction mixture was adjusted to pH 7 with 1M hydrochloric acid, and extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give the object product (1.07 g).

MS (ESI+, m/e) 549 (M+1)

[1070]

In the same manner as in Reference Example 55, the
following compound (Reference Example 173) was obtained.

[1071]

Reference Example 173
tert-butyl (3R,5S)-3-carbamoyl-5-{[1-(2-
5 phenylethyl)-1H-benzimidazol-2-yl]carbonyl}amino)piperidine-1-
carboxylate

[1072]

[1073]

MS (ESI+, m/e) 548 (M+1)

In the same manner as in Example 12, the following
compound (Example 91) was obtained.

[1074]

Example 91
N-{(3S,5R)-5-carbamoylpiperidin-3-yl}-N-(2-methylpropyl)-1-(2-
phenylethyl)-1H-benzimidazole-2-carboxamide dihydrochloride

[1075]

[1076]

MS (ESI+, m/e) 448 (M+1)

In the same manner as in Reference Example 60, the
following compound (Reference Example 174) was obtained.
Reference Example 174

tert-butyl (3R,5S)-3-(hydroxymethyl)-5-[(2-methylpropyl)\{(1-(2-phenylethyl)-1H-benzimidazol-2-yl)carbonyl\}amino]piperidine-1-carboxylate

[1078]

MS (ESI+, m/e) 535 (M+1)

In the same manner as in Example 24, the following compound (Example 92) was obtained.

Example 92

N-[(3S,5R)-5-(hydroxymethyl)piperidin-3-yl]-N-(2-methylpropyl)-1-(2-phenylethyl)-1H-benzimidazole-2-carboxamide dihydrochloride

[1081]

MS (ESI+, m/e) 435 (M+1)

Reference Example 175

tert-butyl (3S,5R)-3-{(2-methylpropyl)\{(1-(2-
[(methyIsulfonfonyloxy)ethyl]-1H-benzimidazol-2-yl]carbonyl]amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[1084]

To a solution of tert-butyl (3S,5R)-3-[[1-(2-hydroxyethyl)-1H-benzimidazol-2-yl]carbonyl](2-
methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (223 mg) and triethylamine (84 µl) in THF (5 ml) was added dropwise methanesulfonyl chloride (37 µl) at room temperature. The reaction mixture was stirred at room temperature for 3 hr, diluted with aqueous sodium bicarbonate, and extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give the object product (288 mg).

MS (ESI+, m/e) 636 (M+1)

[1086]

Reference Example 176
tert-butyl (3S,5R)-3-[(2-methylpropyl){1-[2-(1H-pyrazol-1-yl)ethyl]-1H-benzimidazol-2-yl}carbonyl]amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[1087]
To a solution of tert-butyl (3S,5R)-3-[(2-methylpropyl)[(1-[(2-[(methylsulfonfonyl)oxy]ethyl)-1H-benzimidazol-2-yl]carbonyl]amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (127 mg) and pyrazole (41 mg) in N,N-dimethylacetamide (3 ml) was added cesium carbonate (326 mg), and the mixture was stirred at 60°C for 3 days. The reaction mixture was diluted with water, and extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate was concentrated under reduced pressure to give the object product (72 mg).

MS (ESI+, m/e) 608 (M+1)

In the same manner as in Reference Example 176, the following compound (Reference Example 177) was obtained.

Reference Example 177

tert-butyl (3S,5R)-3-[(1-[2-(1H-imidazol-1-yl)ethyl]-1H-benzimidazol-2-yl]carbonyl)(2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate
In the same manner as in Example 12, the following compounds (Examples 93-94) were obtained.

Example 93

N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1-[2-(1H-pyrazol-1-yl)ethyl]-1H-benzimidazole-2-carboxamide dihydrochloride

Example 94

1-[2-(1H-imidazol-1-yl)ethyl]-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide trihydrochloride
In the same manner as in Example 89, the following compound (Example 95) was obtained.

**Example 95**

1-(3-cyclopropylpropyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide dihydrochloride

**Example 96**

1-(3-hydroxypropyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide dihydrochloride
To a mixed solution of tert-butyl (3S,5R)-3-[(1H-benzimidazol-2-ylcarbonyl)(2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (103 mg), propane-1,3-diol (152 mg) and triphenylphosphine (105 mg) in toluene (5 ml) and THF (5 ml) was added diisopropyl azodicarboxylate (202 μl) at room temperature, and the mixture was stirred at the same temperature for 15 hr. The reaction mixture was diluted with aqueous sodium bicarbonate, and extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to basic silica gel column chromatography, and a fraction eluted with ethyl acetate was concentrated under reduced pressure to give tert-butyl (3S,5R)-3-[[1-(3-hydroxypropyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate. The obtained tert-butyl (3S,5R)-3-[[1-(3-hydroxypropyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate was dissolved in 10 - 20% hydrogen chloride-methanol (3 ml), and the mixture was stirred at room temperature for 3 hr. The reaction mixture was concentrated to give the object product (22 mg).

MS (ESI+, m/e) 472 (M+1)

Reference Example 178
tert-butyl (3S,5R)-3-[[1-(3-ethoxy-3-oxopropyl)-1H-
benzimidazol-2-yl]carbonyl)(2-methylpropyl)amino]-5-
(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[1104]

\[
\text{N} \begin{array}{c}
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\]

5

[1105]

To a solution of tert-butyl (3S,5R)-3-[(1H-benzimidazol-
2-ylcarbonyl)(2-methylpropyl)amino]-5-(morpholin-4-
ylcarbonyl)piperidine-1-carboxylate (257 mg) and ethyl 3-
bromopropanoate (181 mg) in N,N-dimethylacetamide (5 ml) was
added cesium carbonate (489 mg), and the mixture was stirred
at 70°C for 15 hr. Ethyl 3-bromopropanoate (181 mg) was added
to the reaction mixture, and the mixture was further stirred
at 70°C for 5 hr. The reaction mixture was cooled to room
temperature, diluted with water, and extracted with ethyl
acetate. The extract was washed with saturated brine, and
dried over anhydrous sodium sulfate. The solvent was
evaporated under reduced pressure. The residue was subjected
to silica gel column chromatography, and a fraction eluted
with ethyl acetate-hexane (6:4) was concentrated under reduced
pressure to give the object product (225 mg).
MS (ESI+, m/e) 614 (M+1)

[1106]
Reference Example 179

25 tert-butyl (3S,5R)-3-[(1-[3-(2-acetylhydrazino)-3-oxopropyl]-
1H-benzimidazol-2-yl]carbonyl)(2-methylpropyl)amino]-5-
(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[1107]
[1108]
tert-Butyl (3S,5R)-3-[[1-(3-ethoxy-3-oxopropyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (307 mg) was dissolved in ethanol (10 ml), hydrazine monohydrate (243 μl) was added and the mixture was heated under reflux for 6 hr with stirring. The reaction mixture was concentrated, ethyl acetate was added to the residue, and the mixture was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in THF (5 ml), and triethylamine (209 μl) was added. The reaction mixture was cooled to 0°C, acetic anhydride (71 μl) was added dropwise and the mixture was stirred at room temperature for 15 hr. The reaction mixture was dilute with aqueous sodium bicarbonate, and extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give the object product (292 mg).
MS (ESI+, m/e) 642 (M+1)

[1109]
Reference Example 180

tert-butyl (3S,5R)-3-[[1-[2-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl]-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[1110]
[1111]
tert-Butyl (3S,5R)-3-[[1-[3-(2-acetylhydrazino)-3-oxopropyl]-1H-benzimidazol-2-yl]carbonyl] (2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (292 mg) was dissolved in pyridine (5 ml), and trifluoromethanesulfonic anhydride (230 µl) was added dropwise at room temperature. The reaction mixture was stirred at room temperature for 15 hr, and concentrated. The residue was diluted with 10% aqueous citric acid solution, and the mixture was extracted with ethyl acetate. The extract was washed with aqueous sodium bicarbonate and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate was concentrated under reduced pressure to give the object product (117 mg).
MS (ESI+, m/e) 624 (M+1)

[1112]
In the same manner as in Example 23, the following compound (Example 97) was obtained.

[1113]
Example 97

1-[2-((5-methyl-1,3,4-oxadiazol-2-yl)ethyl]-N-(2-methylpropyl)-N-[[3S,5R]-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide

[1114]
[1115]
MS (ESI+, m/e) 524 (M+1)

Reference Example 181
3-(2-[[3S,5R]-1-(tert-butoxycarbonyl)-5-(morpholin-4-y1carbonyl)piperidin-3-yl](2-methylpropyl)carbamoyl)-1H-benimidazol-1-yl)propanoic acid

[1116]

[1117]
To a solution of tert-butyI (3S,5R)-3-[{1-(3-ethoxy-3-oxopropyl)-1H-benimidazol-2-yl}carbonyl](2-methylpropyl)amino]-5-(morpholin-4-y1carbonyl)piperidine-1-carboxylate (225 mg) in ethanol (5 ml) was added 2M aqueous sodium hydroxide solution, and the mixture was stirred at room temperature for 3 days. The reaction mixture was adjusted to pH 7 with 1M hydrochloric acid, and extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give the object product (215 mg).

MS (ESI+, m/e) 586 (M+1)

[1118]
Reference Example 182

 tert-butyl (3S,5R)-3-[[1-(3-amino-3-oxopropyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-\((\text{morpholin-4-yl} \text{carbonyl})\)piperidine-1-carboxylate

![Chemical Structure](image)

[1119]

3-(2-\(((3S,5R)-1-(\text{tert-Butoxycarbonyl})-5-(\text{morpholin-4-yl} \text{carbonyl})\)piperidin-3-yl]\(\text{(2-methylpropyl)carbamoyl})-1H-benzimidazol-1-yl\)propanoic acid (215 mg) and 1H-1,2,3-benzotriazol-1-ol ammonium salt (84 mg) were dissolved in DMF (5 ml), WSC·HCl (142 mg) was added and the mixture was stirred at room temperature for 15 hr. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with 10% aqueous citric acid solution and extracted with ethyl acetate. The extract was washed with aqueous sodium bicarbonate and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate was concentrated under reduced pressure to give the object product (199 mg).

MS (ESI+, m/e) 585 (M+1)

[1121]

Reference Example 183

 tert-butyl (3S,5R)-3-[[1-(2-cyanoethyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-(\text{morpholin-4-yl} \text{carbonyl})piperidine-1-carboxylate

[1122]
[1123]

tert-Butyl (3S,5R)-3-\{[1-(3-amino-3-oxopropyl)-1H-
benzimidazol-2-yl]carbonyl\}(2-methylpropyl)amino]-5-
(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (233 mg) was
dissolved in pyridine (5 ml), trifluoroacetic anhydride (116
μl) was added at 0°C and the mixture was stirred at room
temperature for 2 hr. The reaction mixture was concentrated
under reduced pressure, and diluted with ethyl acetate. 1M
Hydrochloric acid was added, and the mixture was extracted
with ethyl acetate. The extract was washed with aqueous sodium
bicarbonate and saturated brine, dried over anhydrous
magnesium sulfate, and concentrated under reduced pressure.
The residue was subjected to silica gel chromatography, and a
fraction eluted with ethyl acetate-hexane (7:3) was
concentrated under reduced pressure to give the object product
(197 mg).
MS (ESI+, m/e) 567 (M+1)

[1124]

Example 98
N-(2-methylpropyl)-N-\{(3S,5R)-5-(morpholin-4-
ylcarbonyl)piperidin-3-yl\}-1-[2-(1,2,4-oxadiazole-3-yl)ethyl]-
1H-benzimidazole-2-carboxamide dihydrochloride

[1125]
Hydroxylamine hydrochloride (125 mg) was dissolved in dimethyl sulfoxide (5 ml), sodium hydrogen carbonate (463 mg) was added and the mixture was stirred at 50°C for 1 hr. A solution of tert-butyl (3S,5R)-3-[[1-(2-cyanoethyl)-1H-benzimidazol-2-yl]carbonyl] (2-methylpropyl) amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (100 mg) in dimethyl sulfoxide (5 ml) was added to the reaction mixture, and the mixture was stirred at 90°C for 3 hr. The reaction mixture was allowed to cool to room temperature, diluted with water, and extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in trimethyl orthoformate (5 ml) and the mixture was stirred at 100°C for 5 hr. The reaction mixture was concentrated under reduced pressure, and the residue was subjected to basic silica gel chromatography, and a fraction eluted with ethyl acetate was concentrated under reduced pressure to give tert-butyl (3S,5R)-3-[(2-methylpropyl)({1-[2-(1,2,4-oxadiazol-3-yl)ethyl]-1H-benzimidazol-2-yl}carbonyl) amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate. The obtained tert-butyl (3S,5R)-3-[(2-methylpropyl)({1-[2-(1,2,4-oxadiazol-3-yl)ethyl]-1H-benzimidazol-2-yl}carbonyl) amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate was dissolved in 4M hydrogen chloride-ethyl acetate (3 ml), and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated, and the residue was subjected to reversed-phase...
preparative HPLC and the eluted fraction was concentrated under reduced pressure. The residue was diluted with aqueous sodium bicarbonate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. 4M Hydrogen chloride-ethyl acetate (1 ml) was added and the mixture was stirred for 5 min. The solvent was evaporated under reduced pressure to give the object product (35 mg). MS (ESI+, m/e) 510 (M+1)

[1127]
Reference Example 184
tert-butyl (3S,5R)-3-[(1-[2-(ethenyoxy)ethyl]-1H-benzimidazol-2-yl)carbonyl](2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[1128]

[1129]
To a solution of tert-butyl (3S,5R)-3-[(1H-benzimidazol-2-ylcarbonyl)(2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (308 mg), (2-chloroethoxy)ethene (192 mg) and potassium iodide (5 mg) in N,N-dimethylacetamide (5 ml) was added cesium carbonate (586 mg), and the mixture was stirred at 60°C for 15 hr. The reaction mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (6:4) was
concentrated under reduced pressure to give the object product (323 mg).

