

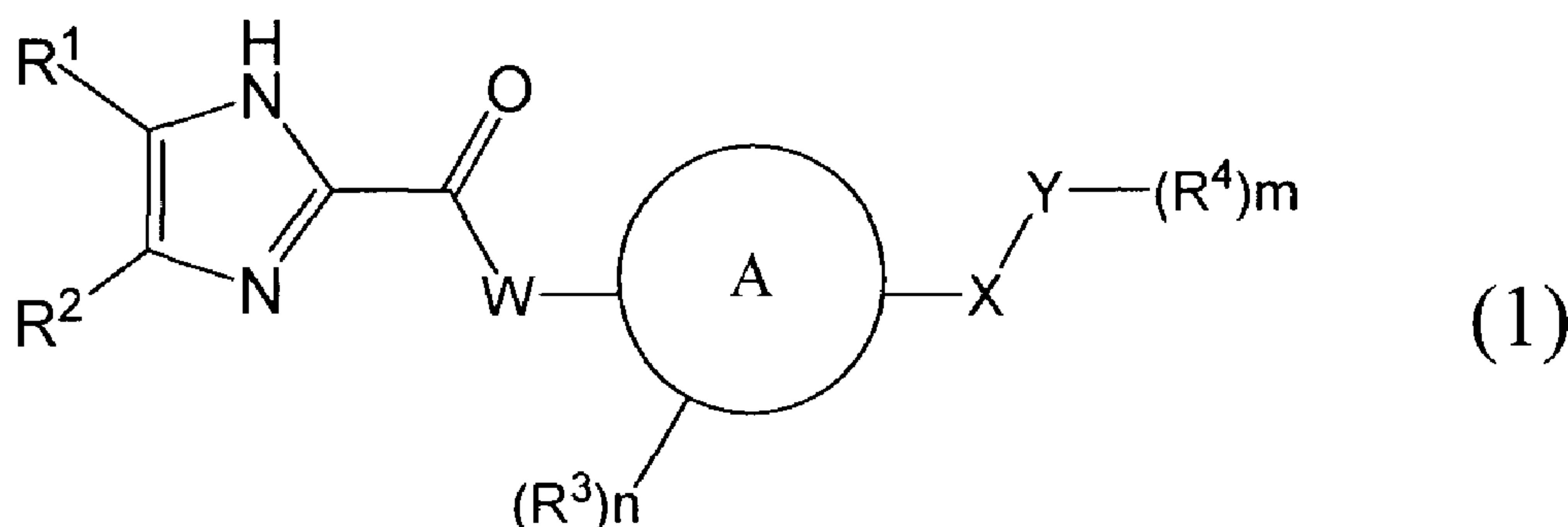


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(54) Titre : COMPOSES A BASE DE CARBONYLE D'IMIDAZOLE ET LEUR UTILISATION POUR LE TRAITEMENT D'INFECTIONS BACTERIENNES
(54) Title: IMIDAZOLE CARBONYL COMPOUNDS AND USE THEREOF FOR TREATING BACTERIAL INFECTIONS



(57) **Abrégé/Abstract:**

To develop an antibiotic having a novel mechanism of action, the present inventors have searched for a compound that has weak cytotoxicity, the physical property of high solubility in water, the effect of inhibiting both DNA gyrase GyrB and topoisomerase IV ParE subunits, and sufficient antibacterial activity. As a result, the present inventors have completed the present invention by finding that a compound of the present invention represented by the general formula (1), a pharmacologically acceptable salt thereof, and a hydrate thereof have desirable properties. The present invention provides a pharmaceutical composition (particularly, a preventive or therapeutic composition for infectious disease) comprising a compound represented by the formula (1), a pharmacologically acceptable salt thereof, or a hydrate thereof as an active ingredient.



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ABSTRACT

To develop an antibiotic having a novel mechanism of action, the present inventors have searched for a compound that has weak cytotoxicity, the physical property of high solubility in water, the effect of inhibiting both DNA gyrase GyrB and topoisomerase IV ParE subunits, and sufficient antibacterial activity. As a result, the present inventors have completed the present invention by finding that a compound of the present invention represented by the general formula (1), a pharmacologically acceptable salt thereof, and a hydrate thereof have desirable properties. The present invention provides a pharmaceutical composition (particularly, a preventive or therapeutic composition for infectious disease) comprising a compound represented by the formula (1), a pharmacologically acceptable salt thereof, or a hydrate thereof as an active ingredient.

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JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
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DESCRIPTION

IMIDAZOLE CARBONYL COMPOUNDS AND USE THEREOF FOR TREATING
BACTERIAL INFECTIONS

Technical Field

[0001]

The present invention relates to compounds that exhibit antibacterial activity, production processes thereof, pharmaceutical compositions comprising the compounds as an active ingredient, and use of the compounds as pharmaceutical agents. Particularly, the present invention relates to compounds useful for the treatment of bacterial infectious disease in a homeothermal animal (e.g., a human) and production and use of pharmaceutical agents used in the treatment of bacterial infectious disease in a homeothermal animal (e.g., a human).

Background Art

[0002]

The problem of bacterial resistance to antibacterial agents has been threatening humans over many years. Examples of such difficult-to-treat resistant bacteria include methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae* (PRSP), and vancomycin-resistant *Enterococcus* (VRE). As existing antibacterial agents such as β -lactam, quinolone, and macrolide agents are used clinically, the number of

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bacteria resistant thereto goes on increasing. On the other hand, the total number of novel antibacterial agents launched has been decreasing since the late 1980s. The problem of bacterial resistance to antibacterial agents is considered as a more critical issue than ever before (Nathan, C. 2004, Nature 431: 899-902). For overcoming the threat of an increasing number of resistant bacteria, there is a need to develop novel antibacterial agents, particularly, antibacterial agents having a novel mechanism of action effective even for various resistant bacteria.

[0003]

Among bacterial infectious diseases, community-acquired respiratory infection occurs with the highest frequency, which is mainly caused by bacteria including a gram-positive bacterium *Streptococcus pneumoniae* and a gram-negative bacterium *Haemophilus influenzae*. Gram-positive bacteria have only a cytoplasmic membrane consisting of a phospholipid bilayer, whereas gram-negative bacteria have, in addition to a cytoplasmic membrane (inner membrane), an outer membrane consisting of an asymmetric bilayer of lipopolysaccharide and phospholipid and therefore exhibit resistance to many antibacterial agents. Only some antibacterial agents used clinically exhibit effectiveness for both *Streptococcus pneumoniae* and *Haemophilus influenzae*. Most novel drugs launched from the 21st century and novel drug candidates under clinical tests are effective only

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for the gram-positive bacterium and are inferior in effectiveness for *Haemophilus influenzae*. There is a demand to develop a novel antibacterial agent that is effective for both *Streptococcus pneumoniae* and *Haemophilus influenzae* and is applicable to community-acquired respiratory infection.

[0004]

Deoxyribonucleic acid (DNA) gyrase is one kind of type II topoisomerase which regulates the topological state of intracellular DNA (Champoux, J.J., 2001, Ann. Rev. Biochem. 70: 369-413). The type II topoisomerase modifies DNA topology by catalyzing a series of reactions through which a DNA duplex is transiently nicked by use of free energy generated as a result of hydrolysis of adenosine triphosphate (ATP); a strand is passed through the nick; and the nicked DNA is reannealed. The DNA gyrase regulates the supercoiling of DNA and relieves topological stress caused by the unwinding of a parent DNA duplex during the replication process. The DNA gyrase is an enzyme essential for growth to be conserved in bacteria and is characterized, among topoisomerases, in the ability to introduce a negative supercoil to DNA.

[0005]

The DNA gyrase is a protein tetramer consisting of two A subunits (GyrA) and two B subunits (GyrB). GyrB consists of an amino-terminal domain having ATP hydrolytic activity and a carboxy-terminal domain which interacts with GyrA and DNA. The supercoiling reaction

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is initiated by ATP binding to GyrB. Subsequently, the ATP is hydrolyzed during this reaction. This ATP binding and the subsequent hydrolysis cause a change in the higher-order structure of the DNA-bound gyrase. This is essential for the activity of DNA gyrase.

[0006]

In contrast to DNA gyrase, eukaryotic type II topoisomerase is a homodimer that is capable of relaxing negative and positive supercoils but not capable of introducing a negative supercoil. Ideally, an antibacterial agent based on the inhibition of bacterial DNA gyrase is selective for this enzyme and has no or relatively weak inhibitory activity against eukaryotic type II topoisomerase.

[0007]

Another bacterial type II topoisomerase is referred to as topoisomerase IV, which is mainly involved in the segregation of catenated closed circular chromosomes produced during replication. The topoisomerase IV is a protein tetramer consisting of two ParC subunits and two ParE subunits. ParE consists of an amino-terminal domain having ATP hydrolytic activity and a carboxy-terminal domain which interacts with ParC. These subunits ParC and ParE are highly homologous to GyrA and GyrB, respectively. The hydrolysis of ATP is required for getting the enzyme back into the initial state and restarting catalytic cycles. TopoIV is highly conserved in bacteria and is essential for bacterial replication

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(Drlica, K. and Zhao, X., 1997, Microbiol. Mol. Biol. Rev. 61: 377-392).

[0008]

DNA gyrase is targeted by quinolone antibacterial agents. Quinolone binds to GyrA to form a tripartite complex of quinolone, DNA gyrase, and DNA. This agent induces cell death by inhibiting DNA replication in this way. Moreover, some members in this class of antibacterial agents also inhibit topoisomerase IV. As a result, these compounds differ in their primary targets among bacterial species and among the compounds. Although the quinolone agents are effective antibacterial agents, they increasingly raise the problem of resistance caused by the mutation of the targets (DNA gyrase and topoisomerase IV) in several kinds of organisms such as *Staphylococcus aureus* and *Streptococcus pneumoniae* (Hooper, D.C., 2002, Lancet Infectious Diseases 2: 530-538). In addition, the quinolone antibacterial agents have been confirmed to have adverse reactions (joint or cartilage disorders) in immature animals and are thus prevented from being used in children (Lipsky, B.A. and Baker, C.A., 1999, Clin. Infect. Dis. 28: 352-364). Examples of other adverse reactions of the quinolone antibacterial agents include cardiotoxicity (prolonged QT interval), decreased blood sugar levels, photosensitivity, and convulsion caused by combined use with a nonsteroidal anti-inflammatory agent.

[0009]

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Many conventional quinolones inhibit topoisomerase IV more strongly than DNA gyrase in many gram-positive bacteria and inhibit DNA gyrase more strongly than topoisomerase IV in many gram-negative bacteria. Some novel quinolones exhibit more equally balanced inhibitory activity against DNA gyrase and topoisomerase IV in one bacterial species. More highly sensitive intracellular (primary target) enzymes become resistant to quinolones as a result of a point mutation. However, a quinolone that equally inhibits DNA gyrase and topoisomerase IV inhibits a secondary target enzyme even if its primary target enzyme is mutated; thus the resistance level is low and limited (Hooper, D.C., 2000, Clin Infect Dis. 31: S24-S28). DNA gyrase and topoisomerase IV are highly homologous in their amino acid sequences. Compounds targeting bacterial type II topoisomerase have the potential to inhibit both these two targets in the cell.

[0010]

There exist several kinds of known natural products that compete with ATP for binding to GyrB and inhibit DNA gyrase (Maxwell, A. and Lawson, D.M., 2003, Curr. Topics in Med. Chem. 3: 283-303). Coumarin antibacterial agents are natural products isolated from the genus *Streptomyces*. Examples thereof include novobiocin, clorobiocin, and coumermycin A1. Although these compounds are potent inhibitors for DNA gyrase, they have toxicity to eukaryotes and low permeability into the bodies of gram-negative bacteria and therefore have low efficacy in

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clinical application (Maxwell, A., 1997, Trends Microbiol. 5: 102-109). Examples of other natural products targeting GyrB include cyclothialidine isolated from *Streptomyces filipinensis* (Watanabe, J. et al., 1994, J. Antibiot. 47: 32-36) and cinodine isolated from the genus *Nocardia* (Martin, J.H. et al., 1978, J. Antibiot. 31: 398-404). Cyclothialidine is an inadequate antibacterial agent that exhibits activity against only a limited number of bacteria (Nakada, N. et al., 1993, Antimicrob. Agents Chemother. 37: 2656-2661). Cinodine has strong toxicity to eukaryotes and is therefore impossible to use clinically (Ellestad, G.A., 2006, Journal of Medicinal Chemistry. 49: 6627-6634). There is a demand to acquire a novel effective GyrB inhibitor that overcomes the disadvantages of these known natural products. Such an inhibitor is an interesting antibacterial agent candidate that is effective even against the spread of resistant bacteria, which besets the existing antibacterial agents. [0011]

In developing antibiotics having a novel mechanism of action, synthetic inhibitors targeting the DNA gyrase GyrB subunit are known in the art. Patent Publication Nos. WO 2005/026149, WO 2006/087543, WO 2006/087544, WO 2006/087548, WO 2006/092599, and WO 2006/092608 describe pyrrole derivatives having antibacterial activity. Patent Publication No. WO 2007/071965 describes bicyclic heteroaromatic compounds. These compounds had the problems of insufficient activity, cytotoxicity, low

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solubility in water, and the production of electrophilic reactive metabolites.

Patent Document 1: WO 2005/026149

Patent Document 2: WO 2006/087543

Patent Document 3: WO 2006/087544

Patent Document 4: WO 2006/087548

Patent Document 5: WO 2006/092599

Patent Document 6: WO 2006/092608

Patent Document 7: WO 2007/071965

Disclosure of the Invention

Problems to be Solved by the Invention

[0012]

To develop an antibiotic having a novel mechanism of action, the present inventors have searched for a compound that has weak cytotoxicity, the physical property of high solubility in water, the effect of inhibiting both DNA gyrase GyrB and topoisomerase IV ParE subunits, and sufficient antibacterial activity. As a result, the present inventors have completed the present invention by finding that compounds of the present invention represented by the general formula (1), pharmacologically acceptable salts thereof, and hydrates thereof have desirable properties.

The present invention provides a pharmaceutical composition (particularly, a preventive or therapeutic composition for infectious disease) comprising a compound represented by the formula (1), a pharmacologically

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acceptable salt thereof, or a hydrate thereof as an active ingredient, use of the compound represented by the formula (1), a pharmacologically acceptable salt thereof, or a hydrate thereof for producing a pharmaceutical composition (particularly, a preventive or therapeutic composition for infectious disease), and a method for preventing or treating disease (particularly, infectious disease), comprising administering a pharmacologically effective amount of the compound represented by the general formula (1), a pharmacologically acceptable salt thereof, or a hydrate thereof to a warm-blooded animal (particularly, a human).

Means for Solving the Problems

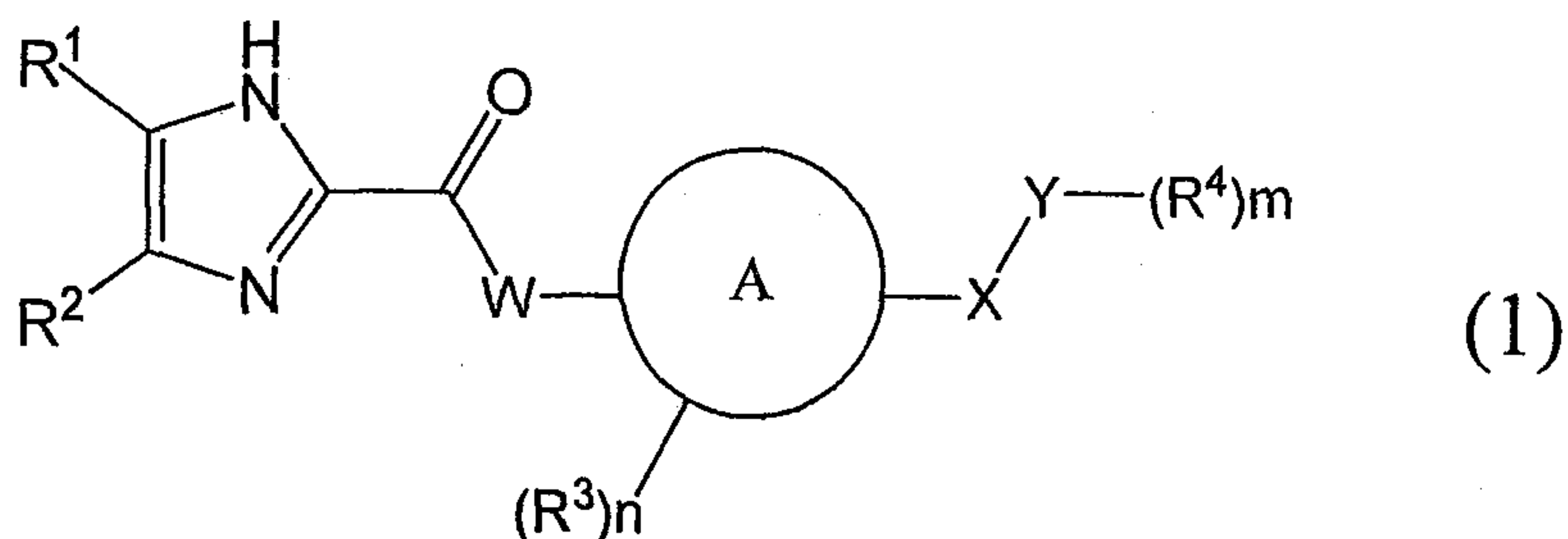
[0013]

Specifically, the present invention provides:

(1) A compound represented by the formula (1), a pharmacologically acceptable salt thereof, or a hydrate thereof:

[0014]

[Formula 1]



[0015]

wherein

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R^1 and R^2 are each independently selected from a hydrogen atom, a nitro group, a hydroxy group, a halogen atom, a cyano group, a (C_1-C_4) alkyl group, a (C_1-C_4) alkoxy group, a (C_2-C_4) alkenyl group, a (C_2-C_4) alkynyl group, a $-CO(C_1-C_4)$ alkyl group, a $-S(O)_a(C_1-C_4)$ alkyl group (wherein a is 0, 1, or 2), and a (C_3-C_6) cycloalkyl group, and R^1 and R^2 may each independently be substituted at their respective carbon atoms with one or more halogen atom(s), cyclopropyl group(s), cyclobutyl group(s), and/or (C_1-C_4) alkoxy group(s);

W represents a single bond, $-O-$, $-NR^5-$, NR^5CH_2- , or $-C(R^6)(R^7)-$;

ring A represents a hydrocarbon ring group or a heterocyclic ring group;

X represents a single bond, $-O-$, $-NR^8-$, $-C(R^9)(R^{10})-$, $-C(O)-$, $-S(O)_p-$ (wherein p is an integer of 0, 1, or 2), $-C(O)NR^{11}-$, $-NR^{12}C(O)-$, $-S(O)_2NR^{13}-$, or $-NR^{14}S(O)_2-$;

Y represents a single bond, a hydrocarbon ring group, or a heterocyclic ring group;

R^3 and R^4 are each independently selected from the following substituents: the substituents are a hydrogen atom, a halogen atom, a nitro group, a cyano group, an oxo group, a hydroxy group, a trifluoromethoxy group, an amino group, a carboxy group, a carbamoyl group, a mercapto group, a sulfamoyl group, a sulfo group, a formyl group, an ureido group, a hydroxyiminomethyl group, a (C_1-C_4) alkoxyiminomethyl group, an N -hydroxyformamide group, a (C_1-C_4) alkylhydrazino group, a

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hydrazinocarbonyl group, an N-hydroxyethanimidoyl group, a (C₁-C₄) alkyl group, a (C₂-C₄) alkenyl group, a (C₂-C₄) alkynyl group, a (C₁-C₄) alkoxy group, -CO(C₁-C₄) alkyl, -OC(O)(C₁-C₄) alkyl, -NH(C₁-C₄) alkyl, -N[di(C₁-C₄) alkyl], -NHC(O)(C₁-C₄) alkyl, -C(O)NH(C₁-C₄) alkyl, -C(O)N[di(C₁-C₄) alkyl], -C(O)NH(C₁-C₄) alkoxy, -NHC(O)NH(C₁-C₄) alkyl, -NHC(O)N[di(C₁-C₄) alkyl], -C(O)N[(C₁-C₄) alkyl][(C₁-C₄) alkoxy], -S(O)_a(C₁-C₄) alkyl (wherein a is 0, 1, or 2), -C(O)(C₁-C₄) alkoxy, -OC(O)(C₁-C₄) alkoxy, -NHC(O)(C₁-C₄) alkoxy, -S(O)₂NH(C₁-C₄) alkyl, -S(O)₂N[di(C₁-C₄) alkyl], -NHSO₂(C₁-C₄) alkyl, -C(O)NHSO₂(C₁-C₄) alkyl, -C(O)NHNH(C₁-C₄) alkyl, -C(O)NHN[di(C₁-C₄) alkyl], =CH(C₁-C₄) alkyl, =C[di(C₁-C₄) alkyl], =N(C₁-C₄) alkoxy, =NN[di(C₁-C₄) alkyl], -R¹⁵-hydrocarbon ring, and -R¹⁶-heterocyclic ring, and R³ and R⁴ may each independently be substituted with one or more R¹⁷ moiety/moieties);

R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, and R¹⁴ each independently represent a hydrogen atom or a (C₁-C₄) alkyl group, wherein the (C₁-C₄) alkyl group may be substituted with R¹⁷;

[0016]

n is an integer of 0, 1, 2, 3, or 4, wherein a plurality of R³ moieties are the same or different;
m is an integer of 0, 1, 2, 3, or 4, wherein a plurality of R⁴ moieties are the same or different;
R¹⁷ is selected from an azide group, a halogen atom, a nitro group, a cyano group, an oxo group, a hydroxy group, a trifluoromethoxy group, an amino group, a carboxy group,

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a carbamoyl group, a mercapto group, a sulfamoyl group, a (C₁-C₄) alkyl group, a (C₂-C₄) alkenyl group, a (C₂-C₄) alkynyl group, a (C₁-C₄) alkoxy group, a -CO(C₁-C₄) alkyl group, a -OC(O)(C₁-C₄) alkyl group, -OC(O)(C₁-C₄) alkoxy, a -NH(C₁-C₄) alkyl group, a -N[di(C₁-C₄) alkyl] group, a -NHC(O)(C₁-C₄) alkyl group, -C(O)NH(C₁-C₄) alkyl, -C(O)N[di(C₁-C₄) alkyl], -C(O)NH(C₁-C₄) alkoxy, -NHC(O)NH(C₁-C₄) alkyl, -NHC(O)N[di(C₁-C₄) alkyl], -C(O)N[(C₁-C₄) alkyl][(C₁-C₄) alkoxy], -S(O)_a(C₁-C₄) alkyl (wherein a is 0, 1, or 2), -C(O)(C₁-C₄) alkoxy, -S(O)₂NH(C₁-C₄) alkyl, -S(O)₂N[di(C₁-C₄) alkyl], -NHS(O)₂(C₁-C₄) alkyl, -NHC(O)(C₁-C₄) alkoxy, =CH(C₁-C₄) alkyl, =C[di(C₁-C₄) alkyl], =N(C₁-C₄) alkoxy, =NN[di(C₁-C₄) alkyl], -R¹⁸-hydrocarbon ring, and -R¹⁹-heterocyclic ring, and R¹⁷ moieties may each independently be substituted with one or more R²⁰ moiety/moieties;

[0017]

R¹⁵, R¹⁶, R¹⁸, and R¹⁹ are each independently selected from a single bond, a double bond, -C(R²¹)(R²²)-, -O-, -N(R²³)-, -C(O)-, -N(R²⁴)C(O)-, -C(O)N(R²⁵)-, -S(O)_p- (wherein p is an integer of 0, 1, or 2), -S(O)₂N(R²⁶)-, -N(R²⁷)S(O)₂-, -O(CO)O-, -C(R²⁸)=, and -N=, wherein R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, and R²⁸ are each independently selected from a hydrogen atom and a (C₁-C₄) alkyl group; and

[0018]

R²⁰ is selected from a halogen atom, a nitro group, a cyano group, an oxo group, a hydroxy group, a

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trifluoromethoxy group, a trifluoromethyl group, an amino group, a carboxy group, a carbamoyl group, a mercapto group, a sulfamoyl group, a methyl group, an ethyl group, a vinyl group, a methoxy group, an ethoxy group, an acetyl group, an acetoxymethyl group, a methylamino group, an ethylamino group, a dimethylamino group, a diethylamino group, -N(methyl)(ethyl), -NHC(O)-methyl, -C(O)NH-methyl, -C(O)NH-ethyl, -C(O)N[di(methyl)], -C(O)N[di(ethyl)], -C(O)N[(methyl)(ethyl)], a methylthio group, an ethylthio group, -S(O)-methyl, -S(O)-ethyl, -S(O)₂-methyl, -S(O)₂-ethyl, a methoxycarbonyl group, an ethoxycarbonyl group, -S(O)₂NH-methyl, -S(O)₂NH-ethyl, -S(O)₂N[di(methyl)], -S(O)₂N[di(ethyl)], and -S(O)₂N[(methyl)(ethyl)].

[0019]

(2) The compound according to (1), a pharmacologically acceptable salt thereof, or a hydrate thereof, wherein W is a single bond.

[0020]

(3) The compound according to (1), a pharmacologically acceptable salt thereof, or a hydrate thereof, wherein W is -NR⁵-.

[0021]

(4) The compound according to any one of (1) to (3), a pharmacologically acceptable salt thereof, or a hydrate thereof, wherein the ring A is a hydrocarbon ring.

[0022]

(5) The compound according to any one of (1) to (3), a pharmacologically acceptable salt thereof, or a hydrate

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thereof, wherein the ring A is a heterocyclic ring.

[0023]

(6) The compound according to any one of (1) to (3), a pharmacologically acceptable salt thereof, or a hydrate thereof, wherein the hydrocarbon ring is an indan ring, a benzene ring, a cyclohexane ring, or a cyclohexene ring.

[0024]

(7) The compound according to any one of (1) to (3), a pharmacologically acceptable salt thereof, or a hydrate thereof, wherein the heterocyclic ring is an azetidine ring, a pyrrolidine ring, a piperidine ring, an azepane ring, a thiazole ring, an oxazole ring, an imidazole ring, a pyrazole ring, a pyridine ring, a pyrimidine ring, a quinoline ring, an isoquinoline ring, a quinazoline ring, a benzoxazole ring, an oxazolopyridine ring, an oxazolopyrimidine ring, a benzimidazole ring, an imidazolopyridine ring, an imidazolopyrimidine ring, a pyrazolopyridine ring, a pyrazolopyrimidine ring, a thienopyridine ring, a thienopyrimidine ring, a benzothiophene ring, a thiazolopyridine ring, a thiazolopyrimidine ring, or a benzothiazole ring.

[0025]

(8) The compound according to any one of (1) to (3), a pharmacologically acceptable salt thereof, or a hydrate thereof, wherein the ring A is an indan ring, a benzene ring, a cyclohexane ring, or a cyclohexene ring.

[0026]

(9) The compound according to any one of (1) to (3),

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a pharmacologically acceptable salt thereof, or a hydrate thereof, wherein the ring A is an azetidine ring, a pyrrolidine ring, or a piperidine ring.

[0027]

(10) The compound according to any one of claims 1 to 9, a pharmacologically acceptable salt thereof, or a hydrate thereof, wherein X is selected from a single bond, $-\text{CH}_2-$, and $-\text{C}(\text{O})-$.

[0028]

(11) The compound according to any one of claims 1 to 10, a pharmacologically acceptable salt thereof, or a hydrate thereof, wherein Y is selected from a single bond, a phenyl group, and a heterocyclic ring group.

[0029]

(12) The compound according to any one of claims 1 to 10, a pharmacologically acceptable salt thereof, or a hydrate thereof, wherein Y is selected from a single bond, a phenyl group, a thiazolyl group, an oxazolyl group, an imidazolyl group, a pyrazolyl group, a quinolinyl group, an isoquinolinyl group, a quinazolyl group, a benzoxazolyl group, an oxazolopyridyl group, an oxazolopyrimidinyl group, a benzimidazolyl group, an imidazolopyridyl group, an imidazolopyrimidinyl group, a pyrazolopyridyl group, a pyrazolopyrimidinyl group, a thiazolopyridyl group, a thiazolopyrimidinyl group, a benzothiazolyl group, a pyrimidinyl group, and a pyridyl group.

[0030]

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(13) A compound represented by the formula (1) selected from the following, or a pharmacologically acceptable salt thereof:

cis(±)-2-(4-{[(4-chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylic acid,

cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylic acid,

cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-ethyl-1,3-thiazole-5-carboxylic acid,

cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-vinyl-1,3-thiazole-5-carboxylic acid,

cis(±)-2-(4-{[(4-chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-ethyl-1,3-thiazole-5-carboxylic acid,

cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylic acid,

cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(methylcarbamoyl)-1,3-thiazole-5-carboxylic acid,

cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-

[(methoxyethyl)carbamoyl]-1,3-thiazole-5-carboxylic acid,

cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-

yl)carbonyl]amino}-3-(2,2-difluoroethoxy)piperidin-1-yl)-
 4-methyl-1,3-thiazole-5-carboxylic acid,
 cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-
 yl)carbonyl]amino}-3-propoxypiperidin-1-yl)-1,3-
 benzothiazole-7-carboxylic acid,
 cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-
 yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-acetyl-1,3-
 thiazole-5-carboxylic acid,
 2-[(3S,4R)-4-{[(4-chloro-5-ethyl-1H-imidazol-2-
 yl)carbonyl]amino}-3-methoxypiperidin-1-yl]-4-methyl-1,3-
 thiazole-5-carboxylic acid,
 cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-
 yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-4-acetyl-1,3-
 thiazole-5-carboxylic acid,
 cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-
 yl)carbonyl]amino}-3-(2,2-difluoropropoxy)piperidin-1-
 yl)-4-methyl-1,3-thiazole-5-carboxylic acid,
 cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-
 yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-4-
 [(methoxyethyl)carbamoyl]-1,3-thiazole-5-carboxylic acid,
 cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-
 yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-
 (dimethylcarbamoyl)-1,3-thiazole-5-carboxylic acid,
 cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-
 yl)carbonyl]amino}-3-propoxypiperidin-1-yl)-4-
 [(methoxyethyl)carbamoyl]-1,3-thiazole-5-carboxylic acid,
 cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-
 yl)carbonyl]amino}-3-propoxypiperidin-1-yl)-4-

(methylcarbamoyl)-1,3-thiazole-5-carboxylic acid,
 cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-4-(ethylcarbamoyl)-1,3-thiazole-5-carboxylic acid,
 cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-4-(isopropylcarbamoyl)-1,3-thiazole-5-carboxylic acid,
 cis(±)-2-[3-(butylamino)-4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}piperidin-1-yl]-1,3-benzothiazole-7-carboxylic acid,
 cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-4-[(2-fluoroethyl)carbamoyl]-1,3-thiazole-5-carboxylic acid,
 2-((3R*,4S*)-4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-4-[(2-methoxy-1-methylethyl)carbamoyl]-1,3-thiazole-5-carboxylic acid,
 cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-4-[(2-ethoxyethyl)carbamoyl]-1,3-thiazole-5-carboxylic acid,
 cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-isopropoxypiperidin-1-yl)-4-(2-methoxyethylcarbamoyl)-1,3-thiazole-5-carboxylic acid,
 cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-[(cyclopropylmethyl)amino]piperidin-1-yl)-1,3-benzothiazole-7-carboxylic acid,
 cis(±)-2-[4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-(pentylamino)piperidin-1-yl]-1,3-benzothiazole-7-carboxylic acid,

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cis(±)-2-[4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-(cyclopentylamino)piperidin-1-yl]-1,3-benzothiazole-7-carboxylic acid,

cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-[(3-methylbutyl)amino]piperidin-1-yl)-1,3-benzothiazole-7-carboxylic acid,

cis(±)-2-[4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-(cyclobutylamino)piperidin-1-yl]-1,3-benzothiazole-7-carboxylic acid, and

2-[(3S,4R)-4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-[(1-ethylpropyl)amino]piperidin-1-yl]-1,3-benzothiazole-7-carboxylic acid.

[0031]

(14) The compound according to any one of (1) to (13), a pharmacologically acceptable salt thereof, or a hydrate thereof, which is intended for use in a method for therapeutically treating a human or animal body.

[0032]

(15) A pharmaceutical agent comprising a compound according to any one of (1) to (13), a pharmacologically acceptable salt thereof, or a hydrate thereof.

[0033]

(16) Use of a compound according to any one of (1) to (13), a pharmacologically acceptable salt thereof, or a hydrate thereof for producing a pharmaceutical agent.

[0034]

(17) A bacterial DNA gyrase inhibitor comprising a compound according to any one of (1) to (13), a

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pharmacologically acceptable salt thereof, or a hydrate thereof.

[0035]

(18) An antibacterial agent comprising a compound according to any one of (1) to (13), a pharmacologically acceptable salt thereof, or a hydrate thereof.

[0036]

(19) A therapeutic agent for infectious disease comprising a compound according to any one of (1) to (13), a pharmacologically acceptable salt thereof, or a hydrate thereof.

[0037]

(20) A method for producing an antibacterial effect in a warm-blooded animal (e.g., a human) in need of treatment which produces an antibacterial effect, the method comprising administering an effective amount of a compound according to any one of (1) to (13), a pharmacologically acceptable salt thereof, or a hydrate thereof to the animal.

[0038]

(21) A method for inhibiting bacterial DNA gyrase in a warm-blooded animal (e.g., a human) in need of treatment which inhibits bacterial DNA gyrase, the method comprising administering an effective amount of a compound according to any one of (1) to (13), a pharmacologically acceptable salt thereof, or a hydrate thereof to the animal.

[0039]

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(22) A method for treating bacterial infection in a warm-blooded animal (e.g., a human) in need of treatment of bacterial infection, the method comprising administering an effective amount of a compound according to any one of (1) to (13), a pharmacologically acceptable salt thereof, or a hydrate thereof to the animal.

[0040]

(23) The compound according to any one of (1) to (13), a pharmacologically acceptable salt thereof, or a hydrate thereof, which is intended for use as a pharmaceutical agent.

[0041]

(24) Use of a compound according to any one of (1) to (13), a pharmacologically acceptable salt thereof, or a hydrate thereof in the production of a pharmaceutical agent used for producing an antibacterial effect in a warm-blooded animal (e.g., a human).

[0042]

(25) Use of a compound according to any one of (1) to (13), a pharmacologically acceptable salt thereof, or a hydrate thereof in the production of a pharmaceutical agent used for inhibiting bacterial DNA gyrase in a warm-blooded animal (e.g., a human).

[0043]

(26) Use of a compound according to any one of (1) to (13), a pharmacologically acceptable salt thereof, or a hydrate thereof in the production of a pharmaceutical agent used for treating bacterial infection in a warm-

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blooded animal (e.g., a human).

[0044]

(27) The compound according to any one of (1) to (13), a pharmacologically acceptable salt thereof, or a hydrate thereof, which is intended for use for producing an antibacterial effect in a warm-blooded animal (e.g., a human).

[0045]

(28) The compound according to any one of (1) to (13), a pharmacologically acceptable salt thereof, or a hydrate thereof, which is intended for use for inhibiting bacterial DNA gyrase in a warm-blooded animal (e.g., a human).

[0046]

(29) The compound according to any one of (1) to (13), a pharmacologically acceptable salt thereof, or a hydrate thereof, which is intended for use for treating bacterial infection in a warm-blooded animal (e.g., a human).

[0047]

(30) A pharmaceutical composition comprising a compound according to any one of (1) to (13), a pharmacologically acceptable salt thereof, or a hydrate thereof, and a pharmaceutically acceptable diluent or carrier.

[0048]

(31) A pharmaceutical composition intended for use for producing an antibacterial effect in a warm-blooded

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animal (e.g., a human), the pharmaceutical composition comprising a compound according to any one of (1) to (13), a pharmacologically acceptable salt thereof, or a hydrate thereof, together with a pharmaceutically acceptable excipient or carrier.

[0049]

(32) A pharmaceutical composition intended for use for inhibiting bacterial DNA gyrase in a warm-blooded animal (e.g., a human), the pharmaceutical composition comprising a compound according to any one of (1) to (13), a pharmacologically acceptable salt thereof, or a hydrate thereof, together with a pharmaceutically acceptable excipient or carrier.

[0050]

(33) A pharmaceutical composition intended for use for treating bacterial infection in a warm-blooded animal (e.g., a human), the pharmaceutical composition comprising a compound according to any one of (1) to (13), a pharmacologically acceptable salt thereof, or a hydrate thereof, together with a pharmaceutically acceptable excipient or carrier.

Advantages of the Invention

[0051]

An imidazole carbonyl compound of the present invention represented by the general formula (1) is useful as a pharmaceutical agent, particularly, a preventive and/or therapeutic agent for infectious

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disease, which has the effect of inhibiting both bacterial DNA gyrase GyrB and topoisomerase IV ParE subunits, is excellent in sufficient antibacterial activity, and has weak cytotoxicity and the physical property of high solubility in water.

Best Mode for Carrying Out the Invention

[0052]

In the present specification, the term "alkyl" encompasses both linear and branched alkyl groups. However, an individual alkyl group, for example, propyl, described herein refers to only the linear form.

[0053]

A similar rule is also applied to other generic names. The term "alkyl" advantageously means a chain having 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms, unless otherwise specified. In the present specification, all the terms "alkenyl", "alkynyl", and "cycloalkenyl" encompass regioisomers and geometric isomers.

[0054]

In the present specification, the term "alkoxy" means such an alkyl group as defined above linked to an oxygen atom.

When arbitrary substituents are selected from 0, 1, 2, or 3 kinds of groups, this definition naturally encompasses all substituents being selected from any one kind of these specified groups or substituents being selected

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from two or more kinds of the specified groups. A similar rule is applied to substituents selected from 0, 1, or 2 kinds of groups; 1, 2, or 3 kinds of substituents; and 1 or 2 kinds of groups.

[0055]

The hydrocarbon ring group refers to a hydrocarbon ring having a monovalent or divalent bond. The term "hydrocarbon ring" refers to a saturated, partially saturated, or unsaturated monocyclic or bicyclic carbon ring containing 3 to 12 carbon atoms, wherein a $-CH_2-$ group may optionally be substituted with $-C(O)-$. Preferably, the hydrocarbon ring is a monocyclic carbon ring containing 5 to 6 atoms or a bicyclic carbon ring containing 9 or 10 atoms. Preferred specific examples thereof include a cyclopropane ring, a cyclobutane ring, a cyclopentane ring, an oxocyclopentane ring, a cyclopentene ring, a cyclohexane ring, a cyclohexene ring, a benzene ring, an indan ring, an oxoindan ring, an indene ring, a tetralin ring, and a naphthalene ring.

[0056]

The heterocyclic ring group refers to a heterocyclic ring having a monovalent or divalent bond. The term "heterocyclic ring" refers to an optionally substituted, saturated or unsaturated monocyclic or bicyclic ring containing 3 to 12 atoms (of them, 1, 2, 3, or 4 ring atoms are selected from nitrogen, sulfur, and oxygen and may be linked carbon, nitrogen, sulfur, or oxygen, unless otherwise specified), wherein a $-CH_2-$ group may

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optionally be substituted with -C(O)-; a sulfur atom in the ring may optionally be oxidized to form an S-oxide; and a nitrogen atom in the ring may optionally be oxidized to form an N-oxide. Specific examples of the heterocyclic ring include an azetidine ring, a morpholine ring, a piperidine ring, a pyridine ring, a pyridyl-N-oxide ring, a pyran ring, a pyrrole ring, an imidazoline ring, a thiazole ring, a thiophene ring, a dioxolane ring, a thiadiazole ring, a piperazine ring, an isothiazole ring, a thiazolidine ring, a triazole ring, a tetrazole ring, an azepane ring, a pyrrolidine ring, an oxazolidine ring, an isoxazolone ring, a thiomorpholine ring, a homopiperazine ring, a 3,5-dioxopiperidine ring, a pyrazolone ring, a tetrahydropyran ring, a tetrahydrothiopyran ring, a 1-oxotetrahydrothiopyran ring, a 1,1-dioxotetrahydrothiopyran ring, a pyrimidine ring, a pyrazine ring, a pyridazine ring, a pyrazole ring, a pyrazoline ring, an isoxazole ring, a 4-oxopyrrolidine ring, a 2-oxopyrrolidine ring, a 4-oxothiazolidine ring, a furan ring, a thiophene ring, an oxazole ring, an oxadiazole ring, a quinoline ring, and a benzothiazole ring.

[0057]

Preferably, the heterocyclic ring group is an azetidine ring group, a morpholine ring group, a pyrrolidine ring group, a piperidine ring group, a pyridine ring group, a pyran ring group, a pyrrole ring

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group, an imidazole ring group, a thiazole ring group, a thiophene ring group, a thiadiazole ring group, a piperazine ring group, an isothiazolidine ring group, a 1,2,4-triazole ring group, a tetrazole ring group, an azepane ring group, a pyrrolidine ring group, a thiomorpholine ring group, a pyrroline ring group, a homopiperazine ring group, a 3,5-dioxopiperidine ring group, a pyrimidine ring group, a pyrazine ring group, a pyridazine ring group, a pyrazole ring group, a pyrazoline ring group, an isoxazole ring group, a 4-oxopyrrolidine ring group, a 2-oxopyrrolidine ring group, a 4-oxothiazolidine ring group, a furan ring group, a thiophene ring group, an oxazole ring group, a 1,3,4-oxadiazole ring group, a 1,2,4-oxadiazole ring group, a quinoline ring group, or a benzothiazole ring group.

[0058]

More preferably, the heterocyclic ring group is an azetidine ring group, a piperidine ring group, a pyrimidine ring group, a pyridine ring group, an oxazole ring group, a thiazole ring group, a quinoline ring group, or a benzothiazole ring group.

[0059]

The halogen atom is, for example, a fluorine, chlorine, bromine, or iodine atom.

[0060]

The (C₁-C₄) alkyl is, for example, methyl, ethyl, propyl, butyl, 1-methylethyl, 1,1-dimethylethyl, 1-methylpropyl, or 2-methylpropyl.

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The (C₁-C₄) alkoxy is, for example, methoxy, ethoxy, propoxy, 1-methylethoxy, butoxy, 2-methylpropoxy, 1,1-dimethylethylethoxy, or 1-methylpropoxy.

Examples of the (C₂-C₄) alkenyl include vinyl, propenyl, allyl, but-2-enyl, and but-3-enyl.

Examples of the (C₂-C₄) alkynyl include ethynyl, prop-2-ynyl, but-2-ynyl, and but-3-ynyl.

Examples of the (C₃-C₆) cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0061]

Hereinafter, R¹ to R⁴, W, ring A, X, Y, m, and n will be illustrated specifically.

[0062]

Specific examples of R¹ and R² each independently include a hydrogen atom, a nitro group, a hydroxy group, a fluorine atom, a chlorine atom, a bromine atom, an iodine atom, a cyano group, a methyl group, an ethyl group, a propyl group, a butyl group, a 1-methylethyl group, a 1,1-dimethylethyl group, a 1-methylpropyl group, a trifluoromethyl group, a 2-methylpropyl group, a methoxy group, a methoxymethyl group, an ethoxy group, a propoxy group, a butoxy group, a vinyl group, a propenyl group, an allyl group, a but-2-enyl group, a but-3-enyl group, an ethynyl group, a prop-2-ynyl group, a but-2-ynyl group, a but-3-ynyl group, an acetyl group, -CO-ethyl, -CO-propyl, -CO-butyl, -CO-1-methylethyl, -CO-1,1-dimethylethyl, -CO-1-methylpropyl, -CO-2-methylpropyl, -S-methyl, -S-ethyl, -S-propyl, -S-butyl, -S-1-methylethyl,

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-S-1,1-dimethylethyl, -S-1-methylpropyl, -S-2-methylpropyl, -S(O)-methyl, -S(O)-ethyl, -S(O)-propyl, -S(O)-butyl, -S(O)-1-methylethyl, -S(O)-1,1-dimethylethyl, -S(O)-1-methylpropyl, -S(O)-2-methylpropyl, -S(O)₂-methyl, -S(O)₂-ethyl, -S(O)₂-propyl, -S(O)₂-butyl, -S(O)₂-1-methylethyl, -S(O)₂-1,1-dimethylethyl, -S(O)₂-1-methylpropyl, -S(O)₂-2-methylpropyl, a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, and a cyclohexyl group. Preferably, R¹ and R² are each independently a hydrogen atom, a methyl group, an ethyl group, a propyl group, a 1-methylethyl group, a methoxymethyl group, a trifluoromethyl group, -S-methyl, a chlorine atom, a bromine atom, or an iodine atom, more preferably a methyl group, an ethyl group, a chlorine atom, or a bromine atom.

[0063]

Specific examples of R³ and R⁴ each independently include a hydrogen atom, a fluorine atom, a chlorine atom, a bromine atom, an iodine atom, a nitro group, a cyano group, an oxo group, a hydroxy group, an acetyl group, a fluoromethyl group, a trifluoromethyl group, a hydroxymethyl group, a trifluoromethoxy group, an amino group, a carboxy group, a carbamoyl group, a mercapto group, a sulfamoyl group, a sulfo group, a formyl group, an ureido group, a hydroxyiminomethyl group, a methoxyiminomethyl group, an ethoxyiminomethyl group, a propoxyiminomethyl group, a butoxyiminomethyl group, an N-hydroxyformamide group, a methylhydrazino group, an ethylhydrazino group, a propylhydrazino group, a

butylhydrazino group, a 1-methylethylhydrazino group, a 1,1-dimethylethylhydrazino group, a 1-methylpropylhydrazino group, a 2-methylpropylhydrazino group, a hydrazinocarbonyl group, an N-hydroxyethanimidoyl group, a methyl group, a cyclopropylmethyl group, an ethyl group, a propyl group, a butyl group, a pentyl group, a hexyl group, a 1-methylethyl group, a 1,1-dimethylethyl group, a 1-methylpropyl group, a 2-methylpropyl group, a 1-ethylpropyl group, a 3-methylbutyl group, a vinyl group, a propenyl group, an allyl group, a but-2-enyl group, a but-3-enyl group, an ethynyl group, a prop-2-ynyl group, a but-2-ynyl group, a but-3-ynyl group, a methoxy group, an ethoxy group, a 1-methylethoxy group, a 1,1-dimethylethoxy group, a 2-difluoroethoxy group, a 2-fluoroethoxy group, a propoxy group, a 1-ethylpropoxy group, a 3-fluoropropoxy group, a 2-difluoropropoxy group, a butoxy group, a 2-methylpropoxy group, a 3-methylbutoxy group, a benzyloxy group, a carboxymethyl group, a 2-carboxyethyl group, a 5-carboxy-4-methyl-1,3-thiazolyl group, a 1-carboxy-cyclopropyl group, -CO-Et, -CO-propyl, -CO-butyl, -CO-1-methylethyl, -CO-1,1-dimethylethyl, -CO-1-methylpropyl, -CO-2-methylpropyl, -CO-Ph, -OC(O)-methyl, -OC(O)-ethyl, -OC(O)-propyl, -OC(O)-butyl, -OC(O)-1-methylethyl, -OC(O)-1,1-dimethylethyl, -OC(O)-1-methylpropyl, -OC(O)-2-methylpropyl, -NHMe, -NH₂Et, -NH-propyl, -NH-cyclopropyl, -NH-cyclopropylmethyl, -NH-butyl, -NHCH(Me)₂, -NH-1,1-dimethylethyl, -NH-1-methylpropyl, -

NH-2-methylpropyl, -NHCH(Et)₂, -NH-3-methylbutyl, -NH-pentyl, -NH-hexyl, -NH-benzyl, -NH-cyclobutyl, -NH-cyclopentyl, -NMe₂, -N[methyl][ethyl], -N[ethyl]₂, -N[methyl][propyl], -N[propyl]₂, -N[butyl]₂, -N[methyl][1-methylethyl], -N[1-methylethyl]₂, -N[1,1-dimethylethyl]₂, -N[1-methylpropyl]₂, -N[2-methylpropyl]₂, -NHAc, -NHC(O)-ethyl, -NHC(O)-propyl, -NHC(O)-butyl, -NHC(O)-1-methylethyl, -NHC(O)-1,1-dimethylethyl, -NHC(O)-1-methylpropyl, -NHC(O)-2-methylpropyl, -C(O)NHMe, -C(O)NH₂Et, -C(O)NH-propyl, -C(O)NH-butyl, -C(O)NHCH(Me)₂, -C(O)NH-1,1-dimethylethyl, -C(O)NH-1-methylpropyl, -C(O)NH-2-methylpropyl, -C(O)NH-Ph, -C(O)NH-cyclopropyl, a piperidin-4-ylcarbamoyl group, -C(O)NHCH₂COOH, -C(O)NH(CH₂)₂F, -C(O)NH(CH₂)₂NMe₂, -C(O)NH(CH₂)₂NEt₂, -C(O)NH(CH₂)₂NHAc, -C(O)NH(CH₂)₂OMe, -C(O)NH(CH₂)₂OEt, -C(O)NH(CH₂)₂CN, -C(O)NHCH(Me)CH₂OH, -C(O)NHCH(Me)CH₂OMe, -C(O)NHCH₂CHF₂, -C(O)NH-2-methylpropyl, -C(O)NMe₂, -C(O)N[methyl][ethyl], -C(O)N[ethyl]₂, -C(O)N[methyl][propyl], -C(O)N[methyl][1-methylethyl], -C(O)N[propyl]₂, -C(O)N[butyl]₂, -C(O)N[1-methylethyl]₂, -C(O)N[1,1-dimethylethyl]₂, -C(O)N[1-methylpropyl]₂, -C(O)N[2-methylpropyl]₂, a 4-methylpiperazin-1-ylcarbonyl group, -C(O)NH-OMe, -C(O)NH-ethoxy, -C(O)NH-propoxy, -C(O)NH-butoxy, -NHC(O)NH-methyl, -NHC(O)NH-ethyl, -NHC(O)NH-propyl, -NHC(O)NH-butyl, -NHC(O)NH-1-methylethyl, -NHC(O)NH-1,1-dimethylethyl, -NHC(O)NH-1-methylpropyl, -NHC(O)NH-2-methylpropyl, -NHC(O)N[methyl]₂, -NHC(O)N[ethyl]₂, -NHC(O)N[propyl]₂, -NHC(O)N[butyl]₂, -

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NHC(O)N[1-methylethyl]₂, -NHC(O)N[1,1-dimethylethyl]₂, -
 NHC(O)N[1-methylpropyl]₂, -NHC(O)N[2-methylpropyl]₂, -
 C(O)N[methyl][methoxy], -C(O)N[ethyl][methoxy], -
 C(O)N[propyl][methoxy], -C(O)N[butyl][methoxy], -C(O)N[1-
 methylethyl][methoxy], -C(O)N[1,1-dimethylethyl][methoxy],
 -C(O)N[1-methylpropyl][methoxy], -C(O)N[2-
 methylpropyl][methoxy], -C(O)N[methyl][ethoxy], -
 C(O)N[ethyl][ethoxy], -C(O)N[propyl][ethoxy], -
 C(O)N[butyl][ethoxy], -C(O)N[1-methylethyl][ethoxy], -
 C(O)N[1,1-dimethylethyl][ethoxy], -C(O)N[1-
 methylpropyl][ethoxy], -C(O)N[2-methylpropyl][ethoxy], -
 C(O)N[methyl][propoxy], -C(O)N[ethyl][propoxy], -
 C(O)N[propyl][propoxy], -C(O)N[butyl][propoxy], -C(O)N[1-
 methylethyl][propoxy], -C(O)N[1,1-dimethylethyl][propoxy],
 -C(O)N[1-methylpropyl][propoxy], -C(O)N[2-
 methylpropyl][propoxy], -C(O)N[methyl][butoxy], -
 C(O)N[ethyl][butoxy], -C(O)N[propyl][butoxy], -
 C(O)N[butyl][butoxy], -C(O)N[1-methylethyl][butoxy], -
 C(O)N[1,1-dimethylethyl][butoxy], -C(O)N[1-
 methylpropyl][butoxy], -C(O)N[2-methylpropyl][butoxy], -
 S-methyl, -S-ethyl, -S-propyl, -S-butyl, -S-1-methylethyl,
 -S-1,1-dimethylethyl, -S-1-methylpropyl, -S-2-
 methylpropyl, -S(O)-methyl, -S(O)-ethyl, -S(O)-propyl, -
 S(O)-butyl, -S(O)-1-methylethyl, -S(O)-1,1-dimethylethyl,
 -S(O)-1-methylpropyl, -S(O)-2-methylpropyl, -S(O)₂-methyl,
 -S(O)₂-ethyl, -S(O)₂-propyl, -S(O)₂-butyl, -S(O)₂-1-
 methylethyl, -S(O)₂-1,1-dimethylethyl, -S(O)₂-1-
 methylpropyl, -S(O)₂-2-methylpropyl, a methoxycarbonyl

group, an ethoxycarbonyl group, -C(O)-propoxy, -C(O)-butoxy, -C(O)(1,1-dimethylethoxy), -OC(O)-methoxy, -OC(O)-ethoxy, -OC(O)-propoxy, -OC(O)-butoxy, -NHC(O)-methoxy, -NHC(O)-ethoxy, -NHC(O)-propoxy, -NHC(O)-butoxy, -NHC(O)-benzyloxy, -S(O)₂NH-methyl, -S(O)₂NH-ethyl, -S(O)₂NH-propyl, -S(O)₂NH-butyl, -S(O)₂NH-1-methylethyl, -S(O)₂NH-1,1-dimethylethyl, -S(O)₂NH-1-methylpropyl, -S(O)₂NH-2-methylpropyl, -S(O)₂N[methyl]₂, -S(O)₂N[ethyl]₂, -S(O)₂N[propyl]₂, -S(O)₂N[butyl]₂, -S(O)₂N[1-methylethyl]₂, -S(O)₂N[1,1-dimethylethyl]₂, -S(O)₂N[1-methylpropyl]₂, -S(O)₂N[2-methylpropyl]₂, -NHSO₂-methyl, -NHSO₂-ethyl, -NHSO₂-propyl, -NHSO₂-butyl, -NHSO₂-1-methylethyl, -NHSO₂-1,1-dimethylethyl, -NHSO₂-1-methylpropyl, -NHSO₂-2-methylpropyl, -C(O)NHSO₂-methyl, -C(O)NHSO₂-ethyl, -C(O)NHSO₂-propyl, -C(O)NHSO₂-butyl, -C(O)NHSO₂-1-methylethyl, -C(O)NHSO₂-1,1-dimethylethyl, -C(O)NHSO₂-1-methylpropyl, -C(O)NHSO₂-2-methylpropyl, -C(O)NHNH-methyl, -C(O)NHNH-ethyl, -C(O)NHNH-propyl, -C(O)NHNH-butyl, -C(O)NHNH-1-methylethyl, -C(O)NHNH-1,1-dimethylethyl, -C(O)NHNH-1-methylpropyl, -C(O)NHNH-2-methylpropyl, -C(O)NHN[methyl]₂, -C(O)NHN[ethyl]₂, -C(O)NHN[propyl]₂, -C(O)NHN[butyl]₂, -C(O)NHN[1-methylethyl]₂, -C(O)NHN[1,1-dimethylethyl]₂, -C(O)NHN[1-methylpropyl]₂, -C(O)NHN[2-methylpropyl]₂, =CH-methyl, =CH-ethyl, =CH-propyl, =CH-butyl, =CH-1-methylethyl, =CH-1,1-dimethylethyl, =CH-1-methylpropyl, =CH-2-methylpropyl, =C[methyl]₂, =C[ethyl]₂, =C[propyl]₂, =C[butyl]₂, =C[1-methylethyl]₂, =C[1,1-dimethylethyl]₂, =C[1-methylpropyl]₂, =C[2-methylpropyl]₂,

=N-methoxy, =N-ethoxy, =N-propoxy, =N-butoxy,
 =NN[methyl]₂, =NN[ethyl]₂, =NN[propyl]₂, =NN[butyl]₂,
 =NN[1-methylethyl]₂, =NN[1,1-dimethylethyl]₂, =NN[1-methylpropyl]₂, =NN[2-methylpropyl]₂, a tetrahydro-2H-pyran-4-ylamino group, a (1E)-3-(methoxyamino)-3-oxoprop-1-en-1-yl group, a (E)-2-carboxyethenyl group, a (E)-2-(4-carboxyphenyl)ethenyl group, a (E)-2-(2-fluoro-4-carboxyphenyl)ethenyl group, a (E)-2-(2-methoxy-4-carboxyphenyl)ethenyl group, a (1E)-N-methoxyethanimidoyl group, a (1Z)-N-methoxyethanimidoyl group, a (Z)-[3-(carboxymethyl)-2,4-dioxo-1,3-thiazolidin-5-ylidene]methyl group, a (Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl group, a (1-acetoxy)ethoxycarbonyl group, a (1,1-dimethylpropionyloxy)methoxycarbonyl group, a 1-[(2-propoxy)carbonyloxy]ethoxycarbonyl group, a 1-(cyclohexyloxy)ethoxycarbonyl group, a cyclopropane ring group, a cyclobutane ring group, a cyclopentane ring group, an oxocyclopentane ring group, a cyclopentene ring group, a cyclohexane ring group, a cyclohexene ring group, a benzene ring group, an indan ring group, an oxoindan ring group, an indene ring group, a tetralone ring group, a naphthalene ring group, an azetidine ring group, a morpholine ring group, a piperidine ring group, a pyridine ring group, a pyridyl-N-oxide ring group, a pyran ring group, a pyrrole ring group, an imidazoline ring group, a thiazole ring group, a thiophene ring group, a dioxolane ring group, a thiadiazole ring group, a piperazine ring group, an

isothiazole ring group, a thiazolidine ring group, a triazole ring group, a tetrazole ring group, an azepane ring group, a pyrrolidine ring group, an oxazolidine ring group, an isoxazolone ring group, a thiomorpholine ring group, a pyrrole ring group, a homopiperazine ring group, a 3,5-dioxopiperidine ring group, a pyrazolone ring group, a tetrahydropyran ring group, a tetrahydrothiopyran ring group, a 1-oxotetrahydrothiopyran ring group, a 1,1-dioxotetrahydrothiopyran ring group, a pyrimidine ring group, a pyrazine ring group, a pyridazine ring group, a pyrazole ring group, a pyrazoline ring group, an isoxazole ring group, a 4-oxopyrrolidine ring group, a 2-oxopyrrolidine ring group, a 4-oxothiazolidine ring group, a furan ring group, a thiophene ring group, an oxazole ring group, an oxadiazole ring group, a quinoline ring group, and a benzothiazole ring group.

Of them, a group having a divalent bond may be bonded when ring A or Y is a saturated or partially saturated hydrocarbon ring or heterocyclic ring or is even an aromatic ring, which must however be, for example, an indene ring or 7H-cyclopenta[c]pyridine ring.

[0064]

Preferably, R^3 is a hydrogen atom, a fluorine atom, a chlorine atom, a methyl group, an ethyl group, a methoxy group, an ethoxy group, a 2-difluoroethoxy group, a 2-fluoroethoxy group, a 1-methylethoxy group, a propoxy group, a 2-methylpropoxy group, a 2-difluoropropoxy group, a 3-fluoropropoxy group, -NH₂, -NHCH(Et)₂, -NHCH(Me)₂, -

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NH-propyl, -NH-butyl, -NH-2-methylpropyl, -NH-3-methylbutyl, -NH-pentyl, -NH-hexyl, -NMe₂, -NH-benzyl, -NHC(O)-benzyloxy, -NH-cyclobutyl, -NH-cyclopentyl, -NH-cyclopropyl, -NH-cyclopropylmethyl, a pyrrolidine ring group, a tetrahydro-2H-pyran-4-ylamino group, a benzyloxy group, a 3-methylbutoxy group, or a butoxy group. More preferred examples of R³ include a chlorine atom, an ethyl group, a methoxy group, an ethoxy group, a 2-fluoroethoxy group, a 2-difluoroethoxy group, a 1-methylethoxy group, a propoxy group, a 2-methylpropoxy group, a 2-difluoropropoxy group, a 3-fluoropropoxy group, -NH-2-methylpropyl, -NHCH(Et)₂, -NH-3-methylbutyl, -NH-butyl, -NH-pentyl, -NH-hexyl, -NH-benzyl, -NH-cyclobutyl, -NH-cyclopentyl, -NH-cyclopropylmethyl, and a butoxy group.

[0065]

Preferably, R⁴ is a hydrogen atom, a chlorine atom, an oxo group, a methyl group, a fluoromethyl group, a trifluoromethyl group, an ethyl group, a vinyl group, a 1-methylethyl group, a butyl group, a propyl group, a methoxy group, a 1,1-dimethylethoxy group, a hydroxymethyl group, a carboxy group, an acetyl group, a 1-carboxy-cyclopropyl group, a carboxymethyl group, a 2-carboxyethyl group, a 5-carboxy-4-methyl-1,3-thiazolyl group, -CO-Et, a carbamoyl group, -C(O)NHMe, -C(O)NH₂, -C(O)NHCH(Me)₂, -C(O)NH-Ph, -C(O)NH-cyclopropyl, a (1E)-N-methoxyethanimidoyl group, a (1Z)-N-methoxyethanimidoyl group, -C(O)NH-OMe, -C(O)NMe₂, a methoxycarbonyl group,

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an ethoxycarbonyl group, $-C(O)(1,1\text{-dimethylethoxy})$, $-C(O)-Ph$, a $(1E)\text{-}3\text{-(methoxyamino)-}3\text{-oxoprop-1-en-1-yl}$ group, $-C(O)NH(CH_2)_2F$, $-C(O)NH(CH_2)_2NMe_2$, $-C(O)NH(CH_2)_2NHAc$, $-C(O)NH(CH_2)_2OMe$, $-C(O)NH(CH_2)_2OEt$, $-C(O)NHCH(Me)CH_2OH$, $-C(O)NHCH(Me)CH_2OMe$, $-C(O)NHCH_2COOH$, $-C(O)NH(CH_2)_2NEt_2$, $-C(O)NHCH_2CHF_2$, $-C(O)NH(CH_2)_2CN$, a 4-methylpiperazin-1-ylcarbonyl group, a methoxyiminomethyl group, a piperidin-4-ylcarbonyl group, a $(E)\text{-}2\text{-carboxyethenyl}$ group, a $(E)\text{-}2\text{-(4-carboxyphenylethenyl)}$ group, a $(E)\text{-}2\text{-(2-fluoro-4-carboxyphenyl)ethenyl}$ group, a $(E)\text{-}2\text{-(2-methoxy-4-carboxyphenyl)ethenyl}$ group, $-NHAc$, a tetrazole ring group, a $(Z)\text{-(}2,4\text{-dioxo-1,3-thiazolidin-5-ylidene)methyl}$ group, or a $(Z)\text{-[}3\text{-(carboxymethyl)-}2,4\text{-dioxo-1,3-thiazolidin-5-ylidene]methyl}$ group.

[0066]

More preferably, R^4 is a hydrogen atom, an oxo group, a methyl group, an ethyl group, a vinyl group, a 1-methylethyl group, a propyl group, a butyl group, an acetyl group, a carbonyl group, $-C(O)NHMe$, $-C(O)NHEt$, $-C(O)NHCH(Me)_2$, $-C(O)NH\text{-cyclopropyl}$, $-C(O)NMe_2$, $-C(O)NH(CH_2)_2F$, $-C(O)NH(CH_2)_2OMe$, $-C(O)NH(CH_2)_2OEt$, $-C(O)NHCH(Me)CH_2OMe$, $-C(O)NHCH_2CHF_2$, $-C(O)NH(CH_2)_2CN$, a carboxy group, a $(1E)\text{-}3\text{-(methoxyamino)-}3\text{-oxoprop-1-en-1-yl}$ group, or a $(Z)\text{-(}2,4\text{-dioxo-1,3-thiazolidin-5-ylidene)methyl}$ group.

[0067]

Specific examples of R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , and R^{11}

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each independently include a hydrogen atom, a methyl group, an ethyl group, a 2-methoxyethyl group, a propyl group, a butyl group, a 1-methylethyl group, a 1,1-dimethylethyl group, a 1-methylpropyl group, and a 2-methylpropyl group.

[0068]

Specific examples of m and n each independently include an integer of 0, 1, 2, 3, or 4. Preferably, m is an integer of 0, 1, 2, or 4, and n is an integer of 0 or 1.

More preferably, m is an integer of 1 or 2, and n is an integer of 1.

[0069]

Specific examples of W include a single bond, -O-, -NH-, -N[methyl]-, -N[ethyl]-, -N[(CH₂)₂OMe]-, -N[propyl]-, -N[butyl]-, -N[1-methylethyl]-, -N[1,1-dimethylethyl]-, -N[1-methylpropyl]-, -N[2-methylpropyl]-, -CH₂-, -C(H)(methyl)-, -C(H)(ethyl)-, -C(H)(propyl)-, -C(H)(butyl)-, -C(H)(1-methylethyl)-, -C(H)(1,1-dimethylethyl)-, -C(H)(1-methylpropyl)-, -C(H)(2-methylpropyl)-, -C(methyl)(methyl)-, -C(methyl)(ethyl)-, -C(methyl)(propyl)-, -C(methyl)(butyl)-, -C(methyl)(1-methylethyl)-, -C(methyl)(1,1-dimethylethyl)-, -C(methyl)(1-methylpropyl)-, -C(methyl)(2-methylpropyl)-, -C(ethyl)(ethyl)-, -C(ethyl)(propyl)-, -C(ethyl)(butyl)-, -C(ethyl)(1-methylethyl)-, -C(ethyl)(1,1-dimethylethyl)-, -C(ethyl)(1-methylpropyl)-, -C(ethyl)(2-methylpropyl)-, -C(propyl)(propyl)-, -C(propyl)(butyl)-, -C(propyl)(1-

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methylethyl)-, -C(propyl)(1,1-dimethylethyl)-, -
 C(propyl)(1-methylpropyl)-, -C(propyl)(2-methylpropyl)-,
 -C(butyl)(butyl)-, -C(butyl)(1-methylethyl)-, -
 C(butyl)(1,1-dimethylethyl)-, -C(butyl)(1-methylpropyl)-,
 -C(butyl)(2-methylpropyl)-, -C(1-methylethyl)(1-
 methylethyl)-, -C(1-methylethyl)(1,1-dimethylethyl)-, -
 C(1-methylethyl)(1-methylpropyl)-, -C(1-methylethyl)(2-
 methylpropyl)-, -C(1,1-dimethylethyl)(1,1-dimethylethyl)-,
 -C(1,1-dimethylethyl)(1-methylpropyl)-, -C(1,1-
 dimethylethyl)(2-methylpropyl)-, -C(1-methylpropyl)(1-
 methylpropyl)-, -C(1-methylpropyl)(2-methylpropyl)-, and
 -C(2-methylpropyl)(2-methylpropyl)-. Preferably, W is a
 single bond, -NH-, -N[methyl]-, -N[(CH₂)₂OMe]-, -
 N[propyl]-, or -N[butyl]-. More preferably, W is a
 single bond, -NH-, -N[propyl]-, or -N[butyl]-.

[0070]

Specific examples of ring A include a cyclopropane ring, a cyclobutane ring, a cyclopentane ring, an oxocyclopentane ring, a cyclopentene ring, a cyclohexane ring, a cyclohexene ring, a benzene ring, an indan ring, an oxoindan ring, an indene ring, a tetralone ring, a naphthalene ring, an azetidine ring, a morpholine ring, a piperidine ring, a pyridine ring, a 1,2,3,4-tetrahydropyridine ring, a pyridyl-N-oxide ring, a pyran ring, a pyrrole ring, an imidazoline ring, a thiazole ring, a thiophene ring, a dioxolane ring, a thiadiazole ring, a piperazine ring, an isothiazole ring, an isoindole ring, a thiazolidine ring, a triazole ring, a

tetrazole ring, an azepane ring, a pyrrolidine ring, an oxazolidine ring, a benzoxazine ring, an isoxazolone ring, a thiomorpholine ring, a pyrrole ring, a homopiperazine ring, a 3,5-dioxopiperidine ring, a pyrazolone ring, a tetrahydropyran ring, a tetrahydrothiopyran ring, a 1-oxotetrahydrothiopyran ring, a 1,1-dioxotetrahydrothiopyran ring, a pyrimidine ring, a pyrazine ring, a pyridazine ring, a pyrazole ring, a pyrazoline ring, an isoxazole ring, a 4-oxopyrrolidine ring, a 2-oxopyrrolidine ring, a 4-oxothiazolidine ring, a 4,5,6,7-tetrahydro-2H-indazole ring, a 4,5,6,7-tetrahydro-1H-indazole ring, a 2,6-diazabicyclo[3.2.0]heptane ring, a furan ring, a benzothiophene ring, a 2H-chromene ring, an oxazole ring, an oxadiazole ring, a quinoline ring, a 1,2,3,4-tetrahydropyridine ring, and a benzothiazole ring.

[0071]

Preferably, the ring A is a benzene ring, a cyclohexane ring, a cyclohexene ring, an azetidine ring, a benzoxazine ring, an indan ring, a 4,5,6,7-tetrahydro-2H-indazole ring, a 4,5,6,7-tetrahydro-1H-indazole ring, a 2,6-diazabicyclo[3.2.0]heptane ring, a benzothiophene ring, a 2H-chromene ring, a 1,2,3,4-tetrahydropyridine ring, a piperidine ring, a pyrrolidine ring, or an isoindole ring, more preferably, a piperidine ring, a benzene ring, a 4,5,6,7-tetrahydro-1H-indazole ring, a 2,6-diazabicyclo[3.2.0]heptane ring, a cyclohexene ring, a benzothiophene ring, a 1,2,3,4-tetrahydropyridine ring,

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or an azetidine ring.

[0072]

Specific examples of X include a single bond, -O-, -NH-, -N(methyl)-, -N(ethyl)-, -N(propyl)-, -N(butyl)-, -N(1-methylethyl)-, -N(1,1-dimethylethyl)-, -N(1-methylpropyl)-, -N(2-methylpropyl)-, -CH₂-, -C(H)(methyl)-, -C(H)(ethyl)-, -C(H)(propyl)-, -C(H)(butyl)-, -C(H)(1-methylethyl)-, -C(H)(1,1-dimethylethyl)-, -C(H)(1-methylpropyl)-, -C(H)(2-methylpropyl)-, -C(methyl)(methyl)-, -C(methyl)(ethyl)-, -C(methyl)(propyl)-, -C(methyl)(butyl)-, -C(methyl)(1-methylethyl)-, -C(methyl)(1,1-dimethylethyl)-, -C(methyl)(1-methylpropyl)-, -C(methyl)(2-methylpropyl)-, -C(ethyl)(ethyl)-, -C(ethyl)(propyl)-, -C(ethyl)(butyl)-, -C(ethyl)(1-methylethyl)-, -C(ethyl)(1,1-dimethylethyl)-, -C(ethyl)(1-methylpropyl)-, -C(ethyl)(2-methylpropyl)-, -C(propyl)(propyl)-, -C(propyl)(butyl)-, -C(propyl)(1-methylethyl)-, -C(propyl)(1,1-dimethylethyl)-, -C(propyl)(1-methylpropyl)-, -C(propyl)(2-methylpropyl)-, -C(butyl)(butyl)-, -C(butyl)(1-methylethyl)-, -C(butyl)(1,1-dimethylethyl)-, -C(butyl)(1-methylpropyl)-, -C(butyl)(2-methylpropyl)-, -C(1-methylethyl)(1-methylethyl)-, -C(1-methylethyl)(1,1-dimethylethyl)-, -C(1-methylethyl)(1-methylpropyl)-, -C(1-methylethyl)(2-methylpropyl)-, -C(1,1-dimethylethyl)(1,1-dimethylethyl)-, -C(1,1-dimethylethyl)(1-methylpropyl)-, -C(1,1-dimethylethyl)(2-methylpropyl)-, -C(1-methylpropyl)(1-methylpropyl)-, -C(1-methylpropyl)(2-methylpropyl)-, -

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C(2-methylpropyl)(2-methylpropyl)-, -C(O)-, -S-, -S(O)-, -S(O)₂-, -C(O)NH-, -C(O)N(methyl)-, -C(O)N(ethyl)-, -C(O)N(propyl)-, -C(O)N(butyl)-, -C(O)N(1-methylethyl)-, -C(O)N(1,1-dimethylethyl)-, -C(O)N(1-methylpropyl)-, -C(O)N(2-methylpropyl)-, -NHC(O)-, -N(methyl)C(O)-, -N(ethyl)C(O)-, -N(propyl)C(O)-, -N(butyl)C(O)-, -N(1-methylethyl)C(O)-, -N(1,1-dimethylethyl)C(O)-, -N(1-methylpropyl)C(O)-, -N(2-methylpropyl)C(O)-, -S(O)₂NH-, -S(O)₂N(methyl)-, -S(O)₂N(ethyl)-, -S(O)₂N(propyl)-, -S(O)₂N(butyl)-, -S(O)₂N(1-methylethyl)-, -S(O)₂N(1,1-dimethylethyl)-, -S(O)₂N(1-methylpropyl)-, -S(O)₂N(2-methylpropyl)-, -NHS(O)₂-, -N(methyl)S(O)₂-, -N(ethyl)S(O)₂-, -N(propyl)S(O)₂-, -N(butyl)S(O)₂-, -N(1-methylethyl)S(O)₂-, -N(1,1-dimethylethyl)S(O)₂-, -N(1-methylpropyl)S(O)₂-, and -N(2-methylpropyl)S(O)₂-.

Preferably, X is a single bond, -NHC(O)-, -CH₂-, or -C(O)-. More preferably, X is a single bond, -CH₂-, or -C(O)-.

[0073]

Specific examples of Y include a single bond, a cyclopropane ring group, a cyclobutane ring group, a cyclopentane ring group, an oxocyclopentane ring group, a cyclopentene ring group, a cyclohexane ring group, a cyclohexene ring group, a benzene ring group, an indan ring group, an oxoindan ring group, an indene ring group, a tetralone ring group, a naphthalene ring group, an azetidine ring group, a morpholine ring group, a piperidine ring group, a pyridine ring group, a pyridyl-

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N-oxide ring group, a pyran ring group, a pyrrole ring group, an imidazoline ring group, a thiazole ring group, a thiophene ring group, a dioxolane ring group, a thiadiazole ring group, a piperazine ring group, an isothiazole ring group, a thiazolidine ring group, a triazole ring group, a tetrazole ring group, an azepane ring group, a pyrrolidine ring group, an oxazolidine ring group, an isoxazolone ring group, a thiomorpholine ring group, a pyrrole ring group, a homopiperazine ring group, a 3,5-dioxopiperidine ring group, a pyrazolone ring group, a tetrahydropyran ring group, a tetrahydrothiopyran ring group, a 1-oxotetrahydrothiopyran ring group, a 1,1-dioxotetrahydrothiopyran ring group, a pyrimidine ring group, a pyrazine ring group, a pyridazine ring group, a pyrazole ring group, a pyrazoline ring group, an isoxazole ring group, a 4-oxopyrrolidine ring group, a 2-oxopyrrolidine ring group, a 4-oxothiazolidine ring group, a furan ring group, a thiophene ring group, an oxazole ring group, a benzoxazole ring group, a benzimidazole ring group, an oxadiazole ring group, a quinoline ring group, a 1,4-dihydroquinoline ring group, a 5,6-dihydro-4H-pyrrolo[3,4-d][1,3]thiazole ring group, a 1,2-dihydropyridine ring group, and a benzothiazole ring group. Preferably, Y is a single bond, a benzene ring group, a cyclopropane ring group, a pyrrolidine ring group, an oxazole ring group, a benzoxazole ring group, a benzimidazole ring group, a thiazole ring group, a thiadiazole ring group, a thiophene ring group, a tetrazole ring group, a

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1,4-dihydroquinoline ring group, a benzothiazole ring group, a pyrimidine ring group, a 5,6-dihydro-4H-pyrrolo[3,4-d][1,3]thiazole ring group, a 1,2-dihydropyridine ring group, or a pyridine ring group. More preferably, Y is a benzothiazole ring group, a thiazole ring group, or a benzene ring group.

[0074]

When a compound of the present invention represented by the general formula (I) has a basic group such as an amino group, a "pharmacologically acceptable salt thereof" can be formed by reacting the compound with an acid. Alternatively, when a compound of the present invention represented by the general formula (I) has an acidic group such as a carboxyl group, a "pharmacologically acceptable salt thereof" can be formed by reacting the compound with a base. Thus, these salts will be shown below.

[0075]

Preferred examples of the salt based on a basic group include: inorganic acid salts such as hydrohalides (e.g., hydrochloride, hydrobromide, and hydroiodide), nitrate, perchlorate, sulfate, and phosphate; organic acid salts such as lower alkanesulfonates (e.g., methanesulfonate, trifluoromethanesulfonate, and ethanesulfonate), arylsulfonates (e.g., benzenesulfonate and p-toluenesulfonate), acetate, malate, fumarate, succinate, citrate, ascorbate, tartrate, oxalate, and maleate; and amino acid salts such as glycine salt,

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lysine salt, arginine salt, ornithine salt, glutamate, and aspartate.

[0076]

On the other hand, preferred examples of the salt based on an acidic group include: metal salts such as alkali metal salts (e.g., sodium salt, potassium salt, and lithium salt), alkaline earth metal salts (e.g., calcium salt and magnesium salt), aluminum salt, and iron salt; amine salts such as inorganic salts (ammonium salt) and organic salts (e.g., t-octylamine salt, dibenzylamine salt, morpholine salt, glucosamine salt, phenylglycine alkyl ester salt, ethylenediamine salt, N-methylglucamine salt, guanidine salt, diethylamine salt, triethylamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, chlorprocaine salt, procaine salt, diethanolamine salt, N-benzylphenethylamine salt, piperazine salt, tetramethylammonium salt, and tris(hydroxymethyl)aminomethane salt); and amino acid salts such as glycine salt, lysine salt, arginine salt, ornithine salt, glutamate, and aspartate.

[0077]

When a compound of the present invention represented by the general formula (I) or the pharmacologically acceptable salt thereof has an asymmetric carbon atom in the molecule, stereoisomers with an R or S configuration are included. Each of these stereoisomers and all mixtures of the stereoisomers at arbitrary ratios are

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also encompassed by the present invention. Such stereoisomers can be prepared, for example, by synthesizing the compound (I) using an optically resolved starting compound or by optically resolving the synthesized compound (I) by a usual optical resolution or separation method, as desired.

The compound of the present invention represented by the general formula (I) or the pharmacologically acceptable salt thereof includes optical isomers. Each of these optical isomers and all mixtures of these optical isomers are also encompassed by the present invention.

The compound of the present invention represented by the general formula (I) or the pharmacologically acceptable salt thereof, when left in the air or recrystallized, may absorb water to associate with adsorbed water or to form a hydrate. Such water-containing compounds and salts are also encompassed by the present invention.

[0078]

According to a further aspect, the present invention provides a compound represented by the formula (1) or a pharmacologically acceptable salt thereof, which is intended for use in a method for therapeutically treating a human or animal body.

[0079]

We have found that compounds of the present invention inhibit bacterial DNA gyrase and are therefore important for antibacterial effects.

[0080]

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According to a further aspect, the present invention provides a method for producing an antibacterial effect in a warm-blooded animal (e.g., a human) in need of treatment which produces an antibacterial effect. This method comprises administering an effective amount of a compound of the present invention or a pharmacologically acceptable salt thereof to the animal.

[0081]

According to a further aspect, the present invention provides a method for inhibiting bacterial DNA gyrase in a warm-blooded animal (e.g., a human) in need of treatment which produces an antibacterial effect. This method comprises administering an effective amount of a compound represented by the formula (1) as defined above or a pharmacologically acceptable salt thereof to the animal.

[0082]

According to a further aspect, the present invention provides a method for treating bacterial infection in a warm-blooded animal (e.g., a human) in need of treatment of bacterial infection. This method comprises administering an effective amount of a compound represented by the formula (1) as defined above or a pharmacologically acceptable salt thereof to the animal.

[0083]

A further aspect of the present invention provides a compound represented by the formula (1) or a pharmacologically acceptable salt thereof, which is

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intended for use as a pharmaceutical agent.
The pharmaceutical agent is appropriately an
antibacterial agent.

[0084]

In a convenient embodiment, this is a compound
represented by the formula (1) or a pharmacologically
acceptable salt thereof, which is intended for use as a
pharmaceutical agent for producing an antibacterial
effect in a warm-blooded animal (e.g., a human).

[0085]

In another convenient embodiment, this is a compound
represented by the formula (1) or a pharmacologically
acceptable salt thereof, which is intended for use as a
pharmaceutical agent for inhibiting bacterial DNA gyrase
in a warm-blooded animal (e.g., a human).

[0086]

Particularly, this is a compound represented by the
formula (1) or a pharmacologically acceptable salt
thereof, which is intended for use as a pharmaceutical
agent for treating bacterial infection in a warm-blooded
animal (e.g., a human).

[0087]

According to a further aspect, the present invention
provides use of a compound represented by the formula (1)
or a pharmacologically acceptable salt thereof in the
production of a pharmaceutical agent used for producing
antibacterial effect in a warm-blooded animal (e.g., a
human).

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[0088]

According to a further aspect, the present invention provides use of a compound represented by the formula (1) or a pharmacologically acceptable salt thereof in the production of a pharmaceutical agent used for inhibiting bacterial DNA gyrase in a warm-blooded animal (e.g., a human).

[0089]

Thus, according to a further aspect, the present invention provides use of a compound represented by the formula (1) or a pharmacologically acceptable salt thereof in the production of a pharmaceutical agent used for treating bacterial infection in a warm-blooded animal (e.g., a human).

[0090]

According to a further aspect, the present invention provides a compound represented by the formula (1) or a pharmacologically acceptable salt thereof, which is intended for use for producing an antibacterial effect in a warm-blooded animal (e.g., a human).

[0091]

According to a further aspect, the present invention provides a compound represented by the formula (1) or a pharmacologically acceptable salt thereof, which is intended for use for inhibiting bacterial DNA gyrase in a warm-blooded animal (e.g., a human).

[0092]

Thus, according to a further aspect, the present

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invention provides a compound represented by the formula (1) or a pharmacologically acceptable salt thereof, which is intended for use for treating bacterial infection in a warm-blooded animal (e.g., a human).

[0093]

The compound represented by the formula (1) or a pharmacologically acceptable salt is used for therapeutically (including preventively) treating a mammal such as a human, particularly, in the treatment of infection (which will be mentioned later in this chapter in relation to the compound or pharmaceutical composition of the present invention). For this purpose, the compound or the salt is usually prepared into a pharmaceutical composition according to standard pharmaceutical practice.

[0094]

Therefore, in an additional aspect, the present invention provides a pharmaceutical composition comprising the compound represented by the formula (1) or a pharmacologically acceptable salt thereof and a pharmaceutically acceptable diluent or carrier.

[0095]

According to a further aspect, the present invention provides a pharmaceutical composition intended for use for inhibiting bacterial DNA gyrase in a warm-blooded animal (e.g., a human), the pharmaceutical composition comprising a compound represented by the formula (1) as defined above or a pharmacologically acceptable salt

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thereof, together with a pharmaceutically acceptable excipient or carrier.

[0096]

According to a further aspect, the present invention provides a pharmaceutical composition intended for use for treating bacterial infection in a warm-blooded animal (e.g., a human), the pharmaceutical composition comprising a compound represented by the formula (1) as defined above or a pharmacologically acceptable salt thereof, together with a pharmaceutically acceptable excipient or carrier.

[0097]

The composition of the present invention may be in a form suitable for oral use (e.g., tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups, and elixirs), topical use (e.g., creams, ointments, gels, and aqueous or oily solutions or suspensions), administration by an inhalation method (e.g., finely grained powders and liquid aerosols), administration by an aeration method (e.g., pulverized powders), or parenteral administration (e.g., sterile aqueous or oily solutions for intravenous, hypodermic, or intramuscular administration and suppositories for rectal administration).