MS (ESI+, m/e) 584 (M+1)

[1130]

Example 99

1-[2-(cyclopropoxy)ethyl]-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide dihydrochloride

[1131]

[1132]

To a solution of tert-butyl (3S,5R)-3-[(1-[2-(ethenylxyloxy)ethyl]-1H-benzimidazol-2-yl)carbonyl] (2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (323 mg) and 1M diethylzinc-hexane solution (2.5 ml) in dichloromethane (5 ml) was added dropwise diiodomethane (443 µl) at room temperature over 5 min, and the mixture was stirred at room temperature for 3 hr. The reaction mixture was diluted with 1M hydrochloric acid, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in methanol (5 ml), 4M hydrogen chloride-ethyl acetate (5 ml) was added and the mixture was stirred at room temperature for 5 hr. The reaction mixture was concentrated, and the residue was subjected to reversed-phase preparative HPLC and the eluted fraction was concentrated under reduced pressure. The residue was diluted with aqueous sodium bicarbonate, and the mixture was extracted with ethyl acetate.
The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. 4M Hydrogen chloride-ethyl acetate (1 ml) was added and the mixture was stirred for 5 min. The solvent was evaporated under reduced pressure to give the object product (35 mg).

MS (ESI+, m/e) 498 (M+1)

[1133]
Reference Example 185
tert-butyl (3S, 5R)-3-[[1-(5-hydroxypentyl)-1H-benzimidazol-2-yl]carbonyl] (2-methylpropyl) amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[1134]

[1135]
To a mixed solution of tert-butyl (3S, 5R)-3-[[1H-benzimidazol-2-ylcarbonyl] (2-methylpropyl) amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (308 mg), pentane-1,5-diol (1.25 g) and triphenylphosphine (472 mg) in toluene (10 ml)-THF (10 ml) was added diisopropyl azodicarboxylate (910 μl) at room temperature, and the mixture was stirred at the same temperature for 15 hr. The reaction mixture was diluted with aqueous sodium bicarbonate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate was concentrated under reduced pressure to give the object product (250 mg).

MS (ESI+, m/e) 600 (M+1)
Example 100

1-(5-hydroxypentyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide dihydrochloride

[1138]

tert-Butyl (3S,5R)-3-[[1-(5-hydroxypentyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (100 mg) was dissolved in 10 - 20% hydrogen chloride-methanol (5 ml), and the mixture was stirred at room temperature for 15 hr. The reaction mixture was concentrated, and the residue was subjected to reversed-phase preparative HPLC and the eluted fraction was concentrated under reduced pressure. The residue was diluted with aqueous sodium bicarbonate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. 10 - 20% Hydrogen chloride-methanol (3 ml) was added and the mixture was stirred for 5 min. The solvent was evaporated under reduced pressure to give the object product (34 mg).

MS (ESI+, m/e) 500 (M+1)

[1139]

Reference Example 186
tert-butyl (3S,5R)-3-[[1-(5-methoxypentyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[1140]
[1141]

To a solution of tert-butyl (3S,5R)-3-[[1-(5-hydroxypentyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (150 mg) and triethylamine (70 µl) in tetrahydrofuran (5 ml) was added methanesulfonyl chloride (725 µl) at 0°C, and the mixture was stirred at room temperature for 2 hr. Aqueous sodium bicarbonate was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in methanol (5 ml), 28% sodium methoxide-methanol solution (482 mg) was added at room temperature and the mixture was stirred at 60°C for 3 days. The reaction mixture was diluted with aqueous sodium bicarbonate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate was concentrated under reduced pressure to give the object product (123 mg).

MS (ESI+, m/e) 614 (M+1)

[1142]

Example 101

1-(5-methoxypentyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide dihydrochloride
[1144]

tert-Butyl (3S,5R)-3-{{1-(5-methoxypentyl)-1H-benzimidazol-2-yl}carbonyl}(2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (123 mg) was dissolved in 4M hydrogen chloride-ethyl acetate (5 ml), and the mixture was stirred at room temperature for 3 hr. The reaction mixture was concentrated, and the residue was subjected to reversed-phase preparative HPLC and the eluted fraction was concentrated under reduced pressure. The residue was diluted with aqueous sodium bicarbonate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. 4M Hydrogen chloride-ethyl acetate (1 ml) was added and the mixture was stirred for 5 min. The solvent was evaporated under reduced pressure to give the object product (76 mg). MS (ESI+, m/e) 514 (M+1)

[1145]

In the same manner as in Reference Example 168, the following compound (Reference Example 187) was obtained.

[1146]

Reference Example 187

tert-butyl (3S,5R)-3-{{1-(4-ethoxy-4-oxobutyl)-1H-benzimidazol-2-yl}carbonyl}(2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[1147]
[1148]
MS (ESI+, m/e) 628 (M+1)

In the same manner as in Reference Example 169, the following compound (Reference Example 188) was obtained.

[1149]
Reference Example 188
tert-butyl (3S,5R)-3-[[1-(4-hydroxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-((morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[1150]

[1151]
MS (ESI+, m/e) 586 (M+1)

In the same manner as in Example 100, the following compound (Example 102) was obtained.

[1152]
Example 102
1-(4-hydroxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-((morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide dihydrochloride

[1153]
[1154]
MS (ESI+, m/e) 486 (M+1)
5 Example 103
1-((4-methoxybutyl)-N-[(3S,5R)-5-(3-methyl-1,2,4-oxadiazol-5-
yl)piperidin-3-yl]-N-(2-methylpropyl)-1H-benzimidazole-2-
carboxamide dihydrochloride

[1155]

10

[1156]
(3R,5S)-1-(tert-Butoxycarbonyl)-5-[[1-((4-methoxybutyl)-
1H-benzimidazol-2-yl)carbonyl](2-
methylpropyl)amino]piperidine-3-carboxylic acid (265 mg), N-
hydroxy acetamidine (56 mg), 1H-benzotriazol-1-ol (95 mg) and
N,N-diisopropylethylamine (259 µl) were dissolved in DMF (10
ml), WSC·HCl (144 mg) was added and the mixture was stirred at
room temperature for 15 hr. The reaction mixture was
20 concentrated under reduced pressure, and the mixture was
extracted with ethyl acetate. The extract was washed with
saturated brine, and dried over anhydrous magnesium sulfate.
The solvent was evaporated under reduced pressure. The residue
was dissolved in toluene (15 ml), and the mixture was refluxed
under heating for 15 hr. The reaction mixture was cooled to
room temperature, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (1:1) was concentrated under reduced pressure to give tert-butyl (3S,5R)-3-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-(3-methyl-1,2,4-oxadiazol-5-yl)piperidine-1-carboxylate (324 mg). The obtained tert-butyl (3S,5R)-3-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-(3-methyl-1,2,4-oxadiazol-5-yl)piperidine-1-carboxylate was dissolved in 4M hydrogen chloride-ethyl acetate (5 ml), and the mixture was stirred at room temperature for 3 hr. The reaction mixture was concentrated, and the residue was diluted with aqueous sodium bicarbonate, and extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to basic silica gel column chromatography, and a fraction eluted with ethyl acetate was concentrated under reduced pressure. The residue was dissolved in methanol (3 ml), 4M Hydrogen chloride-ethyl acetate (1 ml) was added and the mixture was stirred for 5 min. The solvent was evaporated under reduced pressure to give the object product (74 mg).

MS (ESI+, m/e) 469 (M+1)

[1157]

In the same manner as in Example 12, the following compound (Example 104) was obtained.

[1158]

Example 104

N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-yl)carbonyl)piperidin-3-yl]1H-benzimidazole-2-carboxamide dihydrochloride

[1159]
[1160]
MS (ESI+, m/e) 414 (M+1)

Reference Example 189
tert-butyl (3S,5R)-3-[(1-methyl-1H-benzimidazol-2-yl)carbonyl](2-methylpropyl)amino)-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[1161]

[1162]
tert-Butyl (3S,5R)-3-[(1H-benzimidazol-2-ylcarbonyl)(2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (205 mg) was dissolved in dimethylformamide (5 ml), methyl iodide (75 µl) and cesium carbonate (391 mg) were added and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated under reduced pressure, diluted with aqueous sodium bicarbonate, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to silica gel chromatography, and a fraction eluted with ethyl acetate-hexane (6:4) was concentrated under reduced pressure to give the object product (184 mg).
MS (ESI+, m/e) 528 (M+1)

[1163]

In the same manner as in Example 12, the following compound (Example 105) was obtained.

5 [1164]

Example 105

1-methyl-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide dihydrochloride

[1165]

[1166]

MS (ESI+, m/e) 428 (M+1)

Reference Example 190

15 tert-butyl (3S,5R)-3-[[1-2-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]-1H-benzimidazol-2-yl]carbonyl)(2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[1167]

20

[1168]

To a solution of tert-butyl (3S,5R)-3-[[1-(3-ethoxy-3-oxopropyl)-1H-benzimidazol-2-yl]carbonyl)(2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (260 mg) in ethanol (5 ml) was added 2M aqueous
sodium hydroxide solution (1.06 ml), and the mixture was stirred at room temperature for 3 days. The reaction mixture was adjusted to pH 7 with 1M hydrochloric acid, and extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue, N-hydroxy acetamidine (47 mg), 1H-benzotriazol-1-ol (79 mg) and N,N-diisopropylethylamine (217 µl) were dissolved in DMF (5 ml), WSC•HCl (121 mg) was added and the mixture was stirred at 60°C for 2 hr. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with aqueous sodium bicarbonate and extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in toluene (15 ml), and the mixture was refluxed under heating for 15 hr. The reaction mixture was cooled to room temperature, and concentrated under reduced pressure. The residue was subjected to basic silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (7:3) was concentrated under reduced pressure to give the object product (191 mg).

MS (ESI+, m/e) 624 (M+1)

[1169]

In the same manner as in Example 12, the following compound (Example 106) was obtained.

[1170]

Example 106

1-[[2-[(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-y1carbony1)piperidin-3-yl]-1H-benzimidazole-2-carboxamide dihydrochloride

[1171]
[1172]
MS (ESI+, m/e) 524 (M+1)
In the same manner as in Reference Example 69, the following compound (Reference Example 191) was obtained.
Reference Example 191
1-tert-butyl 3-methyl (3R,5S)-5-[[1-(2,2-difluoroethyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino)piperidine-1,3-dicarboxylate

[1173]

[1174]
MS (ESI+, m/e) 523 (M+1)
In the same manner as in Reference Example 172, the following compound (Reference Example 192) was obtained.

[1175]
Reference Example 192
(3R,5S)-1-((tert-butoxycarbonyl)-5-[[1-(2,2-difluoroethyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino)piperidine-3-carboxylic acid

[1176]
In the same manner as in Reference Example 39, the following compounds (Reference Examples 193-194) were obtained.

**[1178]**
Reference Example 193

tert-butyl (3S,5R)-3-[[1-(2,2-difluoroethyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-((morpholin-4-y1)carbonyl)piperidine-1-carboxylate

**[1179]**

**[1180]**

Reference Example 194

tert-butyl (3S,5R)-3-[[1-(2,2-difluoroethyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-((piperidin-1-y1)carbonyl)piperidine-1-carboxylate

**[1181]**
[1182]
MS (ESI+, m/e) 576 (M+1)

In the same manner as in Example 12, the following compounds (Examples 107-108) were obtained.

[1183]
Example 107
1-(2,2-difluoroethyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide dihydrochloride

[1184]

[1185]
MS (ESI+, m/e) 478 (M+1)

Example 108
1-(2,2-difluoroethyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(piperidin-1-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide dihydrochloride

[1186]

[1187]
MS (ESI+, m/e) 476 (M+1)

In the same manner as in Reference Example 60, the following compound (Reference Example 195) was obtained.

[1188]
Reference Example 195
text-butyl (3S,5R)-3-{{[1-(2,2-difluoroethyl)-1H-benzimidazol-2-yl]carbonyl}(2-methylpropyl)amino]-5-(hydroxymethyl)piperidine-1-carboxylate

[1189]

MS (ESI+, m/e) 495 (M+1)

In the same manner as in Example 24, the following compound (Example 109) was obtained.

[1191]
Example 109
1-(2,2-difluoroethyl)-N-[(3S,5R)-5-(hydroxymethyl)piperidin-3-yl]-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide dihydrochloride

[1192]

MS (ESI+, m/e) 395 (M+1)

In the same manner as in Reference Example 69, the following compounds (Reference Examples 196-197) were obtained.

[1194]
Reference Example 196
1-tert-butyl 3-methyl (3R,5S)-5-\{[1-(1-methylethyl)-1H-benzimidazol-2-yl]carbonyl\}(2-methylpropyl)amino)piperidine-1,3-dicarboxylate

[1195]

MS (ESI+, m/e) 501 (M+1)

Reference Example 197

1-tert-butyl 3-methyl (3R,5S)-5-\{(2-methylpropyl)[(1-propyl-1H-benzimidazol-2-yl)carbonyl]amino\}piperidine-1,3-dicarboxylate

[1197]

MS (ESI+, m/e) 501 (M+1)

In the same manner as in Reference Example 189, the following compound (Reference Example 198) was obtained.

Reference Example 198

1-tert-butyl 3-methyl (3R,5S)-5-\{(2-methylpropyl)[(1-(2,2,2-trifluoroethyl)-1H-benzimidazol-2-yl)carbonyl]amino\}piperidine-1,3-dicarboxylate
[1200]

[1201]
MS (ESI+, m/e) 541 (M+1)

In the same manner as in Reference Example 172, the following compounds (Reference Examples 199-201) were obtained.

[1202]
Reference Example 199

(3R,5S)-1-(tert-butoxycarbonyl)-5-[[(1-(1-methylethyl)-1H-benzimidazol-2-yl)carbonyl](2-methylpropyl)amino]piperidine-3-carboxylic acid

[1203]

[1204]
MS (ESI+, m/e) 487 (M+1)

Reference Example 200

(3R,5S)-1-(tert-butoxycarbonyl)-5-{(2-methylpropyl)[(1-propyl-1H-benzimidazol-2-yl)carbonyl]amino}piperidine-3-carboxylic acid

[1205]
[1206]
MS (ESI+, m/e) 487 (M+1)
Reference Example 201
5 (3R,5S)-1-(tert-butoxycarbonyl)-5-[(2-methylpropyl){[1-(2,2,2-
trifluoroethyl)-1H-benzimidazol-2-
yl]carbonyl}amino]piperidine-3-carboxylic acid

[1207]

[1208]
MS (ESI+, m/e) 527 (M+1)

In the same manner as in Reference Example 39, the
following compounds (Reference Examples 202-204) were obtained.

[1209]
Reference Example 202
tert-butyl (3S,5R)-3-[[1-(1-methylethyl)-1H-benzimidazol-2-
yl]carbonyl](2-methylpropyl)amino]-5-(morpholin-4-
ylcarbonyl)piperidine-1-carboxylate

[1210]
[1211]
MS (ESI+, m/e) 556 (M+1)
Reference Example 203
tert-butyl (3S,5R)-3-{(2-methylpropyl) [(1-propyl-1H-
benzimidazol-2-yl)carbonyl] amino} -5 -(morpholin-4-
ylcarbonyl)piperidine-1-carboxylate

[1212]

[1213]
MS (ESI+, m/e) 556 (M+1)
Reference Example 204
tert-butyl (3S,5R)-3-[(2-methylpropyl) {[1-(2,2,2-
trifluoroethyl)-1H-benzimidazol-2-yl] carbonyl} amino] -5-
(morpholin-4-yl carbonyl)piperidine-1-carboxylate

[1214]

[1215]
MS (ESI+, m/e) 596 (M+1)

In the same manner as in Example 12, the following
compounds (Examples 110-112) were obtained.

[1216]
Example 110
1-(1-methylethyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-
(morpholin-
4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide dihydrochloride

[1217]

5 [1218]
MS (ESI+, m/e) 456 (M+1)
Example 111
N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1-propyl-1H-benzimidazole-2-carboxamide dihydrochloride

[1219]

15 Example 112
N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1-(2,2,2-trifluoroethyl)-1H-benzimidazole-2-carboxamide dihydrochloride

[1220]

[1221]
MS (ESI+, m/e) 496 (M+1)

In the same manner as in Reference Example 60, the following compounds (Reference Examples 205-206) were obtained.

Reference Example 205
tert-butyl (3R,5S)-3-(hydroxymethyl)-5-[(2-methylpropyl)[(1-propyl-1H-benzimidazol-2-yl)carbonyl]amino]piperidine-1-carboxylate

MS (ESI+, m/e) 473 (M+1)

Reference Example 206
tert-butyl (3R,5S)-3-(hydroxymethyl)-5-[(2-methylpropyl)\{(1-(2,2,2-trifluoroethyl)-1H-benzimidazol-2-yl)carbonyl\}amino]piperidine-1-carboxylate

MS (ESI+, m/e) 513 (M+1)

In the same manner as in Example 24, the following compounds (Examples 113-114) were obtained.
Example 113
N-[(3S,5R)-5-(hydroxymethyl)piperidin-3-yl]-N-(2-methylpropyl)-1-propyl-1H-benzimidazole-2-carboxamide dihydrochloride

MS (ESI+, m/e) 373 (M+1)

Example 114
N-[(3S,5R)-5-(hydroxymethyl)piperidin-3-yl]-N-(2-methylpropyl)-1-(2,2,2-trifluoroethyl)-1H-benzimidazole-2-carboxamide dihydrochloride

MS (ESI+, m/e) 413 (M+1)

In the same manner as in Reference Example 35, the following compound (Reference Example 207) was obtained.

Reference Example 207
1-cyclopropyl-2-(trichloromethyl)-1H-benzimidazole
[1235]
H-NMR (CDCl₃) δ 1.33-1.42 (2H, m), 1.44-1.54 (2H, m), 3.51-3.61 (1H, m), 7.29-7.43 (2H, m), 7.62-7.68 (1H, m), 7.83-7.90 (1H, m).

In the same manner as in Reference Example 37, the following compound (Reference Example 208) was obtained.

[1236]
Reference Example 208
1-tert-butyl 3-methyl (3R,5S)-5-[(1-cyclopropyl-1H-benzimidazol-2-yl)carbonyl](2-methylpropyl)amino)piperidine-1,3-dicarboxylate

[1237]

[1238]
MS (ESI+, m/e) 499 (M+1)

In the same manner as in Reference Example 172, the following compound (Reference Example 209) was obtained.

[1239]
Reference Example 209
(3R,5S)-1-(tert-butoxycarbonyl)-5-[(1-cyclopropyl-1H-benzimidazol-2-yl)carbonyl](2-methylpropyl)amino)piperidine-3-carboxylic acid

[1240]
[1241]
MS (ESI+, m/e) 485 (M+1)

In the same manner as in Reference Example 39, the following compound (Reference Example 210) was obtained.

[1242]
Reference Example 210
tert-butyl (3S,5R)-3-[(1-cyclopropyl-1H-benzimidazol-2-yl)carbonyl]-(2-methylpropyl)amino)-5-(morpholin-4-yl)carbonyl)piperidine-1-carboxylate

[1243]

[1244]
MS (ESI+, m/e) 554 (M+1)

In the same manner as in Example 12, the following compound (Example 115) was obtained.

[1245]
Example 115
1-cyclopropyl-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-yl)carbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide dihydrochloride

[1246]
[1247]

MS (ESI+, m/e) 454 (M+1)

Reference Example 211

5 ethyl 3-(2-phenylethyl)imidazo[1,2-a]pyridine-2-carboxylate

[1248]

To a solution of ethyl 3-bromo-2-oxo-5-phenylpentanoate (1.9 g) in THF (10 ml) was added 2-aminopyridine (600 mg) at room temperature, and the reaction mixture was heated under reflux for 15 hr. The precipitated crystals were collected by filtration, washed with THF to give 2-amino-1-[3-ethoxy-2,3-dioxo-1-(2-phenylethyl)propyl]pyridinium bromide (1.36 g). 2-Amino-1-[3-ethoxy-2,3-dioxo-1-(2-phenylethyl)propyl]pyridinium bromide (1.36 g) was dissolved in ethanol (10 ml), and the mixture was refluxed under heating for 3 hr. The reaction mixture was concentrated, and dissolved in dichloromethane.

The solution was washed successively with aqueous sodium bicarbonate and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was recrystallized from ethyl acetate-diethyl ether to give the object product (950 mg).

$^1$H-NMR (CDCl$_3$) $\delta$ 1.47 (3H, t), 3.00 (2H, t), 3.57 (2H, t), 4.47 (2H, q), 6.73 (1H, t), 7.12-7.13 (2H, m), 7.16-7.27 (4H, m), 7.65-7.67 (2H, m).
Reference Example 212

ethyl 3-(hydroxymethyl)imidazo[1,2-a]pyridine-2-carboxylate

To a solution of ethyl imidazo[1,2-a]pyridine-2-carboxylate (5.0 g) in acetic acid (30 ml) were added 37% formaldehyde (14 ml) and sodium acetate (8.0 g) at room temperature, and the reaction mixture was heated under reflux for 15 hr. The reaction mixture was cooled to room temperature and dissolved in dichloromethane. The mixture was adjusted to pH 8 with 10% aqueous sodium hydroxide solution at 0°C. The organic layer was separated, washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with dichloromethane-methanol (15:1) was concentrated under reduced pressure to give the object product (2.1 g).

\[^{1}H-NMR\ (CDCl\_3)\ \delta\ 1.43\ (3H, t),\ 4.42\ (2H, t),\ 5.30\ (2H, s),\ 7.06\ (1H, t),\ 7.45\ (1H, t),\ 7.60\ (1H, d),\ 8.50\ (1H, d).\]

Reference Example 213

ethyl 3-(chloromethyl)imidazo[1,2-a]pyridine-2-carboxylate hydrochloride
To a solution of ethyl 3-(hydroxymethyl)imidazo[1,2-a]pyridine-2-carboxylate (2.85 g) in chloroform (40 ml) was added thionyl chloride (8.0 ml) at room temperature, and the mixture was heated under reflux for 12 hr. The reaction solution was cooled to room temperature, and concentrated under reduced pressure. The precipitated crystals were collected by filtration, washed with diethyl ether to give the object product (3.50 g).

\(^1\)H-NMR (CDCl\(_3\)) \(\delta\) 1.37 (3H, t), 4.40 (2H, t), 5.57 (2H, s), 7.34 (1H, t), 7.67 (1H, t), 7.82 (1H, m), 8.71 (1H, d).

Reference Example 214

ethyl 3-(phenoxy)methyl]imidazo[1,2-a]pyridine-2-carboxylate

A solution of a mixture of phenol (2.20 g) and sodium hydride (95 wt%, 500 mg) in DMF (40 ml) was added dropwise to a solution of ethyl 3-(chloromethyl)imidazo[1,2-a]pyridine-2-carboxylate hydrochloride (3.5 g) in DMF (50 ml) at 0°C. Triethylamine (2.7 ml) was added at the same temperature over 30 min. The reaction mixture was stirred at 50°C for 3 hr, and the reaction mixture was diluted with water and extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (6:1) was concentrated under reduced pressure to give the object product (1.5 g).

\(^1\)H-NMR (CDCl\(_3\)) \(\delta\) 1.31 (3H, t), 4.34 (2H, t), 5.80 (2H, s), 6.97
(1H, t), 7.06-7.08 (2H, m), 7.12 (1H, t), 7.29-7.33 (2H, m), 7.44-7.48 (1H, m), 7.70 (1H, d), 8.54 (1H, d).

[1259]
Reference Example 215

ethyl 3-[(1E)-4-methoxybut-1-en-1-yl]imidazo[1,2-a]pyridine-2-carboxylate

[1260]

\[
\text{Me}
\]

CO\text{Et}  

[1261]

To a suspension of (3-methoxypropyl)(triphenyl)phosphonium bromide (3.56 g) in THF (50 ml) was added potassium tert-butoxide (0.38 g) at -78°C, and the mixture was stirred at the same temperature for 30 min. Ethyl 3-formylimidazo[1,2-a]pyridine-2-carboxylate (1.7 g) was added to the reaction mixture, and the mixture was stirred at room temperature for 12 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate was concentrated under reduced pressure to give the object product (256 mg).

MS (ESI+, m/e) 275 (M+1)

[1262]
Reference Example 216

ethyl 3-(4-methoxybutyl)imidazo[1,2-a]pyridine-2-carboxylate

[1263]
Ethyl 3-[(1E)-4-methoxybut-1-en-1-yl]imidazo[1,2-a]pyridine-2-carboxylate (530 mg) and diphenyl sulfide (3.6 mg) were dissolved in ethyl acetate (13 ml), 10% palladium carbon (50% in water) (53 mg) was added and the mixture was stirred in a hydrogen stream at ambient temperature and normal pressure for 2.5 hr. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate was concentrated under reduced pressure to give the object product (260 mg).

$^1$H-NMR (CDCl$_3$) $\delta$ 1.46 (3H, t), 1.67-1.78 (4H, m), 3.32-3.34 (2H, m), 3.33 (3H, s), 3.42 (2H, t), 4.46 (2H, q), 6.88 (1H, t), 7.22 (1H, dd), 7.67 (1H, d), 7.99 (1H, d).

Reference Example 217

ethyl 3-(4-methoxybutyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylate

Ethyl 3-[(1E)-4-methoxybut-1-en-1-yl]imidazo[1,2-a]pyridine-2-carboxylate (1.40 g) was dissolved in ethyl acetate (30 ml), 10% palladium carbon (50% in water) (510 mg) was added and the mixture was stirred in a hydrogen stream at ambient temperature and normal pressure for 12 hr. The
catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-methanol (5:1) was concentrated under reduced pressure to give the object product (1.14 g).

$^1$H-NMR (CDCl$_3$) δ 1.39 (3H, t), 1.62-1.67 (4H, m), 1.89-1.92 (2H, m), 1.99-2.01 (2H, m), 2.89 (2H, t), 2.92-2.96 (2H, m), 3.32 (3H, s), 3.38-3.41 (2H, m), 3.82-3.85 (2H, m), 4.35 (2H, q).

[1268]

Reference Example 218

tert-butyl (3S,5R)-3-[(2-methylpropyl){[3-(2-phenylethyl)imidazo[1,2-a]pyridin-2-yl]carbonyl}amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[1269]

[1270]

Ethyl 3-(2-phenylethyl)imidazo[1,2-a]pyridine-2-carboxylate (883 mg) was dissolved in ethanol (50 ml), 2N aqueous sodium hydroxide solution (3 ml) was added, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was concentrated under reduced pressure, neutralized with 1N hydrochloric acid, subjected to DIAION HP-20 (manufactured by Mitsubishi Chemical), and washed with water. The fraction eluted with acetone was concentrated under reduced pressure to give 3-(2-phenylethyl)imidazo[1,2-a]pyridine-2-carboxylic acid (1.03 g). The obtained 3-(2-phenylethyl)imidazo[1,2-a]pyridine-2-carboxylic acid (341 mg), tert-butyl (3S,5R)-3-[(2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (370 mg) and N,N-
diisopropylethylamine (862 µl) were dissolved in acetonitrile (20 ml), chloro-N,N,N',N'-tetramethylformamidinium hexafluorophosphate (561 mg) was added and the mixture was stirred at room temperature for 15 hr. The reaction mixture was concentrated, and the residue was diluted with aqueous sodium bicarbonate. The mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to basic silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (9:1) was concentrated under reduced pressure to give the object product (522 mg).