[0098]

The compositions of the present invention can also be obtained by conventional approaches using conventional

pharmaceutical excipients well known in the art.

[0099]

Thus, the compositions intended for oral use may contain, for example, one or more coloring agent(s), sweetener(s), corrigent(s), and/or preservative(s).

[0100]

Examples of the pharmaceutically acceptable excipients suitable for tablet preparation include: inert diluents, for example, lactose, sodium carbonate, calcium phosphate, and calcium carbonate; granulating agents and disintegrants, for example, corn starch and alginic acid; binders, for example, starch; lubricants, for example, magnesium stearate, stearic acid, and talc; preservatives, for example, ethyl p-hydroxybenzoate and propyl p-hydroxybenzoate; and antioxidants, for example, ascorbic acid.

[0101]

The prepared tablets may be uncoated or may be coated for altering their disintegration, and subsequent enteral absorption of the active ingredient, or for improving their stability and/or appearance. In both cases, conventional coating agents and approaches well known in the art are used.

[0102]

The compositions intended for oral use may be in the form of a hard gelatin capsule. In this case, the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate, or kaolin.

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Alternatively, for use as a soft gelatin capsule, the active ingredient is mixed with water or oil, for example, peanut oil, liquid paraffin, or olive oil.

[0103]

The aqueous suspensions generally comprise the active ingredient in a pulverized form, together with one or more suspending agent(s), for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, tragacanth gum, and gum arabic; and dispersant(s) or wetting agent(s), for example, lecithin, condensation products of alkylene oxides and fatty acids (e.g., polyoxyethylene stearate), condensation products of ethylene oxide and long-chain aliphatic alcohols (e.g., heptadecaethylene oxycetanol), condensation products of ethylene oxide and partial esters derived from fatty acids and hexitols (e.g., polyoxyethylene sorbitol monooleate), and condensation products of ethylene oxide and partial esters derived from fatty acids and hexitol anhydrides (e.g., polyethylene sorbitan monooleate).

[0104]

The aqueous suspensions may also contain one or more preservative(s) (e.g., ethyl p-hydroxybenzoate and propyl

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p-hydroxybenzoate), antioxidant(s) (e.g., ascorbic acid), coloring agent(s), corrigent(s), and/or sweetener(s) (e.g., sucrose, saccharine, and aspartame).

[0105]

The oily suspensions may be prepared by suspending the active ingredient in a plant oil (e.g., peanut oil, olive oil, sesame oil, or coconut oil) or a mineral oil (e.g., liquid paraffin). The oily suspensions may also contain a thickener such as beeswax, solid paraffin, or cetyl alcohol. To provide palatable oral preparations, such sweetener(s) and corrigent(s) as described above may be added thereto. These compositions may be stored by adding thereto an antioxidant such as ascorbic acid.

[0106]

The dispersible powders and granules suitable for producing aqueous suspensions by the addition of water generally comprise the active ingredient, together with a dispersant or wetting agent, a suspending agent, and one or more preservative(s). Appropriate dispersants or wetting agents and suspending agents are already shown above. Moreover, additional excipients such as sweeteners, corrigents, and coloring agents may be contained therein.

[0107]

Moreover, the pharmaceutical compositions of the present invention may be in the form of a water-in-oil emulsion. The oil phase can be a plant oil (e.g., olive oil or peanut oil) or a mineral oil (e.g., liquid

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paraffin), or any mixture thereof. Appropriate emulsifying agents can be, for example, naturally existing gums (e.g., gum arabic and tragacanth gum), naturally existing phosphatides (e.g., soybean and lecithin), esters or partial esters derived from fatty acids and hexitol anhydrides (e.g., sorbitan monooleate), and condensation products of the partial esters and ethylene oxide (e.g., polyoxyethylene sorbitan monolaurate). The emulsions may also contain a sweetener, a corrigent, and a preservative.

[0108]

The syrups and the elixirs may be prepared together with a sweetener such as glycerol, propylene glycol, sorbitol, aspartame, or sucrose and may contain a demulcent, a preservative, a corrigent, and/or a coloring agent.

[0109]

The present pharmaceutical compositions may be in the form of a sterile injectable aqueous or oily suspension. These suspensions may be prepared according to known approaches using one or more of the appropriate dispersants or wetting agents and suspending agents described above.

Moreover, the sterile injectable formulations may be sterile injectable solutions or suspensions in a nontoxic, parenterally acceptable diluent or solvent and are, for example, 1,3-butanediol solutions.

[0110]

The compositions for use in administration by an inhalation method may be in the form of a conventional pressurized aerosol that is adjusted to distribute the active ingredient either as an aerosol containing pulverized solid or as an aerosol containing liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used. An aerosol apparatus is appropriately adjusted to distribute a constant amount of the active ingredient.

[0111]

For further information about preparation, the readers can refer to the chapter 25.2 in vol. 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; editor in chief), Pergamon Press, 1990.

[0112]

The amount of the active ingredient contained together with one or more excipient(s) for producing one dosage form is inevitably predicted to vary according to the host to be treated and the particular administration route. For example, a preparation intended for oral administration to a human is generally predicted to comprise, for example, 0.5 mg to 2 g of the active ingredient formulated together with an appropriate and convenient amount of excipient(s). In this context, the amount of the excipients can vary within the range of approximately 5 to approximately 98% by weight of the total weight of the composition. A unit dosage form is generally predicted to comprise approximately 1 mg to

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approximately 500 mg of the active ingredient. For further information about administration routes and dose schedules, the readers can refer to the chapter 25.3 in vol. 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; editor in chief), Pergamon Press, 1990.

[0113]

The pharmaceutical compositions of the present invention may also comprise, in addition to a compound of the present invention, one or more known agent(s) selected from other clinically useful antibacterial agents (e.g., macrolide, quinolone, β -lactam, and aminoglycoside agents) and/or other anti-infective agents (e.g., anti-fungal triazoles and amphotericin) or may be coadministered with these agents (simultaneously, continuously, or separately). Examples of these known agents include carbapenems, for example, meropenem and imipenem. Use of these agents can expand the therapeutic effectiveness of the pharmaceutical compositions of the present invention. The compounds of the present invention may also comprise a bactericidal/permeability-increasing protein (BPI) product or an efflux pump inhibitor for improving their activity against gram-negative bacteria and bacterial resistance to the antibacterial agent, or may be coadministered with these agents.

[0114]

As described above, the magnitude of the dose necessary for the therapeutic or preventive treatment of

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a particular condition is inevitably predicted to vary according to the host to be treated, the administration route, and the severity of disease to be treated.

Preferably, the daily dose is used within the range of 1 to 50 mg/kg. However, the daily dose is inevitably predicted to vary according to the host to be treated, the particular administration route, and the severity of the disease to be treated. Thus, the optimum dose may be determined by any general practitioner that provides treatment to the patient.

[0115]

Moreover, the compounds represented by the formula (1) and the pharmacologically acceptable salts thereof are useful not only for use in therapeutic agents but also as pharmacological tools for development and standardization of *in-vitro* and *in-vivo* test systems for evaluating the effect of a DNA gyrase inhibitor in experimental animals (e.g., cats, dogs, rabbits, monkeys, rats, or mice) as part of a search for novel therapeutic agents.

[0116]

Alternative preferred embodiments of the compounds of the present invention described herein are also applied to the aspects of additional pharmaceutical compositions, processes, methods, uses, and production of pharmaceutical agents other than those described above.

[0117]

The present invention provides synthesis methods for producing the compounds represented by the formula (1) or

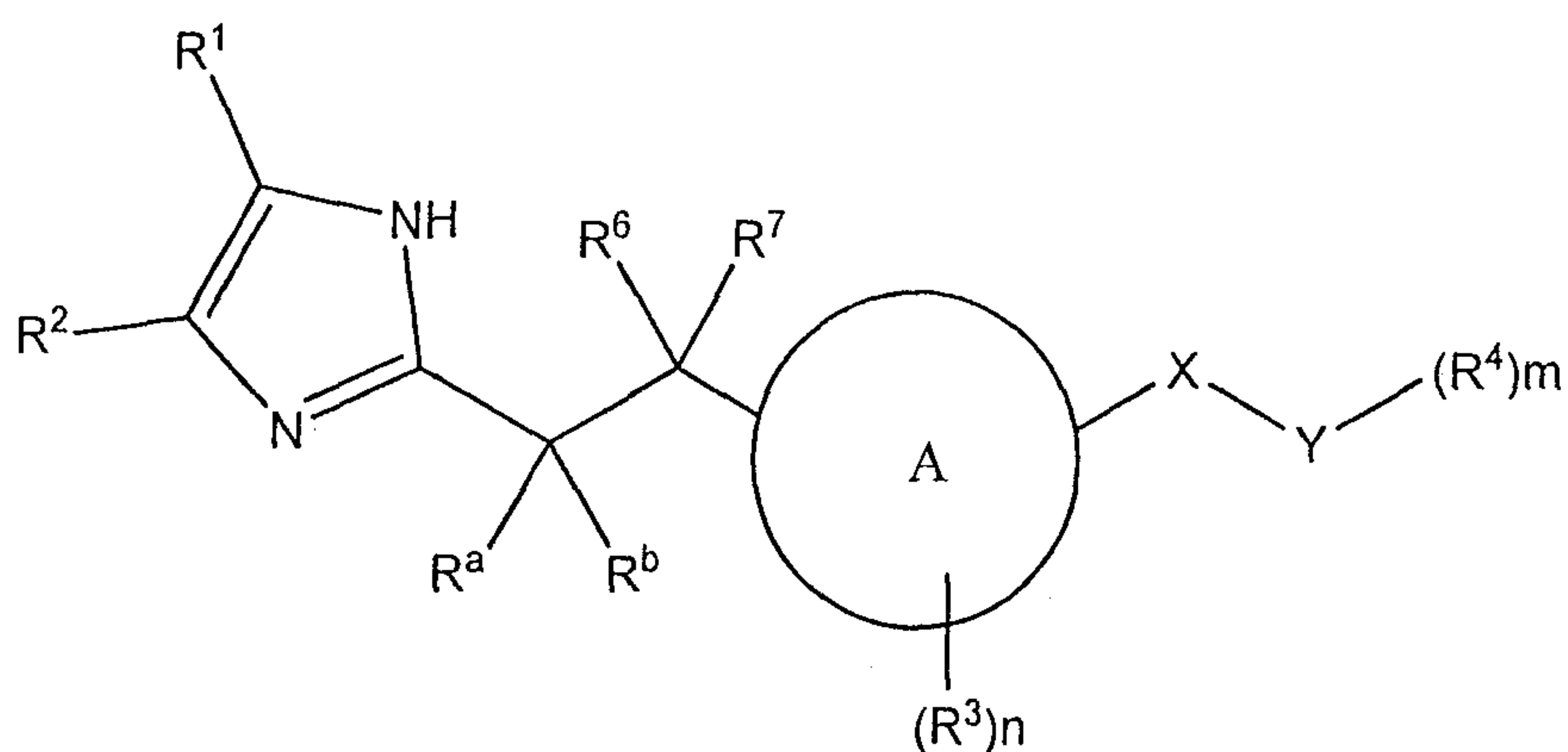
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the pharmacologically acceptable salts thereof.

Synthesis Method 1)

A compound represented by the formula (1) wherein W is -C(R⁶)(R⁷)- is converted from a compound represented by the formula (2):

[0118]



(2)

[0119]

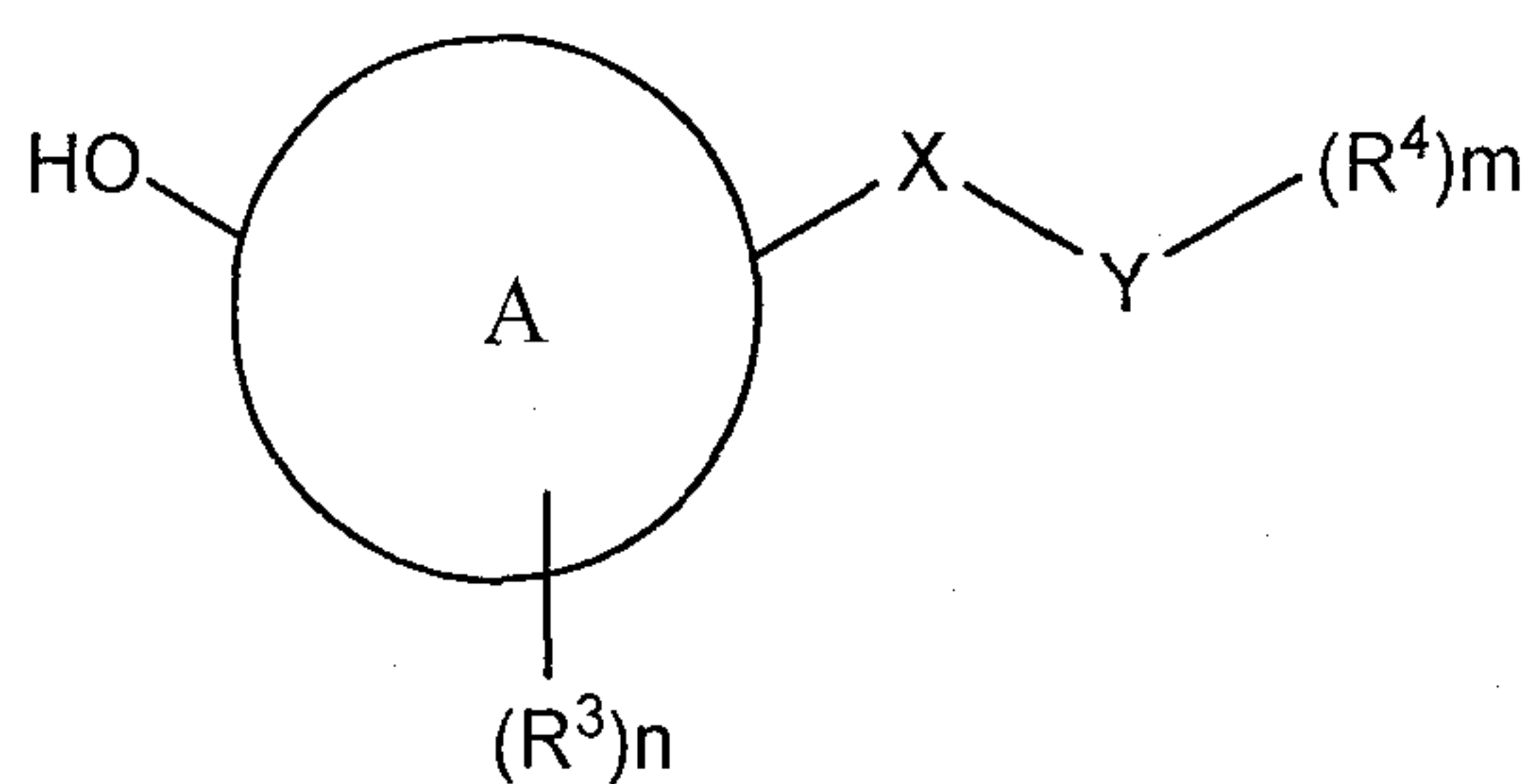
wherein R^a is cyano, and R^b is dimethylamino or diethylamino; or R^a and R^b are each independently selected from -S(C₁-C₄) alkyl groups; or R^a and R^b may together form a 1,3-dithiane ring or a 1,3-dithiolane ring.

[0120]

Synthesis Method 2)

A compound represented by the formula (1) wherein W is -O- is synthesized from a compound represented by the formula (3):

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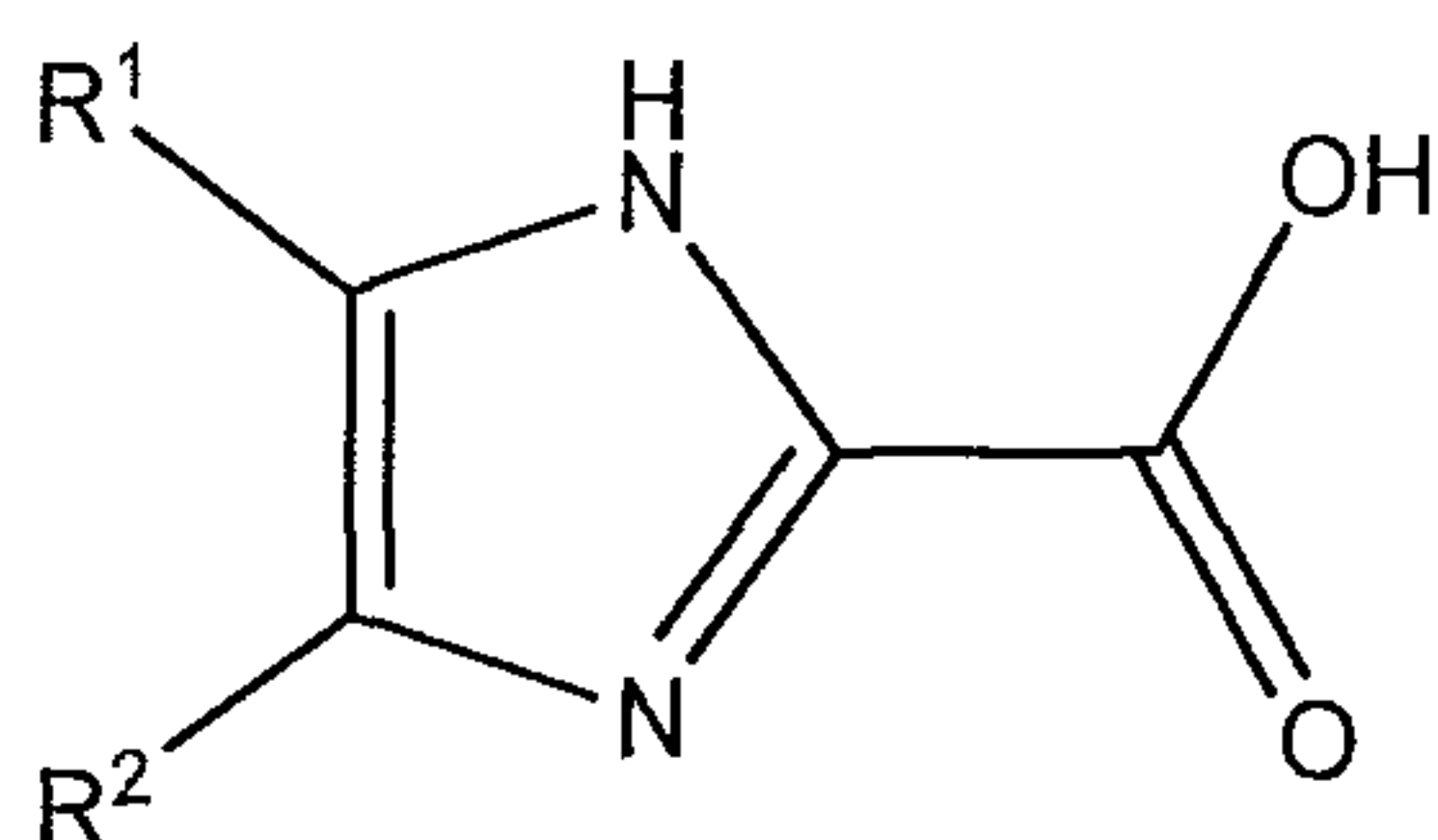


(3)

[0121]

and a carboxylic acid represented by the formula (4):

[0122]

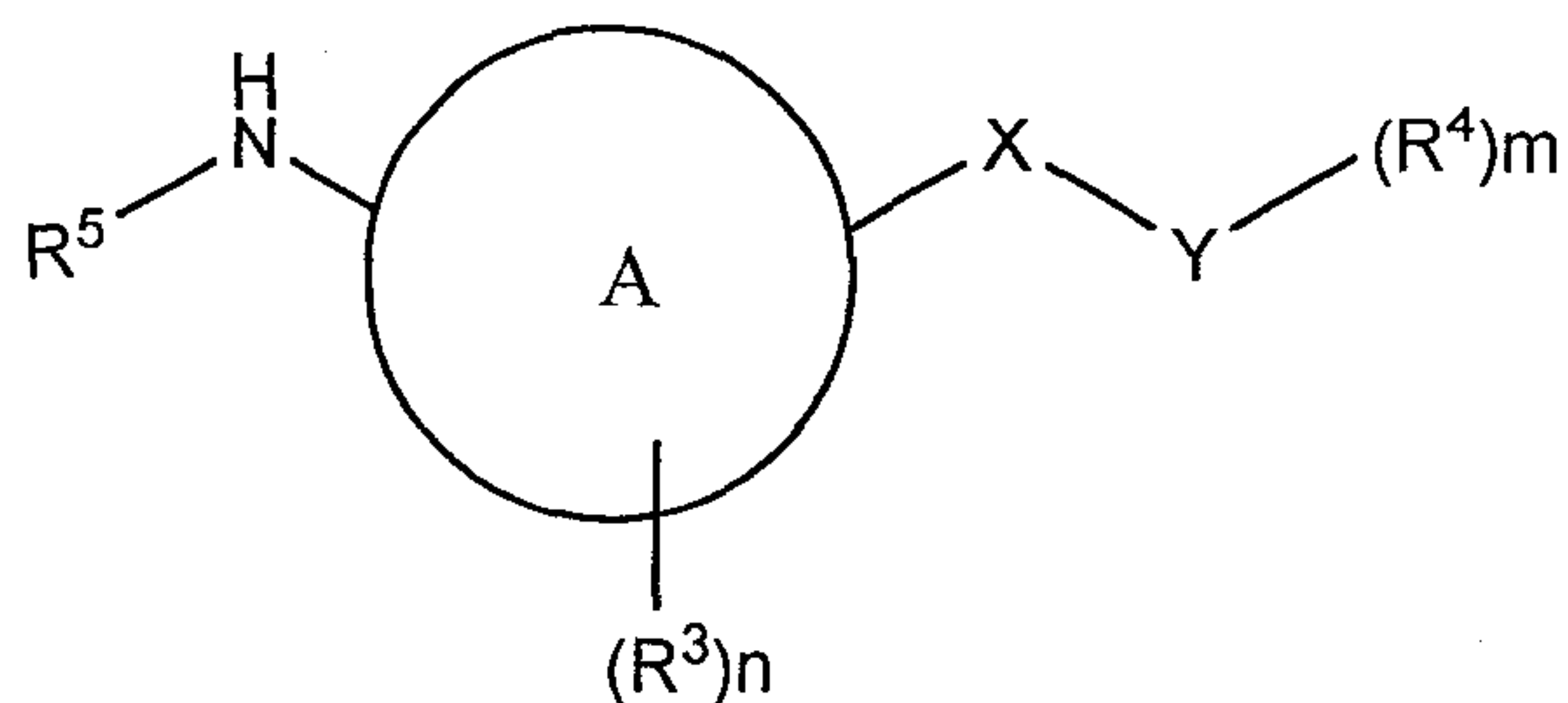


(4)

[0123]

Synthesis Method 3)

A compound represented by the formula (1) wherein W is -N(R⁵) is synthesized from a compound represented by the formula (5):



(5)

[0124]

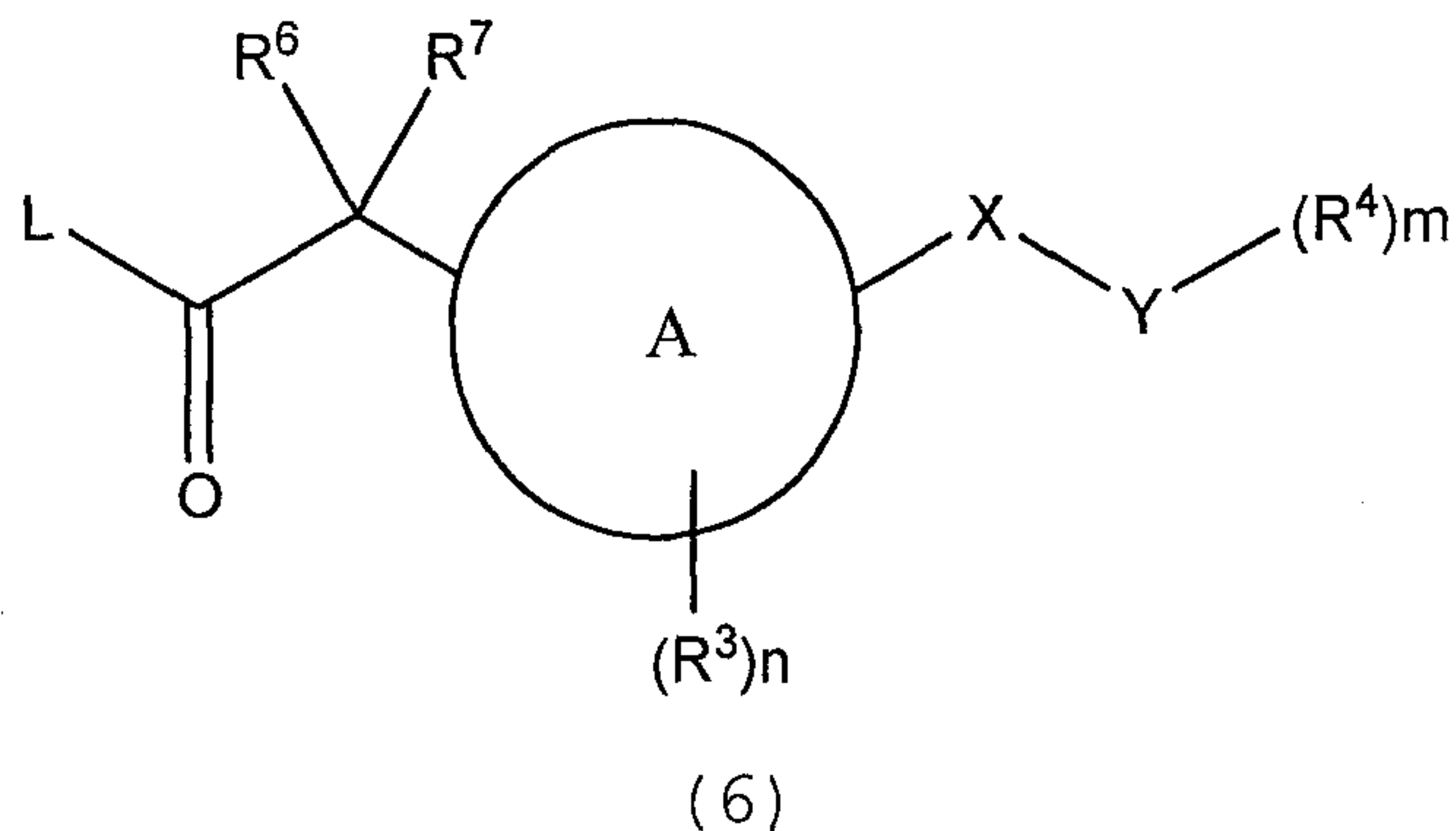
and the carboxylic acid represented by the formula (4) or an activated derivative thereof.

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[0125]

Synthesis Method 4)

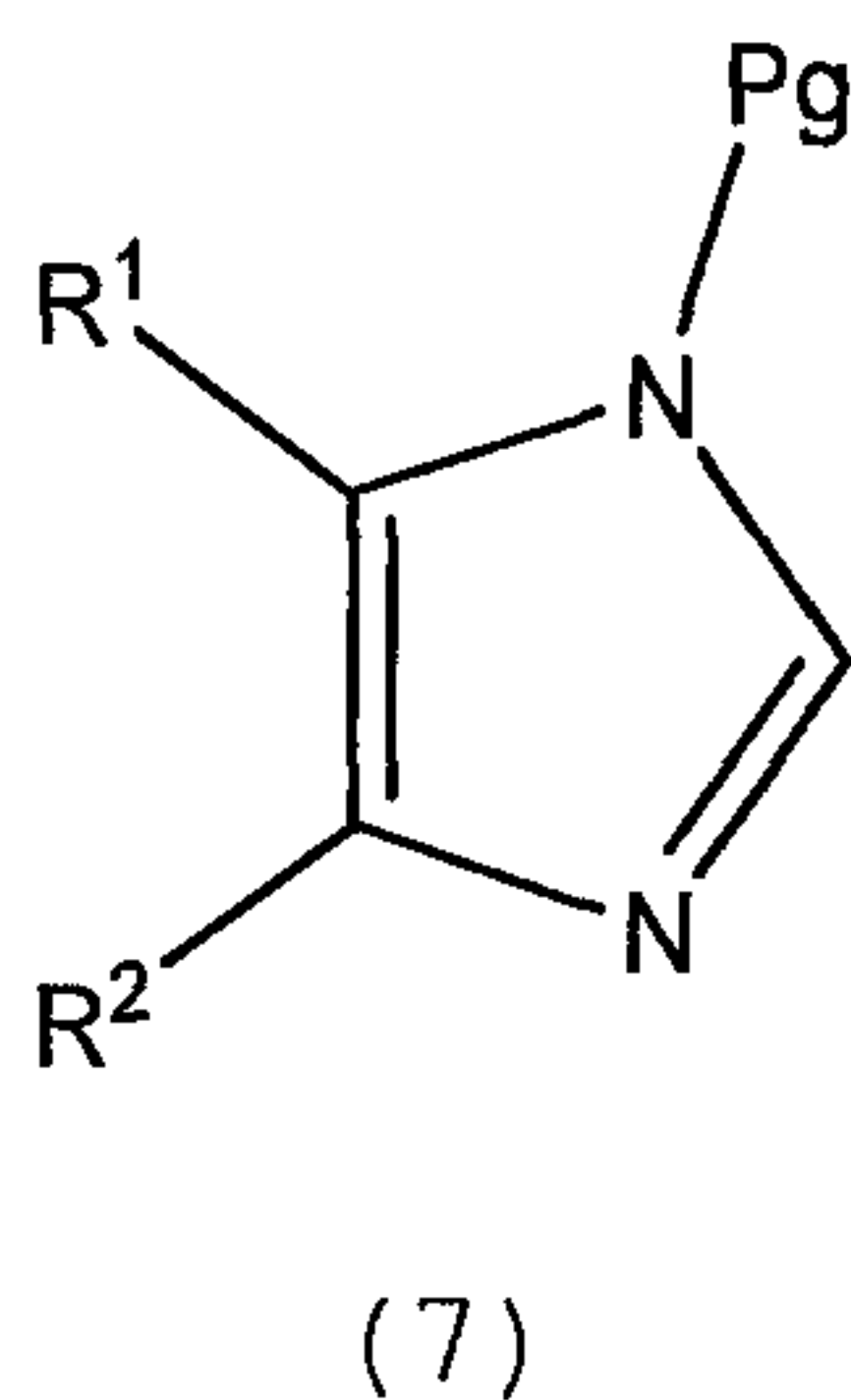
A compound represented by the formula (1) wherein W is -C(R⁶)(R⁷)- is synthesized from a compound represented by the formula (6):



[0126]

wherein L is a group which may be substituted, and a compound represented by the formula (7):

[0127]



[0128]

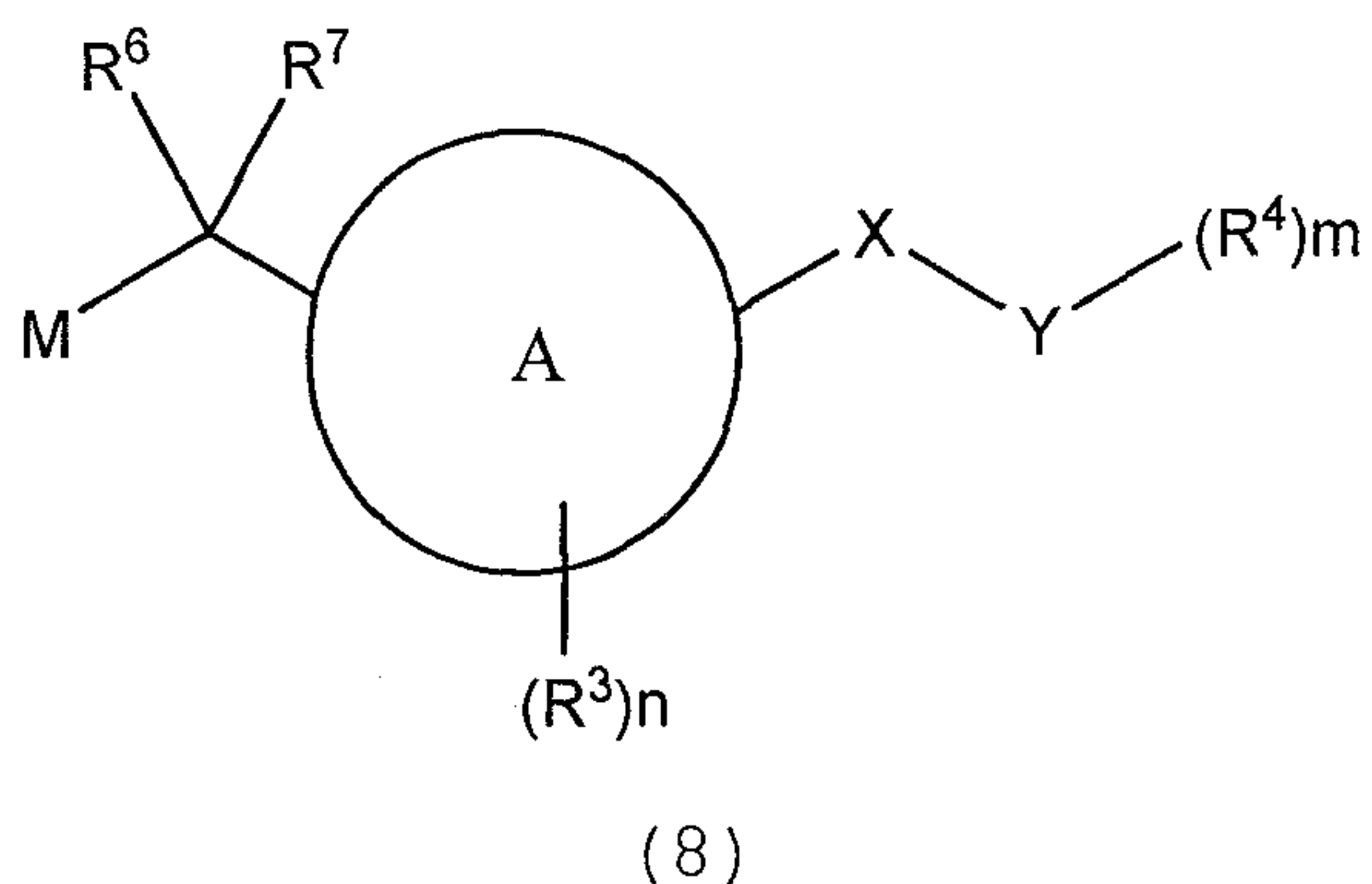
wherein Pg is a protecting group.

[0129]

Synthesis Method 5)

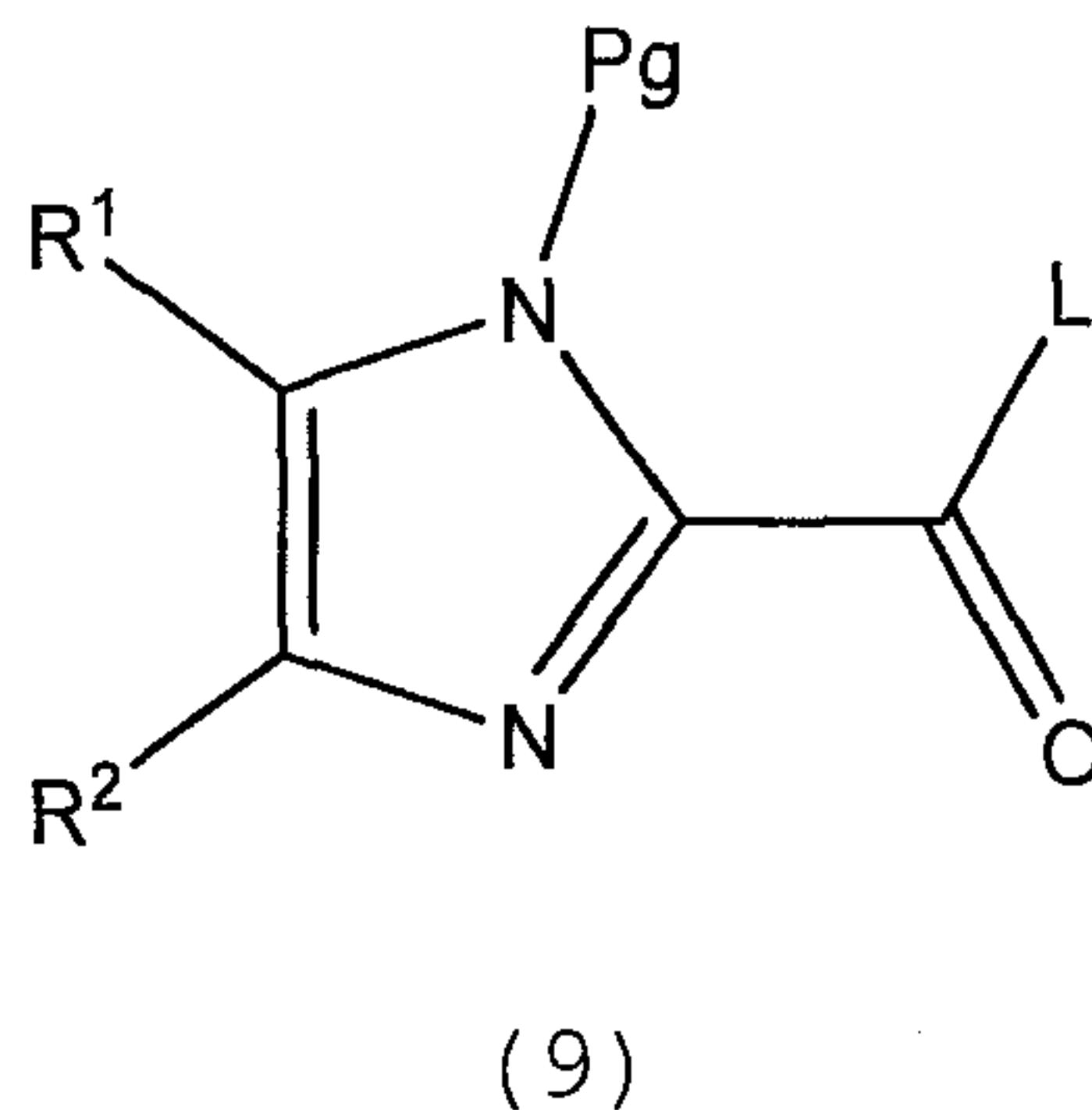
A compound represented by the formula (1) wherein W is -C(R⁶)(R⁷)- is synthesized from a compound represented by the formula (8):

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[0130]

wherein M is an organometal species, and
a compound represented by the formula (9):



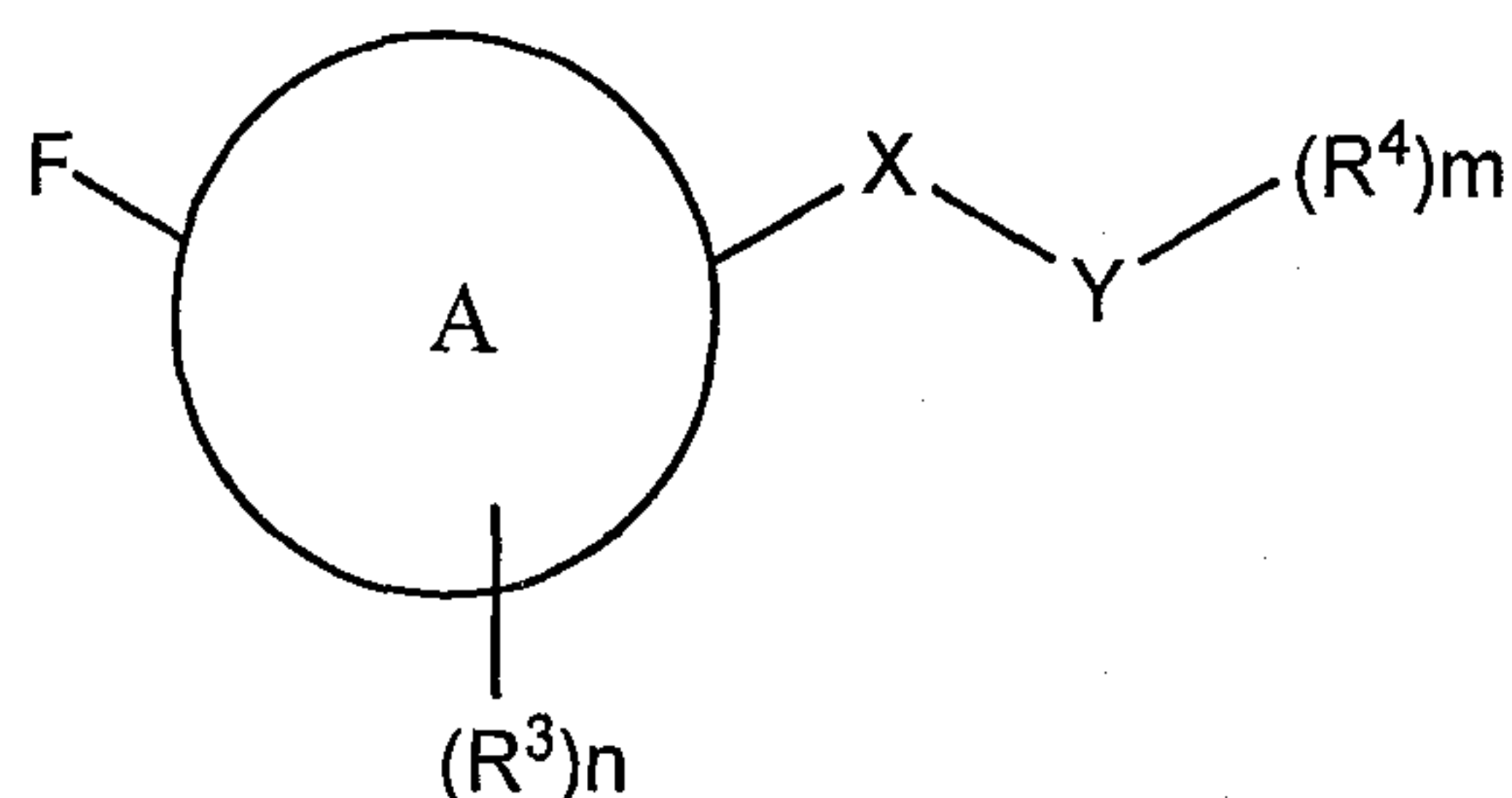
[0131]

wherein L is a group which may be substituted, and Pg is
a protecting group.