MS (ESI+, m/e) 618 (M+1)

[1271]

Reference Example 219
tert-butyl (3S,5R)-3-[(2-methylpropyl)({[3-(phenoxy)methyl]imidazo[1,2-a]pyridin-2-yl]carbonyl}amino)-5-(morpholin-4-yl)carbonyl]piperidine-1-carboxylate

[1272]

[1273]

Ethyl 3-(phenoxy)methyl]imidazo[1,2-a]pyridine-2-carboxylate (889 mg) was dissolved in ethanol (50 ml), 2N aqueous sodium hydroxide solution (3 ml) was added, and the mixture was stirred at room temperature for 15 hr. The precipitated crystals were collected by filtration, and washed with ethanol to give sodium 3-(phenoxy)methyl]imidazo[1,2-a]pyridine-2-carboxylate (680 g). The obtained sodium 3-(phenoxy)methyl]imidazo[1,2-a]pyridine-2-carboxylate (290 mg),
tert-butyl (3S,5R)-3-[(2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (370 mg) and N,N-diisopropylethylamine (862 µl) were dissolved in acetonitrile (20 ml), chloro-N,N,N’,N’-tetramethylformamidinium hexafluorophosphate (561 mg) was added and the mixture was stirred at room temperature for 15 hr. The reaction mixture was concentrated, and the residue was diluted with aqueous sodium bicarbonate, and extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to basic silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (9:1) was concentrated under reduced pressure to give the object product (563 mg).

\(^1\)H-NMR (CDCl\(_3\)) \(\delta\) 0.65-1.06 (6H, m), 1.15-1.54 (9H, m), 1.72-2.53 (4H, m), 2.57-3.01 (2H, m), 3.16-5.00 (12H, m), 5.51-5.73 (2H, m), 6.86-7.07 (4H, m), 7.23-7.35 (4H, m), 7.45-7.66 (1H, m), 8.27 (1H, t).

MS (ESI+, m/e) 620 (M+1)

[1274]

In the same manner as in Example 12, the following compound (Example 116) was obtained.

[1275]

Example 116

N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-3-(2-phenylethyl)imidazo[1,2-al]pyridine-2-carboxamide dihydrochloride

[1276]

![Chemical Structure](image)

[1277]
MS (ESI+, m/e) 518 (M+1)

Example 117

N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-3-(phenoxymethyl)imidazo[1,2-5a]pyridine-2-carboxamide dihydrochloride

[1278]

[1279]

tert-Butyl (3S,5R)-3-[(2-methylpropyl){[3-(phenoxymethyl)imidazo[1,2-a]pyridin-2-yl]carbonyl}amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (290 mg) was dissolved in 4M hydrogen chloride-ethyl acetate (5 ml), and the mixture was stirred at room temperature for 3 hr. The reaction mixture was concentrated to give the object product (278 mg).

1H-NMR (DMSO-d6) δ 0.63-0.97 (6H, m), 1.74-2.45 (3H, m), 2.81-4.66 (17H, m), 5.51-5.61 (2H, m), 6.95-7.11 (3H, m), 7.19-7.38 (3H, m), 7.56-7.81 (2H, m), 8.57-8.69 (1H, m), 9.07-9.69 (2H, m).

MS (ESI+, m/e) 520 (M+1)

[1280]

Reference Example 220
tert-butyl (3S,5R)-3-[[3-(4-methoxybutyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-2-yl]carbonyl]{(2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[1281]
[1282]

Ethyl 3-(4-methoxybutyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylate (56 mg) was dissolved in ethanol (5 ml), lithium hydroxide monohydrate (42 mg) was added and the mixture was stirred at 50°C for 6 hr. 8N Aqueous sodium hydroxide solution (0.1 ml) was added to the reaction mixture, and the mixture was stirred at 60°C for 15 hr, and concentrated under reduced pressure. The residue was dissolved in acetonitrile (5 ml), tert-butyl (3S,5R)-3-[(2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (74 mg), N,N-diisopropylethylamine (172 μl) and chloro-N,N,N',N'-tetramethylformamidinium hexafluorophosphate (112 mg) were added and the mixture was stirred at room temperature for 5 hr. The reaction mixture was concentrated, and the residue was diluted with aqueous sodium bicarbonate, and extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to basic silica gel column chromatography, and a fraction eluted with ethyl acetate was concentrated under reduced pressure to give the object product (26 mg).

MS (ESI+, m/e) 604 (M+1)

[1283]

In the same manner as in Example 12, the following compound (Example 118) was obtained.

[1284]

Example 118

3-(4-methoxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-5,6,7,8-tetrahydroimidazo[1,2-
a) pyridine-2-carboxamide dihydrochloride

[1285]

[1286]
MS (ESI+, m/e) 504 (M+1)
Reference Example 221
1-tert-butyl 3-methyl (3R,5S)-5-[[3-(4-
methoxybutyl)imidazo[1,2-a]pyridin-2-yl]carbonyl](2-
methylpropyl)amino]piperidine-1,3-dicarboxylate

[1287]

[1288]
Ethyl 3-(4-methoxybutyl)imidazo[1,2-a]pyridine-2-
carboxylate (183 mg) was dissolved in ethanol (5 ml), lithium
hydroxide monohydrate (139 mg) was added and the mixture was
stirred at 60°C for 15 hr. The reaction mixture was
concentrated under reduced pressure, and the residue was
dissolved in acetonitrile (5 ml). 1-tert-Butyl 3-methyl
(3R,5S)-5-[[2-methylpropyl]amino]piperidine-1,3-dicarboxylate
(208 mg), N,N-diisopropylethylamine (570 μl) and chloro-
N,N,N',N'-tetramethylformamidinium hexafluorophosphate (370
mg) were added and the mixture was stirred at room temperature
for 15 hr. The reaction mixture was concentrated, and the
residue was diluted with aqueous sodium bicarbonate, and extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to basic silica gel column chromatography, and a fraction eluted with ethyl acetate was concentrated under reduced pressure to give the object product (224 mg).

MS (ESI+, m/e) 545 (M+1)

[1289]

In the same manner as in Reference Example 172, the following compound (Reference Example 222) was obtained.

[1290]

Reference Example 222
(3R,5S)-1-(tert-butoxycarbonyl)-5-[[3-(4-methoxybutyl)imidazo[1,2-a]pyridin-2-yl]carbonyl](2-methylpropyl)amino]piperidine-3-carboxylic acid

[1291]

[1292]

MS (ESI+, m/e) 531 (M+1)

In the same manner as in Reference Example 39, the following compounds (Reference Examples 223-224) were obtained.

[1293]

Reference Example 223
tert-butyl (3S,5R)-3-[[3-(4-methoxybutyl)imidazo[1,2-a]pyridin-2-yl]carbonyl](2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[1294]
[1295]
MS (ESI+, m/e) 600 (M+1)

Reference Example 224
tert-butyl (3S,5R)-3-[[3-(4-methoxybutyl)imidazo[1,2-a]pyridin-2-yl]carbonyl](2-methylpropyl)amino]-5-(pyrrolidin-1-ylcarbonyl)piperidine-1-carboxylate

[1296]

[1297]
MS (ESI+, m/e) 584 (M+1)

In the same manner as in Example 12, the following compounds (Examples 119-120) were obtained.

[1298]
Example 119
3-(4-methoxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]imidazo[1,2-a]pyridine-2-carboxamide dihydrochloride

[1299]
Example 120

3-(4-methoxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(pyrrolidin-1-ylcarbonyl)piperidin-3-yl]imidazo[1,2-a]pyridine-2-carboxamide dihydrochloride

Example 121

N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]quinoline-2-carboxamide 2 TFA salt
A 0.08M solution (1000 µL, 80 µmol) of tert-butyl (3S,5R)-3-[(2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate in DMF and quinoline-2-carboxylic acid (15.2 mg, 88 µmol) were mixed, a 0.32M solution (500 µL, 160 µmol) of chloro-N,N,N',N'-tetramethylformamidinium hexafluorophosphate and N,N-diisopropylethylamine in DMF was added at room temperature and the mixture was stirred for 16 hr. After completion of the reaction, 2% aqueous sodium hydrogen carbonate solution (1.0 ml) was added, and extracted with ethyl acetate (3.5 ml). The organic layer was separated by upper layer Phase Septube (manufactured by Wako Pure Chemical Industries, Ltd.). The solvent was evaporated under reduced pressure, and the residue was dissolved in DMSO-methanol (1:1) (1 ml), purified by preparative HPLC, and the object fraction was concentrated to give a protected title compound. 1M MSA acetonitrile solution (3 ml) was added to the obtained protected compound, and the mixture was stirred at room temperature for 16 hr. After completion of the reaction, 1M DIEA acetonitrile solution (3.5 ml) was added, and the reaction mixture was directly developed by preparative HPLC to give the object product (12.3 mg).

MS (ESI+): 425 (M+H)

In the same manner as in Example 121, the following compounds (Examples 122-124) were obtained.

Example 122

N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl] isoquinoline-3-carboxamide 2TFA salt

377
[1308]
MS(ESI+): 425 (M+H)

Example 123
5-fluoro-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide TFA salt

[1309]

[1310]
MS(ESI+): 432 (M+H)

Example 124
5-chloro-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide TFA salt

[1311]
[1312]
MS(ESI+): 448 (M+H)

[1313]
Example 125
N-{(3S,5R)-5-[(1R)-1-hydroxy-2-methoxyethyl]piperidin-3-yl}-1-(4-methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide dihydrochloride (Example 125-1)
and

N-{(3S,5R)-5-[(1S)-1-hydroxy-2-methoxyethyl]piperidin-3-yl}-1-(4-methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide dihydrochloride (Example 125-2)

[1314]

[1315]
tert-Butyl (3R,5S)-3-(1-hydroxy-2-methoxyethyl)-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino]piperidine-1-carboxylate (7.3 g) and vinyl acetate (146 ml) were dissolved in isopropanol (292 ml), lipase (Toyobo, LIP-301, 20 g) was added at room temperature, and the mixture was stirred at room temperature for 24 hr. The completion of the reaction was confirmed by HPLC, and the reaction mixture was filtered. The filtrate was concentrated
under reduced pressure, and the residue was subjected to
silica gel column chromatography, and a fraction eluted with
ethyl acetate-hexane (1:9 - 1:0) was concentrated under
reduced pressure to give a first elution component (3.76 g)
and a second elution component (3.15 g). It was confirmed that
the first elution component was a compound of Example 73-1
wherein the hydroxyl group was acetylated, and the second
elution component (99.9%de) was the same as the compound of
Example 73-2.

The obtained first elution component (100 mg) was
dissolved in methanol (1 ml), 1M aqueous sodium hydroxide
solution (1 ml) was added and the mixture was stirred at room
temperature for 1 hr. 1M Hydrochloric acid (1 ml) was added to
the reaction mixture for neutralization and methanol was
evaporated under reduced pressure. The concentrate was diluted
with water, and the mixture was extracted with ethyl acetate.
The extract was washed with saturated brine, dried over
anhydrous sodium sulfate, and concentrated under reduced
pressure. The residue was dissolved in ethanol (1 ml), 12M
hydrochloric acid (0.50 ml) was added and the mixture was
stirred at room temperature for 1 hr. The reaction mixture was
concentrated under reduced pressure, the residue was dissolved
in ethanol, and ethanol was evaporated under reduced pressure.
This operation was repeated twice to give the object product

[1316]

Example 125-1 spectrum data

\(^1\text{H}-\text{NMR (CDCl}_3\) \(\delta 0.71 \ (2 \ H, \ dd), 0.95 \ (4 \ H, \ dd), 1.38 - 1.63 \ (2 \\
H, \ m), 1.66 - 1.86 \ (3 \ H, \ m), 1.86 - 2.04 \ (1 \ H, \ m), 2.12 \ (2 \ H, \\
dd), 2.59 - 2.91 \ (1 \ H, \ m), 3.02 \ (1 \ H, \ d), 3.09 - 3.22 \ (4 \ H, \ m), \\
3.24 - 3.39 \ (9 \ H, \ m), 3.50 \ (2 \ H, \ br \ s), 3.62 \ (1 \ H, \ br \ s), 4.15 \\
(2 \ H, \ br \ s), 4.21 - 4.39 \ (2 \ H, \ m), 7.15 - 7.53 \ (2 \ H, \ m), 7.55 \\
- 7.87 \ (2 \ H, \ m), 8.33 - 9.18 \ (1 \ H, \ m), 9.43 \ (1 \ H, \ br \ s)

MS (ESI+, m/e) 461 (M+1)

[1317]
The obtained second elution component (447 mg) was dissolved in ethanol (1 ml), 12M hydrochloric acid (0.70 ml) was added and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in ethanol, and ethanol was evaporated under reduced pressure. This operation was repeated twice to give the object product (365 mg) of Example compound 125-2.

[1318]

Example 125-2 spectrum data

$^1$H-NMR (CDCl$_3$) δ 0.71 (2 H, dd), 0.81 - 1.12 (4 H, m), 1.31 - 1.61 (2 H, m), 1.62 - 1.98 (5 H, m), 1.98 - 2.23 (2 H, m), 2.57 - 2.87 (1 H, m), 3.14 (1 H, d), 3.18 - 3.23 (3 H, m), 3.23 - 3.39 (10 H, m), 3.39 - 3.63 (3 H, m), 4.23 - 4.38 (3 H, m), 7.16 - 7.51 (2 H, m), 7.55 - 7.86 (2 H, m), 8.29 - 9.11 (1 H, m), 9.38 (1 H, br s)

MS (ESI+, m/e) 461 (M+1)

[1319]

Example 126

N-{(3S,5R)-5-[{(1S)-1-hydroxyethyl)piperdin-3-yl]}-1-(4-methoxybutyl)-N-{(2-methylpropyl)-1H-benzimidazole-2-carboxamide dihydrochloride (Example 126-1)

and

N-{(3S,5R)-5-[{(1R)-1-hydroxyethyl)piperdin-3-yl]}-1-(4-methoxybutyl)-N-{(2-methylpropyl)-1H-benzimidazole-2-carboxamide dihydrochloride (Example 126-2)

[1320]

[1321]
tert-Butyl (3R,5S)-3-(1-hydroxyethyl)-5-[[1-((4-methoxybutyl)-1H-benzimidazol-2-yl)carbonyl] (2-methylpropyl)aminopiperidine-1-carboxylate (39.95 g) and vinyl acetate (789 ml) were dissolved in isopropanol (1.6 l), lipase (Toyobo, LIP-301, 120 g) was added at room temperature, and the mixture was stirred at room temperature for 15 hr. The completion of the reaction was confirmed by HPLC, and the reaction mixture was filtered. The filtrate was concentrated under reduced pressure, and the residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (1:9 - 1:0) was concentrated under reduced pressure to give a first elution component (23.3 g) and a second elution component (18.3 g). It was confirmed that the first elution component was a compound of Example 74-1 wherein the hydroxyl group was acetylated, and the second elution component (99.8%de) was the same as the compound of Example 74-2.

The obtained first elution component (100 mg) was dissolved in methanol (1 ml), 1M aqueous sodium hydroxide solution (1 ml) was added and the mixture was stirred at room temperature for 1 hr. 1M Hydrochloric acid (1 ml) was added to the reaction mixture for neutralization and methanol was evaporated under reduced pressure. The concentrate was diluted with water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was dissolved in ethanol (1 ml), 12M hydrochloric acid (0.50 ml) was added and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in ethanol, and ethanol was evaporated under reduced pressure. This operation was repeated twice to give the object product (75 mg) of Example compound 126-1.

[1322]

Example 126-1 spectrum data
The obtained second elution component (1.0 g) was dissolved in 10% hydrogen chloride containing methanol solution (40 ml), and the mixture was stirred at room temperature for 15 hr. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in ethanol, and ethanol was evaporated under reduced pressure. This operation was repeated twice to give the object product (0.86 g) of Example compound 126-2.

Example 126-2 spectrum data

\[ ^1H\text{-NMR (CDCl}_3\text{)} \delta 0.71 (3 \text{ H, dd), 0.94 (3 \text{ H, d), 1.09 (3 \text{ H, dd), 1.27 - 1.64 (3 \text{ H, m), 1.70 (1 \text{ H, s), 1.74 - 2.00 (4 \text{ H, m), 2.00 - 2.29 (1 \text{ H, m), 2.54 - 2.76 (1 \text{ H, m), 3.11 (1 \text{ H, d), 3.20 (4 \text{ H, d), 3.24 - 3.62 (7 \text{ H, m), 4.32 (3 \text{ H, d), 7.16 - 7.54 (2 \text{ H, m), 7.72 (2 \text{ H, q), 8.27 - 9.22 (1 \text{ H, m), 9.36 - 9.56 (1 \text{ H, m)}}.} \\]

MS (ESI+, m/e) 431 (M+1)

Example 127

N-{(3S,5R)-5-\{(1S)-1-hydroxypropyl\}piperidin-3-yl}-1-(4-methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide dihydrochloride (Example 127-1)

and

N-{(3S,5R)-5-\{(1R)-1-hydroxypropyl\}piperidin-3-yl}-1-(4-methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide dihydrochloride (Example 127-2)
tert-Butyl (3R,5S)-3-(1-hydroxypropyl)-5-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl](2-methylpropyl)amino)piperidine-1-carboxylate (16.4 g) and vinyl acetate (328 ml) were dissolved in isopropanol (656 ml), lipase (Toyobo, LIP-301, 65.6 g) and molecular sieves 4A (65.6 g) were added at room temperature, and the mixture was stirred at room temperature for 77 hr. Lipase (Toyobo, LIP-301, 8.2 g) was added to the reaction mixture, and the mixture was stirred at room temperature for 118 hr. Lipase (Toyobo, LIP-301, 16.4 g) was again added to the reaction mixture, and the mixture was stirred at room temperature for 140 hr. Lipase (Toyobo, LIP-301, 16.4 g) was further added to the reaction mixture, and the mixture was stirred at room temperature for 333 hr. The completion of the reaction was confirmed by HPLC, and the reaction mixture was filtered. The filtrate was concentrated under reduced pressure, and the residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (1:9 - 3:2) was concentrated under reduced pressure to give a first elution component (9.5 g) and a second elution component (8.0 g). It was confirmed that the first elution component was a compound of Example 75-1 wherein the hydroxyl group was acetylated, and the second elution component (99.7% de) was the same as the compound of Example 75-2.

The obtained first elution component (100 mg) was dissolved in methanol (1 ml), 1M aqueous sodium hydroxide solution (1 ml) was added and the mixture was stirred at room temperature for 1 hr. 1M Hydrochloric acid (1 ml) was added to
the reaction mixture for neutralization and methanol was evaporated under reduced pressure. The concentrate was diluted with water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was dissolved in ethanol (1 ml), 12M hydrochloric acid (0.50 ml) was added and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in ethanol, and ethanol was evaporated under reduced pressure. This operation was repeated twice to give the object product (62 mg) of Example compound 127-1.

Example 127-1 spectrum data

$^1$H-NMR (CDCl$_3$) δ 0.71 (2 H, dd), 0.79 – 1.11 (7 H, m), 1.32 – 1.58 (4 H, m), 1.60 – 1.68 (1 H, m), 1.70 – 1.85 (3 H, m), 1.87 – 2.20 (2 H, m), 2.59 – 2.87 (1 H, m), 3.00 (1 H, d), 3.08 – 3.23 (4 H, m), 3.23 – 3.41 (6 H, m), 3.49 (1 H, d), 3.89 – 4.23 (2 H, m), 4.23 – 4.55 (2 H, m), 7.16 – 7.52 (2 H, m), 7.55 – 7.86 (2 H, m), 8.24 – 9.18 (1 H, m), 9.21 – 9.57 (1 H, m)

MS (ESI+, m/e) 445 (M+1)

The obtained second elution component (0.85 g) was dissolved in ethanol (2 ml), 12M hydrochloric acid (1.5 ml) was added, and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in ethanol, and ethanol was evaporated under reduced pressure. This operation was repeated twice to give the object product (0.64 g) of Example compound 127-2.

Example 127-2 spectrum data

$^1$H-NMR (CDCl$_3$) δ 0.71 (2 H, dd), 0.78 – 1.01 (7 H, m), 1.26 – 1.66 (4 H, m), 1.66 – 1.86 (4 H, m), 1.93 (1 H, d), 2.02 –
2.23 (1 H, m), 2.53 - 2.84 (1 H, m), 3.03 - 3.24 (5 H, m), 3.31 (5 H, q), 3.37 - 3.56 (2 H, m), 4.16 (2 H, br s), 4.22 - 4.44 (2 H, m), 7.16 - 7.54 (2 H, m), 7.54 - 7.87 (2 H, m), 8.16 - 9.27 (1 H, m), 9.36 - 9.84 (1 H, m)

MS (ESI+, m/e) 445 (M+1)

[1331]

In the same manner as in Reference Example 82, the following compound (Reference Example 225) was obtained.

[1332]

Reference Example 225

 tert-butyl (3S,5R)-3-[[1-(4-methoxybutyl)-1H-benzimidazol-2-yl]carbonyl]{2-methylpropyl}amino]-5-[(4-methoxypiperidin-1-yl)carbonyl]piperidine-1-carboxylate

[1333]

\[ \begin{align*}
\text{\includegraphics[width=100px]{formula.png}} \\
\end{align*} \]

[1334]

MS (ESI+, m/e) 628 (M+1)

In the same manner as in Example 25, the following compound (Example 128) was obtained.

[1335]

Example 128

1-(4-methoxybutyl)-N-[(3S,5R)-5-[(4-methoxypiperidin-1-yl)carbonyl]piperidin-3-yl]-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide dihydrochloride

[1336]
[1337]
MS (ESI+, m/e) 528 (M+1)

Example 129
1-(3-ethoxypropyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide trifluoroacetate

[1338]

[1339]
A 0.16M solution (500 µL, 80 µmol) of tert-butyl (3S,5R)-3-[(2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate in toluene, a 0.32M solution (500 µL, 160 µmol) of triphenylphosphine in toluene, and a 0.32M solution (500 µL, 160 µmol) of 3-ethoxypropan-1-ol in toluene were mixed, diisopropyl azodicarboxylate (30 µL, 160 µmol) was added at room temperature and the mixture was stirred for 16 hr. 4N Hydrochloric acid-ethyl acetate solution (2.0 ml) was added to the reaction mixture, and the mixture was further stirred at room temperature for 5 hr. 4N Aqueous sodium hydroxide solution (2.0 ml) was added, and the mixture was neutralized and extracted. The organic layer was separated by upper layer Phase Septube (manufactured by Wako Pure
Chemical Industries, Ltd.). The solvent was evaporated under reduced pressure, and the residue was dissolved in DMSO-methanol (1:1) (1 ml) and purified by preparative HPLC. The object fraction was concentrated, and the residue was diluted with aqueous calcium carbonate solution and extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give the title compound (38.4 mg).

MS (ESI+): 500 (M+H)

[1340]

In the same manner as in Example 129, the following compounds (Examples 130-146) were obtained.

[1341]

Example 130

1-(4-methoxybutyl)-N-(2-methylpropyl)-N-[((3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide trifluoroacetate

[1342]

MS (ESI+, m/e) 500 (M+H)

Example 131

1-(3-methoxypropyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide trifluoroacetate

[1344]
[1345]
MS (ESI+, m/e) 486 (M+1)
Example 132
N-(2-methylpropyl)-1-[3-(methylsulfanyl)propyl]-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide trifluoroacetate

[1346]

[1347]
MS (ESI+, m/e) 502 (M+1)
Example 133
N-(2-methylpropyl)-1-[2-(methylsulfanyl)ethyl]-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide trifluoroacetate

[1348]

[1349]
MS (ESI+, m/e) 488 (M+1)
Example 134
1-ethyl-N-(2-methylpropyl)-N-[(3R,5S)-5-(morpholin-4-
ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide
trifluoroacetate

[1350]

[1351]
MS (ESI+, m/e) 442 (M+1)

Example 135
1-(1-methylethyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-
4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide
trifluoroacetate

[1352]

[1353]
MS (ESI+, m/e) 456 (M+1)

Example 136
N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-
ylcarbonyl)piperidin-3-yl]-1-propyl-1H-benzimidazole-2-
carboxamide trifluoroacetate

[1354]
[1355]

MS (ESI+, m/e) 456 (M+1)

Example 137

1-butyl-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide trifluoroacetate

[1356]

[1357]

MS (ESI+, m/e) 470 (M+1)

Example 138

N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1-(pent-3-yn-1-yl)-1H-benzimidazole-2-carboxamide trifluoroacetate

[1358]
[1359]
MS (ESI+, m/e) 480 (M+1)
Example 139
1-[(2-methylcyclopropyl)methyl]-N-(2-methylpropyl)-N-[(3S,5R)-
5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-
carboxamide trifluoroacetate

[1360]

[1361]
MS (ESI+, m/e) 482 (M+1)
Example 140
1-(2,2-difluoroethyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-
(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-
carboxamide trifluoroacetate

[1362]

[1363]
MS (ESI+, m/e) 478 (M+1)
Example 141
N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-
ylcarbonyl)piperidin-3-yl]-1-(3,3,3-trifluoropropyl)-1H-
benzimidazole-2-carboxamide trifluoroacetate

[1364]
[1365]
MS (ESI+, m/e) 510 (M+1)

Example 142
N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1-(4,4,4-trifluorobutyl)-1H-benzimidazole-2-carboxamide trifluoroacetate

[1366]

[1367]
MS (ESI+, m/e) 524 (M+1)

Example 143
N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1-(4-oxopentyl)-1H-benzimidazole-2-carboxamide trifluoroacetate

[1368]
[1369]
MS (ESI+, m/e) 498 (M+1)
Example 144
N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylicarbonyl)piperidin-3-yl]-1-(2-(pyridin-2-yl)ethyl)-1H-benzimidazole-2-carboxamide ditrifluoroacetate

[1370]

[1371]
MS (ESI+, m/e) 519 (M+1)
Example 145
N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylicarbonyl)piperidin-3-yl]-1-(2-(pyridin-3-yl)ethyl)-1H-benzimidazole-2-carboxamide ditrifluoroacetate

[1372]

[1373]
MS (ESI+, m/e) 519 (M+1)
Example 146
N-(2-methylpropyl)-1-[2-(4-methyl-1,3-thiazol-5-yl)ethyl]-N-[(3S,5R)-5-(morpholin-4-ylicarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide trifluoroacetate

[1374]
MS (ESI+, m/e) 539 (M+1)
Reference Example 225

Ethyl 2-tert-butyl-6-oxo-1,6-dihydropyrimidine-5-carboxylate

To a solution of diethyl 2,2-dimethylpropanimidamide hydrochloride (1.36 g) and (ethoxymethylene)malonate (2.16 g) in ethanol (100 ml) was added 20% sodium ethoxide-ethanol solution (6.8 g) under ice-cooling, and the mixture was stirred at 80°C for 5 hr. The reaction mixture was concentrated under reduced pressure, 1M hydrochloric acid (10 ml) was added under ice-cooling, and the mixture was extracted with ethyl acetate. The extract was concentrated under reduced pressure, hexane was added to the residue, and the precipitate was collected by filtration to give the object product (1.65 g) as a powder.

MS (ESI+, m/e) 225 (M+1)

$^1$H-NMR (CDCl$_3$) $\delta$ 1.33-1.41 (3H, m), 1.43 (9H, s), 4.32-4.41 (2H, m), 8.72 (1H, s).