[0132]

Synthesis Method 6)

A compound represented by the formula (1) wherein W is a
single bond is synthesized from a compound represented by
the formula (10):



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(10)

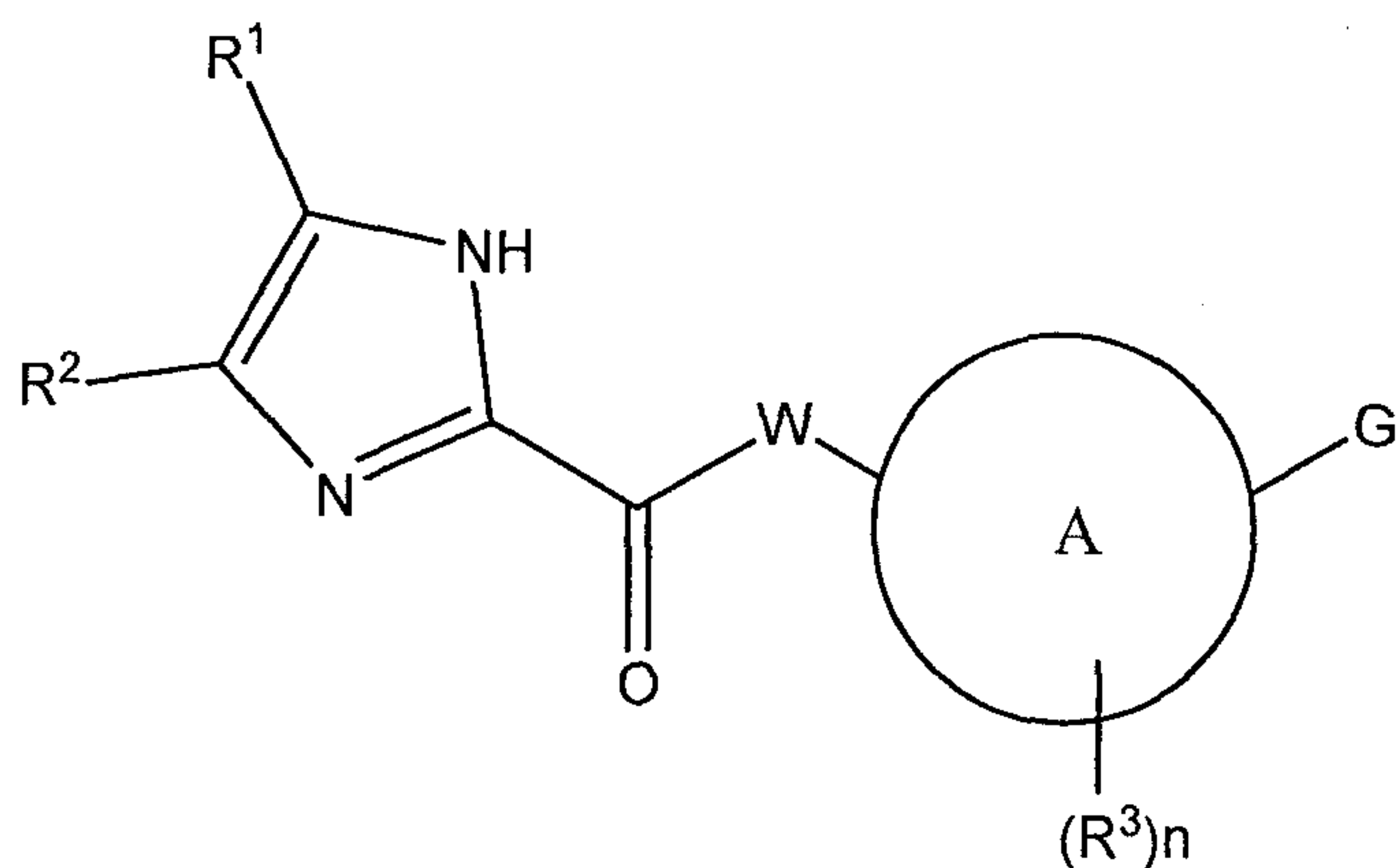
[0133]

wherein F is hydrogen or an organometal species, and the carboxylic acid represented by the formula (4) or an activated derivative thereof.

[0134]

Synthesis Method 7)

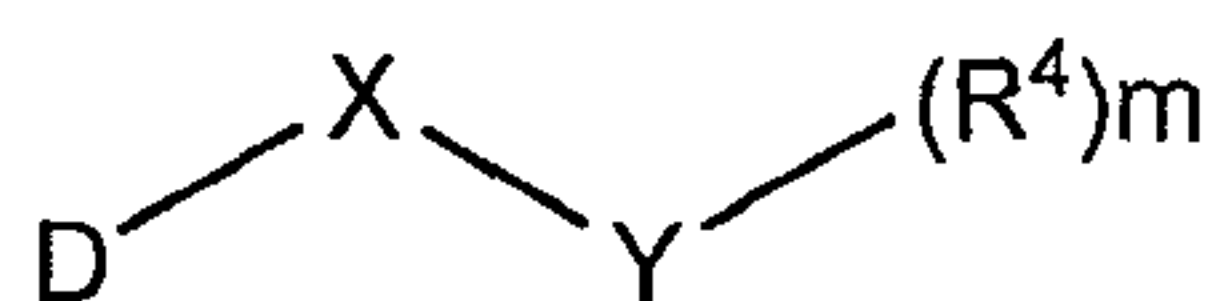
A compound represented by the formula (1) is synthesized from a compound represented by the formula (11):



(11)

[0135]

wherein G is an organometal species or hydrogen, and a compound represented by the formula (12):



(12)

[0136]

wherein D is a group which may be substituted.

[0137]

Synthesis Method 8)

A compound represented by the formula (1) wherein X is -

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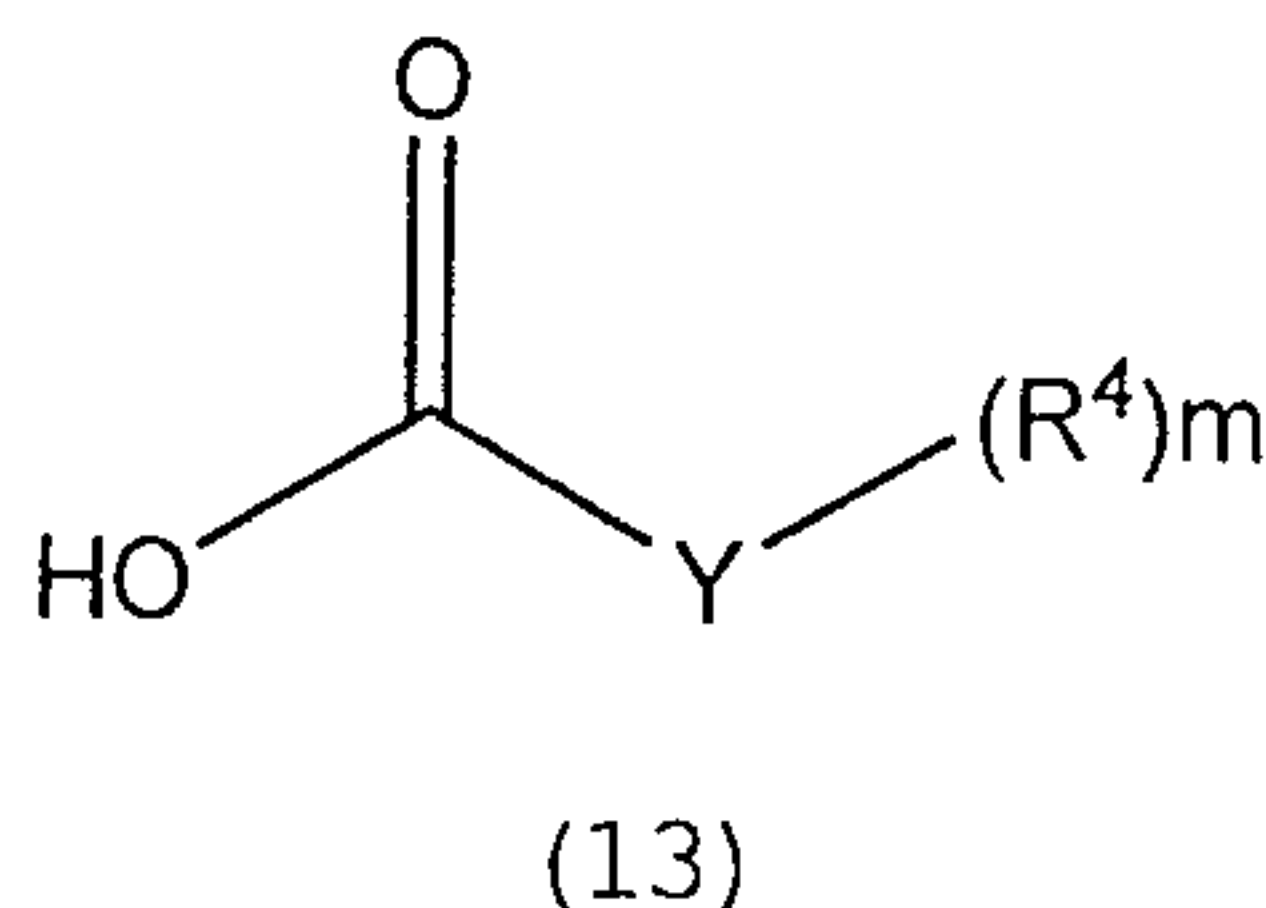
C(O)- is synthesized from the compound represented by the formula (11):

[0138]

wherein G is hydrogen or an organometal species, and

a carboxylic acid represented by the formula (13):

[formula (11)]



or an activated derivative thereof.

[0139]

Synthesis Method 9)

Conversion From The Compound Represented By The Formula (1) To
Another Compound Represented By The Formula (1)

Synthesis Method 10)

Conversion To The Compound Represented By The Formula (1) By
Removal Of The Protecting Group

Synthesis Method 11)

Conversion To A Pharmacologically Acceptable Salt Containing
The Compound Represented By The Formula (1)

Description of Abbreviations

L represents a group which may be substituted and encompasses
halo as an appropriate example, and examples
thereof include chloro, bromo, pentafluorophenoxy, and 2,5-
oxopyrrolidin-1-yloxy.

D represents a group which may be substituted and encompasses
halo as an appropriate example, and examples

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thereof include chloro, bromo, iodo, p-toluenesulfonyloxy, and methanesulfonyloxy.

Pg represents a protecting group for the functional group and encompasses trimethylsilylethoxymethyl or benzyloxycarbonyl as an appropriate example, and examples thereof include methoxymethyl, tetrahydropyranyl, and t-butyloxycarbonyl.

M encompasses an organocopper compound as an appropriate example, and examples thereof include copper lithium, organozinc compounds, zinc, and Grignard reagents (e.g., magnesium chloride).

F represents a group which may be substituted and encompasses hydrogen or an organocopper compound as an appropriate example, and examples thereof include copper lithium, organozinc compounds, zinc, and Grignard reagents (e.g., magnesium chloride).

G represents a group which may be substituted and encompasses hydrogen or an organoboron compound as an appropriate example, and examples thereof include -
 $B(OR^a)_2$ (wherein R^a is hydrogen or C_1 - C_4 alkyl), organocopper compounds (e.g., copper lithium), organozinc, zinc, Grignard reagents (e.g., magnesium chloride), and organotin compounds (e.g., trimethyltin and tributyltin).

[0140]

Special reaction conditions for the reactions will be shown below.

Synthesis Method 1)

Conversion Of The Compound Represented By The Formula (1)

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Wherein W Is $-C(R^6)(R^7)-$ From The Compound Represented By The Formula (2)

For The Case Where R^a Is Cyano, And R^b Is Dimethylamino Or Diethylamino

For example, the compound represented by the formula (2) is treated in an appropriate solvent, for example, aqueous methanol, at room temperature in the presence of a base such as sodium hydroxide.

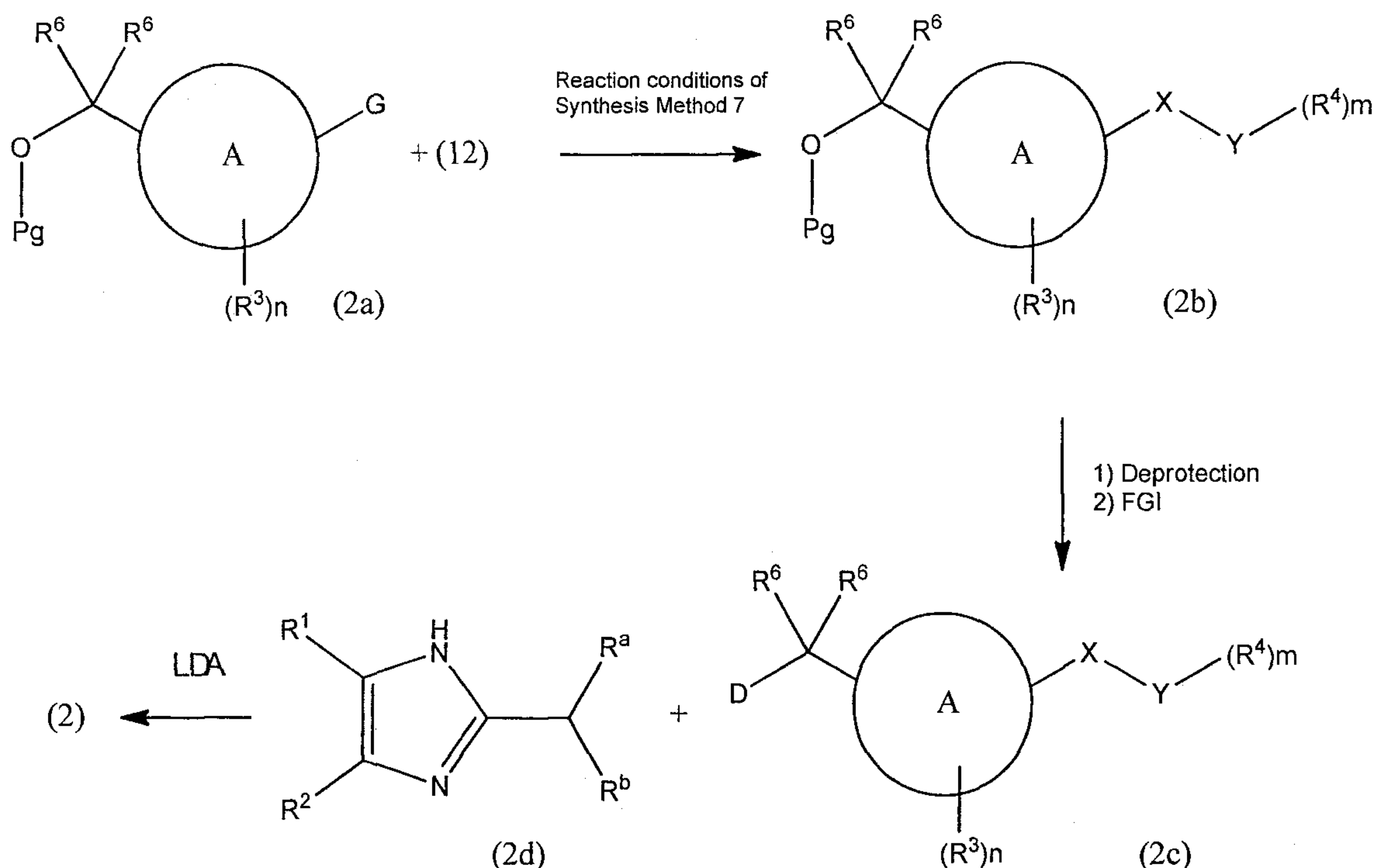
For The Case Where R^a And R^b Are Each Independently Selected from $-S(C_1-C_4)$ Alkyl Groups; Or R^a And R^b Together Form A 1,3-Dithiane Ring Or A 1,3-Dithiolane Ring

For example, the compound represented by the formula (2) is treated in an appropriate solvent, for example, methanol, ethanol, or acetone, in the range of room temperature to reflux temperature in the presence of a mercury salt, copper salt, or silver salt such as mercury (II) perchlorate, copper (II) chloride, silver nitrate, or silver oxide.

[0141]

The compound represented by the formula (2) is synthesized according to scheme 1.

[0142]



Scheme 1

[0143]

wherein Pg is a protecting group for a hydroxyl group and is defined above as a protecting group for the functional group; and D is defined above as a group which may be substituted.

The deprotection of the hydroxyl group is well known in the art.

FGI means functional group interconversion. The interconversion from the hydroxyl group to the group D in the scheme is well known in the art and can be practised by those skilled in the art.

The compounds represented by the formula (2a) or (2b) are compounds known in documents or compounds synthesized by standard synthesis methods well known in the art.

[0144]

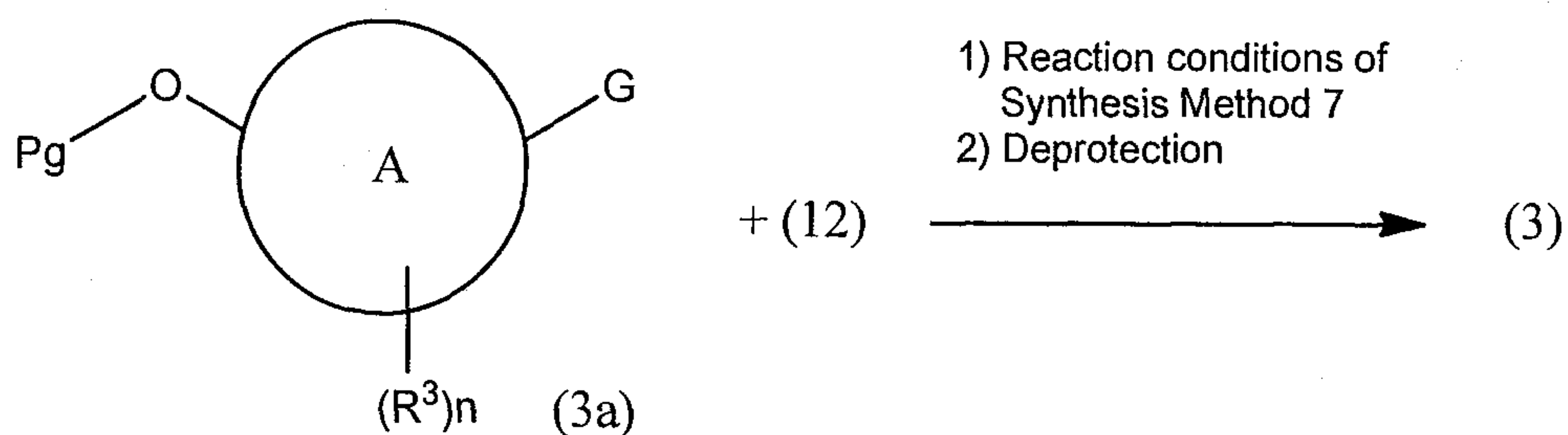
Synthesis Method 2)

The compound represented by the formula (3) and the compound represented by the formula (4) can be reacted in an appropriate solvent, for example, methylene chloride, THF, or diethyl ether, in the presence of a condensing agent such as dicyclohexylcarbodiimide or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI).

[0145]

The compound represented by the formula (3) is synthesized according to scheme 2.

[0146]



Scheme 2

[0147]

wherein Pg is a protecting group for a hydroxyl group and is defined above as a protecting group for the functional group.

The deprotection of the hydroxyl group is described in documents well known in the art.

The compounds represented by the formula (3a) or (4) are commercially available compounds, compounds known in documents, or compounds synthesized by standard synthesis methods well known in the art.

[0148]

Synthesis Method 3)

The compound represented by the formula (5) and the compound represented by the formula (4) can be condensed in the presence of an appropriate condensing agent. A standard peptide coupling reagent known in the art can be used as an appropriate coupling reagent. Alternative examples of the coupling reagent include carbonyldiimidazole, dicyclohexyl-carbodiimide, and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI). The reaction may be performed optionally in the presence of a catalyst (e.g., 1-hydroxy-benzotriazole, HOBT, dimethylaminopyridine, or 4-pyrrolidinopyridine) and optionally in the presence of a base (e.g., triethylamine, di-isopropylethylamine, pyridine, or 2,6-di-alkyl-pyridine (e.g., 2,6-lutidine or 2,6-di-tert-butylpyridine)).

Examples of an appropriate solvent include dimethylacetamide, methylene chloride, toluene, N-methylpyrrolidone, tetrahydrofuran, and dimethylformamide. The coupling reaction is performed in the temperature range of -40°C to 40°C.

[0149]

Appropriate examples of the activated derivative of the acid include acid halides, for example, acid chlorides. Alternative examples thereof include active esters, for example, pentafluorophenyl esters. The reaction of these types of compounds with amines is well

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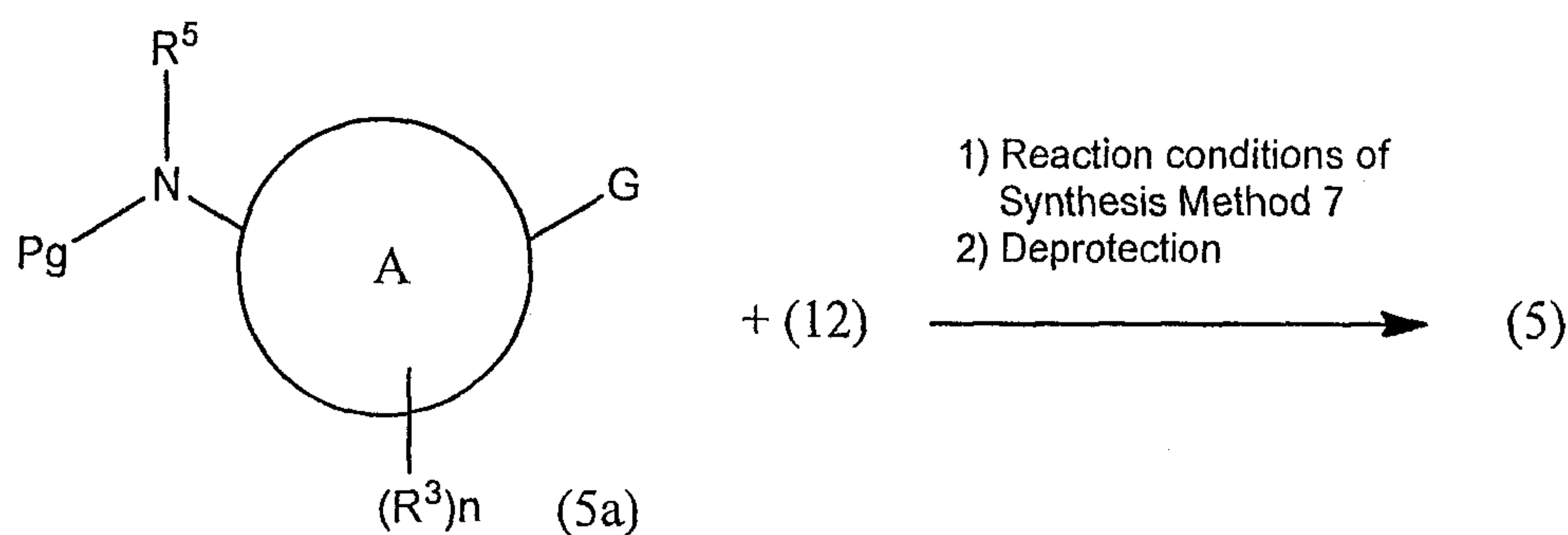
known in the art. For example, they can be reacted in an appropriate solvent (e.g., such a solvent as described above) in the presence of a base (e.g., such a base as described above).

Such a reaction is performed in the temperature range of -40°C to 40°C.

[0150]

The compound represented by the formula (5) is synthesized according to scheme 3.

[0151]



Scheme 3

[0152]

wherein Pg is a protecting group for the amino group and is defined above as a protecting group for the functional group. Those skilled in the art can understand here that an appropriate protecting group needs to be introduced when R^5 is hydrogen.

The deprotection of the amino group is described in documents well known in the art.

The compounds represented by the formula (5a) are commercially available compounds, compounds known in documents, or compounds synthesized by standard synthesis

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methods well known in the art.

[0153]

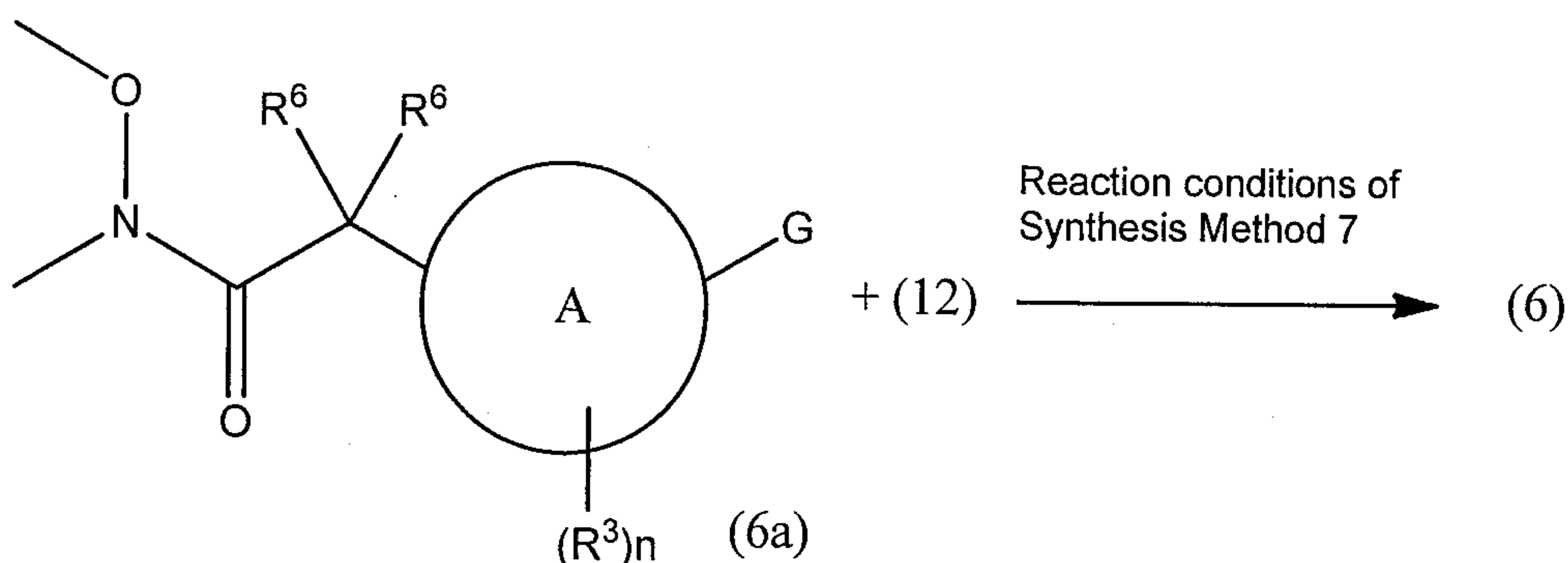
Synthesis Method 4)

The compound represented by the formula (6) and the compound represented by the formula (7) can be reacted in the range of -80°C to 0°C in an appropriate solvent, for example, THF or diethyl ether, in the presence of an alkyl lithium such as butyl lithium.

[0154]

The compound represented by the formula (6) is synthesized according to scheme 4.

[0155]



Scheme 4

[0156]

The compounds represented by the formula (6a) or (7) are commercially available compounds, compounds known in documents, or compounds synthesized by standard synthesis methods well known in the art.

[0157]

Synthesis Method 5)

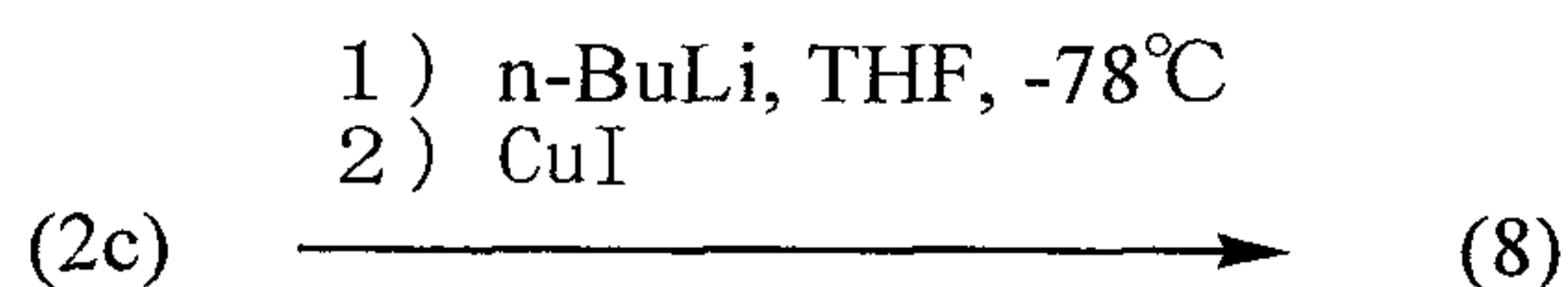
The compound represented by the formula (8) and the compound represented by the formula (9) can be reacted in

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the range of -80°C to 0°C in an appropriate aprotic solvent, for example, THF or diethyl ether.

The compound represented by the formula (8) is synthesized from a compound represented by the formula (2c) under standard conditions well known in the art. For example, the compound represented by the formula (8) wherein M is an organocopper compound can be synthesized according to scheme 5.

[0158]



Scheme 5

[0159]

The compounds represented by the formula (9) are commercially available compounds, compounds known in documents, or compounds synthesized by standard synthesis methods well known in the art.

[0160]

Synthesis Method 6)

Reaction Between The Compound Represented By The Formula (10) And The Compound Represented By The Formula (4)

For The Case Where F In The Compound Represented By The Formula (10) Is Bound To A Nitrogen Atom

F in the compound represented by the formula (10) is hydrogen, and the compound represented by the formula (10) and the compound represented by the formula (4) can be reacted under the reaction conditions of Synthesis Method 3).

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For The Case Where F In The Compound Represented By The Formula (10) Is Bound To A Carbon Atom

F in the compound represented by the formula (10) is an organometal species and encompasses an organocopper compound as an appropriate organometal compound. For example, the compound represented by the formula (10) wherein F is an organocopper compound can be synthesized with reference to the scheme 5. For example, the compound represented by the formula (10) and the activated derivative (e.g., acid chloride) of the carboxylic acid represented by the formula (4) can be reacted in the range of -80°C to 0°C in an appropriate aprotic solvent, for example, THF or diethyl ether.

[0161]

Synthesis Method 7)

Reaction Between The Compound Represented By The Formula (11) And The Compound Represented By The Formula (12)

For The Case Where G In The Compound Represented By The Formula (11) Is Bound To A Nitrogen Atom

G in the compound represented by the formula (11) is hydrogen, and the compound represented by the formula (11) and the compound represented by the formula (12) can be reacted in an appropriate solvent, for example, dioxane, DMF, or dimethylaminoacetamide, in the presence of a base such as triethylamine, diisopropylethylamine, or cesium carbonate and optionally in the presence of a catalyst such as copper (I) iodide or palladium (II) acetate under heating conditions or using a microwave

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irradiation reactor.

For The Case Where G In The Compound Represented By The Formula (11) Is Bound To A Carbon Atom

G in the compound represented by the formula (11) is an organometal species and encompasses an organoboron compound as an appropriate organometal compound.

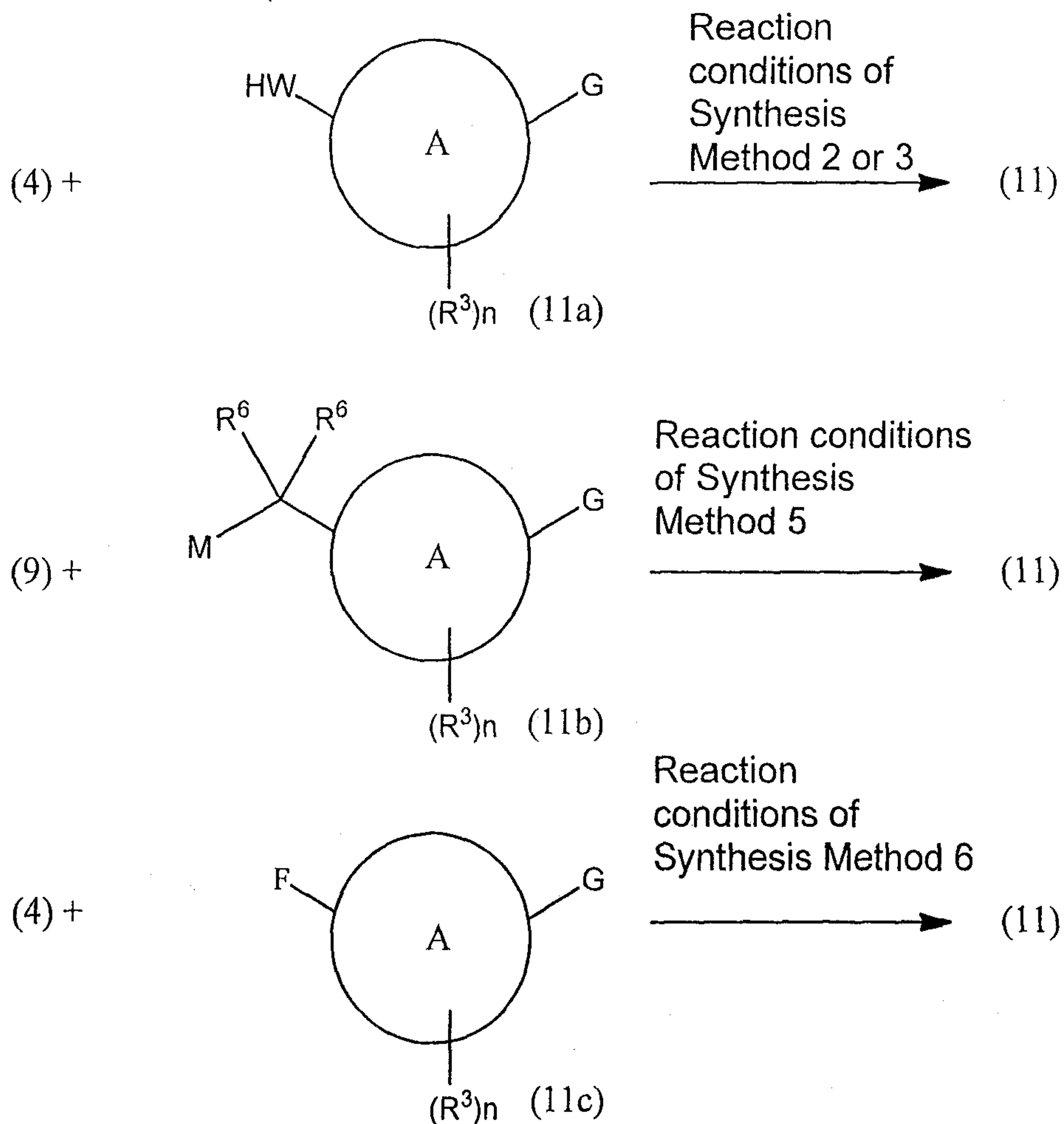
Examples thereof include $-B(OR^a)_2$ (wherein R^a is hydrogen or C_1 - C_4 alkyl), organocopper compounds (e.g., copper lithium), organozinc, zinc, Grignard reagents (e.g., magnesium chloride), and organotin compounds (e.g., trimethyltin and tributyltin). The compound represented by the formula (11) and the compound represented by the formula (12) can be reacted in an appropriate solvent, for example, dioxane, THF, toluene, or DMF, optionally in the presence of a base such as cesium carbonate or sodium carbonate, in the presence of a catalyst such as tetrakis(triphenylphosphine)palladium, and optionally in the presence of water under heating conditions or using a microwave irradiation reactor.

[0162]

The compound represented by the formula (11) is synthesized according to scheme 6.

[0163]

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Scheme 6

[0164]

wherein M is defined above as an organometal species. The compounds represented by the formula (11a), (11b), (11c), or (12) are commercially available compounds, compounds known in documents, or compounds synthesized by standard synthesis methods well known in the art.

[0165]

Synthesis Method 8)

Reaction Between The Compound Represented By The Formula (11) And The Compound Represented By The Formula (13)
For The Case Where G In The Compound Represented By The

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Formula (11) Is Bound To A Nitrogen Atom

G in the compound represented by the formula (11) is hydrogen, and the compound represented by the formula (11) and the compound represented by the formula (13) can be reacted under the conditions of Synthesis Method 3).

For The Case Where G In The Compound Represented By The Formula (11) Is Bound To A Carbon Atom

G in the compound represented by the formula (11) is an organometal species and encompasses an organocopper compound as an appropriate organometal compound. For example, the compound represented by the formula (11) wherein G is an organocopper compound can be synthesized with reference to the scheme 5. Moreover, the compound represented by the formula (13) can be converted to an acid chloride by a standard synthesis method known in the art. For example, the compound represented by the formula (11) and the acid chloride converted from the compound represented by the formula (13) can be reacted in the range of -80°C to 0°C in an appropriate aprotic solvent, for example, THF or diethyl ether.

[0166]

In this context, the compounds represented by the formula (13) are commercially available compounds, compounds known in documents, or compounds synthesized by standard synthesis methods well known in the art.

[0167]

A synthesis method for producing the pharmacologically acceptable salt is within the skill

routinely used by usual organic chemists.

[0168]

Of course, substituents for various predetermined rings in the compound of the present invention may be introduced through standard aromatic substitution reaction either prior to the synthesis methods or immediately thereafter such that they are contained in the embodiments of the synthesis methods of the present invention. Alternatively, these substituents may be formed by the conventional modification of the functional groups.

Reagents used for introducing such substituents for rings are either commercially available or produced by synthesis methods known in the art.

[0169]

A certain compound represented by the formula (1) can be converted to another compound represented by the formula (1).

Examples of such reaction and modification include introduction of substituents through aromatic substitution reaction, reduction of substituents, alkylation of substituents, oxidation of substituents, esterification of substituents, amination of substituents, and formation of heteroaryl rings.

Reagents and reaction conditions for such approaches are well known in the chemical field.

Examples of the particular aromatic substitution reaction include introduction of alkoxide, diazotization reaction,

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and introduction of thiol, alcohol, or halogen groups. Examples of the modification include oxidation of alkylthio into alkylsulfinyl or alkylsulfonyl.

[0170]

Skilled organic chemists can presumably obtain necessary starting materials and products by using reference documents described below, Examples described therein, information contained in Examples described herein, and information referred to in these Examples and adjusting them.

[0171]

When starting materials necessary for such approaches as described above are not commercially available, they may be formed by an approach selected from standard organic chemical techniques, techniques similar to the synthesis of structurally similar known compounds, and techniques similar to approaches described in the procedures described above or in Examples.

[0172]

It should be noted that many starting materials for the synthesis methods are commercially available and/or have been reported widely in scientific documents or can be formed from commercially available products by appropriately using synthesis methods reported in scientific documents. As a general guide to reaction conditions or reagents, further see Advanced Organic Chemistry, vol. 4 (Jerry March, ed., published by John Wiley and Sons, 1992).

[0173]

Of course, for some of the reactions described herein, the protection of every highly reactive group in the compound is also predicted to be required or desired in some cases.

The case where such protection is required or desired is known as a method suitable for such protection by those skilled in the art.

Conventional protecting groups can be used according to standard techniques (for the illustrative purpose, see T.W. Greene, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991).

[0174]

Examples of the protecting groups suitable for the hydroxy group include acyl groups, for example, alkanoyl groups (e.g., acetyl), aroyl groups (e.g., benzoyl), silyl groups (e.g., trimethylsilyl), and arylmethyl groups (e.g., benzyl).

Deprotection conditions for the protecting groups are inevitably predicted to vary according to the selection of the protecting groups.

Thus, for example, acyl groups such as alkanoyl or aroyl groups may be removed, for example, by hydrolysis with an appropriate base such as an alkali metal hydroxide (e.g., lithium hydroxide or sodium hydroxide).

Alternatively, silyl groups such as trimethylsilyl may be removed using, for example, fluoride or an aqueous acid solution; or arylmethyl groups such as a benzyl

group may be removed, for example, by the addition of hydrogen in the presence of a palladium-supported catalyst (e.g., active carbon).

[0175]

Examples of the protecting groups suitable for the amino group include acyl groups, for example, alkanoyl groups (e.g., acetyl), alkoxycarbonyl groups (e.g., methoxycarbonyl, ethoxycarbonyl, and t-butoxycarbonyl), arylmethoxycarbonyl groups (e.g., benzyloxycarbonyl), and aroyl groups (e.g., benzoyl).

Deprotection conditions for the protecting groups inevitably vary according to the selection of the protecting groups.

Thus, for example, acyl groups such as alkanoyl or alkoxycarbonyl groups or aroyl groups may be removed, for example, by hydrolysis with an appropriate base such as an alkali metal hydroxide (e.g., lithium hydroxide or sodium hydroxide).

Alternatively, alkoxycarbonyl groups (e.g., a t-butoxycarbonyl group) may be removed, for example, by treatment with an appropriate acid such as hydrochloric acid, sulfuric acid, phosphoric acid, or trifluoroacetic acid. Arylmethoxycarbonyl groups (e.g., a benzyloxycarbonyl group) may be removed, for example, by the addition of hydrogen in the presence of a palladium-supported catalyst (e.g., active carbon) or by treatment with a Lewis acid, for example, boron tris(trifluoroacetate).

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Moreover, examples of the protecting groups suitable for the primary amino group include a phthaloyl group, which may be removed by treatment with an alkylamine (e.g., dimethylaminopropylamine or 2-hydroxyethylamine) or hydrazine.

[0176]

Examples of the protecting groups suitable for the carboxyl group include esterifiable substituents, for example, methyl, ethyl, t-butyl, and benzyl groups. Deprotection conditions for the protecting groups are inevitably predicted to vary according to the selection of the protecting groups.