Reference Example 226

2-tert-butyl-6-oxo-1,6-dihydropyrimidine-5-carboxylic acid
Ethyl 2-tert-butyl-6-oxo-1,6-dihydropyrimidine-5-carboxylate (43.9 g) was dissolved in ethanol (200 ml), 2M aqueous sodium hydroxide solution (330 ml) was added and the mixture was stirred at room temperature for 40 hr. The reaction mixture was concentrated under reduced pressure, and aqueous layer of the mixture was adjusted to pH 8 with 6M hydrochloric acid. The mixture was concentrated under reduced pressure and azeotroped with 2-propanol. The residue was suspended in acetone, and insoluble powder was collected by filtration. The obtained powder was suspended in 1M hydrochloric acid and the mixture was adjusted to pH 3, and concentrated under reduced pressure. The residue was azeotroped with 2-propanol, and the insoluble material was suspended in acetone and filtered off. The filtrate was concentrated under reduced pressure to give the object product (32.8 g) as a powder.

$^1$H-NMR (DMSO-$d_6$) δ 1.45 (9H, s), 8.99 (1H, s), 10.59 (1H, br s), 12.47 (1H, br s).

Reference Example 227

1-tert-butyl 3-methyl (3R,5S)-5-[[2-tert-butyl-4-chloropyrimidin-5-yl]carbonyl]((isobutyl)amino)piperidine-1,3-dicarboxylate

[1382]
2-tert-Butyl-6-oxo-1,6-dihydropyrimidine-5-carboxylic acid (3.25 g) was dissolved in THF (60 ml), thionyl chloride (4.3 ml) and DMF (5 drops) were added and the mixture was heated under reflux with stirring for 2.5 hr. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, and the residue was azeotroped with toluene. The obtained residue was suspended in THF (50 ml), and the suspension was added to a solution of 1-tert-butyl 3-methyl (3R,5S)-5-(isobutylamino)piperidine-1,3-dicarboxylate (4.13 g) and diisopropylethylamine (9.15 µl) in THF (50 ml) and the mixture was stirred at room temperature for 8 hr. The reaction mixture was concentrated under reduced pressure, diluted with water, and extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (1:19 - 2:3) was concentrated under reduced pressure to give the object product (6.29 g).

MS (ESI+, m/e) 511 (M+1)

Reference Example 228
1-tert-butyl 3-methyl (3R,5S)-5-([(2-tert-butyl-4-(hex-1-yn-1-yl)pyrimidin-5-yl)carbonyl](2-methylpropyl)amino)piperidine-1,3-dicarboxylate

[1385]
[1386]

1-tert-Butyl 3-methyl (3R,5S)-5-[(2-tert-butyl-4-chloropyrimidin-5-yl)carbonyl](isobutyl)amino)piperidine-1,3-dicarboxylate (300 mg), dichloro[bis(triphenylphosphine)]palladium (412 mg), copper iodide (112 mg) and N,N-diisopropylethylamine (0.51 µL) were dissolved in DMF (8 ml), and the mixture was stirred at room temperature for 15 min. 1-Hexyne (0.08 ml) was added and the mixture was stirred at room temperature 2 hr, and further at 70°C for 8 hr. The mixture was cooled to room temperature, adsorbed to silica gel (10 g), and a fraction eluted with ethyl acetate was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with hexane-ethyl acetate (95:5 - 30:70) was concentrated under reduced pressure to give the object product (218 mg).

MS (ESI+, m/e) 557 (M+1)

[1387]

Reference Example 229
1-tert-butyl 3-methyl (3R,5S)-5-[(2-tert-butyl-4-hexylpyrimidin-5-yl)carbonyl](2-methylpropyl)amino)piperidine-1,3-dicarboxylate

[1388]
1-tert-Butyl 3-methyl (3R,5S)-5-([(2-tert-butyl-4-(hex-1-yln-1-yl)pyrimidin-5-yl)carbonyl](2-methylpropyl)amino)piperidine-1,3-dicarboxylate (218 mg) and palladium-carbon (20 mg) were suspended in methanol and the mixture was stirred under a hydrogen atmosphere (1 atom) at room temperature for 16 hr. The palladium catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give the object product (219 mg) as a solid. MS (ESI+, m/e) 561 (M+1)

Reference Example 230

tert-butyl (3S,5R)-3-([(2-tert-butyl-4-hexylpyrimidin-5-yl)carbonyl](2-methylpropyl)amino)-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

1-tert-Butyl 3-methyl (3R,5S)-5-([(2-tert-butyl-4-hexylpyrimidin-5-yl)carbonyl](2-methylpropyl)amino)piperidine-1,3-dicarboxylate (219 mg) was dissolved in methanol (3 ml) and THF (2 ml), 1M aqueous sodium hydroxide solution (2 ml)
was added and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated under reduced pressure, and the aqueous layer of the mixture was adjusted to pH 5-6 with saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The obtained residue, morpholine (41 µl), 1H-benzotriazol-1-ol (30 mg) and triethylamine (140 µl) were dissolved in 1,2-dichloroethane (4 ml), WSC·HCl (115 mg) was added and the mixture was stirred at room temperature for 3 days. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (5:95 - 80:20) was concentrated under reduced pressure to give the object product (88 mg).

MS (ESI+, m/e) 616 (M+1)

[1393]
Reference Example 231
4-chloro-1-(4-methoxybutyl)-2-phenyl-1H-imidazole-5-carbaldehyde

[1394]

[1395]
To a solution of 4-chloro-2-phenyl-1H-imidazole-5-carbaldehyde (500 mg) and 4-methoxybutyl methanesulfonate (660 mg) in N,N-dimethylacetamide (10 ml) was added cesium
carbonate (2.4 g); and the mixture was stirred at 90°C for 7 hr. After cooling to room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (5:95 - 3:7) was concentrated under reduced pressure to give the object product (702 mg).

\[ ^{1}H\text{-NMR (CDCl}_{3} \text{) }\delta: 1.43-1.58 \text{ (2H, m), 1.76-1.88 (2H, m), 3.27 (3H, s), 3.30 (2H, t), 4.31-4.40 (2H, m), 7.52 (2H, d), 7.41-7.56 (1H, m), 7.56-7.69 (2H, m), 9.85 (1H, s).} \]

MS (ESI+, m/e) 293 (M+1)

[1396]

In the same manner as in the method shown in Reference Example 231, the following compound (Reference Example 232) was obtained.

[1397]
Reference Example 232

2-butyl-4-chloro-1-((4-methoxybutyl)-1H-imidazole-5-carbaldehyde

[1398]

\[ \text{Cl} \]

\[ \text{N} = \text{N} \]

\[ \text{O} \]

[1399]

\[ ^{1}H\text{-NMR (CDCl}_{3} \text{) }\delta: 0.96 (3H, t), 1.33-1.49 (2H, m), 1.60 (2H, d), 1.68-1.85 (2H, m), 1.76 (2H, quin), 2.67 (1H, d), 2.67 (1H, s), 3.33 (3H, s), 3.41 (2H, t), 4.27 (1H, s), 4.23 (1H, d), 9.72 (1H, s).} \]

MS (ESI+, m/e) 273 (M+1)

[1400]
Reference Example 233
4-chloro-1-(4-methoxybutyl)-2-phenyl-1H-imidazole-5-carboxylic acid

[1401]

5

[1402]
To a solution of 4-chloro-1-(4-methoxybutyl)-2-phenyl-1H-imidazole-5-carbaldehyde (790 mg) in tert-butanol (15 ml) and 2-methyl-2-butene (1.5 ml) was added aqueous solution (4 ml) of sodium chlorite (300 mg) and sodium dihydrogen phosphate (400 mg), and the mixture was stirred at room temperature for 12 hr. 1M Hydrochloric acid was added, and the mixture was adjusted to pH 3, and extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give the object product (730 mg). MS (ESI+, m/e) 309 (M+1)

[1403]
In the same manner as in the method shown in Reference Example 233, the following compound (Reference Example 234) was obtained.

[1404]
Reference Example 234
2-butyl-4-chloro-1-(4-methoxybutyl)-1H-imidazole-5-carboxylic acid

[1405]
[1406]
MS (ESI+, m/e) 289 (M+1)
Reference Example 235
tert-butyl (3S,5R)-3-[[[4-chloro-1-(4-methoxybutyl)-2-phenyl-1H-imidazol-5-yl]carbonyl](2-methylpropyl)amino]-5-[(morpholin-4-yl)carbonyl]piperidine-1-carboxylate

[1407]

[1408]
4-Chloro-1-(4-methoxybutyl)-2-phenyl-1H-imidazole-5-carboxylic acid (309 mg), tert-butyl (3S,5R)-3-[(2-methylpropyl)amino]-5-[(morpholin-4-yl)carbonyl]piperidine-1-carboxylate (370 mg) obtained in Reference Example 22 and N,N-diisopropylethylamine (270 μl) were dissolved in 1,2-dichloroethane (8 ml), chloro-N,N,N',N'-tetramethylformamidinium hexafluorophosphate (340 mg) was added and the mixture was stirred at room temperature for 4 days. The reaction mixture was diluted with saturated aqueous sodium hydrogen carbonate solution and extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (10:90 - 100:0) was concentrated under reduced pressure to give the object product (425 mg). MS (ESI+, m/e) 661 (M+1)

[1409]
In the same manner as in the method shown in Reference Example 235, the following compound (Reference Example 236)
was obtained.

[1410]
Reference Example 236
tert-butyl (3S,5R)-3-[[2-butyl-4-chloro-1-(4-methoxybutyl)-1H-imidazol-5-yl]carbonyl](2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[1411]

[1412]
MS (ESI+, m/e) 641 (M+1)
Reference Example 237
tert-butyl (3S,5R)-3-[[1-(4-methoxybutyl)-2-phenyl-1H-imidazol-5-yl]carbonyl](2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[1413]

[1414]
tert-Butyl (3S,5R)-3-[[4-chloro-1-(4-methoxybutyl)-2-phenyl-1H-imidazol-5-yl]carbonyl](2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (200 mg), palladium(II) hydroxide-carbon (20 mg) and potassium acetate (30 mg) were suspended in methanol (10 ml), and the mixture was stirred under a hydrogen atmosphere (1 atom) at room
temperature for 1 day. The palladium catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was suspended in water, and the suspension was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (10:90 - 80:20) was concentrated under reduced pressure to give the object product (90 mg).

MS (ESI+, m/e) 626 (M+1)

In the same manner as in the method shown in Reference Example 237, the following compound (Reference Example 238) was obtained.

Reference Example 238
tert-butyl (3S,5R)-3-[(2-butyl-1-(4-methoxybutyl)-1H-imidazol-5-yl)carbonyl]-(2-methylpropyl)amino]-5-(morpholin-4-yl)carbonyl)piperidine-1-carboxylate

MS (ESI+, m/e) 606 (M+1)

Reference Example 239
tert-butyl N-[cyclohexyl(imino)methyl]glycinate
[1420]

To a solution of cyclohexanecarboximidamide hydrochloride (2.00 g) and tert-butyl glycinate hydrochloride (2.06 g) in DMF (16 ml) was added triethylamine (4.30 ml) at room temperature, and the mixture was stirred at 60°C for 3 hr. The reaction mixture was cooled to room temperature, diluted with water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give the object product (0.84 g).

\[ ^1H-NMR \text{ (CDCl}_3\text{)} \delta: 1.26-1.34 \text{ (4H, m), 1.48 (7H, d), 1.63-1.78 (2H, m), 1.79-1.91 (1H, m), 1.84 (2H, dd), 1.97 (2H, d), 2.43 (1H, t), 3.93-4.02 (1H, m), 4.09 (2H, d).} \]

[1421]

Reference Example 240

4-chloro-2-cyclohexyl-1H-imidazole-5-carbaldehyde

[1422]

[1423]

tert-Butyl N-(cyclohexyl(imino)methyl)glycinate (830 mg) was dissolved in a solution (10%, 15 ml) of trifluoroacetic acid in 1,2-dichloroethane and the mixture was stirred at room temperature for 1 day. The reaction mixture was concentrated under reduced pressure. The residue was suspended in toluene, phosphorus oxychloride (3.21 ml) was added and the mixture was stirred at 80°C for 30 min. DMF (2.67 ml) was added and the
mixture was stirred at 100°C for 5 hr. The reaction mixture was ice-cooled, basified by pouring into an aqueous sodium hydroxide solution, and extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (10:90 - 100:0) was concentrated under reduced pressure to give the object product (495 mg).

\(^1\text{H-NMR (CDCl}_3\) δ: 1.22-1.34 (1H, m), 1.39 (1H, dt), 1.57 (2H, qd), 1.74 (1H, ddd), 1.80-1.89 (1H, m), 1.83 (2H, dd), 2.02 (1H, d), 2.06 (1H, d), 2.79 (1H, tt), 9.65 (1H, s), 10.59 (1H, br s).}

[1424]

In the same manner as in the method shown in Reference Example 231, the following compound (Reference Example 241) was obtained.

[1425]

Reference Example 241

4-chloro-2-cyclohexyl-1-(4-methoxybutyl)-1H-imidazole-5-carbaldehyde

[1426]

\[\text{Cl} \quad \text{N} \quad \text{N} \quad \text{Cl} \quad \text{O} \quad \text{O} \quad \text{H}\]

[1427]

\(^1\text{H-NMR (CDCl}_3\) δ: 1.27-1.43 (3H, m), 1.60-1.67 (3H, m), 1.69-1.81 (6H, m), 1.84-1.89 (2H, m), 2.65 (1H, tt), 3.29-3.46 (6H, m), 4.25 (2H, t), 9.71 (1H, s).

In the same manner as in the method shown in Reference Example 233, the following compound (Reference Example 242) was obtained.
[1428]
Reference Example 242
4-chloro-2-cyclohexyl-1-(4-methoxybutyl)-1H-imidazole-5-carboxylic acid

[1429]

[1430]
MS (ESI+, m/e) 315 (M+1)
In the same manner as in the method shown in Reference Example 235, the following compound (Reference Example 243) was obtained.

[1431]
Reference Example 243
tert-butyl (3S,5R)-3-[[4-chloro-2-cyclohexyl-1-(4-methoxybutyl)-1H-imidazol-5-yl]carbonyl](2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[1432]

[1433]
MS (ESI+, m/e) 667 (M+1)
In the same manner as in the method shown in Reference Example 237, the following compound (Reference Example 244) was obtained.
[1434]
Reference Example 244
tert-butyl (3S,5R)-3-{{[2-cyclohexyl-1-(4-methoxybutyl)-1H-imidazol-5-yl]carbonyl}{2-methylpropyl}amino}-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[1435]

[1436]
10 MS (ESI+, m/e) 632 (M+1)
Reference Example 245
methyl 2-diazo-7-methoxy-3-oxoheptanoate

[1437]

[1438]
To a solution (100 ml) of methyl 7-methoxy-3-oxoheptanoate (5.00 g) and 4-(acetylamino)benzenesulfonyl azide (7.02 g) in acetonitrile was added triethylamine (11.1 ml) and the mixture was stirred at room temperature for 2 days. Insoluble material was filtered through celite, and the filtrate was concentrated under reduced pressure. The residue was suspended in diethyl ether and the insoluble material was filtered off. The filtrate was concentrated under reduced pressure to give the object product (6.93 g).

^1H-NMR (CDCl₃) δ: 1.49-1.83 (4H, m), 2.88 (2H, t), 3.32 (3H, s), 3.39 (2H, t), 3.84 (3H, s).

[1439]
Reference Example 246
methyl 5-(4-methoxybutyl)-2-oxo-1-phenyl-2,3-dihydro-1H-imidazole-4-carboxylate

![Chemical Structure](image)

Methyl 2-diazoo-7-methoxy-3-oxoheptanoate (6.93 g) and 1-phenylurea (5.41 g) were suspended in toluene (30 ml)-1,2-dichloroethane (30 ml), rhodium tetraacetate (230 mg) was added and the mixture was stirred at 80°C for 2 hr. After cooling to room temperature, trifluoroacetic acid (7.5 ml) was added and the reaction mixture was stirred at room temperature for 1 day. The reaction mixture was concentrated under reduced pressure, and the residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (15:85 - 100:0) was concentrated under reduced pressure to give the object product (7.40 g).

MS (ESI+, m/e) 305 (M+1)

Reference Example 247
methyl 2-chloro-5-(4-methoxybutyl)-1-phenyl-1H-imidazole-4-carboxylate

![Chemical Structure](image)
Methyl 5-(4-methoxybutyl)-2-oxo-1-phenyl-2,3-dihydro-1H-imidazole-4-carboxylate (1.50 g) was dissolved in phosphorus oxychloride (18 ml) and the mixture was stirred at 100°C for 10 hr. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was diluted with saturated aqueous sodium hydrogen carbonate solution and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (10:90 - 100:0) was concentrated under reduced pressure to give the object product (454 mg).

$^1$H-NMR (CDCl$_3$) δ: 1.37-1.53 (4H, m), 2.72-2.88 (2H, m), 3.16-3.33 (5H, m), 3.92 (3H, s), 7.17-7.33 (2H, m), 7.51-7.57 (3H, m).

Reference Example 248

2-chloro-5-(4-methoxybutyl)-1-phenyl-1H-imidazole-4-carboxylic acid

![Chemical Structure](image)

Methyl 2-chloro-5-(4-methoxybutyl)-1-phenyl-1H-imidazole-4-carboxylate (450 mg) was dissolved in methanol (5 ml), 1M aqueous sodium hydroxide solution (4.2 ml) was added and the mixture was stirred at 80°C for 2 hr. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was acidified with 1M hydrochloric acid and extracted with ethyl acetate. The
extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give the object product (372 mg).

MS (ESI+, m/e) 309 (M+1)

[1448]

In the same manner as in the method shown in Reference Example 235, the following compound (Reference Example 249) was obtained.

[1449]

Reference Example 249
tert-butyl (3S,5R)-3-[[2-chloro-5-(4-methoxybutyl)-1-phenyl-1H-imidazol-4-yl]carbonyl](2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[1450]

MS (ESI+, m/e) 661 (M+1)

In the same manner as in the method shown in Reference Example 237, the following compound (Reference Example 250) was obtained.

[1452]

Reference Example 250
tert-butyl (3S,5R)-3-[[5-(4-methoxybutyl)-1-phenyl-1H-imidazol-4-yl]carbonyl](2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[1453]
[1454]
MS (ESI+, m/e) 626 (M+1)

In the same manner as in the method shown in Reference Example 231, the following compound (Reference Example 251) was obtained.

Reference Example 251
ethyl 1-(4-methoxybutyl)-1H-imidazole-2-carboxylate

[1455]

[1456]
$^1$H-NMR (CDCl$_3$) δ: 1.43 (3H, t), 1.59 (2H, dd), 1.89 (2H, quin), 3.32 (3H, s), 3.39 (2H, t), 4.34-4.50 (4H, m), 7.12 (2H, d).

[1457]

[1458]

Ethyl 1-(4-methoxybutyl)-1H-imidazole-2-carboxylate (2.18 g) was dissolved in acetonitrile (30 ml), N-bromosuccinimide (1.71 g) was added and the mixture was stirred at 60°C for 14
hr. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (10:90 - 70:30) was concentrated under reduced pressure to give the object product (689 mg).

$^1$H-NMR (CDCl$_3$) δ: 1.42 (3H, t), 1.60 (2H, dd), 1.89 (2H, quin), 3.33 (3H, s), 3.40 (2H, t), 4.34-4.50 (4H, m), 7.08 (1H, s).

MS (ESI+, m/e) 306 (M+1)

[1459]

Reference Example 253
tert-butyl (3S,5R)-3-[[4-bromo-1-(4-methoxybutyl)-1H-imidazol-2-yl]carbonyl](2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

![Chemical Structure](image)

[1460]

Ethyl 4-bromo-1-(4-methoxybutyl)-1H-imidazole-2-carboxylate (290 mg) and lithium hydroxide monohydrate (60 mg) were suspended in THF (2 ml), ethanol (2 ml) and water (1 ml) and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated under reduced pressure. The obtained residue and tert-butyl (3S,5R)-3-[[2-methylpropyl]amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate (355 mg) obtained in Reference Example 22 were suspended in 1,2-dichloroethane (3 ml), chloro-N,N,N',N'-tetramethylformamidinium hexafluorophosphate (405 mg) was added and the mixture was stirred at room temperature for 3 days. The reaction mixture was diluted with saturated aqueous
sodium hydrogen carbonate solution and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (10:90 - 100:0) was concentrated under reduced pressure. The obtained residue was purified by reversed-phase preparative HPLC, and the object fraction was concentrated under reduced pressure. The residue was basified with 3.5M aqueous potassium carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give the object product (117 mg).

MS (ESI+, m/e) 629 (M+1)

Reference Example 254

methyl 2-methoxy-5-(4-methoxybutyl)-1-phenyl-1H-imidazole-4-carboxylate

![Chemical Structure](image)

Methyl 5-(4-methoxybutyl)-2-oxo-1-phenyl-2,3-dihydro-1H-imidazole-4-carboxylate (2.00 g) was dissolved in dichloromethane (14 ml), trimethylsloxonium tetrafluoroborate (2.00 g) was added and the mixture was stirred at room temperature for 16 hr. Saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous
magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (10:90 - 100:0) was concentrated under reduced pressure to give the object product (585 mg).

1H-NMR (CDCl₃) δ: 1.35-1.51 (4H, m), 2.72-2.81 (2H, m), 3.14-3.30 (5H, m), 3.90 (3H, s), 4.02 (3H, s), 7.20-7.33 (3H, m), 7.42-7.55 (2H, m).

MS (ESI+, m/e) 319 (M+1)

[1465]

Reference Example 255

methyl 2-ethoxy-5-(4-methoxybutyl)-1-phenyl-1H-imidazole-4-carboxylate

[1466]

[1467]

Methyl 5-(4-methoxybutyl)-2-oxo-1-phenyl-2,3-dihydro-1H-imidazole-4-carboxylate (740 mg) was dissolved in acetonitrile (8 ml), a 1M solution (6.1 ml) of trimethyloxonium tetrafluoroborate in dichloromethane was added and the reaction mixture was stirred at room temperature for 3 days. Saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (10:90 - 80:20) was concentrated under reduced pressure to give the object product (79 mg).

MS (ESI+, m/e) 333 (M+1)
[1468] In the same manner as in the method shown in Reference Example 248, the following compounds (Reference Examples 256-257) were obtained.

[1469] Reference Example 256
2-methoxy-5-(4-methoxybutyl)-1-phenyl-1H-imidazole-4-carboxylic acid

[1470]

[1471] MS (ESI+, m/e) 305 (M+1)
Reference Example 257

[1472] 2-ethoxy-5-(4-methoxybutyl)-1-phenyl-1H-imidazole-4-carboxylic acid

[1473] MS (ESI+, m/e) 319 (M+1)
In the same manner as in the method shown in Reference Example 235, the following compounds (Reference Examples 258-259) were obtained.

[1474] Reference Example 258
tert-butyl (3S,5R)-3-[[2-methoxy-5-(4-methoxybutyl)-1-phenyl-1H-imidazol-4-y]carbonyl][2-methylpropyl]amino]-5-(morpholin-
[1475]

4-ylcarbonyl)piperidine-1-carboxylate

[1476]

MS (ESI+, m/e) 656 (M+1)
Reference Example 259
tert-butyl (3S,5R)-3-[[2-ethoxy-5-(4-methoxybutyl)-1-phenyl-1H-imidazol-4-yl]carbonyl] (2-methylpropyl)amino]-5- (morpholin-4-yl)carbonyl)piperidine-1-carboxylate

[1477]

[1478]

MS (ESI+, m/e) 670 (M+1)
Reference Example 260
methyl 2-(hydroxyimino)-7-methoxy-3-oxoheptanoate

[1479]

[1480]

To an aqueous solution (20 ml) of sodium nitrite (2.20 g) was added dropwise a solution of methyl 7-methoxy-3-
oxoheptanoate (5.00 g) obtained in Reference Example 359 in acetic acid (5 ml) under ice-cooling, and the reaction mixture was stirred at room temperature for 3 hr. The reaction mixture was diluted with water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give the object product (5.91 g).

$^1$H-NMR (CDCl$_3$) δ: 1.60-1.79 (4H, m), 2.82 (2H, t), 3.38 (3H, s), 3.46 (2H, t), 3.90 (3H, s).

[1481]
Reference Example 261
methyl 2-(acetylamino)-7-methoxy-3-oxoheptanoate

[1482]

[1483]
Methyl 2-(hydroxyimino)-7-methoxy-3-oxoheptanoate (5.70 g) and palladium-carbon (900 mg) were suspended in acetic acid (60 ml)-acetic anhydride (25 ml) and the mixture was stirred under a hydrogen atmosphere (1 atom) at room temperature for 14 hr. The palladium catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give the object product (5.48 g).

$^1$H-NMR (CDCl$_3$) δ: 1.54-1.62 (2H, m), 1.65-1.75 (2H, m), 2.07 (3H, s), 2.75 (2H, q), 3.26-3.43 (5H, m), 3.81 (3H, s), 5.26 (1H, d), 6.65 (1H, br s).

[1484]
Reference Example 262
methyl 5-(4-methoxybutyl)-2-methyl-1-phenyl-1H-imidazole-4-carboxylate

[1485]
Methyl 2-(acetylamino)-7-methoxy-3-oxoheptanoate (5.45 g), aniline (3.01 ml) and trifluoroacetic acid (2.48 ml) were dissolved in butyronitrile (30 ml), and the reaction mixture was heated under reflux for 2 hr. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. 3.6M Aqueous potassium carbonate solution was added to the obtained residue and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (10:90 - 100:0) was concentrated under reduced pressure to give the object product (3.88 g).

$^1$H-NMR (CDCl$_3$) δ: 1.36-1.53 (4H, m), 1.71 (2H, td), 2.21 (3H, s), 2.76 (2H, t), 3.13-3.30 (3H, m), 3.91 (3H, s), 7.16-7.25 (2H, m), 7.47-7.61 (3H, m).

MS (ESI+, m/e) 303 (M+1)

Reference Example 263

[1487]  
5-(4-methoxybutyl)-2-methyl-1-phenyl-1H-imidazole-4-carboxylic acid

[1488]
Methyl 5-(4-methoxybutyl)-2-methyl-1-phenyl-1H-imidazole-4-carboxylate (3.85 g) was dissolved in methanol (26 ml)-water (24 ml), lithium hydroxide monohydrate (800 mg) was added and the mixture was heated under reflux for 2 hr. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was adjusted to pH=7 with 1M hydrochloric acid, subjected to DIAION HP-20 (manufactured by Mitsubishi Chemical), washed with water and a fraction eluted with acetone was concentrated under reduced pressure to give the object product (1.08 g).

\[^1\text{H-NMR (DMSO-d}_6\text{)} \delta: 1.28 (5H, br s), 2.07 (3H, s), 2.50 (1H, br s), 2.69 (2H, br s), 3.08 (3H, s), 7.41 (2H, d), 7.51-7.67 (3H, m).\]

MS (ESI+, m/e) 289 (M+1)

[1490]

In the same manner as in the method shown in Reference Example 235, the following compound (Reference Example 264) was obtained.