Thus, for example, a methyl ester or ethyl ester group may be removed, for example, by hydrolysis with an appropriate base such as sodium hydroxide. For example, a t-butyl ester group may be removed, for example, by treatment with an organic acid such as trifluoroacetic acid. A benzyl ester group may be removed, for example, by the addition of hydrogen in the presence of a palladium-supported catalyst (e.g., active carbon).

[0177]

These protecting groups may be removed at any convenient stage of synthesis using conventional techniques well known in the chemical field. Alternatively, the protecting groups may be removed in subsequent reaction steps or during workup.

[0178]

The removal of every protecting group and the

- 82 -

formation of the pharmacologically acceptable salt are within the ability of usual organic chemists to use standard techniques.

Further information about these steps is described above.

[0179]

When an optically active form of the compound of the present invention is required, this form may be obtained by subjecting an optically active starting material (e.g., formed by asymmetric derivatization in an appropriate reaction step) to any one of the approaches described above; or by resolving a racemic form of the present compound or an intermediate thereof using standard procedures; or by separating a diastereoisomer, if formed, by chromatography.

Moreover, enzymatic techniques can also be useful in the production of the optically active compound and/or intermediate.

[0180]

Likewise, when a pure regioisomer of the compound of the present invention is required, this isomer may be obtained by subjecting a pure regioisomer as a starting material to any one of the approaches described above or by resolving a mixture of regioisomers or intermediates thereof using standard procedures.

Examples

[0181]

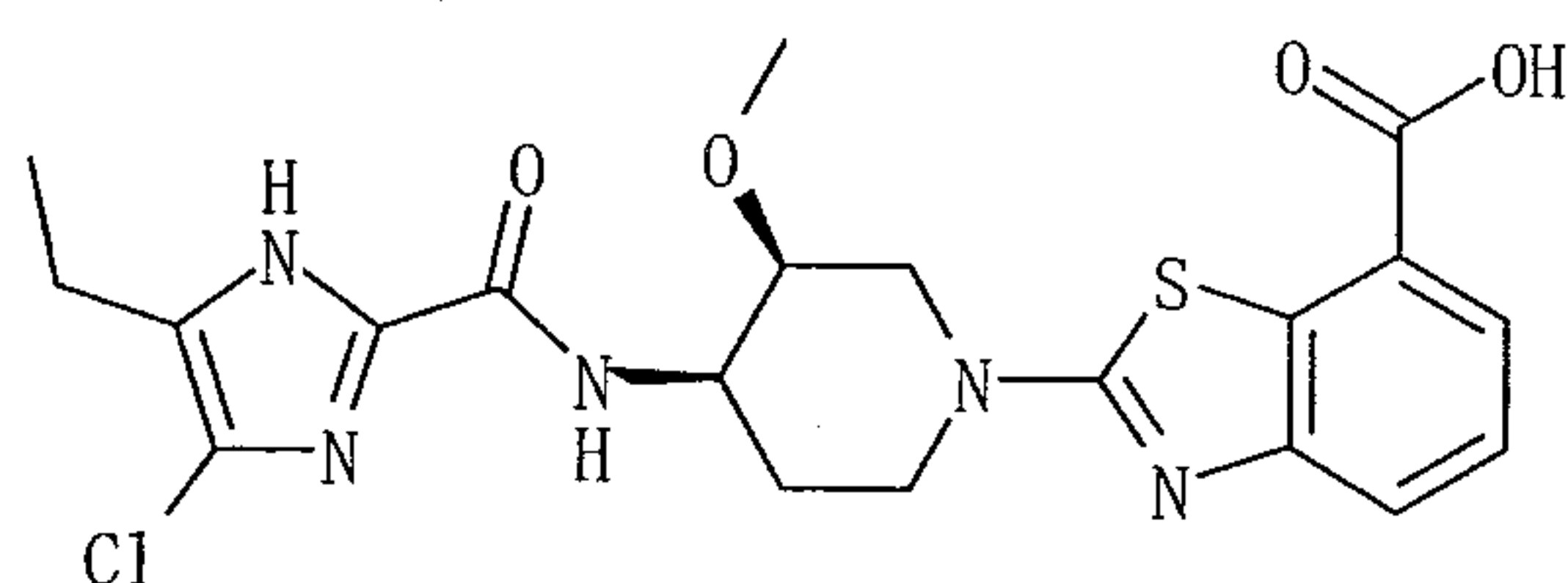
The present invention will be described in more

detail below with reference to Examples, Reference Examples and Test Examples; however, the scope of the present invention is not limited thereto.

[0182]

(Example 1) cis($\pm$)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylic acid

(Exemplified Compound No. 1)



[0183]

(1a) 1-Amino-butan-2-one hydrochloride

The compound was synthesized according to the method described in the following document.

[0184]

Synlett., 11, 2004, 2031-2033

(1b) Ethyl 5-ethyl-1H-imidazole-2-carboxylate

Sodium acetate (9.3 g, 113.4 mmol) was added to a solution of 1-amino-butan-2-one hydrochloride (3.41 g, 27.60 mmol) and ethyl imino(methylthio)acetate tetrafluoroborate (7.45 g, 31.84 mmol) synthesized according to the method described in the document (J. Med. Chem., 38, 1995, 2196-2201) in acetic acid (120 mL), and the mixture was stirred at 100°C for four hours. The reaction solution was concentrated under reduced pressure and then saturated aqueous sodium bicarbonate solution

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was added to the reaction solution, followed by extraction with ethyl acetate. Then, the organic layer was washed with brine and dried over anhydrous sodium sulfate. Following concentration under reduced pressure, the residue was purified by silica gel column chromatography (elution solvent: hexane/ethyl acetate = 5/1, 2/1, 1/2) to obtain 3.35 g of the title compound as a pale yellow solid (72%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.28 (3H, t, J = 7.66 Hz), 1.42 (3H, t, J = 7.15 Hz), 2.70 (2H, q, J = 7.66 Hz), 4.42 (2H, q, J = 7.15 Hz), 6.96 (1H, s).

(1c) Ethyl 4-chloro-5-ethyl-1H-imidazole-2-carboxylate

NCS (3.15 g, 23.59 mmol) was added to a solution of ethyl 5-ethyl-1H-imidazole-2-carboxylate obtained in Example (1b) (3.35 g, 19.92 mmol) in chloroform (100 mL), and the mixture was stirred at room temperature for 28 hours. Saturated aqueous sodium bicarbonate solution was added to the reaction solution, followed by extraction with chloroform. Then, the organic layer was washed with brine and dried over anhydrous sodium sulfate. Following concentration under reduced pressure, the residue was purified by silica gel column chromatography (elution solvent: hexane/ethyl acetate = 4/1, 3/1) to obtain 1.81 g of the title compound as a pale yellow solid (45%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.27 (3H, t, J = 7.61 Hz), 1.41 (3H, t, J = 7.12 Hz), 2.71 (2H, q, J = 7.61 Hz), 4.42 (2H, q, J = 7.12 Hz), 10.46 (1H, s).

(1d) 4-Chloro-5-ethyl-1H-imidazole-2-carboxylic acid

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Ethyl 4-chloro-5-ethyl-1H-imidazole-2-carboxylate obtained in Example (1c) (0.52 g, 2.56 mmol) was dissolved in methanol (8 mL) and dichloromethane (2 mL), and the solution was slowly added dropwise to a 3 N aqueous lithium hydroxide solution (3.5 mL, 10.5 mmol) heated to 70°C. Following stirring at that temperature for 40 minutes, the reaction solution was concentrated under reduced pressure and 1 N hydrochloric acid was added dropwise until the pH was 7. Thereafter, purification by reverse phase silica gel column chromatography (elution solvent: distilled water) gave 0.48 g of the title compound as a white solid (100%).
¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 1.10 (3H, t, J = 7.32 Hz), 2.44-2.51 (2H, m).

(1e) tert-Butyl cis(±)-4-amino-3-methoxypiperidine-1-carboxylate

The compound was synthesized according to the method described in the following document.

[0185]

WO 2006/087543 A1

(1f) Ethyl 2-bromo-1,3-benzothiazole-7-carboxylate

The compound was synthesized according to the method described in the following document.

[0186]

WO 2006/087543 A1

(1g) tert-Butyl cis(±)-4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate

WSC hydrochloride (580 mg, 3.02 mmol) and DMAP (125

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mg, 1.02 mmol) were added to a solution of tert-butyl cis(±)-4-amino-3-methoxypiperidine-1-carboxylate obtained in Example (1e) (230 mg, 0.99 mmol) and ethyl 4-chloro-5-ethyl-1H-imidazole-2-carboxylate obtained in Example (1d) (85 mg, 0.49 mmol) in DMA (5 mL), and the mixture was stirred at room temperature for three hours. Dilute hydrochloric acid was added to the reaction solution, followed by extraction with ethyl acetate. Then, the organic layer was washed with water, saturated aqueous sodium bicarbonate solution and brine, and dried over anhydrous sodium sulfate. Following concentration under reduced pressure, the residue was purified by silica gel column chromatography (elution solvent: hexane/ethyl acetate = 1/1, ethyl acetate) to obtain 117 mg of the title compound as a pale yellow solid (62%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.26 (3H, t, J = 7.62 Hz), 1.47 (9H, s), 1.57-1.70 (1H, m), 1.78-1.92 (1H, m), 2.68 (2H, q, J = 7.62 Hz), 2.74-2.84 (2H, m), 3.33-3.39 (2H, m), 3.41 (3H, s), 4.05-4.50 (2H, m), 7.44-7.52 (1H, m), 11.27 (1H, s).

(1h) Ethyl cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylate

tert-Butyl cis(±)-4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate obtained in Example (1g) (117 mg, 0.30 mmol) was dissolved in methanol (2 mL). A 4 N hydrochloric acid/ethyl acetate solution (5 mL) was added, and the

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mixture was stirred at room temperature for one hour.

Following concentration under reduced pressure, the residue was dissolved in DMF (3 mL).

Diisopropylethylamine (0.32 mL, 1.84 mmol) and ethyl 2-bromo-1,3-benzothiazole-7-carboxylate obtained in Example (1f) (87 mg, 0.30 mmol) were added, and the mixture was stirred at 70°C for two hours. Dilute hydrochloric acid was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with water, saturated aqueous sodium bicarbonate solution and brine, and dried over anhydrous sodium sulfate. Following concentration under reduced pressure, the residue was purified by silica gel column chromatography (elution solvent: hexane/ethyl acetate = 5/1, ethyl acetate) to obtain 97 mg of the title compound as a pale yellow solid (65%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.28 (3H, t, J = 7.57 Hz), 1.44 (3H, t, J = 7.12 Hz), 1.82-1.88 (1H, m), 2.05-2.16 (1H, m), 2.70 (2H, q, J = 7.57 Hz), 3.20-3.33 (2H, m), 3.45 (3H, s), 3.55 (1H, br s), 4.23-4.34 (2H, m), 4.45 (2H, q, J = 7.12 Hz), 4.58-4.67 (1H, m), 7.31-7.41 (1H, m), 7.53 (1H, d, J = 9.03 Hz), 7.70 (1H, dd, J = 7.93, 1.10 Hz), 7.74-7.83 (1H, m), 11.33 (1H, s).

(1i) cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylic acid

Ethyl cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-

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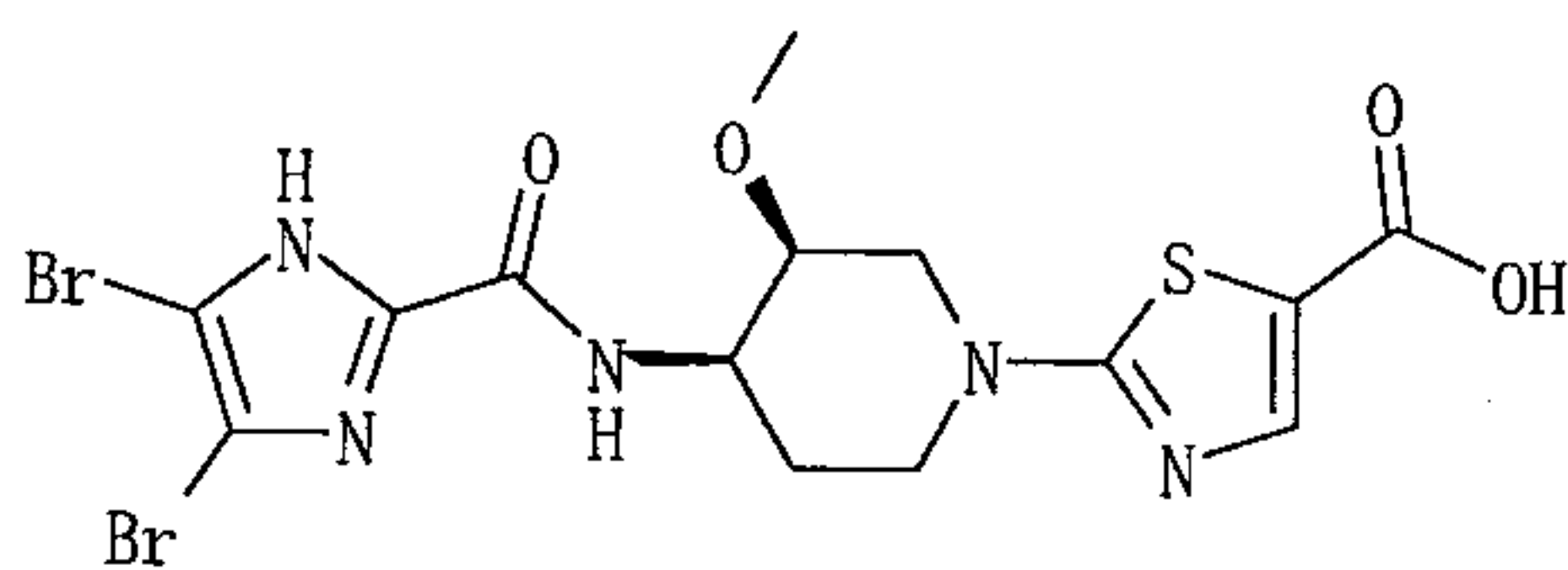
benzothiazole-7-carboxylate obtained in Example (1h) (95 mg, 0.19 mmol) was dissolved in methanol (5 mL) and dichloromethane (2 mL). A 2 N aqueous lithium hydroxide solution (3 mL) was added, and the mixture was stirred at 70°C for 1.5 hours. The organic solvent was evaporated under reduced pressure and 1 N hydrochloric acid was added until the pH of the solution was about 4. The resulting solid was collected by filtration and washed with distilled water to obtain 75 mg of the title compound as a white solid (84%).

¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 1.14 (3H, t, J = 7.56 Hz), 1.68-1.77 (1H, m), 1.85-1.99 (1H, m), 2.55 (2H, q, J = 7.56 Hz), 3.35-3.45 (5H, m), 3.60 (1H, br s), 4.07-4.17 (1H, m), 4.20-4.30 (1H, m), 4.36-4.48 (1H, m), 7.36-7.43 (1H, m), 7.63-7.71 (3H, m), 13.38 (1H, br s), 13.48 (1H, br s).

mass spectrum (ESI): m/z 464 (M+H)⁺.

(Example 2) cis(±)-2-(4-{[(4,5-Dibromo-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 2)



[0187]

(2a) 4,5-Dibromoimidazole-2-carboxylic acid

The compound was synthesized according to the method described in the following document.

[0188]

J. Heterocycle. Chem., 17, 1980, 409-411

(2b) tert-Butyl cis(±)-4-{[(4,5-dibromo-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate

The same operation as in Example (1g) was performed using tert-butyl cis(±)-4-amino-3-methoxypiperidine-1-carboxylate obtained by the method described in Example (1e) (300 mg, 1.30 mmol), 4,5-dibromoimidazole-2-carboxylic acid obtained in Example (2a) (300 mg, 1.11 mmol), WSC hydrochloride (460 mg, 2.40 mmol) and DMAP (50 mg, 0.41 mmol), to obtain 384 mg of the title compound as a white solid (72%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.48 (9H, s), 1.68-1.71 (1H, m), 1.86-1.93 (1H, m), 2.72-2.85 (2H, m), 3.39-3.42 (1H, m), 3.42 (3H, s), 4.18-4.21 (2H, m), 4.37-4.44 (1H, m), 7.55 (1H, brs).

(2c) Ethyl cis(±)-2-(4-{[(4,5-dibromo-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis(±)-4-{[(4,5-dibromo-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate obtained in Example (2b) (384 mg, 0.80 mmol), a 4 N hydrochloric acid/ethyl acetate solution (8 ml), diisopropylethylamine (0.7 mL, 4.02 mmol) and ethyl 2-bromo-1,3-thiazole-5-carboxylate (0.15 mL, 1.00 mmol), to obtain 249 mg of the title compound as an orange solid substance (58%).

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^1H NMR spectrum (400 MHz, DMSO- d_6) δ ppm: 1.25 (3H, t, J = 7.05 Hz), 1.67-1.71 (1H, m), 1.87-1.92 (1H, m), 3.32 (3H, s), 3.59 (1H, brs), 3.93-4.05 (2H, m), 4.21 (2H, q, J = 7.05 Hz), 4.21-4.25 (2H, m), 4.31-4.36 (1H, m), 7.82 (1H, s), 7.87 (1H, d, J = 8.20 Hz).

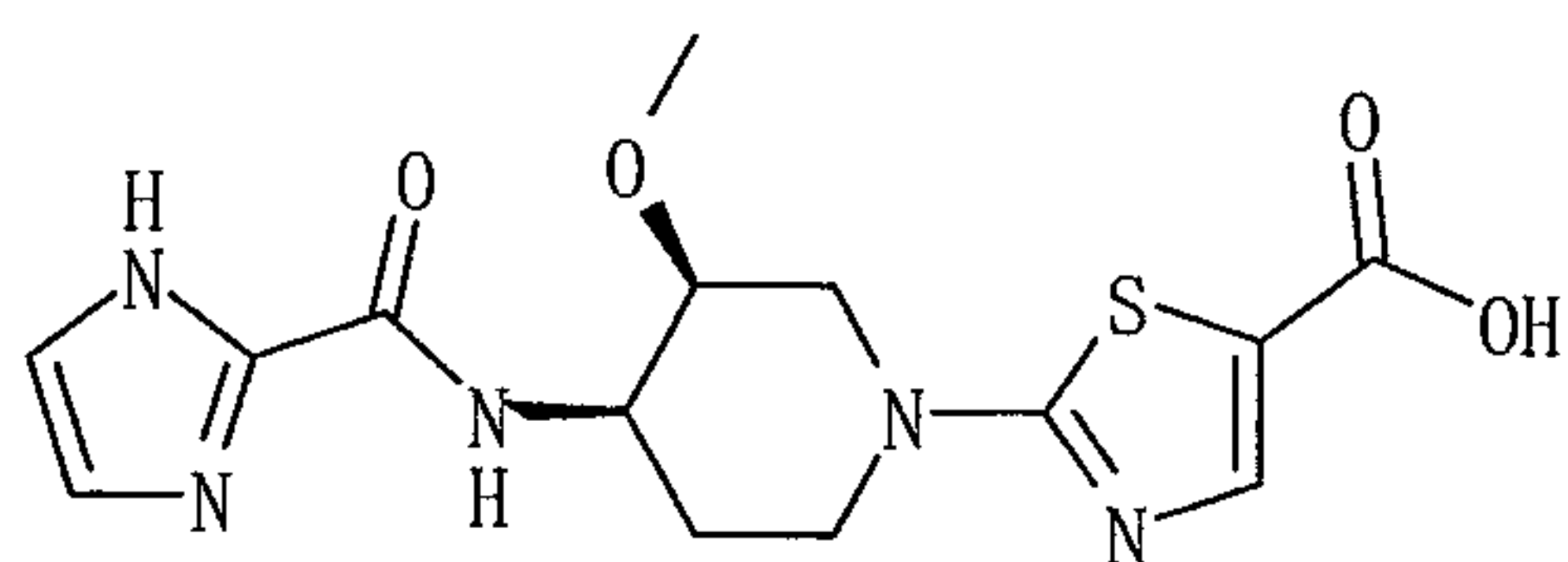
(2d) cis($\pm$)-2-(4-{[(4,5-Dibromo-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid

The same operation as in Example (1i) was performed using ethyl cis($\pm$)-2-(4-{[(4,5-dibromo-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate obtained in Example (2c) (249 mg, 0.46 mmol) and a 2 N aqueous lithium hydroxide solution (10 mL), to obtain 164 mg of the title compound as a white solid (69%).

^1H NMR spectrum (400 MHz, DMSO- d_6) δ ppm: 1.67-1.70 (1H, m), 1.85-1.93 (1H, m), 3.29-3.34 (2H, m), 3.33 (3H, s), 3.58 (1H, brs), 3.91-3.94 (1H, m), 4.19-4.23 (1H, m), 4.30-4.33 (1H, m), 7.74 (1H, s), 7.83 (1H, d, J = 8.20 Hz), 12.61 (1H, brs).

mass spectrum (FAB): m/z 510 ($M+H$) $^+$.

(Example 3) cis($\pm$)-{4-[(1H-Imidazol-2-ylcarbonyl)amino]-3-methoxypiperidin-1-yl}-1,3-thiazole-5-carboxylic acid
(Exemplified Compound No. 3)



[0189]

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(3a) 1H-Imidazol-2-carboxylic acid

The compound was synthesized according to the method described in the following document.

[0190]

J. Org. Chem., 60, 1995, 1090-1092

(3b) tert-Butyl cis(±)-4-[(1H-imidazol-2-ylcarbonyl)amino]-3-methoxypiperidine-1-carboxylate

The same operation as in Example (1g) was performed using tert-butyl cis(±)-4-amino-3-methoxypiperidine-1-carboxylate obtained by the method described in Example (1e) (0.20 g, 0.87 mmol), 1H-imidazole-2-carboxylic acid obtained in Example (3a) (91 mg, 0.81 mmol), WSC hydrochloride (0.36 g, 1.88 mmol) and DMAP (10 mg, 0.083 mmol), to obtain 138 mg of the title compound as a white solid (58%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.47 (9H, s), 1.80-1.93 (1H, m), 2.04-2.17 (1H, m), 2.72-3.01 (2H, m), 3.35-3.41 (1H, m), 3.42 (3H, s), 3.97-4.20 (2H, m), 4.33-4.56 (1H, m), 7.15-7.16 (2H, m), 7.60 (1H, brs).

(3c) Ethyl cis(±)-{4-[(1H-imidazol-2-ylcarbonyl)amino]-3-methoxypiperidin-1-yl}-1,3-thiazole-5-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis(±)-4-[(1H-imidazol-2-ylcarbonyl)amino]-3-methoxypiperidine-1-carboxylate obtained in Example (3b) (135 mg, 0.42 mmol), a 4 N hydrochloric acid /ethyl acetate solution (7 ml), diisopropylethylamine (0.3 mL, 1.72 mmol) and ethyl 2-bromo-1,3-thiazole-5-carboxylate (0.06 mL, 0.41 mmol), to

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obtain 67 mg of the title compound as an orange solid substance (43%).

¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 1.25 (3H, t, J = 7.07 Hz), 1.67-1.77 (1H, m), 1.78-1.90 (1H, m), 3.28-3.41 (2H, m), 3.34 (3H, s), 3.58 (1H, br s), 3.90-3.99 (1H, m), 4.20-4.28 (1H, m), 4.21 (2H, q, J = 7.07 Hz), 4.31-4.41 (1H, m), 7.04 (1H, br s), 7.29 (1H, br s), 7.68 (1H, d, J = 8.78 Hz), 7.82 (1H, s), 13.13 (1H, br s).

(3d) cis(±)-{4-[(1H-Imidazol-2-ylcarbonyl)amino]-3-methoxypiperidin-1-yl}-1,3-thiazole-5-carboxylic acid

The same operation as in Example (1i) was performed using ethyl cis(±)-{4-[(1H-imidazol-2-ylcarbonyl)amino]-3-methoxypiperidin-1-yl}-1,3-thiazole-5-carboxylate obtained in Example (3c) (67 mg, 0.18 mmol) and a 2 N aqueous lithium hydroxide solution (4 mL), to obtain 45 mg of the title compound as a white solid (71%).

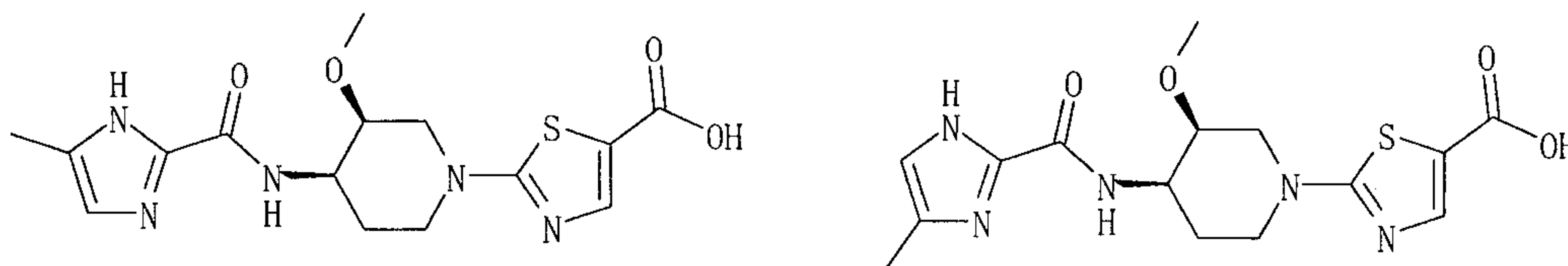
¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 1.64-1.74 (1H, m), 1.77-1.89 (1H, m), 3.10-3.21 (2H, m), 3.34 (3H, s), 3.53 (1H, br s), 3.76-3.86 (1H, m), 4.11-4.25 (2H, m), 7.03 (1H, br s), 7.13 (1H, s), 7.28 (1H, br s), 7.65 (1H, d, J = 8.54 Hz), 13.12 (1H, br s).

mass spectrum (FAB): m/z 352 (M+H)⁺.

(Example 4) cis(±)-(3-Methoxy-4-{[(4-methyl-1H-imidazol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylic acid and cis(±)-(3-methoxy-4-{[(5-methyl-1H-imidazol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 4)

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[0191]

(4a) 1-{[2-(Trimethylsilyl)ethoxy]methyl}-4-methylimidazole and 1-{[2-(trimethylsilyl)ethoxy]methyl}-5-methylimidazole

The compounds were synthesized according to the method described in the following document.

[0192]

J. Org. Chem., 38, 1973, 1437-1438

(4b) Ethyl 4-methyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazole-2-carboxylate and ethyl 5-methyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazole-2-carboxylate

A solution of the about 1:1 mixture of 1-{[2-(trimethylsilyl)ethoxy]methyl}-4-methylimidazole and 1-{[2-(trimethylsilyl)ethoxy]methyl}-5-methylimidazole obtained in Example (4a) (1.93 g, 9.01 mmol) in THF (50 mL) was cooled to -78°C . A n-butyllithium/1.58 M hexane solution (6 mL, 9.48 mmol) was added dropwise and the mixture was stirred for one hour. Thereafter, ethyl chloroformate (1 mL, 10.46 mmol) was added, and the mixture was heated to room temperature and further stirred for one hour. Brine was added to the reaction solution, followed by extraction with ethyl acetate. Then, the organic layer was washed with brine and dried over anhydrous sodium sulfate. Following concentration under reduced pressure, the residue was purified by

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silica gel column chromatography (elution solvent: hexane/ethyl acetate = 3/1, 2/1, 1/1) to obtain 0.50 g of the title compound as an about 1:1 mixture and as a pale yellow oily substance (20%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: -0.01 (9H x1/2, s), 0.00 (9H x1/2, s), 0.86-1.00 (2H, m), 1.44 (3H, t, J = 7.07 Hz), 2.30 (3H x1/2, s), 2.35 (3H x1/2, s), 3.55-3.60 (2H, m), 4.39-4.46 (2H, m), 5.76 (2H x1/2, s), 5.83 (2H x1/2, s), 6.97 (1H x1/2, s), 7.02 (1H x1/2, s).

(4c) tert-Butyl cis(±)-3-methoxy-4-{[(4-methyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazol-2-yl)carbonyl]amino}piperidine-1-carboxylate and tert-butyl cis(±)-3-methoxy-4-{[(5-methyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazol-2-yl)carbonyl]amino}piperidine-1-carboxylate

The about 1:1 mixture of ethyl 4-methyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazole-2-carboxylate and ethyl 5-methyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazole-2-carboxylate obtained in Example (4b) (0.35 g, 1.23 mmol) was dissolved in methanol (8 ml). A 1 N aqueous sodium hydroxide solution (8 mL, 8 mmol) was added, and the mixture was stirred at room temperature for one hour. The reaction solution was concentrated under reduced pressure and 1 N hydrochloric acid was added dropwise until the pH was 7. Thereafter, purification by reverse phase silica gel column chromatography (elution solvent: distilled water, acetonitrile/distilled water: 3/7) gave 0.12 g of

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carboxylic acid. The resulting carboxylic acid (0.12 g, 0.48 mmol) and tert-butyl cis($\pm$)-4-amino-3-methoxy piperidine-1-carboxylate obtained by the method described in Example (1e) (0.20 g, 0.87 mmol) were dissolved in dichloromethane. WSC hydrochloride (0.19 g, 0.99 mmol), triethylamine (0.2 mL, 1.43 mmol) and DMAP (10 mg, 0.083 mmol) were added, and the mixture was stirred at room temperature for 2.5 hours. Dilute hydrochloric acid was added to the reaction solution, followed by extraction with dichloromethane. Then, the organic layer was washed with saturated aqueous sodium bicarbonate solution and brine, and dried over anhydrous sodium sulfate.

Following concentration under reduced pressure, the residue was purified by silica gel column chromatography (elution solvent: hexane/ethyl acetate = 5/1, 1/1) to obtain 92 mg of the title compound as an about 3:1 mixture and as a pale yellow oily substance (16%).

^1H NMR spectrum (400 MHz, CDCl_3) δ ppm: -0.04 (9H x1/4, s), -0.02 (9H x3/4, s), 0.86-0.94 (2H, m), 1.47 (9H x3/4, s), 1.60 (9H x1/4, s), 1.62-1.71 (1H, m), 1.78-1.92 (1H, m), 2.23 (3H x3/4, s), 2.31 (3H x1/4, s), 3.32-3.40 (2H, m), 3.41 (3H x1/4, s), 3.43 (3H x3/4, s), 3.53-3.61 (3H, m), 4.07-4.52 (3H, m), 5.81 (2H x3/4, s), 5.91 (2H x1/4, s), 6.80 (1H x1/4, s), 6.92 (1H x3/4, s), 7.70 (1H, brs).

(4d) Ethyl cis($\pm$)-(3-methoxy-4-{[(4-methyl-1H-imidazol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylate and ethyl cis($\pm$)-(3-methoxy-4-{[(5-methyl-1H-imidazol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-

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thiazole-5-carboxylate

The same operation as in Example (1h) was performed using the about 3:1 mixture of tert-butyl cis(±)-3-methoxy-4-{[(4-methyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazol-2-yl)carbonyl]amino}piperidine-1-carboxylate and tert-butyl cis(±)-3-methoxy-4-{[(5-methyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazol-2-yl)carbonyl]amino}piperidine-1-carboxylate obtained in Example (4c) (90 mg, 0.19 mmol), a 4 N hydrochloric acid/ethyl acetate solution (4 mL, 16 mmol), diisopropylethylamine (0.14 mL, 0.80 mmol) and ethyl 2-bromo-1,3-thiazole-5-carboxylate (0.045 mL, 0.30 mmol), to obtain 80 mg of the title compound as an about 3:1 mixture and as a yellow oily substance (80%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: -0.03 (9H x1/4, s), -0.02 (9H x3/4, s), 0.86-0.96 (2H, m), 1.34 (3H, t, J = 7.11 Hz), 1.55-1.58 (1H, m), 1.78-1.87 (1H, m), 2.23 (3H, s), 2.32 (3H x3/4, s), 3.12-3.19 (1H x1/4, m), 3.20-3.30 (1H, m), 3.43 (3H x1/4, s), 3.44 (3H x3/4, s), 3.52-3.62 (3H, m), 3.93-4.02 (1H, m), 4.21-4.31 (1H, m), 4.29 (2H, q, J = 7.11 Hz), 4.49-4.58 (1H, m), 5.82 (2H x3/4, s), 5.90 (2H x1/4, s), 6.81 (1H x1/4, s), 6.93 (1H x3/4, s), 7.68-7.78 (1H, m), 7.84 (1H, s).

(4e) cis(±)-(3-Methoxy-4-{[(4-methyl-1H-imidazol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylic acid and cis(±)-(3-methoxy-4-{[(5-methyl-1H-imidazol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-

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thiazole-5-carboxylic acid

The about 3:1 mixture of ethyl cis($\pm$)-(3-methoxy-4-
{[(4-methyl-1H-imidazol-2-yl)carbonyl]amino}piperidin-1-
yl)-1,3-thiazole-5-carboxylate and ethyl cis($\pm$)-(3-
methoxy-4-
{[(5-methyl-1H-imidazol-2-
yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-
carboxylate obtained in Example (4d) (79 mg, 0.15 mmol)
was dissolved in ethanol (1 mL). A 4 N hydrochloric
acid/ethyl acetate solution (5 mL, 20 mmol) was added,
and the mixture was heated under reflux for four hours.
The reaction solution was concentrated under reduced
pressure, diluted with dichloromethane, washed with
saturated aqueous sodium bicarbonate solution and brine,
and dried over anhydrous sodium sulfate. Following
concentration under reduced pressure, the residue was
dissolved in methanol (5 mL) and dichloromethane (2 mL).
The solution was subjected to the same operation as in
Example (1i) using a 2 N aqueous lithium hydroxide
solution (4 mL, 8 mmol), to obtain 42 mg of the title
compound as an about 3:2 mixture and as a white solid
(77%).

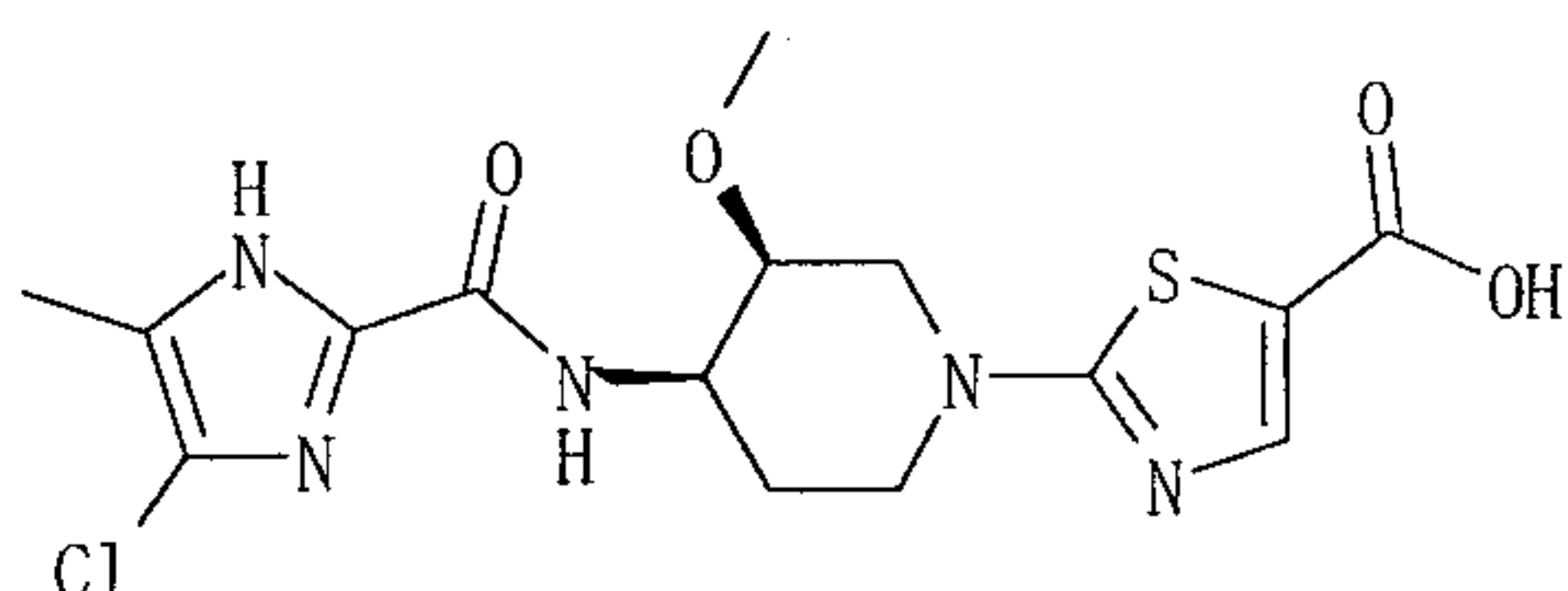
^1H NMR spectrum (400 MHz, DMSO- d_6) δ ppm: 1.70-1.86 (2H,
m), 2.14 (3H x2/5, s), 2.18 (3H x3/5, s), 3.26-3.40 (2H,
m), 3.31 (3H, s), 3.57 (1H, br s), 3.88-3.97 (1H, m),
4.16-4.40 (2H, m), 6.73 (1H x2/5, s), 6.99 (1H x3/5, s),
7.52-7.62 (1H, m), 7.73 (1H, s), 12.55-12.68 (1H, m),
12.75-12.90 (1H, m).

mass spectrum (FAB): m/z 366 ($M+H$) $^+$.

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(Example 5) cis($\pm$)-2-(4-{[(4-Chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 5)



[0193]

(5a) Ethyl 5-methyl-1H-imidazole-2-carboxylate

The compound was synthesized according to the method described in the following document.

[0194]

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(5b) Ethyl 4-chloro-5-methyl-1H-imidazole-2-carboxylate

The same operation as in Example (1c) was performed using ethyl 5-methyl-1H-imidazole-2-carboxylate obtained in Example (5a) (0.50 g, 3.23 mmol) and NCS (0.44 g, 3.25 mmol), to obtain 0.50 g of the title compound as a white solid (82%).

^1H NMR spectrum (400 MHz, CDCl_3) δ ppm: 1.41 (3H, t, J = 7.15 Hz), 2.32 (3H, s), 4.42 (2H, q, J = 7.15 Hz), 10.53 (1H, br s).

(5c) 4-Chloro-5-methyl-1H-imidazole-2-carboxylic acid

The same operation as in Example (1d) was performed using ethyl 4-chloro-5-methyl-1H-imidazole-2-carboxylate obtained in Example (5b) (0.50 g, 2.65 mmol) and a 3 N aqueous lithium hydroxide solution (4 mL), to obtain 0.35 g of the title compound as a white solid (82%).

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¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 2.21 (3H, s), 10.02 (1H, brs).

(5d) Ethyl cis(±)-2-(4-amino-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis(±)-4-amino-3-methoxypiperidine-1-carboxylate obtained by the method described in Example (1e) (3.00 g, 13.03 mmol), a 4 N hydrochloric acid/ethyl acetate solution (120 ml, 480 mmol), diisopropylethylamine (13 mL, 78.16 mmol) and ethyl 2-bromo-4-methyl-1,3-thiazole-5-carboxylate (3.23 g, 13.68 mmol), to obtain 2.41 g of the title compound as a yellow oily substance (65%).

¹H NMR spectrum (400 MHz, CD₃OD) δ ppm: 1.32 (3H, t, J = 7.20 Hz), 1.66-1.85 (2H, m), 2.96-3.03 (1H, m), 3.20-3.26 (2H, m), 3.42 (3H, s), 3.42-3.46 (1H, m), 3.89-3.99 (1H, m), 4.23-4.38 (3H, m), 7.77 (1H, s).

(5e) Ethyl cis(±)-2-(4-{[(4-chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate

The same operation as in Example (1g) was performed using ethyl cis(±)-2-(4-amino-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate obtained in Example (5d) (0.21 g, 0.73 mmol), 4-chloro-5-methyl-1H-imidazole-2-carboxylic acid obtained in Example (5c) (0.10 g, 0.64 mmol), WSC hydrochloride (0.27 g, 1.41 mmol) and DMAP (10 mg, 0.083 mmol), to obtain 54 mg of the title compound as a pale yellow solid (20%).

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¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.34 (3H, t, J = 7.12 Hz), 1.78-1.86 (1H, m), 1.99-2.13 (1H, m), 2.30 (3H, s), 3.11-3.17 (1H, m), 3.20-3.30 (1H, m), 3.42 (3H, s), 3.53 (1H, br s), 3.95-4.04 (1H, m), 4.22-4.32 (1H, m), 4.30 (2H, q, J = 7.12 Hz), 4.52-4.60 (1H, m), 7.43-7.49 (1H, m), 7.84 (1H, s), 11.01 (1H, br s).

(5f) cis(±)-2-(4-{[(4-Chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid

The same operation as in Example (1i) was performed using ethyl cis(±)-2-(4-{[(4-chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate obtained in Example (5e) (54 mg, 0.12 mmol) and a 2 N aqueous lithium hydroxide solution (2 mL), to obtain 11 mg of the title compound as a white solid (22%).