[1491]

Reference Example 264

tert-butyl (3S,5R)-3-[[5-(4-methoxybutyl)-2-methyl-1-phenyl-1H-imidazol-4-yl]carbonyl](2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate

[1492]

[1493]

\[^1\text{H-NMR (CDCl}_3\text{)} \delta: 0.94 (6H, br s), 1.35-1.52 (4H, m), 1.45 (9H, d), 1.83 (3H, br s), 2.02-2.19 (4H, m), 2.62 (2H, d), 2.72-2.85 (3H, m), 3.11-3.27 (6H, m), 3.49 (2H, br s), 3.58-3.75 (2H, m), 3.69 (5H, dd), 4.06-4.21 (2H, m), 7.17-7.33 (2H, m),]
7.45-7.62 (3H, m).  
MS (ESI+, m/e) 640 (M+1)

[1494]  
Reference Example 265

5-[(benzyloxy)methyl]-1-phenyl-1H-1,2,3-triazole-4-carboxylic acid  

[N]  

[1495]

Methyl 4-(benzyloxy)-3-oxobutanoate (5.00 g) and azidobenzene (2.68 g) were dissolved in methanol (30 ml), sodium methanolate (28% methanol solution, 6.5 g) was added and the mixture was stirred at room temperature for 2 hr, and then heated under reflux for 18 hr. 1M Aqueous sodium hydroxide solution (10 ml) was added and the mixture was heated under reflux for 2 hr. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in water and washed with ethyl acetate-hexane (1:1, v/v). The obtained aqueous solution was acidified with 1M hydrochloric acid, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give the object product (6.03 g).  

\[^1H\text{-NMR}\ (\text{CDCl}_3) \delta: 4.62 \ (2H, s), 4.88 \ (2H, s), 7.22-7.39 \ (5H, m), 7.47-7.62 \ (3H, m), 7.68 \ (2H, d.d).\]

MS (ESI+, m/e) 310 (M+1)

[1497]  
Reference Example 266

1-tert-butyl 3-methyl (3R,5S)-5-[[5-[(benzyloxy)methyl]-1-phenyl-1H-1,2,3-triazol-4-yl]carbonyl] (2-
methylpropylamino)piperidine-1,3-dicarboxylate

[1498]

5-[(Benzzyloxy)methyl]-1-phenyl-1H-1,2,3-triazole-4-carboxylic acid (6.00 g) was dissolved in THF (50 ml), thionyl chloride (2.15 ml) and DMF (5 drops) were added and the mixture was heated under reflux with stirring for 2 hr. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, and the residue was azeotroped with toluene. The obtained residue was suspended in THF (20 ml), and the suspension was added to a solution of 1-tert-butyl 3-methyl (3R,5S)-5-(isobutylamino)piperidine-1,3-dicarboxylate (6.10 g) and diisopropylethylamine (10.0 μl) in THF (30 ml) and the mixture was stirred at room temperature for 14 hr. The reaction mixture was concentrated under reduced pressure, diluted with water, and extracted with ethyl acetate. The extract was washed successively with 1M hydrochloric acid and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography, and a fraction eluted with ethyl acetate-hexane (5:95 - 70:30) was concentrated under reduced pressure to give the object product (7.70 g).

1H-NMR (CDCl3) δ: 0.77-1.06 (6H, m), 1.36-1.53 (9H, m), 1.57 (2H, br s), 1.80-2.00 (1H, m), 2.14-2.33 (1H, m), 2.63 (2H, br s), 2.82 (1H, br s), 3.30 (1H, d), 3.56 (1H, br s), 3.71 (3H, s), 4.21-4.37 (2H, m), 4.54 (2H, s), 4.76 (2H, d), 7.17-7.22 (2H, m), 7.24-7.36 (3H, m), 7.46-7.57 (3H, m), 7.59-7.68 (2H,
m).

MS (ESI+, m/e) 606 (M+1)

[1500]

Reference Example 267

5 1-tert-butyl 3-methyl (3R,5S)-5-[[5-(hydroxymethyl)-1-phenyl-1H-1,2,3-triazol-4-yl]carbonyl](2-methylpropyl)amino)piperidine-1,3-dicarboxylate

[1501]

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

[1502]

1-tert-Butyl 3-methyl (3R,5S)-5-[[5-[(benzyloxy)methyl]-1-phenyl-1H-1,2,3-triazol-4-yl]carbonyl](2-methylpropyl)amino)piperidine-1,3-dicarboxylate (2.92 g) and palladium(II) hydroxide-carbon (500 mg) were suspended in methanol, and the mixture was stirred under a hydrogen atmosphere (5 atom) at room temperature for 10 hr. The palladium catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give the object product (2.39 g) as a solid.

\(^1\)H-NMR (CDCl\(_3\)) \(\delta\): 0.96 (6H, dd), 1.46 (9H, d), 1.60-1.95 (1H, m), 2.19 (1H, dt), 2.60 (1H, d), 2.68-2.93 (2H, m), 3.28 (1H, br s), 3.54 (1H, br s), 3.72 (3H, s), 4.32 (2H, br s), 4.65 (2H, d), 4.82-4.98 (2H, m), 7.57 (5H, s).

MS (ESI+, m/e) 516 (M+1)

[1503]

Reference Example 268

(3R,5S)-1-(tert-butoxycarbonyl)-5-[[5-(hydroxymethyl)-1-phenyl-1H-1,2,3-triazol-4-yl]carbonyl](2-methylpropyl)amino)piperidine-3-carboxylic acid
1-tert-Butyl 3-methyl (3R,5S)-5-{[5-(hydroxymethyl)-1-phenyl-1H-1,2,3-triazol-4-yl]carbonyl}(2-methylpropyl)amino)piperidine-1,3-dicarboxylate (2.25 g) was dissolved in THF (10 ml)-methanol (10 ml)-water (8 ml), 8M aqueous sodium hydroxide solution (1.5 ml) was added and the reaction mixture was stirred at room temperature for 3 hr. The reaction mixture was neutralized with saturated aqueous ammonium chloride solution, acidified with 1M hydrochloric acid and extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give the object product (2.18 g). MS (ESI+, m/e) 502 (M+1)

Reference Example 269
tert-butyl (3S,5R)-3-{[5-(hydroxymethyl)-1-phenyl-1H-1,2,3-triazol-4-yl]carbonyl}(2-methylpropyl)amino]-5-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate
DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D’UN TOME.

CECI EST LE TOME 1 DE 2
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NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:
CLAIMS:

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

   ![Chemical Structure](image)

   (I)

   wherein

   5 \( R^1 \) is a \( \text{C}_{1-6} \) alkyl group;

   \( R^2 \) is

   (i) a \( \text{C}_{1-6} \) alkyl group optionally having 1 to 3 substituents selected from

   (a) a hydroxy group,

   (b) a halogen atom,

   (c) a \( \text{C}_{1-6} \) alkoxy group,

   (d) a \( \text{C}_{1-6} \) alkyl-carbonyloxy group,

   (e) an aromatic heterocyclic group optionally having 1 to 3 halogen atoms,

15   (f) a \( \text{C}_{3-10} \) cycloalkyl group, and
(g) a cyclic amino group optionally having an oxo group,

(2) a 3- to 10-membered heterocyclic group optionally having 1 to 3 substituents selected from a C₁₋₆ alkyl group and an oxo group,

(3) a carboxy group,

(4) a C₁₋₆ alkoxy-carbonyl group optionally having 1 to 3 substituents selected from a nonaromatic heterocyclic group optionally having 1 to 3 substituents selected from a C₁₋₆ alkyl group and oxo group,

(5) a C₁₋₆ alkyl-carbonyl group, or

(6) a group represented by the formula: -CO-NR’R” wherein R’ and R” are each a hydrogen atom, or R’ and R” form, together with the nitrogen atom bonded thereto, a nitrogen-containing heterocycle optionally having 1 to 3 substituents selected from halogen atom(s); and

X is

(1) a hydrogen atom;

(2) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from

(a) a halogen atom,

(b) a hydroxy group,
(c) a C₁₋₆ alkoxy group optionally having a C₁₋₆ alkoxy group or a halogen atom,
(d) a C₁₋₆ alkylthio group,
(e) an aryl group,
(f) an aryloxy group optionally having a C₁₋₆ alkoxy group or a halogen atom, and
(g) a heteroaryl group; or

(3) a C₃₋₁₀ cycloalkyl group,

or a salt thereof.

2. A compound represented by the formula (II):

![Chemical Structure](image)

wherein

R¹ is a C₁₋₆ alkyl group;
R³ is a C₁₋₆ alkoxy group optionally substituted by a C₁₋₆ alkoxy group or a halogen atom, a C₁₋₆ alkylthio group, a C₃₋₁₀ cycloalkyl group optionally substituted by a C₁₋₆ alkyl group,
27103-683

an aryl group or a heteroaryl group optionally substituted by a C₁₋₆ alkyl group;

X¹ is a C₁₋₆ alkyene group; and

the group represented by

\[ \text{Diagram: } \text{Group Representation} \]

is a group represented by

\[ \text{Diagram: } \text{Group Representation} \]

wherein \( R^4 \) is

1. a hydrogen atom,
2. a cyano (nitrile) group,
3. a C₁₋₆ alkyl group optionally having 1 to 3 substituents selected from
   a. a hydroxy group,
   b. a C₁₋₆ alkoxy group,
   c. a C₁₋₆ alkyl-carbonyloxy group,
   d. an aromatic heterocyclic group optionally having 1 to 3 halogen atoms,
(e) a C₃₋₁₀ cycloalkyl group, and

(f) a cyclic amino group optionally having an oxo group,

(4) a 3- to 10-membered heterocyclic group optionally having 1 to 3 substituents selected from a C₁₋₆ alkyl group and an oxo group,

(5) a carboxy group,

(6) a C₁₋₆ alkoxy-carbonyl group optionally having 1 to 3 substituents selected from a nonaromatic heterocyclic group optionally having 1 to 3 substituents selected from a C₁₋₆ alkyl group and oxo group or

(7) a group represented by the formula: -CO-NR’R” wherein R’ and R” are each a hydrogen atom, or

R’ and R” form, together with the nitrogen atom bonded thereto, a nitrogen-containing heterocycle optionally having 1 to 3 substituents selected from halogen atom(s), or a salt thereof.

3. The compound of claim 2, or salt thereof, wherein the group represented by

is a group represented by
wherein \( R^i \) is

1. a cyano (nitrile) group,

2. a \( C_{1-6} \) alkyl group optionally having 1 to 3 substituents selected from

   (a) a hydroxy group,
   
   (b) a \( C_{1-6} \) alkoxy group,
   
   (c) a \( C_{1-6} \) alkyl-carbonyloxy group,
   
   (d) an aromatic heterocyclic group optionally having 1 to 3 halogen atoms,
   
   (e) a \( C_{3-10} \) cycloalkyl group, and
   
   (f) a cyclic amino group optionally having an oxo group,

3. a 3- to 10-membered heterocyclic group optionally having 1 to 3 substituents selected from a \( C_{1-6} \) alkyl group and an oxo group,

4. a carboxy group,

5. a \( C_{1-6} \) alkoxy-carbonyl group optionally having 1 to 3 substituents selected from a nonaromatic heterocyclic
group optionally having 1 to 3 substituents selected from a C₁₋₆ alkyl group and an oxo group or

(6) a group represented by the formula: -CO-NR'R''

wherein R' and R'' are each a hydrogen atom, or

R' and R'' form, together with the nitrogen atom bonded thereto, a nitrogen-containing heterocycle optionally having 1 to 3 substituents selected from halogen atom(s).

4. The compound of claim 2, or salt thereof, wherein the group represented by

![Diagram](image)

is a group represented by

![Diagram](image)

wherein Rᵣ is -CO-NR'R'' wherein R' and R'' are each a hydrogen atom, or R' and R'' form, together with the nitrogen atom bonded thereto, a nitrogen-containing heterocycle optionally having 1 to 3 substituents selected from halogen atom(s).

5. A compound, wherein the compound is N-[(3S,5R)-5-carbamoylpiperidin-3-yl]-1-(4-methoxybutyl)-N-(2-
methylpropyl)-1H-benzimidazole-2-carboxamide or a salt thereof.

6. A compound, wherein the compound is N-[(3S,5R)-5-[1-hydroxyethyl]piperidin-3-yl]-1-(4-methoxybutyl)-N-(2-methylpropyl)-1H-benzimidazole-2-carboxamide or a salt thereof.

7. A compound, wherein the compound is 1-(4-Methoxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide or a salt thereof.

8. A compound, wherein the compound is 1-(4-Hydroxybutyl)-N-(2-methylpropyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-1H-benzimidazole-2-carboxamide or a salt thereof.

9. A compound, wherein the compound is 1-(4-Methoxybutyl)-N-[(3S,5R)-5-(morpholin-4-ylcarbonyl)piperidin-3-yl]-N-propyl-1H-benzimidazole-2-carboxamide or a salt thereof.

10. A pharmaceutical composition comprising the compound of any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

11. The pharmaceutical composition of claim 10, for use as a renin inhibitor.

12. The pharmaceutical composition of claim 10, for use in the prophylaxis or treatment of a circulatory disease.
13. The pharmaceutical composition of claim 10, which is a prophylactic or therapeutic agent of hypertension and/or various organ damages attributable to hypertension.

14. Use of the compound of any one of claims 1 to 9, or a pharmacetically acceptable salt thereof, for the prophylaxis or treatment of a circulatory disease in a mammal.

15. Use of the compound of any one of claims 1 to 9, or a pharmacetically acceptable salt thereof, for the prophylaxis or treatment of hypertension and/or various organ damages attributable to hypertension in a mammal.

16. Use of the compound of any one of claims 1 to 9, or a pharmacetically acceptable salt thereof, for the production of a prophylactic or therapeutic agent for a circulatory disease.

17. Use of the compound of any one of claims 1 to 9, or a pharmacetically acceptable salt thereof, for the production of a prophylactic or therapeutic agent for hypertension and/or various organ damages attributable to hypertension.

18. Use of the compound of any one of claims 1 to 9, or a pharmacetically acceptable salt thereof, for inhibiting renin activity.
(I)

(II)