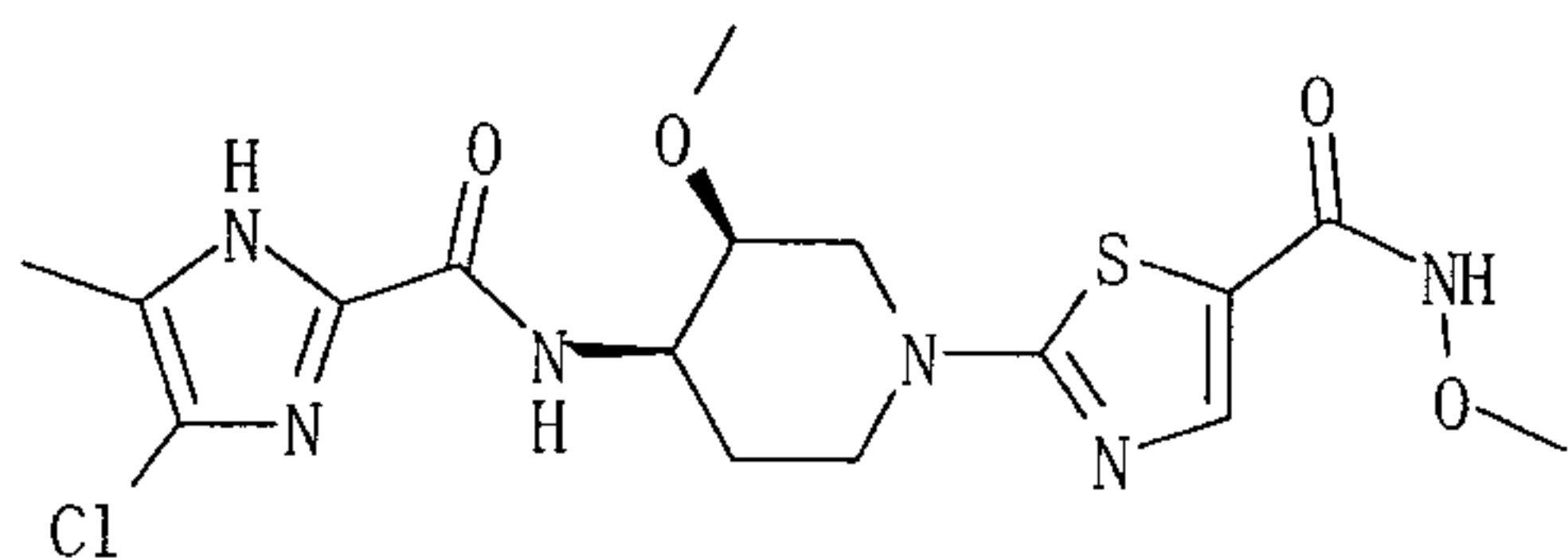
¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 1.65-1.74 (2H, m), 1.81-1.94 (2H, m), 2.16 (3H, s), 3.30-3.34 (1H, m), 3.32 (3H, s), 3.57 (1H, br s), 3.87-3.97 (1H, m), 4.17-4.38 (2H, m), 7.66 (1H, d, J = 8.54 Hz), 7.72 (1H, s), 13.35 (1H, br s).

mass spectrum (FAB): m/z 400 (M+H)⁺.

(Example 6) cis(±)-2-(4-{[(4-Chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-N-methoxy-1,3-thiazole-5-carboxamide

(Exemplified Compound No. 6)

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[0195]

(6a) cis(±)-2-(4-{{[(4-Chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxamide

The same operation as in Example (1g) was performed using cis(±)-2-(4-{{[(4-chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid obtained by the method described in Example (5f) (17 mg, 0.045 mmol), O-methylhydroxylamine (15 mg, 0.18 mmol), WSC hydrochloride (0.46 g, 0.24 mmol) and DMAP (5 mg, 0.042 mmol), to obtain 3.5 mg of the title compound as a white solid (18%).

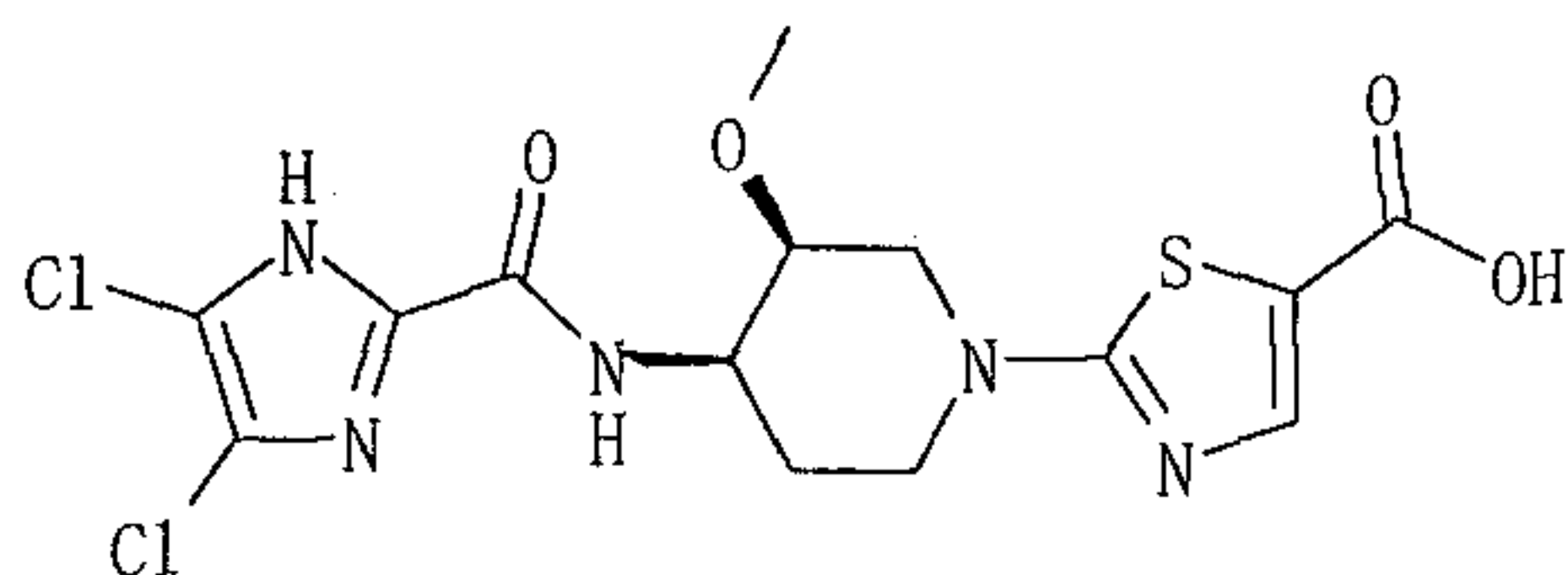
¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.78-1.87 (1H, m), 1.98-2.11 (1H, m), 2.30 (3H, s), 3.12-3.18 (1H, m), 3.20-3.30 (1H, m), 3.42 (3H, s), 3.53 (1H, br s), 3.83 (3H, s), 3.96-4.04 (1H, m), 4.22-4.32 (1H, m), 4.52-4.62 (1H, m), 7.26 (OH, s), 7.43-7.50 (1H, m), 7.88 (1H, s), 8.29 (1H, br s), 10.87 (1H, br s).

mass spectrum (ESI): m/z 429 (M+H)⁺.

(Example 7) cis(±)-2-(4-{{[(4,5-Dichloro-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 7)

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[0196]

(7a) 2-Bromo-4,5-dichloro-1-([2-(trimethylsilyl)ethoxy]methyl)-1H-imidazole

2-Bromo-4,5-dichloro-1H-imidazole (1.1 g, 5.09 mmol) was dissolved in THF (30 mL), and sodium hydride (0.29 g, 6.65 mmol) was added under ice-cooling, followed by stirring for 15 minutes. 2-

(Chloromethoxy)ethyltrimethylsilane (1 mL, 5.65 mmol) was added to the reaction solution, and the mixture was heated to room temperature and stirred for 40 minutes. Aqueous ammonium chloride solution was added to the reaction solution, followed by extraction with ethyl acetate. Then, the organic layer was washed with saturated aqueous sodium bicarbonate solution and brine, and dried over anhydrous sodium sulfate. Following concentration under reduced pressure, the residue was purified by silica gel column chromatography (elution solvent: hexane/ethyl acetate = 20/1, 10/1) to obtain 1.76 g of the title compound as a pale yellow oily substance (100%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 0.00 (9H, s), 0.93 (2H, t, J = 8.23 Hz), 3.60 (2H, t, J = 8.23 Hz), 5.29 (2H, s).

(7b) Ethyl 4,5-dichloro-1-([2-(trimethylsilyl)ethoxy]methyl)-1H-imidazole-2-carboxylate

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The same operation as in Example (4b) was performed using 2-bromo-4,5-dichloro-1-([2-(trimethylsilyl)ethoxy]methyl)-1H-imidazole obtained in Example (7a) (0.95 g, 2.55 mmol), a n-butyllithium/1.58 M hexane solution (1.9 mL, 3.00 mmol) and ethyl cyanoformate (0.33 mL, 3.34 mmol), to obtain 0.59 g of the title compound as a pale yellow oily substance (67%).
¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 0.01 (9H, s), 0.90-0.99 (2H, m), 1.46 (3H, t, J = 7.17 Hz), 3.61-3.68 (2H, m), 4.47 (2H, q, J = 7.17 Hz), 5.87 (2H, s).

(7c) Ethyl 4,5-dichloroimidazole-2-carboxylate

Ethyl 4,5-dichloro-1-([2-(trimethylsilyl)ethoxy]methyl)-1H-imidazole-2-carboxylate obtained in Example (7b) (0.61 g, 1.79 mmol) was dissolved in ethanol (3 mL). A 4 N hydrochloric acid/ethyl acetate solution (15 mL) was added, and the mixture was heated under reflux for one hour. The reaction solution was concentrated under reduced pressure, diluted with ethyl acetate, washed with brine and dried over anhydrous sodium sulfate. Following concentration under reduced pressure, the residue was purified by silica gel column chromatography (elution solvent: hexane/ethyl acetate = 10/1, 1/1) to obtain 0.24 g of the title compound as a pale yellow oily substance (65%).
mass spectrum (FAB): m/z 210 (M+H)⁺.

(7d) 4,5-Dichloroimidazole-2-carboxylic acid

The same operation as in Example (1d) was performed using ethyl 4,5-dichloroimidazole-2-carboxylate obtained

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in Example (7c) (0.24 g, 1.16 mmol) and a 2 N aqueous lithium hydroxide solution (5 mL), to obtain 0.16 g of the title compound as a white solid (76%).

mass spectrum (FAB): m/z 181 (M+H)+.

(7e) Ethyl cis(±)-2-(4-{[(4,5-dichloro-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate

The same operation as in Example (1g) was performed using ethyl cis(±)-2-(4-amino-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate obtained by the method described in Example (5d) (0.23 g, 0.81 mmol), 4,5-dichloroimidazole-2-carboxylic acid obtained in Example (7d) (84 mg, 0.46 mmol), WSC hydrochloride (0.24 g, 1.25 mmol) and DMAP (10 mg, 0.083 mmol), to obtain 49 mg of the title compound as a pale yellow solid (24%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.34 (3H, t, J = 7.12 Hz), 1.79-1.88 (1H, m), 1.99-2.10 (1H, m), 3.10-3.17 (1H, m), 3.20-3.30 (1H, m), 3.43 (3H, s), 3.53 (1H, br s), 3.94-4.04 (1H, m), 4.23-4.32 (1H, m), 4.30 (2H, q, J = 7.12 Hz), 4.52-4.61 (1H, m), 7.48 (1H, d, J = 8.79 Hz), 7.84 (1H, s).

(7f) cis(±)-2-(4-{[(4,5-Dichloro-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid

The same operation as in Example (1i) was performed using ethyl cis(±)-2-(4-{[(4,5-dichloro-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate obtained in Example (7e) (49 mg, 0.11 mmol)

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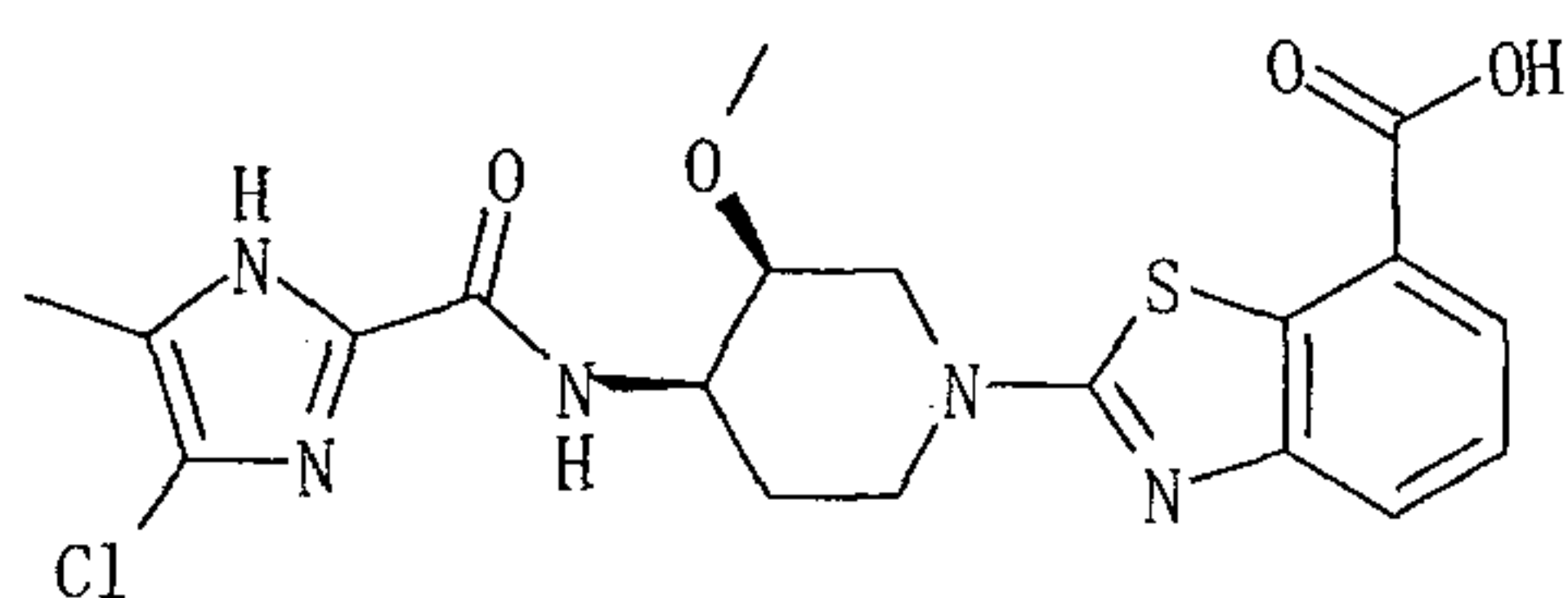
and a 2 N aqueous lithium hydroxide solution (2 mL), to obtain 18 mg of the title compound as a white solid (38%).

^1H NMR spectrum (400 MHz, DMSO- d_6) δ ppm: 1.63-1.73 (1H, m), 1.80-1.93 (1H, m), 3.27-3.36 (2H, m), 3.30 (3H, s), 3.56 (3H, br s), 3.87-3.98 (1H, m), 4.15-4.25 (1H, m), 4.27-4.38 (1H, m), 7.70-7.77 (1H, m), 7.74 (1H, s).

mass spectrum (ESI): m/z 421 ($M+H$) $^+$.

(Example 8) cis($\pm$)-2-(4-{[(4-Chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylic acid

(Exemplified Compound No. 8)



[0197]

(8a) tert-Butyl cis($\pm$)-4-{[(4-chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate

The same operation as in Example (1g) was performed using tert-butyl cis($\pm$)-4-amino-3-methoxypiperidine-1-carboxylate obtained by the method described in Example (1e) (1 g, 4.34 mmol), 4-chloro-5-methyl-1H-imidazole-2-carboxylic acid obtained by the method described in Example (5c) (0.35 g, 2.17 mmol), WSC hydrochloride (1.25 g, 6.52 mmol) and HOBt (0.30 g, 2.22 mmol), to obtain 0.68 g of the title compound as a white solid (84%).

^1H NMR spectrum (400 MHz, CDCl_3) δ ppm: 1.47 (9H, s), 1.57-1.70 (1H, m), 1.78-1.92 (1H, m), 2.30 (3H, s), 2.74-

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2.84 (2H, m), 3.35-3.39 (2H, m), 3.42 (3H, s), 4.05-4.50 (2H, m), 7.44-7.52 (1H, m), 11.25 (1H, s).

(8b) Ethyl cis(±)-2-(4-{[(4-chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis(±)-4-{[(4-chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate obtained in Example (8a) (48 mg, 0.13 mmol), a 4 N hydrochloric acid/ethyl acetate solution (4 mL), diisopropylethylamine (0.1 mL, 0.52 mmol) and ethyl 2-bromo-1,3-benzothiazole-7-carboxylate obtained by the method described in Example (1f) (42 mg, 0.15 mmol), to obtain 38 mg of the title compound as an orange solid substance (61%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.44 (3H, t, J = 7.11 Hz), 1.80-1.89 (1H, m), 2.01-2.14 (1H, m), 2.30 (3H, s), 3.20-3.34 (2H, m), 3.46 (3H, s), 3.55 (1H, br s), 4.21-4.34 (2H, m), 4.45 (2H, q, J = 7.11 Hz), 4.57-4.68 (1H, m), 7.34-7.44 (2H, m), 7.69 (2H, d, J = 7.80 Hz), 7.79 (2H, d, J = 8.05 Hz), 10.42 (1H, br s).

(8c) cis(±)-2-(4-{[(4-Chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylic acid

The same operation as in Example (1i) was performed using ethyl cis(±)-2-(4-{[(4-chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylate obtained in Example (8b) (38

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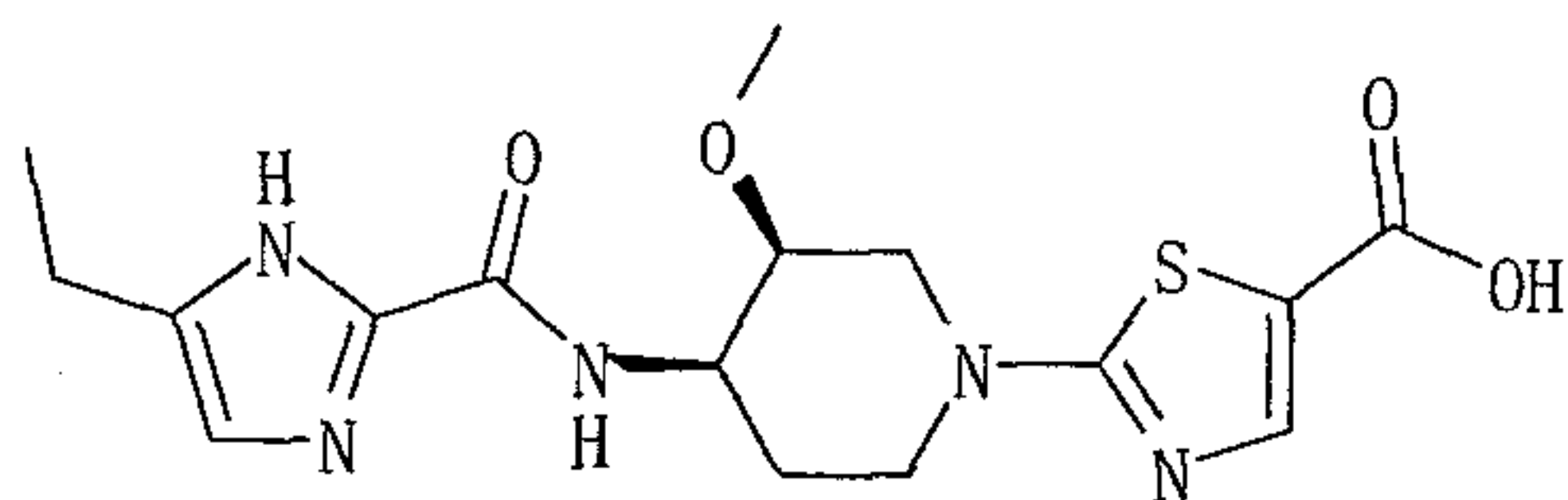
mg, 0.079 mmol) and a 4 N aqueous lithium hydroxide solution (2 mL), to obtain 21 mg of the title compound as a white solid (59%).

^1H NMR spectrum (400 MHz, DMSO- d_6) δ ppm: 1.67-1.83 (1H, m), 1.87-2.02 (1H, m), 2.16 (3H, s), 3.26-3.54 (2H, m), 3.38 (3H, s), 3.57-3.67 (1H, m), 4.06-4.57 (3H, m), 7.36-7.48 (1H, m), 7.61-7.77 (3H, m), 13.29-13.51 (1H, m).

mass spectrum (ESI): m/z 450 ($M+H$) $^+$.

(Example 9) cis($\pm$)-2-(4-{[5-Ethyl-1H-imidazol-2-yl]carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 9)



[0198]

(9a) 5-Ethyl-1H-imidazole-2-carboxylic acid

The same operation as in Example (1d) was performed using ethyl 5-ethyl-1H-imidazole-2-carboxylate obtained by the method described in Example (1b) (0.15 g, 0.89 mmol) and a 2 N aqueous lithium hydroxide solution (2 mL), to obtain 0.12 g of the title compound as a white solid (100%).

^1H NMR spectrum (400 MHz, DMSO- d_6) δ ppm: 1.28 (3H, t, J = 7.66 Hz), 2.70 (2H, q, J = 7.66 Hz), 10.01 (1H, br s).

(9b) Ethyl cis($\pm$)-2-(4-{[5-ethyl-1H-imidazol-2-yl]carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate

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The same operation as in Example (1g) was performed using ethyl cis($\pm$)-2-(4-amino-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate obtained by the method described in Example (5d) (0.21 g, 0.73 mmol), 5-ethyl-1H-imidazole-2-carboxylic acid obtained in Example (9a) (82 mg, 0.44 mmol), WSC hydrochloride (0.53 g, 2.76 mmol) and DMAP (0.12 g, 0.94 mmol), to obtain 107 mg of the title compound as a pale yellow solid (60%).

^1H NMR spectrum (400 MHz, CDCl_3) δ ppm: 1.23-1.30 (3H, m), 1.34 (3H, t, $J = 7.07$ Hz), 1.80-1.88 (1H, m), 2.01-2.07 (1H, m), 2.61-2.72 (2H, m), 3.11-3.18 (1H, m), 3.22-3.32 (1H, m), 3.43 (3H, s), 3.54 (1H, br s), 3.95-4.04 (1H, m), 4.24-4.35 (1H, m), 4.29 (2H, q, $J = 7.07$ Hz), 4.50-4.60 (1H, m), 6.84-6.91 (1H, m), 7.52-7.59 (1H, m), 7.84 (1H, s), 10.42-10.63 (1H, m).

(9c) cis($\pm$)-2-(4-{[5-Ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid

The same operation as in Example (1i) was performed using ethyl cis($\pm$)-2-(4-{[5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate obtained in Example (9b) (106 mg, 0.26 mmol) and a 2 N aqueous lithium hydroxide solution (2 mL) to obtain 63 mg of the title compound as a white solid (64%).

^1H NMR spectrum (400 MHz, $\text{DMSO}-d_6$) δ ppm: 1.12-1.21 (3H, m), 1.66-1.76 (1H, m), 1.78-1.90 (1H, m), 2.51-2.60 (2H, m), 3.29-3.37 (2H, m), 3.34 (3H, s), 3.57 (1H, br s),

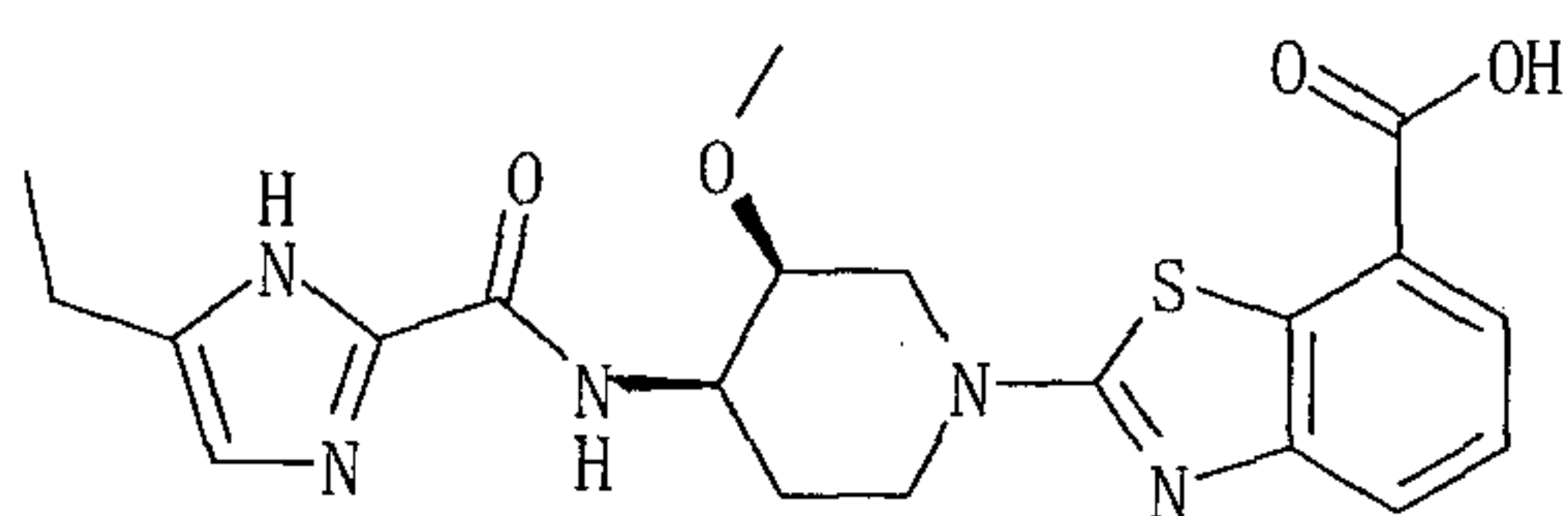
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3.88-3.98 (1H, m), 4.18-4.40 (2H, m), 6.73-7.02 (1H, m),
7.54-7.60 (1H, m), 7.74 (1H, s), 12.52-12.63 (1H, m),
12.80-12.92 (1H, m).

mass spectrum (FAB): m/z 380 (M+H)⁺.

(Example 10) cis(±)-2-(4-{[5-Ethyl-1H-imidazol-2-yl]carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylic acid

(Exemplified Compound No. 10)



[0199]

(10a) tert-Butyl cis(±)-4-{[(5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate

The same operation as in Example (1g) was performed using tert-butyl cis(±)-4-amino-3-methoxypiperidine-1-carboxylate obtained by the method described in Example (1e) (0.20 g, 0.87 mmol), 5-ethyl-1H-imidazole-2-carboxylic acid obtained in Example (1b) (85 mg, 0.44 mmol), WSC hydrochloride (0.55 g, 2.87 mmol) and DMAP (115 mg, 0.94 mmol), to obtain 85 mg of the title compound as a pale yellow solid (55%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.24-1.30 (3H, m), 1.47 (9H, s), 1.64-1.72 (1H, m), 1.78-1.92 (1H, m), 2.60-2.72 (2H, m), 3.34-3.44 (5H, m), 4.10-4.22 (2H, m), 4.35-4.54 (2H, m), 6.83-6.89 (1H, m), 7.48-7.59 (1H, m), 10.27-10.50 (1H, m).

(10b) Ethyl cis(±)-2-(4-{[5-Ethyl-1H-imidazol-2-

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yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis($\pm$)-4-{[(5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate obtained in Example (10a) (84 mg, 0.24 mmol), a 4 N hydrochloric acid/ethyl acetate solution (3 mL), diisopropylethylamine (0.25 mL, 1.43 mmol) and ethyl 2-bromo-1,3-benzothiazole-7-carboxylate obtained by the method described in Example (1f) (71 mg, 0.24 mmol), to obtain 65 mg of the title compound as a yellow solid substance (58%).

^1H NMR spectrum (400 MHz, CDCl_3) δ ppm: 1.23-1.32 (3H, m), 1.44 (3H, t, $J = 7.18$ Hz), 1.83-1.91 (1H, m), 2.02-2.19 (1H, m), 2.60-2.73 (2H, m), 3.22-3.36 (2H, m), 3.46 (3H, s), 3.57 (1H, br s), 4.21-4.37 (2H, m), 4.45 (2H, q, $J = 7.18$ Hz), 4.56-4.66 (1H, m), 6.83-6.92 (1H, m), 7.33-7.39 (1H, m), 7.52-7.59 (1H, m), 7.69 (1H, d, $J = 8.06$ Hz), 7.78 (1H, dd, $J = 7.81, 0.98$ Hz), 10.20-10.37 (1H, m).

(10c) cis($\pm$)-2-(4-{[5-Ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylic acid

The same operation as in Example (1i) was performed using ethyl cis($\pm$)-2-(4-{[5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylate obtained in Example (10b) (65 mg, 0.14 mmol) and a 2 N aqueous lithium hydroxide solution (2 mL, 4 mmol), to obtain 38 mg of the title

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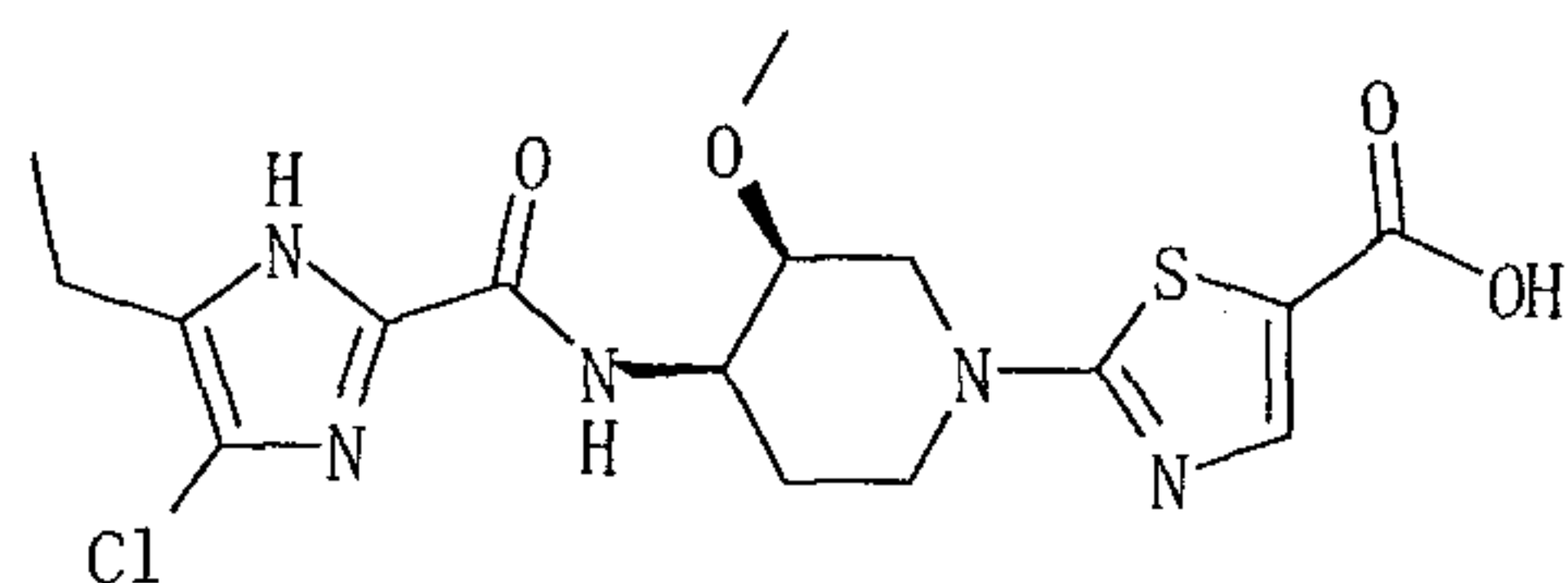
compound as a pale yellow solid (62%).

^1H NMR spectrum (400 MHz, DMSO-d_6) δ ppm: 1.17 (3H, t, $J = 7.56$ Hz), 1.71-1.80 (1H, m), 1.84-1.90 (1H, m), 2.52-2.60 (2H, m), 3.28-3.46 (2H, m), 3.38 (3H, s), 3.60 (1H, br s), 4.07-4.17 (1H, m), 4.21-4.31 (1H, m), 4.37-4.50 (1H, m), 6.84-7.00 (1H, m), 7.36-7.43 (1H, m), 7.61-7.71 (3H, m), 13.47 (1H, br s).

mass spectrum (ESI): m/z 430 ($\text{M}+\text{H}$) $^+$.

(Example 11) cis($\pm$)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 11)



[0200]

(11a) Ethyl cis($\pm$)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate

The same operation as in Example (1g) was performed using ethyl cis($\pm$)-2-(4-amino-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate obtained by the method described in Example (5d) (0.22 g, 0.77 mmol), 4-chloro-5-ethyl-1H-imidazole-2-carboxylic acid obtained by the method described in Example (1d) (85 mg, 0.49 mmol), WSC hydrochloride (0.56 g, 2.92 mmol) and DMAP (0.13 g, 1.02 mmol), to obtain 0.15 g of the title compound as a pale yellow solid (71%).

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¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.26 (3H, t, J = 7.56 Hz), 1.34 (3H, t, J = 7.19 Hz), 1.75-1.86 (1H, m), 2.03-2.09 (1H, m), 2.69 (2H, q, J = 7.56 Hz), 3.09-3.17 (1H, m), 3.19-3.31 (1H, m), 3.42 (3H, s), 3.52 (1H, brs), 3.95-4.05 (1H, m), 4.22-4.34 (3H, m), 4.51-4.61 (1H, m), 7.41-7.49 (1H, m), 7.84 (1H, s), 10.71 (1H, s).

(11b) cis(±)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid

The same operation as in Example (1i) was performed using ethyl cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate obtained in Example (11a) (0.15 g, 0.34 mmol) and a 2 N aqueous lithium hydroxide solution (2 mL), to obtain 0.12 g of the title compound as a white solid (87%).

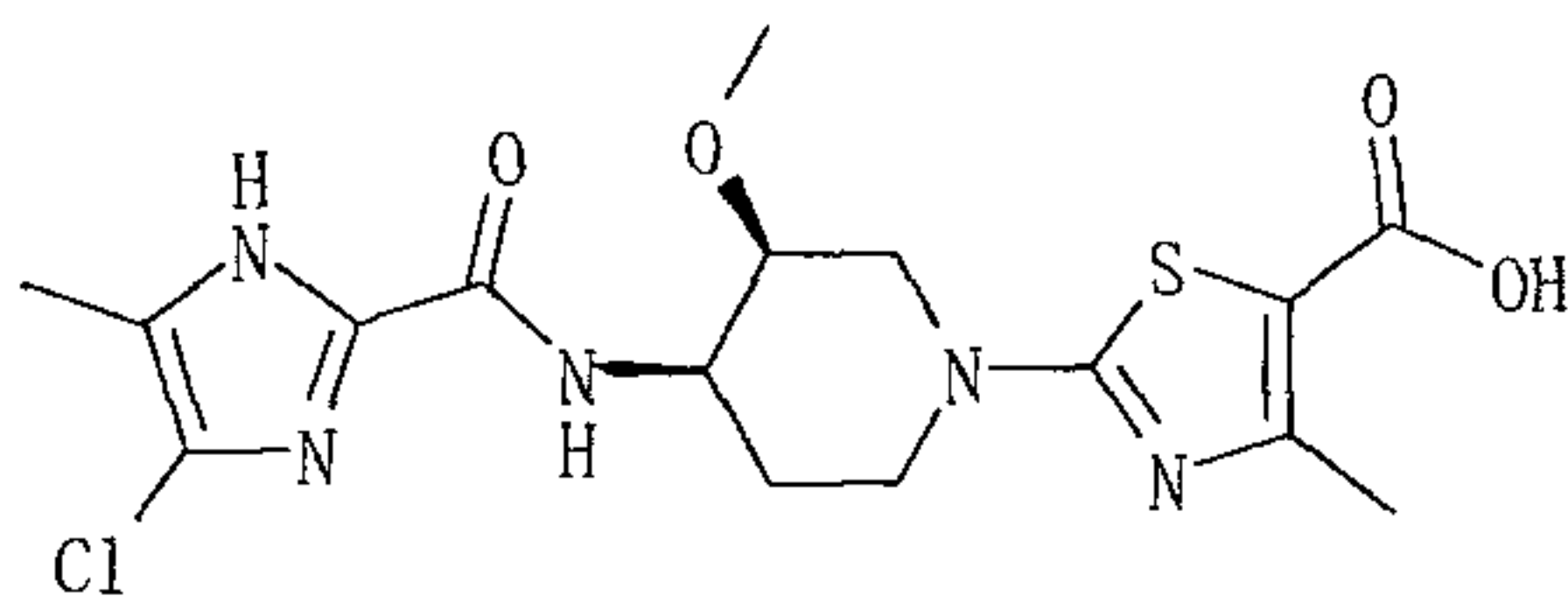
¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 1.14 (3H, t, J = 7.57 Hz), 1.64-1.73 (1H, m), 1.85-1.91 (1H, m), 2.52-2.60 (2H, m), 3.28-3.36 (2H, m), 3.32 (3H, s), 3.58 (1H, br s), 3.88-3.97 (1H, m), 4.18-4.26 (1H, m), 4.29-4.38 (1H, m), 7.65-7.70 (1H, m), 7.74 (1H, s), 13.37 (1H, br s).

mass spectrum (FAB): m/z 414 (M+H)⁺.

(Example 12) cis(±)-2-(4-{[(4-Chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 12)

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[0201]

(12a) Ethyl cis(±)-2-(4-{[(4-chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis(±)-4-{[(4-chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate obtained by the method described in Example (8a) (42 mg, 0.11 mmol), a 4 N hydrochloric acid/ethyl acetate solution (4 ml), diisopropylethylamine (0.1 mL, 0.57 mmol) and ethyl 2-bromo-4-methyl-1,3-thiazole-5-carboxylate (40 mg, 0.16 mmol), to obtain 33 mg of the title compound as a yellow solid substance (66%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.33 (3H, t, J = 7.19 Hz), 1.74-1.84 (1H, m), 2.00-2.05 (1H, m), 2.29 (3H, s), 2.54 (3H, s), 3.06-3.14 (1H, m), 3.16-3.25 (1H, m), 3.42 (3H, s), 3.51 (1H, br s), 3.95-4.04 (1H, m), 4.21-4.28 (3H, m), 4.46-4.55 (1H, m), 7.38-7.45 (1H, m), 10.32-10.46 (1H, m).

(12b) cis(±)-2-(4-{[(4-Chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid

The same operation as in Example (1i) was performed using ethyl cis(±)-2-(4-{[(4-chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-

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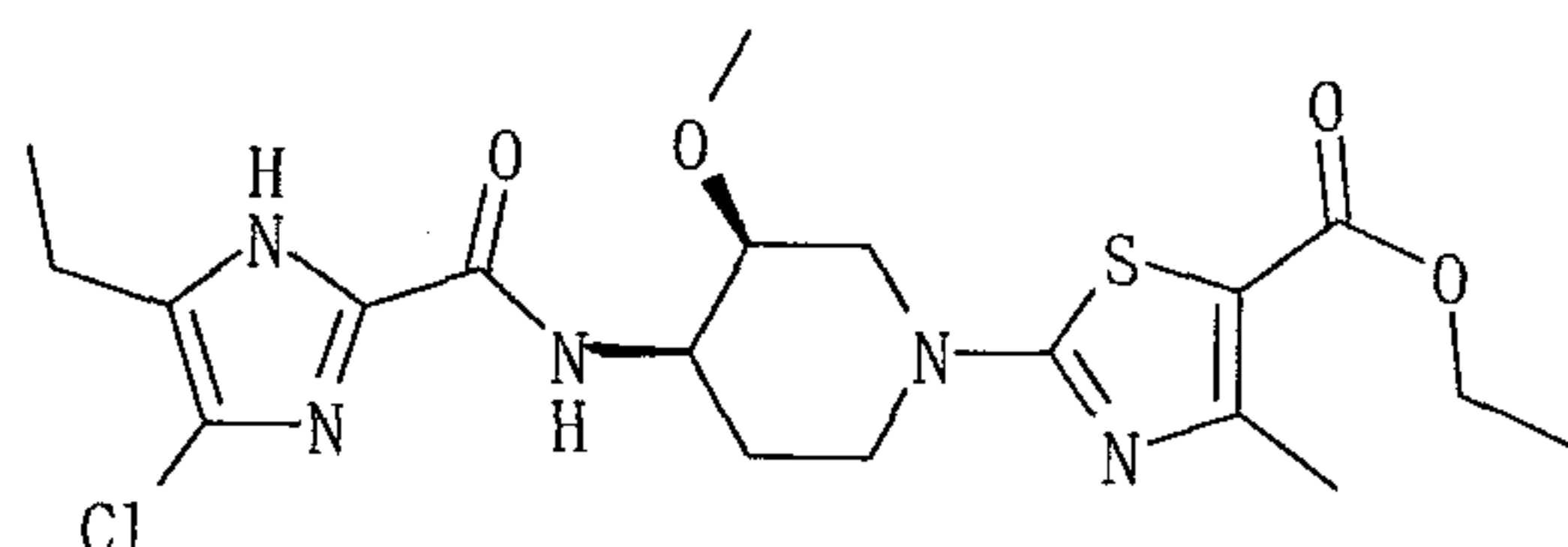
1,3-thiazole-5-carboxylate obtained in Example (12a) (32 mg, 0.072 mmol) and a 2 N aqueous lithium hydroxide solution (2 mL), to obtain 24 mg of the title compound as a white solid (80%).

^1H NMR spectrum (400 MHz, DMSO- d_6) δ ppm: 1.63-1.72 (1H, m), 1.77-1.92 (1H, m), 2.16 (3H, s), 2.41 (3H, s), 3.22-3.36 (2H, m), 3.32 (3H, s), 3.56 (1H, brs), 3.87-3.98 (1H, m), 4.17-4.27 (2H, m), 7.65 (1H, d, $J = 8.29$ Hz), 12.39 (1H, br s), 13.35 (1H, br s).

mass spectrum (ESI): m/z 414 ($M+H$) $^+$.

(Example 13) Ethyl cis($\pm$)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate

(Exemplified Compound No. 13)



[0202]

(13a) Ethyl cis($\pm$)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis($\pm$)-4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate obtained by the method described in Example (1g) (57 mg, 0.15 mmol), a 4 N hydrochloric acid/ethyl acetate solution (3 mL), diisopropylethylamine (0.1 mL, 0.57 mmol) and ethyl 2-bromo-4-methyl-1,3-thiazole-5-

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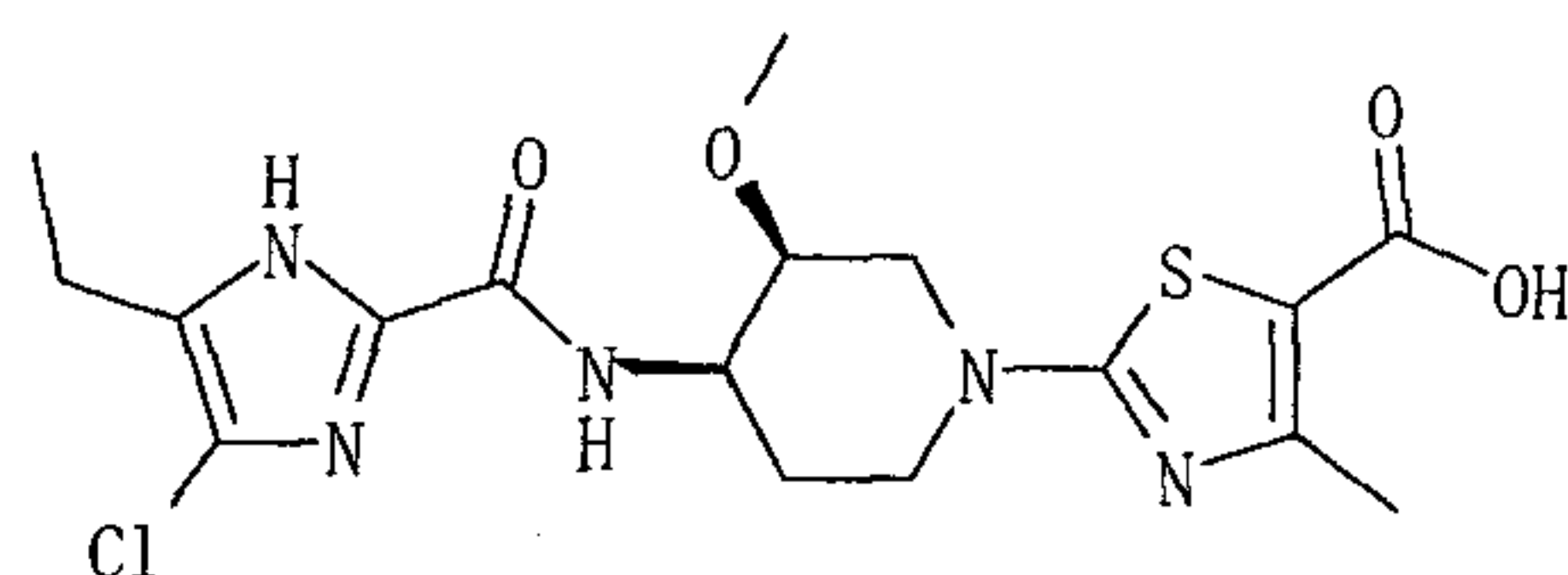
carboxylate (45 mg, 0.18 mmol), to obtain 52 mg of the title compound as a yellow solid substance (78%).

^1H NMR spectrum (400 MHz, CDCl_3) δ ppm: 1.27 (3H, t, $J = 7.66$ Hz), 1.33 (3H, t, $J = 7.19$ Hz), 1.72-1.81 (1H, m), 1.97-2.11 (1H, m), 2.54 (3H, s), 2.69 (2H, q, $J = 7.66$ Hz), 3.06-3.13 (1H, m), 3.14-3.24 (1H, m), 3.42 (3H, s), 3.51 (1H, br s), 3.96-4.06 (1H, m), 4.21-4.31 (3H, m), 4.46-4.56 (1H, m), 7.54 (1H, d, $J = 9.02$ Hz), 11.61 (1H, br s).

mass spectrum (ESI): m/z 456 ($\text{M}+\text{H}$) $^+$

(Example 14) cis($\pm$)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 14)



[0203]

(14a) cis($\pm$)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid

The same operation as in Example (1i) was performed using ethyl cis($\pm$)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate obtained by the method described in Example (13a) (52 mg, 0.12 mmol) and a 2 N aqueous lithium hydroxide solution (2 mL), to obtain 32 mg of the title compound as a white solid (65%).

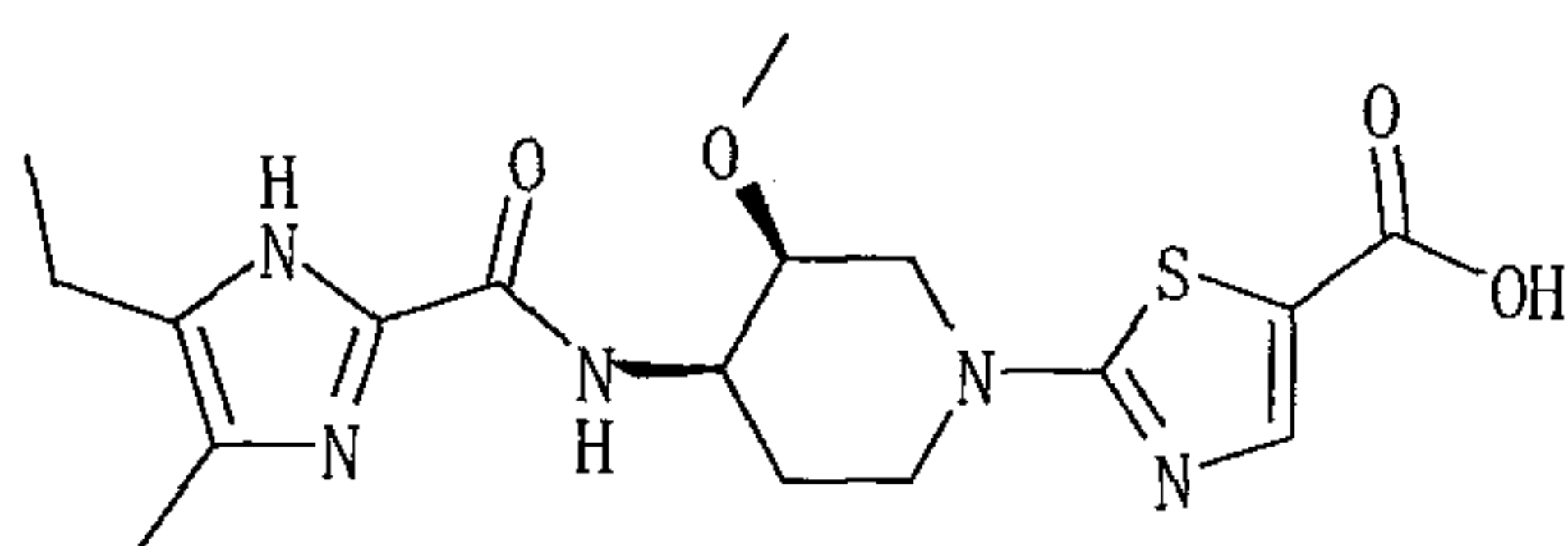
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^1H NMR spectrum (400 MHz, DMSO-d_6) δ ppm: 1.14 (3H, t, $J = 7.56$ Hz), 1.62-1.72 (1H, m), 1.81-1.87 (1H, m), 2.41 (3H, s), 2.55 (2H, q, $J = 7.56$ Hz), 3.22-3.36 (2H, m), 3.34 (3H, s), 3.56 (1H, br s), 3.86-3.98 (1H, m), 4.15-4.29 (2H, m), 7.64 (1H, d, $J = 8.54$ Hz), 12.38 (1H, br s), 13.36 (1H, br s).

mass spectrum (ESI): m/z 428 ($\text{M}+\text{H}$) $^+$.

(Example 15) cis($\pm$)-2-(4-{[(5-Ethyl-4-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 15)



[0204]

(15a) 2-Bromo-pentan-3-one

The compound was synthesized according to the method described in the following document.

[0205]

J. Org. Chem., 40, 1975, 1294-1298

(15b) 2-(1-Methyl-2-oxobutyl)-1H-isoindole-1,3(2H)-dione

2-Bromo-pentan-3-one obtained in Example (15a) (8.47 g, 35.57 mmol) was dissolved in DMF (120 mL). Potassium phthalimide (6.9 g, 37.25 mmol) was added, and the mixture was stirred at room temperature for 10 hours. Ethyl acetate was added to the reaction solution, and the organic layer was washed with 1 N hydrochloric acid and brine, and dried over anhydrous sodium sulfate.

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Following concentration under reduced pressure, the residue was washed with hexane to obtain 6.5 g of the title compound as a white solid (79%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.08 (3H, t, J = 7.19 Hz), 1.68 (3H, d, J = 7.32 Hz), 2.45-2.56 (2H, m), 4.82 (1H, q, J = 7.32 Hz), 7.74-7.80 (2H, m), 7.84-7.92 (2H, m).

(15c) 2-Amino-pentan-3-one hydrochloride

2-(1-Methyl-2-oxobutyl)-1H-isoindole-1,3(2H)-dione obtained in Example (15b) (2.3 g, 9.95 mmol) was dissolved in acetic acid (20 mL). 6 N hydrochloric acid (20 mL) was added, and the mixture was heated under reflux for seven hours. The reaction solution was left to stand overnight and the precipitated phthalic acid was separated by filtration. The filtrate was concentrated under reduced pressure to obtain the title compound as a white solid. The resulting compound was used for the next reaction without purification.

[0206]

(15d) Ethyl 5-ethyl-4-methyl-1H-imidazole-2-carboxylate

The same operation as in Example (1b) was performed using 2-amino-pentan-3-one hydrochloride obtained in Example (15c) (about 10 mmol) and ethyl imino(methylthio)acetate tetrafluoroborate obtained according to a method known in the literature (J. Med. Chem., 38, 1995, 2196-2201) (about 10 mmol), to obtain 1.1 g of the title compound as a yellow solid (60%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.23 (3H, t, J =

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7.56 Hz), 1.41 (3H, t, $J = 7.17$ Hz), 2.24 (3H, s), 2.61 (2H, br s), 4.41 (2H, q, $J = 7.17$ Hz), 9.88 (1H, br s).

(15e) 5-Ethyl-4-methyl-1H-imidazole-2-carboxylic acid

The same operation as in Example (1d) was performed using ethyl 5-ethyl-4-methyl-1H-imidazole-2-carboxylate obtained in Example (15d) (0.30 g, 1.66 mmol) and a 3 N aqueous lithium hydroxide solution (2.5 mL), to obtain 0.26 g of the title compound as a white solid (100%).

^1H NMR spectrum (400 MHz, DMSO- d_6) δ ppm: 1.12 (3H, t, $J = 7.44$ Hz), 2.13 (3H, s), 2.50-2.54 (2H, m).

(15f) tert-Butyl cis($\pm$)-4-{[(5-ethyl-4-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate

The same operation as in Example (1g) was performed using tert-butyl cis($\pm$)-4-amino-3-methoxypiperidine-1-carboxylate obtained by the method described in Example (1e) (0.77 g, 3.32 mmol), 5-ethyl-4-methyl-1H-imidazole-2-carboxylic acid obtained in Example (15e) (0.26 g, 1.66 mmol), WSC hydrochloride (1.85 g, 9.65 mmol) and DMAP (0.2 g, 1.64 mmol), to obtain 0.43 g of the title compound as a white foamy substance (70%).

^1H NMR spectrum (400 MHz, CDCl_3) δ ppm: 1.19-1.28 (3H, m), 1.47 (9H, s), 1.58-1.71 (1H, m), 1.78-1.92 (1H, m), 2.19 (3H, s), 2.48-2.66 (2H, m), 3.34-3.44 (2H, m), 3.41 (3H, s), 3.97-4.25 (3H, m), 4.33-4.56 (1H, m), 7.41-7.51 (1H, m), 10.21-10.38 (1H, m).

(15g) Ethyl cis($\pm$)-2-(4-{[(5-ethyl-4-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-

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thiazole-5-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis($\pm$)-4-{[(5-ethyl-4-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate obtained in Example (15f) (0.11 g, 0.26 mmol), a 4 N hydrochloric acid/ethyl acetate solution (2 mL), diisopropylethylamine (0.2 mL, 1.15 mmol) and ethyl 2-bromo-1,3-thiazole-5-carboxylate (0.05 mL, 0.33 mmol), to obtain 97 mg of the title compound as a yellow solid (79%).

^1H NMR spectrum (400 MHz, CDCl_3) δ ppm: 1.26 (3H, t, J = 7.07 Hz), 1.34 (3H, t, J = 7.07 Hz), 1.78-1.87 (1H, m), 2.00-2.09 (1H, m), 2.18-2.26 (3H, m), 2.50-2.65 (2H, m), 3.12-3.19 (1H, m), 3.20-3.30 (1H, m), 3.42 (3H, s), 3.54 (1H, br s), 3.95-4.03 (1H, m), 4.23-4.33 (1H, m), 4.29 (3H, q, J = 7.07 Hz), 4.50-4.57 (1H, m), 7.42-7.49 (1H, m), 7.84 (1H, s), 10.00-10.13 (1H, m).

(15h) cis($\pm$)-2-(4-{[(5-Ethyl-4-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid

The same operation as in Example (1i) was performed using ethyl cis($\pm$)-2-(4-{[(5-ethyl-4-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate obtained in Example (15g) (95 mg, 0.19 mmol) and a 2 N aqueous lithium hydroxide solution (3 mL), to obtain 64 mg of the title compound as a white solid (72%).

^1H NMR spectrum (400 MHz, $\text{DMSO}-d_6$) δ ppm: 1.10 (3H, t, J

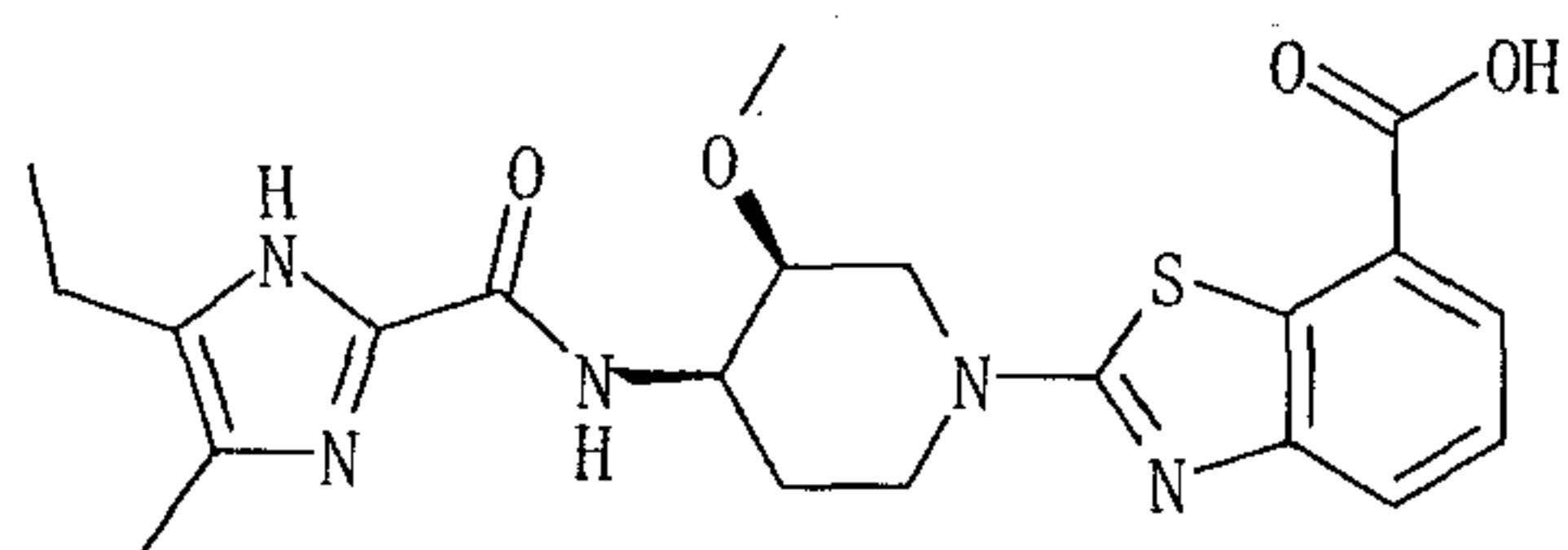
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= 7.44 Hz), 1.66-1.75 (1H, m), 1.77-1.87 (1H, m), 2.05-2.16 (3H, m), 2.46-2.55 (2H, m), 3.28-3.37 (2H, m), 3.34 (3H, s), 3.56 (1H, br s), 3.88-3.97 (1H, m), 4.18-4.23 (1H, m), 4.29-4.40 (1H, m), 7.41-7.51 (1H, m), 7.74 (1H, s), 12.57-12.67 (2H, m).

mass spectrum (ESI): m/z 394 (M+H)⁺.

(Example 16) cis(±)-2-(4-{[(5-Ethyl-4-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylic acid

(Exemplified Compound No. 16)



[0207]

(16a) Ethyl cis(±)-2-(4-{[(5-ethyl-4-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis(±)-4-{[(5-ethyl-4-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate obtained by the method described in Example (15f) (0.11 g, 0.26 mmol), a 4 N hydrochloric acid/ethyl acetate solution (2 mL), diisopropylethylamine (0.2 mL, 1.15 mmol) and ethyl 2-bromo-1,3-benzothiazole-7-carboxylate obtained by the method described in Example (1f) (88 mg, 0.31 mmol), to obtain 80 mg of the title compound as a yellow solid (58%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.21-1.28 (3H, m),

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1.44 (3H, t, $J = 7.14$ Hz), 1.81-1.90 (1H, m), 2.03-2.28 (4H, m), 2.48-2.68 (2H, m), 3.22-3.37 (2H, m), 3.46 (3H, s), 3.57 (1H, br s), 4.19-4.36 (2H, m), 4.45 (2H, q, $J = 7.14$ Hz), 4.54-4.64 (1H, m), 7.33-7.39 (1H, m), 7.43-7.54 (1H, m), 7.69 (1H, dd, $J = 7.80, 1.04$ Hz), 7.78 (1H, dd, $J = 7.68, 1.04$ Hz), 10.05-10.21 (1H, m).

(16b) cis($\pm$)-2-(4-{[(5-Ethyl-4-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylic acid

The same operation as in Example (1i) was performed using ethyl cis($\pm$)-2-(4-{[(5-ethyl-4-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylate obtained in Example (16a) (78 mg, 0.17 mmol) and a 2 N aqueous lithium hydroxide solution (2 mL), to obtain 36 mg of the title compound as a white solid (49%).

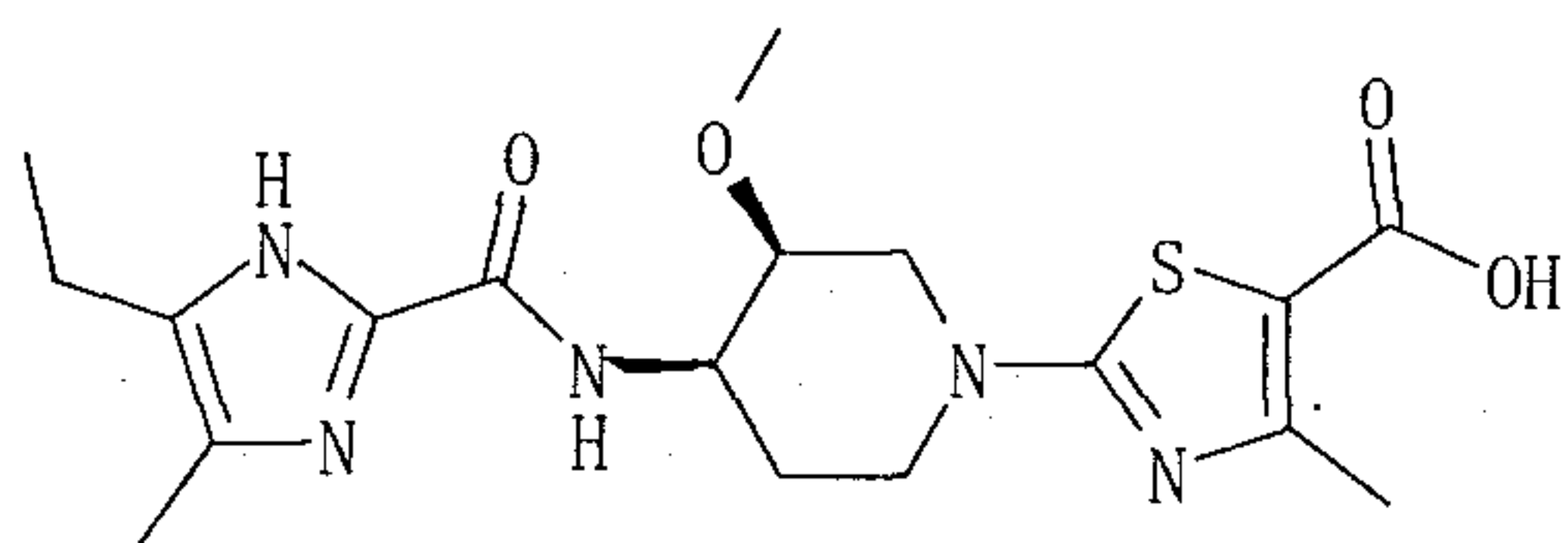
^1H NMR spectrum (400 MHz, DMSO- d_6) δ ppm: 1.22 (3H, t, $J = 7.56$ Hz), 1.33 (3H, t, $J = 7.07$ Hz), 1.76-1.85 (1H, m), 1.98-2.10 (1H, m), 2.16-2.28 (3H, m), 2.54 (3H, s), 2.62 (2H, q, $J = 7.56$ Hz), 3.09-3.15 (1H, m), 3.18-3.25 (1H, m), 3.43 (3H, s), 3.52 (1H, br s), 3.95-4.03 (1H, m), 4.21-4.31 (3H, m), 4.46-4.53 (1H, m), 7.41-7.49 (1H, m), 9.95-10.07 (1H, m).

mass spectrum (ESI): m/z 444 ($M+H$) $^+$.

(Example 17) cis($\pm$)-2-(4-{[(5-Ethyl-4-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 17)

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[0208]

(17a) Ethyl cis(±)-2-(4-{{[(5-ethyl-4-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis(±)-4-{{[(5-ethyl-4-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate obtained by the method described in Example (15f) (0.11 g, 0.26 mmol), a 4 N hydrochloric acid/ethyl acetate solution (2 mL), diisopropylethylamine (0.2 mL, 1.15 mmol) and ethyl 2-bromo-4-methyl-1,3-thiazole-5-carboxylate (83 mg, 0.33 mmol), to obtain 78 mg of the title compound as a yellow solid (61%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.22 (3H, t, J = 7.56 Hz), 1.33 (3H, t, J = 7.07 Hz), 1.76-1.85 (1H, m), 1.98-2.10 (1H, m), 2.16-2.28 (3H, m), 2.54 (3H, s), 2.62 (2H, q, J = 7.56 Hz), 3.09-3.15 (1H, m), 3.18-3.25 (1H, m), 3.43 (3H, s), 3.52 (1H, br s), 3.95-4.03 (1H, m), 4.21-4.31 (3H, m), 4.46-4.53 (1H, m), 7.41-7.49 (1H, m), 9.95-10.07 (1H, m).

(17b) cis(±)-2-(4-{{[(5-Ethyl-4-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid

The same operation as in Example (1i) was performed using ethyl cis(±)-2-(4-{{[(5-ethyl-4-methyl-1H-imidazol-

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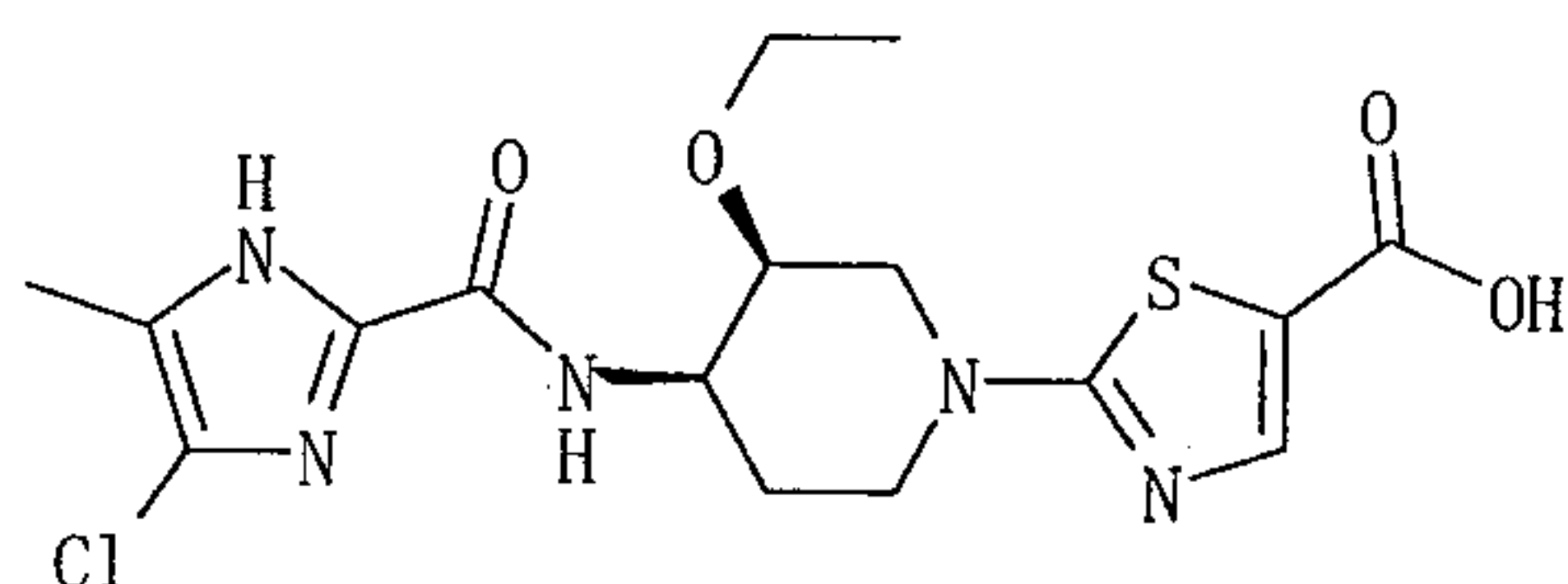
2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate obtained in Example (17a) (75 mg, 0.17 mmol) and a 2 N aqueous lithium hydroxide solution (2 mL), to obtain 60 mg of the title compound as a white solid (85%).

¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 1.10 (3H, t, J = 7.56 Hz), 1.69 (1H, s), 1.81-1.85 (1H, m), 2.06-2.12 (3H, m), 2.40 (3H, s), 2.46-2.53 (2H, m), 3.26-3.37 (2H, m), 3.34 (3H, s), 3.90 (1H, br s), 4.12-4.32 (2H, m), 7.37-7.49 (1H, m), 12.33-12.43 (1H, m), 12.58-12.67 (1H, m).

mass spectrum (ESI): m/z 408 (M+H)⁺.

(Example 18) cis(±)-2-(4-{[(4-Chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 18)



[0209]

(18a) tert-Butyl cis(±)-4-amino-3-ethoxypiperidine-1-carboxylate

The compound was synthesized according to the method described in the following document.

[0210]

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(18b) tert-Butyl cis(±)-4-{[(4-chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidine-1-

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carboxylate

The same operation as in Example (1g) was performed using tert-butyl cis($\pm$)-4-amino-3-ethoxypiperidine-1-carboxylate obtained in Example (18a) (0.34 g, 1.37 mmol), 4-chloro-5-methyl-1H-imidazole-2-carboxylic acid obtained by the method described in Example (5c) (0.16 g, 0.91 mmol), WSC hydrochloride (1.18 g, 6.15 mmol) and DMAP (0.12 g, 0.94 mmol), to obtain 0.23 g of the title compound as a pale yellow solid (43%).

^1H NMR spectrum (400 MHz, CDCl_3) δ ppm: 1.17-1.29 (3H, m), 1.47 (9H, s), 1.56-1.69 (1H, m), 1.81-1.95 (1H, m), 2.28 (3H, s), 2.68-2.90 (2H, m), 3.40 (2H, m), 3.68-3.81 (1H, m), 4.00-4.51 (3H, m), 7.39-7.50 (1H, m), 10.93 (1H, brs).

(18c) Ethyl cis($\pm$)-2-(4-{[(4-chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis($\pm$)-4-{[(4-chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidine-1-carboxylate obtained in Example (18b) (82 mg, 0.21 mmol), a 4 N hydrochloric acid/ethyl acetate solution (5 ml), diisopropylethylamine (0.2 mL, 1.15 mmol) and ethyl 2-bromo-1,3-thiazole-5-carboxylate (0.004 mL, 0.27 mmol), to obtain 79 mg of the title compound as a yellow solid substance (85%).

^1H NMR spectrum (400 MHz, CDCl_3) δ ppm: 1.15 (3H, t, J = 6.95 Hz), 1.34 (3H, t, J = 7.17 Hz), 1.76-1.84 (1H, m), 2.02-2.14 (1H, m), 2.30 (3H, s), 3.13-3.20 (1H, m), 3.20-

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3.29 (1H, m), 3.39-3.49 (1H, m), 3.62 (1H, brs), 3.68-3.78 (1H, m), 3.98-4.06 (1H, m), 4.20-4.34 (1H, m), 4.30 (2H, q, $J = 7.17$ Hz), 4.41-4.51 (0H, m), 7.43 (1H, d, $J = 9.02$ Hz), 7.84 (1H, s), 10.65 (1H, br s).

(18d) cis($\pm$)-2-(4-{[(4-Chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid

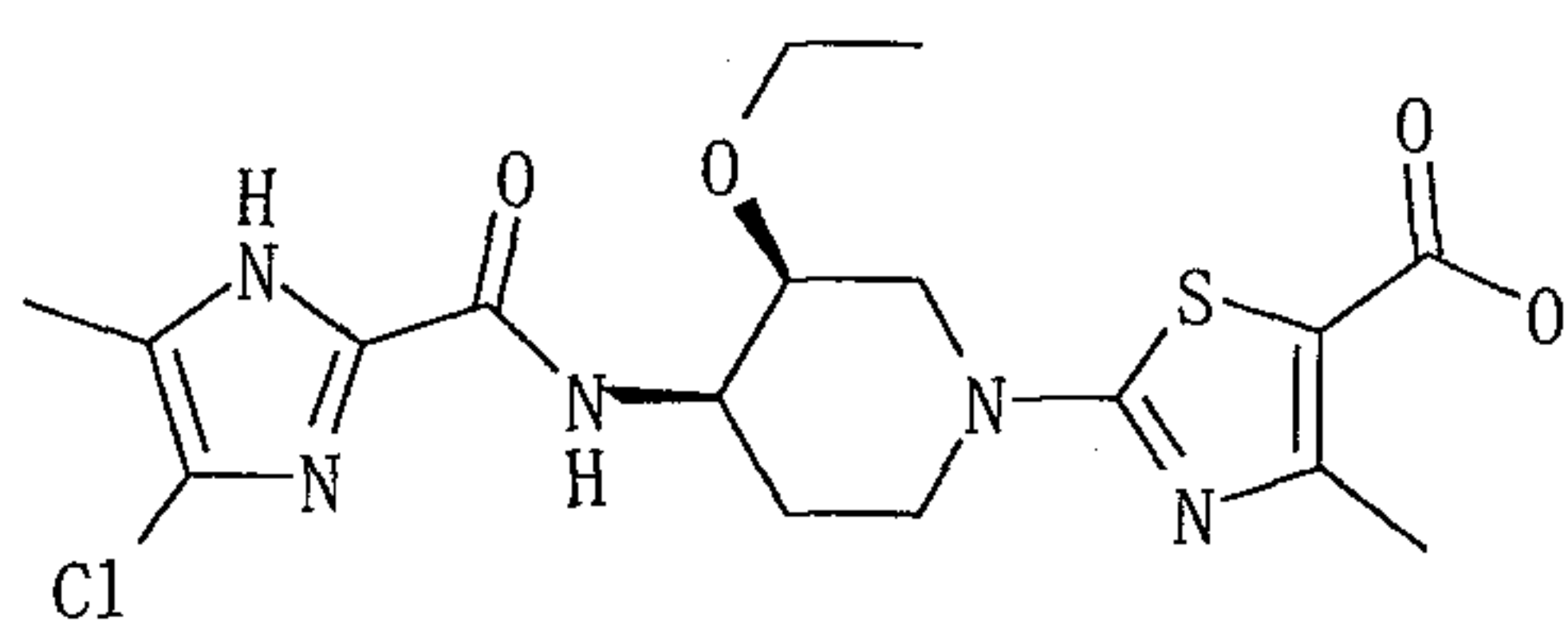
The same operation as in Example (1i) was performed using ethyl cis($\pm$)-2-(4-{[(4-chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate obtained in Example (18c) (78 mg, 0.18 mmol) and a 2 N aqueous lithium hydroxide solution (2 mL), to obtain 50 mg of the title compound as a pale yellow solid (68%).

^1H NMR spectrum (400 MHz, DMSO- d_6) δ ppm: 1.04 (3H, t, $J = 6.95$ Hz), 1.65-1.74 (1H, m), 1.84-1.90 (1H, m), 2.16 (3H, s), 3.25-3.48 (3H, m), 3.58-3.67 (2H, m), 3.92-4.04 (1H, m), 4.14-4.27 (2H, m), 7.64 (1H, d, $J = 8.29$ Hz), 7.73 (1H, s), 12.59 (1H, br s), 13.34 (1H, brs).

mass spectrum (ESI): m/z 414 ($M+H$) $^+$.

(Example 19) cis($\pm$)-2-(4-{[(4-Chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 19)



[0211]

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(19a) Ethyl cis($\pm$)-2-(4-{[(4-chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis($\pm$)-4-{[(4-chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidine-1-carboxylate obtained by the method described in Example (18b) (82 mg, 0.21 mmol), a 4 N hydrochloric acid/ethyl acetate solution (5 mL), diisopropylethylamine (0.2 mL, 1.15 mmol) and ethyl 2-bromo-4-methyl-1,3-thiazole-5-carboxylate (58 mg, 0.23 mmol), to obtain 74 mg of the title compound as a yellow solid (76%).

^1H NMR spectrum (400 MHz, CDCl_3) δ ppm: 1.16 (3H, t, J = 6.95 Hz), 1.33 (3H, t, J = 7.07 Hz), 1.74-1.83 (1H, m), 2.01-2.12 (1H, m), 2.29 (3H, s), 2.54 (3H, s), 3.08-3.26 (2H, m), 3.39-3.47 (1H, m), 3.61 (1H, br s), 3.70-3.78 (1H, m), 3.96-4.06 (1H, m), 4.19-4.30 (3H, m), 4.36-4.45 (1H, m), 7.40-7.47 (1H, m), 10.75 (1H, br s).

(19b) cis($\pm$)-2-(4-{[(4-Chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid

The same operation as in Example (1i) was performed using ethyl cis($\pm$)-2-(4-{[(4-chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate obtained in Example (19a) (70 mg, 0.15 mmol) and a 2 N aqueous lithium hydroxide solution (2 mL), to obtain 31 mg of the title compound as a white solid (47%).

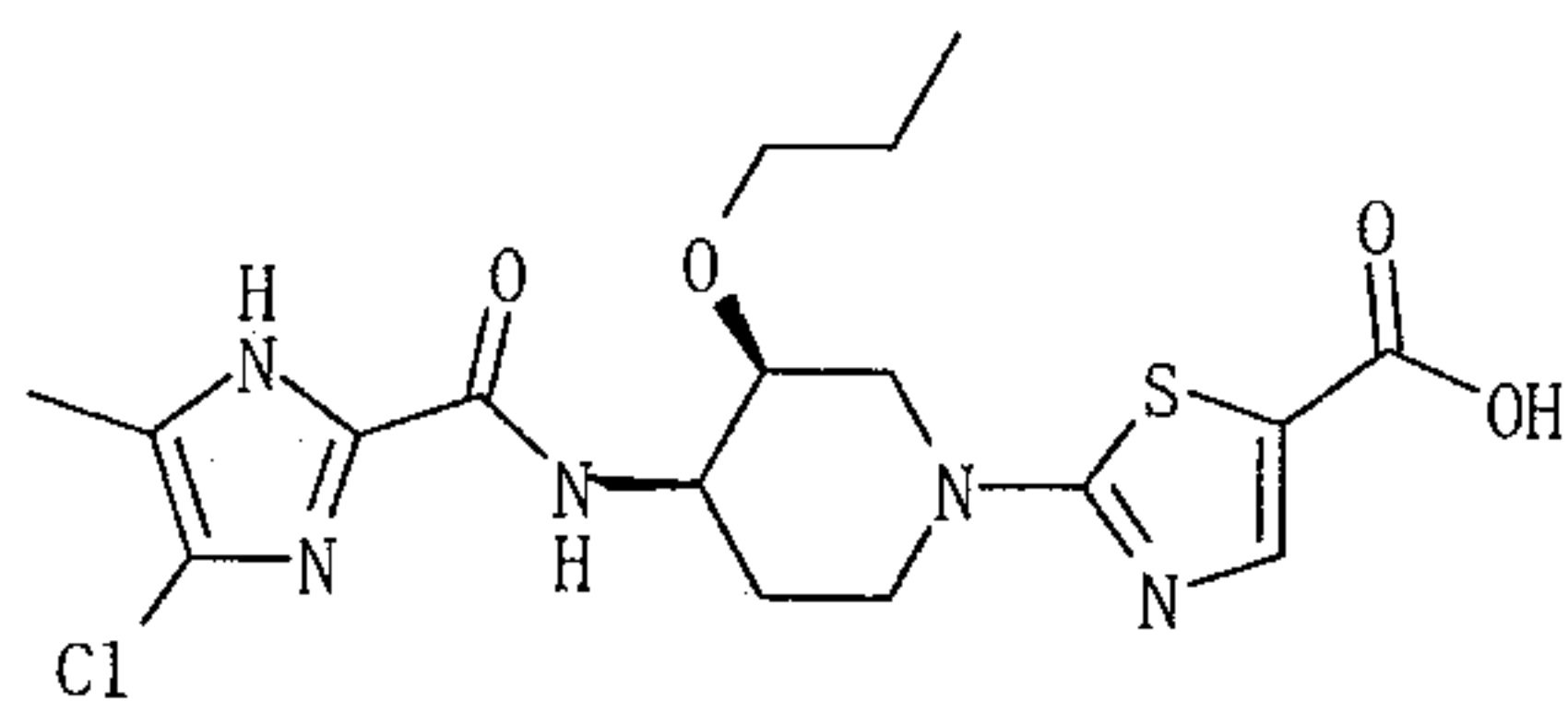
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^1H NMR spectrum (400 MHz, DMSO- d_6) δ ppm: 1.04 (3H, t, J = 7.08 Hz), 1.61-1.72 (1H, m), 1.78-1.92 (1H, m), 2.16 (3H, s), 2.40 (3H, s), 3.22-3.47 (3H, m), 3.59-3.65 (2H, m), 3.91-4.01 (1H, m), 4.09-4.22 (2H, m), 7.62 (1H, d, J = 8.54 Hz), 13.34 (1H, br s).

mass spectrum (ESI): m/z 428 ($M+H$) $^+$.

(Example 20) cis($\pm$)-2-(4-{[(4-Chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-propoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 20)



[0212]

(20a) tert-Butyl cis($\pm$)-4-amino-3-propoxypiperidine-1-carboxylate

The compound was synthesized according to the method described in the following document.

[0213]

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(20b) tert-Butyl cis($\pm$)-4-{[(4-chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-propoxypiperidine-1-carboxylate

The same operation as in Example (1g) was performed using tert-butyl cis($\pm$)-4-amino-3-propoxypiperidine-1-carboxylate obtained in Example (20a) (0.22 g, 0.85 mmol), 4-chloro-5-methyl-1H-imidazole-2-carboxylic acid obtained by the method described in Example (5c) (0.11 g, 0.64

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mmol), WSC hydrochloride (0.63 g, 3.28 mmol) and DMAP (84 mg, 0.69 mmol), to obtain 0.15 g of the title compound as a pale yellow solid (60%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 0.90-0.99 (3H, m), 1.46 (9H, s), 1.57-1.67 (3H, m), 1.80-1.95 (1H, m), 2.28 (3H, s), 2.65-2.93 (2H, m), 3.22-3.31 (1H, m), 3.45 (1H, br s), 3.64 (1H, br s), 3.95-4.46 (3H, m), 7.40-7.51 (1H, m), 10.98 (1H, br s).

(20c) Ethyl cis(±)-2-(4-{[(4-chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-propoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis(±)-4-{[(4-chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-propoxypiperidine-1-carboxylate obtained in Example (20b) (76 mg, 0.19 mmol), a 4 N hydrochloric acid/ethyl acetate solution (3 ml), diisopropylethylamine (0.15 mL, 0.86 mmol) and ethyl 2-bromo-1,3-thiazole-5-carboxylate (0.004 mL, 0.27 mmol), to obtain 65 mg of the title compound as a yellow solid substance (74%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 0.86 (3H, t, J = 7.44 Hz), 1.34 (3H, t, J = 7.13 Hz), 1.49-1.60 (2H, m), 1.79-1.88 (1H, m), 2.05-2.16 (1H, m), 2.29 (3H, s), 3.14-3.36 (3H, m), 3.59-3.67 (2H, m), 3.96-4.06 (1H, m), 4.20-4.34 (1H, m), 4.30 (2H, q, J = 7.13 Hz), 4.43-4.52 (1H, m), 7.50 (1H, d, J = 8.78 Hz), 7.84 (1H, s), 11.33 (1H, br s).

(20d) cis(±)-2-(4-{[(4-Chloro-5-methyl-1H-imidazol-2-

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yl)carbonyl]amino}-3-propoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid

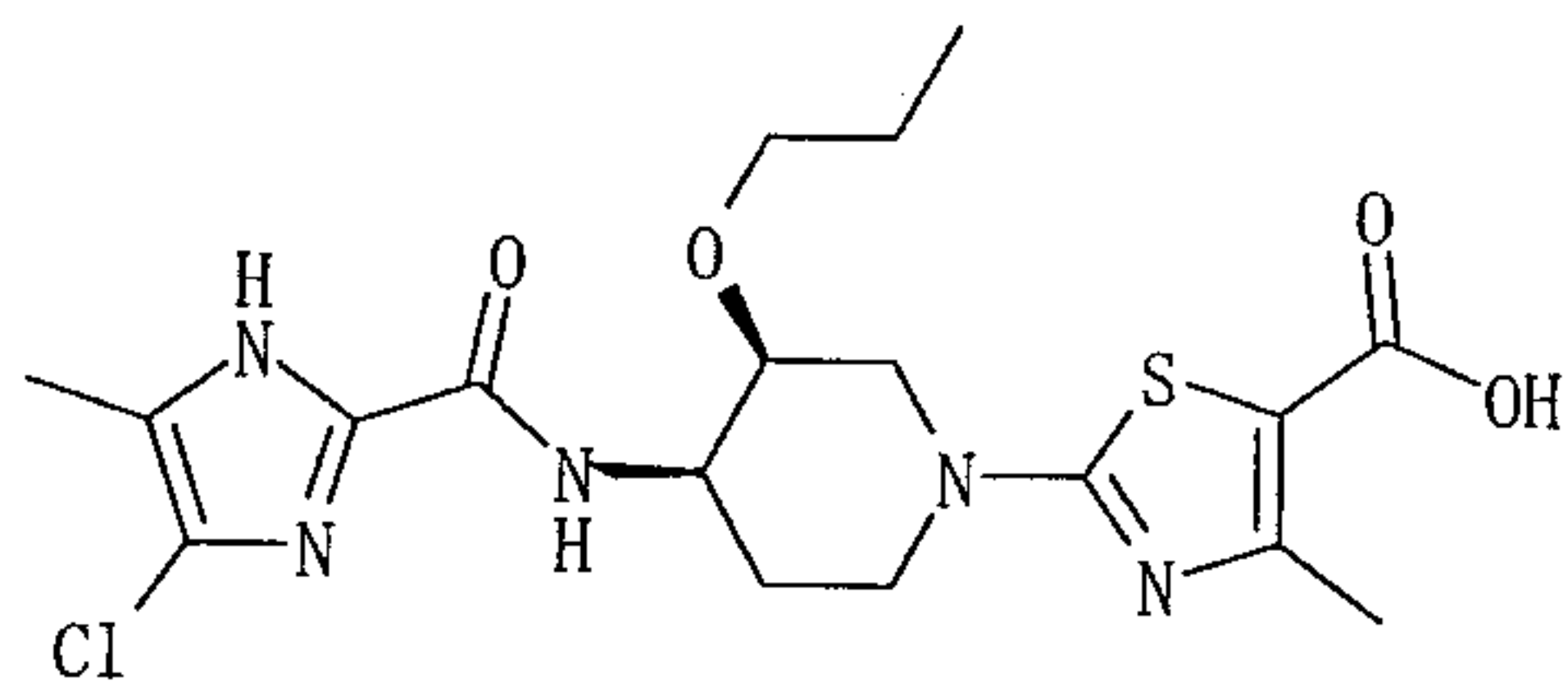
The same operation as in Example (1i) was performed using ethyl cis($\pm$)-2-(4-{[(4-chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-propoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate obtained in Example (20c) (60 mg, 0.13 mmol) and a 2 N aqueous lithium hydroxide solution (2 mL), to obtain 43 mg of the title compound as a pale yellow solid (76%).

^1H NMR spectrum (400 MHz, DMSO- d_6) δ ppm: 0.80 (3H, t, J = 7.44 Hz), 1.38-1.49 (2H, m), 1.64-1.74 (1H, m), 1.81-1.96 (1H, m), 2.15 (3H, s), 3.28-3.35 (3H, m), 3.50-3.59 (1H, m), 3.66 (1H, br s), 3.89-4.00 (1H, m), 4.16-4.26 (2H, m), 7.63 (1H, d, J = 8.54 Hz), 7.73 (1H, s), 12.58 (1H, br s), 13.33 (1H, br s).

mass spectrum (ESI): m/z 428 ($M+H$) $^+$.

(Example 21) cis($\pm$)-2-(4-{[(4-Chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-propoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 21)



[0214]

(21a) Ethyl cis($\pm$)-2-(4-{[(4-chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-propoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate

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The same operation as in Example (1h) was performed using tert-butyl cis($\pm$)-4-{[(4-chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-propoxypiperidine-1-carboxylate obtained by the method described in Example (20b) (76 mg, 0.19 mmol), a 4 N hydrochloric acid/ethyl acetate solution (3 ml), diisopropylethylamine (0.15 mL, 0.86 mmol) and ethyl 2-bromo-4-methyl-1,3-thiazole-5-carboxylate (63 mg, 0.25 mmol), to obtain 79 mg of the title compound as a yellow solid (89%).

^1H NMR spectrum (400 MHz, CDCl_3) δ ppm: 0.86 (3H, t, J = 7.44 Hz), 1.33 (3H, t, J = 7.07 Hz), 1.49-1.62 (2H, m), 1.76-1.81 (1H, m), 2.04-2.18 (1H, m), 2.29 (3H, s), 2.53 (3H, s), 3.10-3.35 (3H, m), 3.60-3.67 (2H, m), 3.95-4.06 (1H, m), 4.20-4.29 (3H, m), 4.40-4.50 (1H, m), 7.51 (1H, d, J = 8.78 Hz), 11.40 (1H, br s).

(21b) cis($\pm$)-2-(4-{[(4-Chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-propoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid

The same operation as in Example (1i) was performed using ethyl cis($\pm$)-2-(4-{[(4-chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-propoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate obtained in Example (21a) (75 mg, 0.16 mmol) and a 2 N aqueous lithium hydroxide solution (2.5 mL), to obtain 56 mg of the title compound as a white solid (80%).

^1H NMR spectrum (400 MHz, $\text{DMSO}-d_6$) δ ppm: 0.81 (3H, t, J = 7.44 Hz), 1.39-1.46 (2H, m), 1.64-1.73 (1H, m), 1.80-1.93 (1H, m), 2.15 (3H, s), 2.40 (3H, s), 3.22-3.36 (3H,

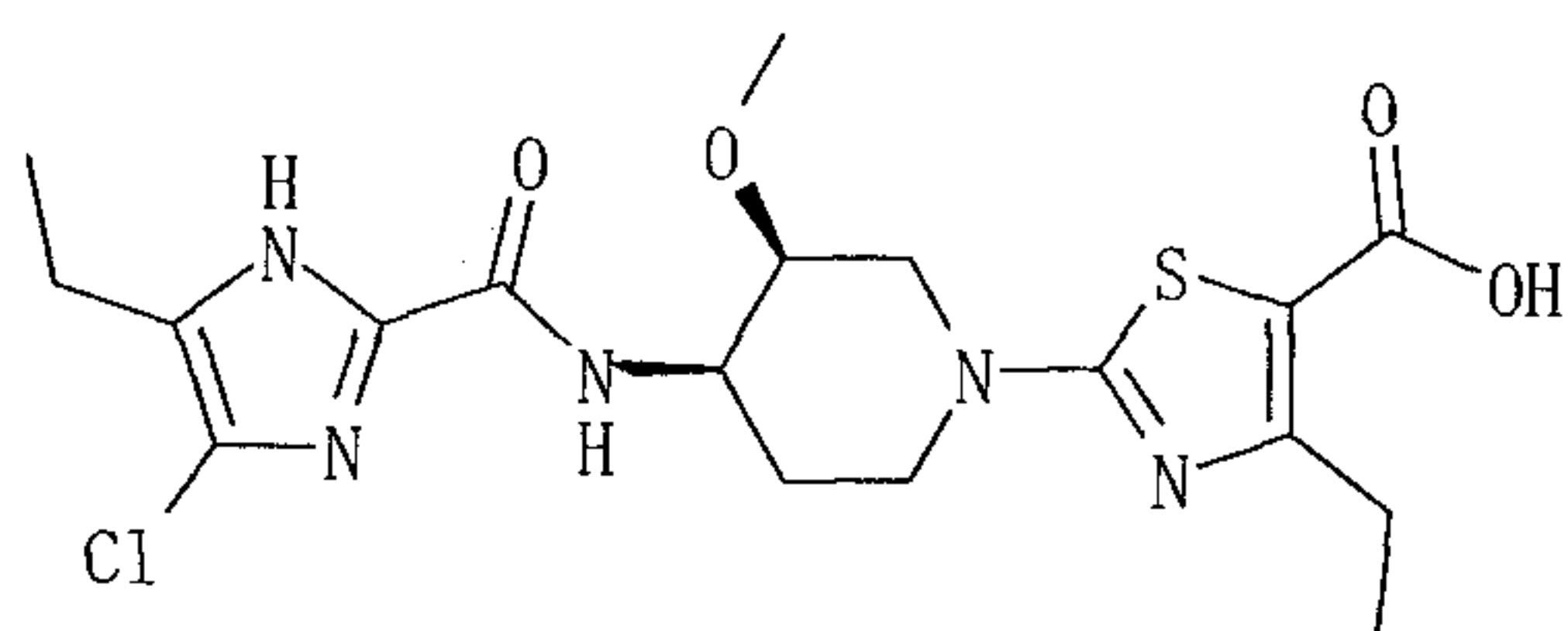
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m), 3.51-3.59 (1H, m), 3.62-3.67 (1H, m), 3.88-4.00 (1H, m), 4.12-4.24 (2H, m), 7.62 (1H, d, $J = 8.54$ Hz), 12.37 (1H, br s), 13.33 (1H, br s).

mass spectrum (ESI): m/z 442 ($M+H$)⁺.

(Example 22) cis($\pm$)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-ethyl-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 22)



[0215]

(22a) Methyl 2-chloro-3-oxo-pentanoate

The compound was synthesized according to the method described in the following document.

[0216]

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(22b) Methyl 2-amino-4-ethyl-1,3-thiazole-5-carboxylate

Methyl 2-chloro-3-oxo-pentanoate obtained in Example (22a) (1.91 g, 11.57 mmol) was dissolved in ethanol (50 mL). Thiourea (0.77 g, 10.09 mmol) was added, and the mixture was heated under reflux for 1.5 hours. The reaction solution was concentrated under reduced pressure, diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate solution and brine, and dried over anhydrous sodium sulfate. Following concentration under reduced pressure, the residue was washed with

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hexane/ethyl acetate: 5/1 to obtain 1.78 g of the title compound as a pale yellow solid (95%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.23 (3H, t, J = 7.53 Hz), 2.97 (2H, q, J = 7.53 Hz), 3.80 (3H, s), 5.44 (2H, br s).

(22c) Methyl 2-bromo-4-ethyl-1,3-thiazole-5-carboxylate

Methyl 2-amino-4-ethyl-1,3-thiazole-5-carboxylate obtained in Example (22b) (0.5 g, 2.68 mmol) was suspended in acetonitrile (25 mL). Copper bromide (0.9 g, 4.03 mmol) and tert-butyl nitrite (0.48 mL, 4.04 mmol) were added, and the mixture was stirred at room temperature for two hours. The reaction solution was concentrated under reduced pressure, diluted with ethyl acetate, washed with 1 N hydrochloric acid and brine, and dried over anhydrous sodium sulfate. Following concentration under reduced pressure, the residue was purified by silica gel column chromatography (elution solvent: hexane/ethyl acetate = 97/3, 95/5) to obtain 0.63 g of the title compound as a white solid (94%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.28 (3H, t, J = 7.53 Hz), 3.13 (2H, q, J = 7.53 Hz), 3.87 (3H, s).

(22d) Methyl cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-ethyl-1,3-thiazole-5-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis(±)-4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate obtained by the method described in Example

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(1g) (67 mg, 0.17 mmol), a 4 N hydrochloric acid/ethyl acetate solution (3 ml), diisopropylethylamine (0.12 mL, 0.69 mmol) and methyl 2-bromo-4-ethyl-1,3-thiazole-5-carboxylate obtained in Example (22c) (48 mg, 0.19 mmol), to obtain 49 mg of the title compound as a yellow solid (61%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.19-1.34 (6H, m), 1.74-1.87 (1H, m), 1.98-2.10 (1H, m), 2.69 (2H, q, J = 7.64 Hz), 3.40-3.57 (4H, m), 3.43 (3H, s), 3.78-3.86 (1H, m), 3.79 (3H, s), 3.93-4.02 (2H, m), 4.20-4.34 (1H, m), 4.55-4.69 (1H, m), 4.85 (1H, br s), 7.50-7.60 (1H, m), 11.43 (1H, br s).

(22e) cis(±)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-ethyl-1,3-thiazole-5-carboxylic acid

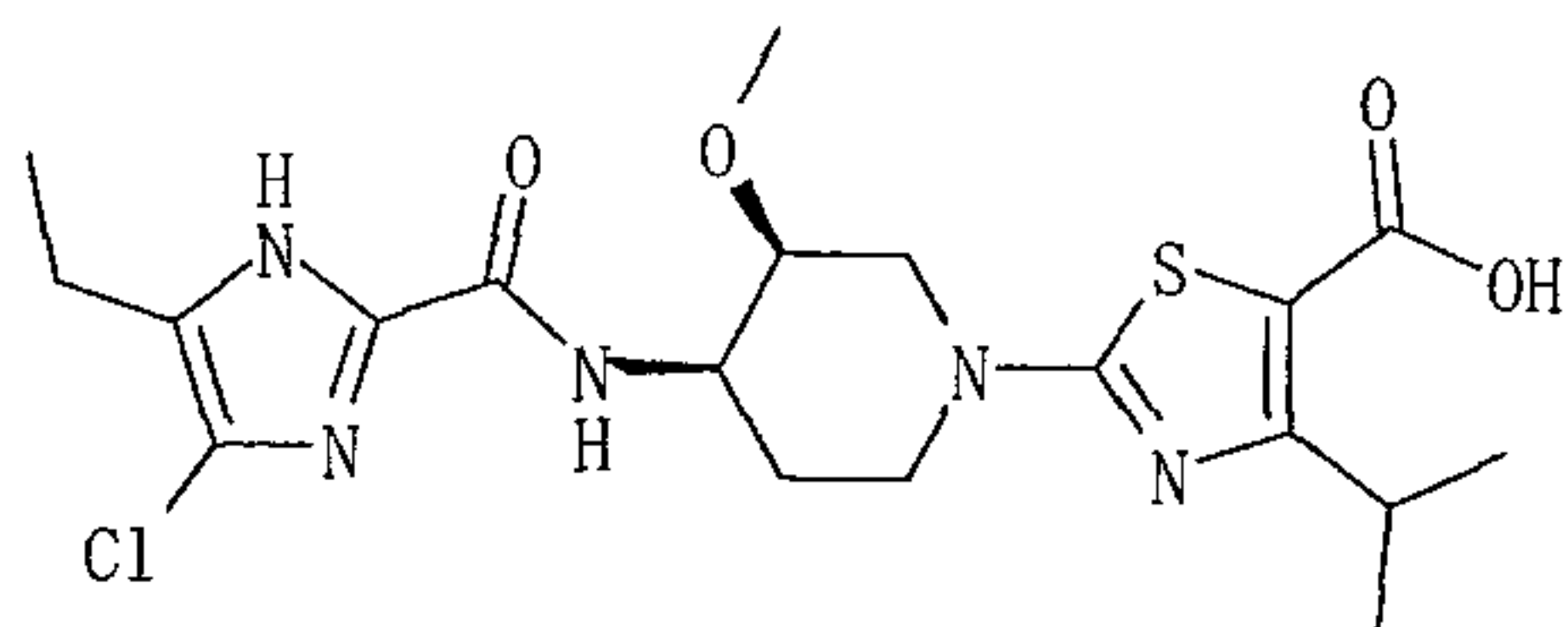
The same operation as in Example (1i) was performed using methyl cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-ethyl-1,3-thiazole-5-carboxylate obtained in Example (22d) (49 mg, 0.11 mmol) and a 2 N aqueous lithium hydroxide solution (1.5 mL), to obtain 31 mg of the title compound as a white solid (65%).

¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 1.10-1.17 (6H, m), 1.65-1.72 (1H, m), 1.79-1.92 (1H, m), 2.51-2.59 (2H, m), 2.74-2.96 (2H, m), 3.24-3.36 (2H, m), 3.34 (3H, s), 3.56 (1H, br s), 3.82-3.88 (1H, m), 4.16-4.25 (1H, m), 4.28-4.40 (1H, m), 7.64 (1H, d, J = 8.54 Hz), 12.38 (1H, br s), 13.37 (1H, br s).

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mass spectrum (ESI): m/z 442 ($M+H$)⁺.

(Example 23) *cis*(±)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-isopropyl-1,3-thiazole-5-carboxylic acid
(Exemplified Compound No. 23)



[0217]

(23a) Ethyl 2-amino-4-isopropyl-1,3-thiazole-5-carboxylate

The compound was synthesized according to the method described in the following document.

[0218]

J. Heterocycl. Chem., 1985, 1621-1630

(23b) Ethyl 2-bromo-4-isopropyl-1,3-thiazole-5-carboxylate

The same operation as in Example (22c) was performed using ethyl 2-amino-4-isopropyl-1,3-thiazole-5-carboxylate obtained in Example (23a) (0.5 g, 2.33 mmol), copper bromide (0.79 g, 3.53 mmol) and tert-butyl nitrite (0.42 mL, 3.53 mmol), to obtain 0.60 g of the title compound as a white solid (92%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.28 (6H, d, J = 6.84 Hz), 1.36 (3H, t, J = 7.12 Hz), 3.89-3.99 (1H, m), 4.32 (2H, q, J = 7.12 Hz).

(23c) Ethyl *cis*(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-

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isopropyl-1,3-thiazole-5-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis($\pm$)-4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate obtained by the method described in Example (1g) (67 mg, 0.17 mmol), a 4 N hydrochloric acid/ethyl acetate solution (3 ml), diisopropylethylamine (0.12 mL, 0.69 mmol) and ethyl 2-bromo-4-isopropyl-1,3-thiazole-5-carboxylate obtained in Example (23b) (55 mg, 0.19 mmol), to obtain 55 mg of the title compound as a yellow solid (65%).

^1H NMR spectrum (400 MHz, CDCl_3) δ ppm: 1.10-1.43 (9H, m), 1.76-1.97 (1H, m), 1.94-2.10 (1H, m), 2.69 (2H, q, $J = 7.64$ Hz), 2.97-3.06 (1H, m), 3.10-3.29 (1H, m), 3.43 (3H, s), 3.49-3.52 (1H, m), 3.81-3.99 (2H, m), 4.21-4.30 (3H, m), 4.71-4.80 (1H, m), 7.47-7.53 (1H, m), 11.19 (1H, br s).

(23d) cis($\pm$)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-isopropyl-1,3-thiazole-5-carboxylic acid

The same operation as in Example (1i) was performed using ethyl cis($\pm$)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-isopropyl-1,3-thiazole-5-carboxylate obtained in Example (23c) (55 mg, 0.11 mmol) and a 2 N aqueous lithium hydroxide solution (2 mL), to obtain 32 mg of the title compound as a white solid (62%).

^1H NMR spectrum (400 MHz, $\text{DMSO}-d_6$) δ ppm: 1.11-1.18 (9H,

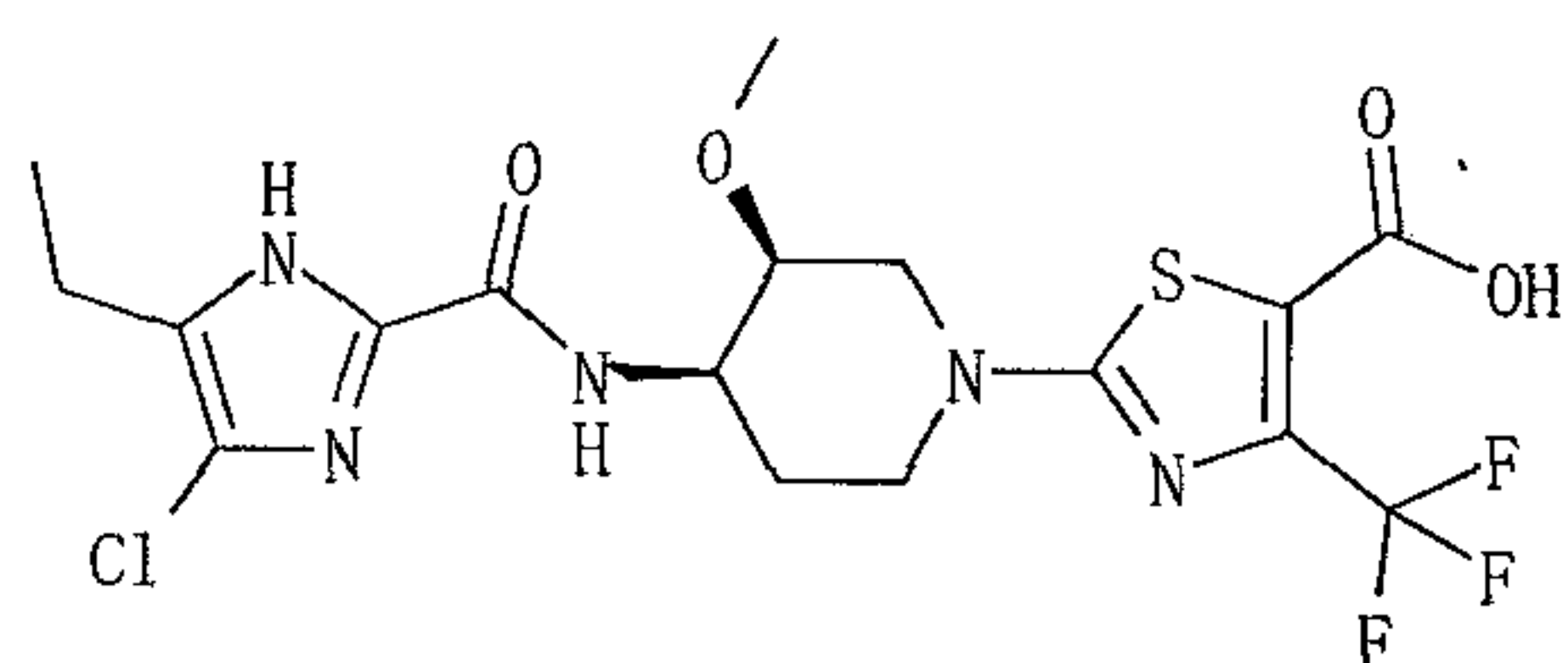
- 136 -

m), 1.62-1.72 (1H, m), 1.79-1.92 (1H, m), 2.51-2.59 (2H, m), 3.21-3.37 (2H, m), 3.34 (3H, s), 3.55 (1H, br s), 3.76-3.87 (2H, m), 4.14-4.25 (1H, m), 4.36-4.51 (1H, m), 7.64 (1H, d, $J = 8.54$ Hz), 12.40 (1H, br s), 13.37 (1H, br s).

mass spectrum (ESI): m/z 456 ($M+H$)⁺.

(Example 24) cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-trifluoromethyl-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 24)



[0219]

(24a) Ethyl cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-trifluoromethyl-1,3-thiazole-5-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis(±)-4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate obtained in Example (1g) (77 mg, 0.20 mmol), a 4 N hydrochloric acid/ethyl acetate solution (3 ml), diisopropylethylamine (0.14 mL, 0.80 mmol) and ethyl 2-chloro-4-trifluoromethyl-1,3-thiazole-5-carboxylate (62 mg, 0.24 mmol), to obtain 88 mg of the title compound as a yellow solid (86%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.23-1.37 (6H, m),

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1.77-1.94 (1H, m), 1.96-2.06 (1H, m), 2.69 (2H, q, J = 7.56 Hz), 3.06-3.15 (1H, m), 3.22-3.34 (1H, m), 3.42 (3H, s), 3.49-3.55 (1H, m), 3.88-4.00 (1H, m), 4.21-4.35 (3H, m), 4.57-4.67 (1H, m), 7.39-7.47 (1H, m), 10.58 (1H, br s).

(24b) cis(±)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-trifluoromethyl-1,3-thiazole-5-carboxylic acid

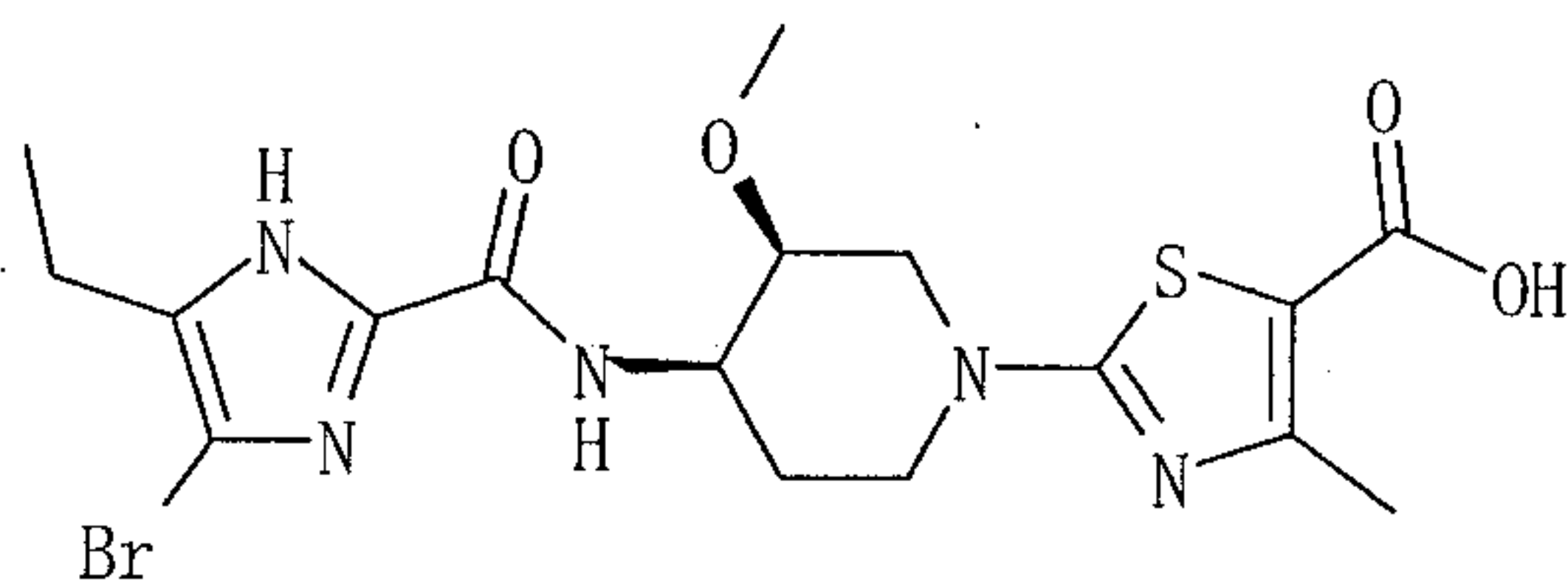
The same operation as in Example (1i) was performed using ethyl cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-trifluoromethyl-1,3-thiazole-5-carboxylate obtained in Example (24a) (85 mg, 0.17 mmol) and a 2 N aqueous lithium hydroxide solution (1.5 mL), to obtain 51 mg of the title compound as a white solid (63%).

¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 1.14 (3H, t, J = 7.51 Hz), 1.65-1.74 (1H, m), 1.81-1.95 (1H, m), 2.55 (2H, q, J = 7.51 Hz), 3.26-3.42 (5H, m), 3.59 (1H, br s), 3.82-3.99 (1H, m), 4.17-4.36 (2H, m), 7.69 (1H, d, J = 8.30 Hz), 13.35-13.46 (2H, m).

mass spectrum (ESI): m/z 482 (M+H)⁺.

(Example 25) cis(±)-2-(4-{[(4-Bromo-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 25)



[0220]

(25a) Ethyl 4-bromo-5-ethyl-1H-imidazole-2-carboxylate

The same operation as in Example (1c) was performed using ethyl 5-ethyl-1H-imidazole-2-carboxylate obtained by the method described in Example (1b) (0.29 g, 1.30 mmol) and NBS (0.28 g, 1.28 mmol), to obtain 0.22 g of the title compound as a white solid (69%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.27 (3H, t, J = 7.67 Hz), 1.41 (3H, t, J = 7.12 Hz), 2.70 (2H, q, J = 7.67 Hz), 4.42 (2H, q, J = 7.12 Hz), 10.39 (1H, br s).

(25b) 4-Bromo-5-ethyl-1H-imidazole-2-carboxylic acid

The same operation as in Example (1d) was performed using ethyl 4-bromo-5-ethyl-1H-imidazole-2-carboxylate obtained in Example (25a) (0.22 g, 0.87 mmol) and a 3 N aqueous lithium hydroxide solution (3 mL), to obtain 0.18 g of the title compound as a white solid (95%).

¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 1.10 (3H, t, J = 7.45 Hz), 2.30-2.56 (2H, m).

(25c) tert-Butyl cis(±)-4-{[(4-bromo-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate

The same operation as in Example (1g) was performed using tert-butyl cis(±)-4-amino-3-methoxypiperidine-1-carboxylate obtained by the method described in Example (1e) (0.39 g, 1.67 mmol), 4-bromo-5-ethyl-1H-imidazole-2-

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carboxylic acid obtained in Example (25b) (0.18 g, 0.82 mmol), WSC hydrochloride (0.49 g, 2.53 mmol) and HOBT (0.11 g, 0.84 mmol), to obtain 0.33 g of the title compound as a white solid (92%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.25 (3H, t, J = 7.61 Hz), 1.47 (9H, s), 1.60-1.67 (1H, m), 1.79-1.92 (1H, m), 2.61-2.90 (2H, m), 2.67 (2H, q, J = 7.61 Hz), 3.32-3.45 (2H, m), 3.41 (3H, s), 4.01-4.27 (1H, m), 4.34-4.57 (1H, m), 7.45-7.54 (1H, m), 11.22 (1H, br s).

(25d) Ethyl cis(±)-2-(4-{[(4-bromo-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis(±)-4-{[(4-bromo-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate obtained in Example (25c) (74 mg, 0.17 mmol), a 4 N hydrochloric acid/ethyl acetate solution (3 ml), diisopropylethylamine (0.12 mL, 0.69 mmol) and ethyl 2-bromo-4-methyl-1,3-thiazole-5-carboxylate (56 mg, 0.22 mmol), to obtain 71 mg of the title compound as an orange solid substance (83%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.26 (3H, t, J = 7.61 Hz), 1.33 (3H, t, J = 7.08 Hz), 1.75-1.83 (1H, m), 1.98-2.10 (1H, m), 2.54 (3H, s), 2.68 (2H, q, J = 7.61 Hz), 3.07-3.13 (1H, m), 3.15-3.24 (1H, m), 3.42 (3H, s), 3.51 (1H, br s), 3.97-4.05 (1H, m), 4.21-4.30 (3H, m), 4.47-4.56 (1H, m), 7.48-7.53 (1H, m), 11.17 (1H, br s).

(25e) cis(±)-2-(4-{[(4-Bromo-5-ethyl-1H-imidazol-2-

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yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid

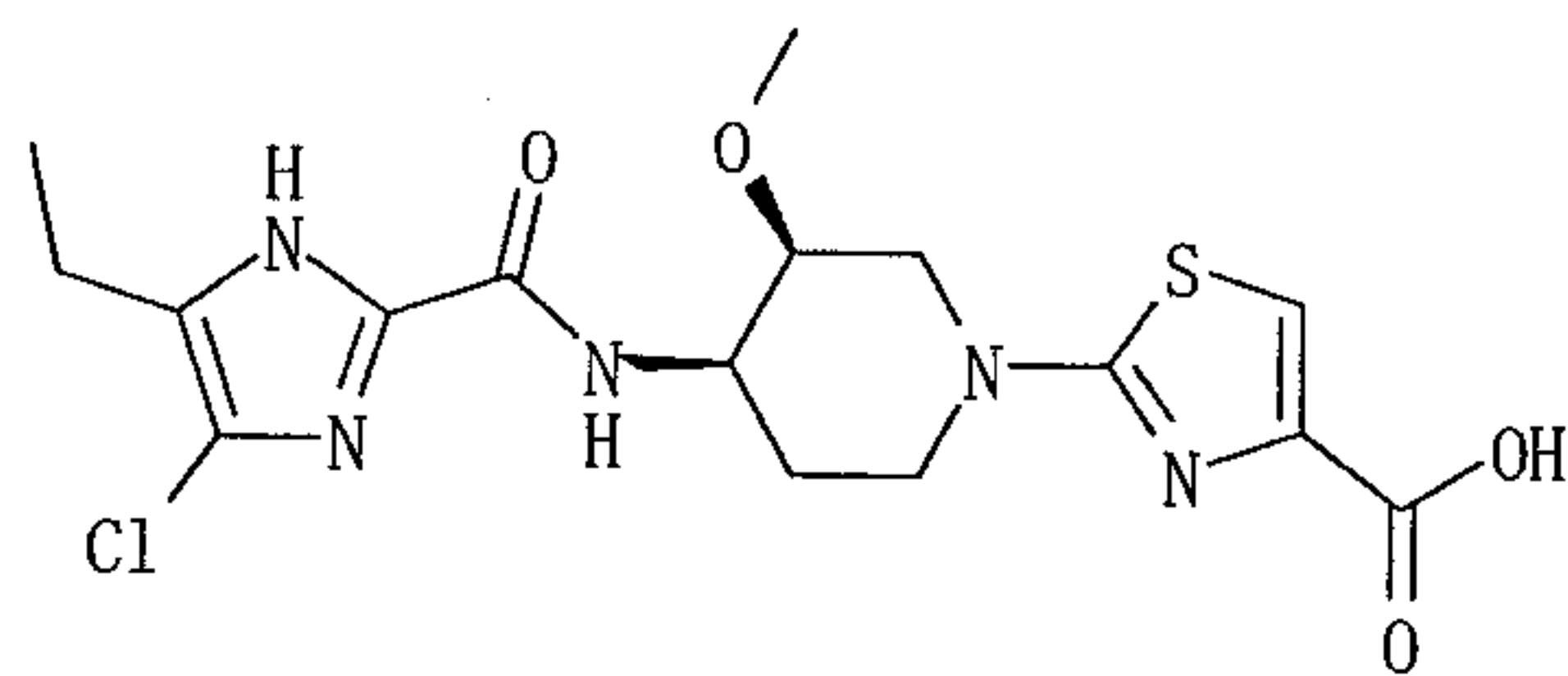
The same operation as in Example (1i) was performed using ethyl cis($\pm$)-2-(4-{[(4-bromo-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate obtained in Example (25d) (70 mg, 0.14 mmol) and a 2 N aqueous lithium hydroxide solution (2 mL), to obtain 36 mg of the title compound as a white solid (56%).

^1H NMR spectrum (400 MHz, DMSO- d_6) δ ppm: 1.13 (3H, t, J = 7.44 Hz), 1.63-1.72 (1H, m), 1.79-1.92 (1H, m), 2.40 (3H, s), 2.50-2.57 (2H, m), 3.24-3.36 (2H, m), 3.34 (3H, s), 3.55 (1H, br s), 3.86-3.97 (1H, m), 4.14-4.29 (2H, m), 7.66 (1H, d, J = 8.54 Hz), 13.41 (1H, br s).

mass spectrum (ESI): m/z 473 ($M+H$) $^+$.

(Example 26) cis($\pm$)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-4-carboxylic acid

(Exemplified Compound No. 26)



[0221]

(26a) Ethyl cis($\pm$)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-4-carboxylate

The same operation as in Example (1h) was performed

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using tert-butyl cis($\pm$)-4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate obtained by the method described in Example (1g) (0.12 g, 0.30 mmol), a 4 N hydrochloric acid/ethyl acetate solution (3 mL), diisopropylethylamine (0.21 mL, 1.21 mmol), and ethyl 2-bromo-1,3-thiazole-4-carboxylate (75 mg, 0.32 mmol), to obtain 30 mg of the title compound as a yellow solid (22%).

^1H NMR spectrum (400 MHz, CDCl_3) δ ppm: 1.26 (3H, t, J = 7.60 Hz), 1.37 (3H, t, J = 7.19 Hz), 1.75-1.85 (1H, m), 2.01-2.15 (1H, m), 2.69 (2H, q, J = 7.60 Hz), 3.11-3.25 (2H, m), 3.43 (3H, s), 3.50-3.54 (1H, m), 3.96-4.04 (1H, m), 4.20-4.29 (1H, m), 4.31-4.40 (2H, m), 4.45-4.52 (1H, m), 7.43 (1H, s), 7.46-7.54 (1H, m), 11.21 (1H, br s).

(26b) cis($\pm$)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-4-carboxylic acid

The same operation as in Example (1i) was performed using ethyl cis($\pm$)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-4-carboxylate obtained in Example (26a) (30 mg, 0.068 mmol) and a 2 N aqueous lithium hydroxide solution (1 mL), to obtain 16 mg of the title compound as a white solid (58%).

^1H NMR spectrum (400 MHz, $\text{DMSO}-d_6$) δ ppm: 1.14 (3H, t, J = 7.56 Hz), 1.61-1.73 (1H, m), 1.84-1.93 (1H, m), 2.55 (2H, q, J = 7.56 Hz), 3.23-3.36 (2H, m), 3.33 (3H, s), 3.56 (1H, br s), 3.82-3.91 (1H, m), 4.14-4.25 (2H, m),

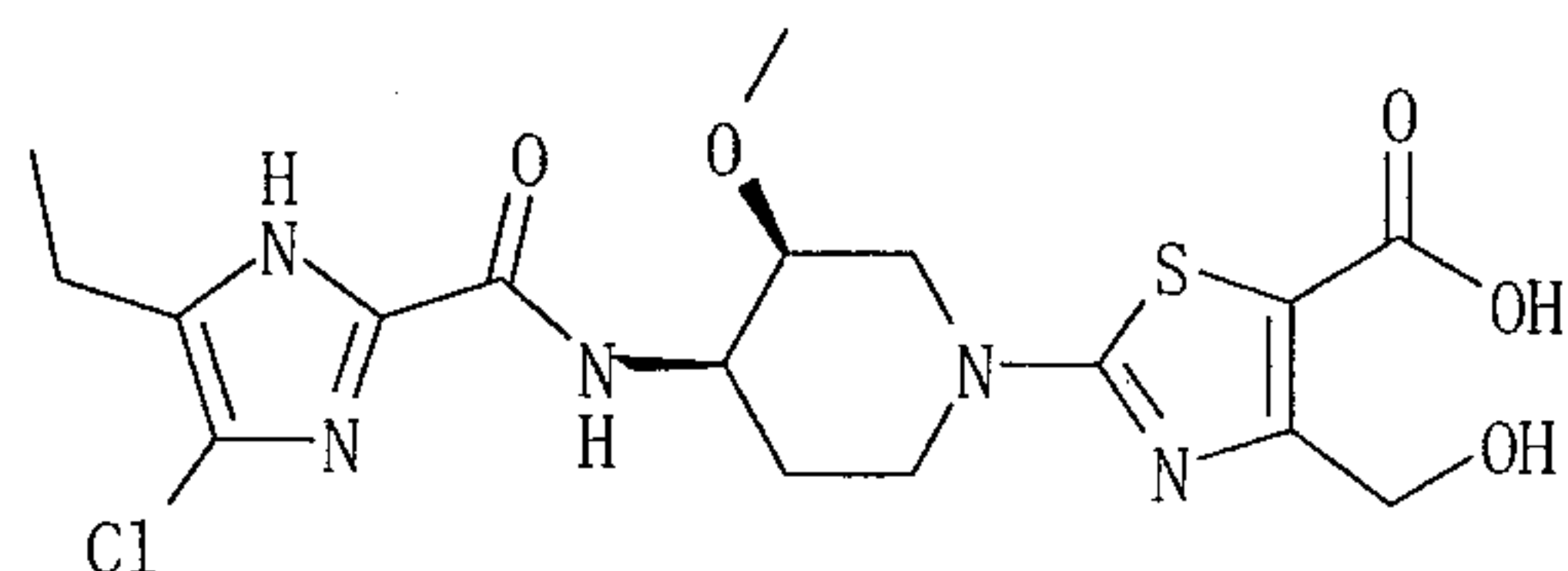
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7.56 (1H, s), 7.65 (1H, d, $J = 8.29$ Hz).

mass spectrum (ESI): m/z 414 ($M+H$)⁺.

(Example 27) cis(±)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(hydroxymethyl)-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 27)



[0222]

(27a) Ethyl 2-chloro-4-(hydroxymethyl)-1,3-thiazole-5-carboxylate

The compound was synthesized according to the method described in the following document.

[0223]

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(27b) Ethyl cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(hydroxymethyl)-1,3-thiazole-5-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis(±)-4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate obtained by the method described in Example (1g) (0.23 g, 0.60 mmol), a 4 N hydrochloric acid/ethyl acetate solution (9 ml), diisopropylethylamine (0.42 mL, 2.41 mmol) and ethyl 2-chloro-4-(hydroxymethyl)-1,3-thiazole-5-carboxylate obtained in Example (27a) (0.27 g, 1.01 mmol), to obtain 0.20 g of the title compound as a

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yellow solid (72%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.27 (3H, t, J = 7.56 Hz), 1.34 (3H, t, J = 7.19 Hz), 1.76-1.85 (1H, m), 1.97-2.10 (1H, m), 2.69 (2H, q, J = 7.56 Hz), 3.09-3.16 (1H, m), 3.19-3.28 (1H, m), 3.42 (3H, s), 3.52 (1H, br s), 3.96-4.02 (1H, m), 4.22-4.32 (3H, m), 4.50-4.61 (1H, m), 4.79 (2H, d, J = 6.34 Hz), 7.44 (1H, d, J = 8.78 Hz), 10.71 (1H, br s).

(27c) cis(±)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(hydroxymethyl)-1,3-thiazole-5-carboxylic acid

The same operation as in Example (1i) was performed using ethyl cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(hydroxymethyl)-1,3-thiazole-5-carboxylate obtained in Example (27b) (30 mg, 0.064 mmol) and a 2 N aqueous lithium hydroxide solution (0.8 mL), to obtain 16 mg of the title compound as a white solid (57%).

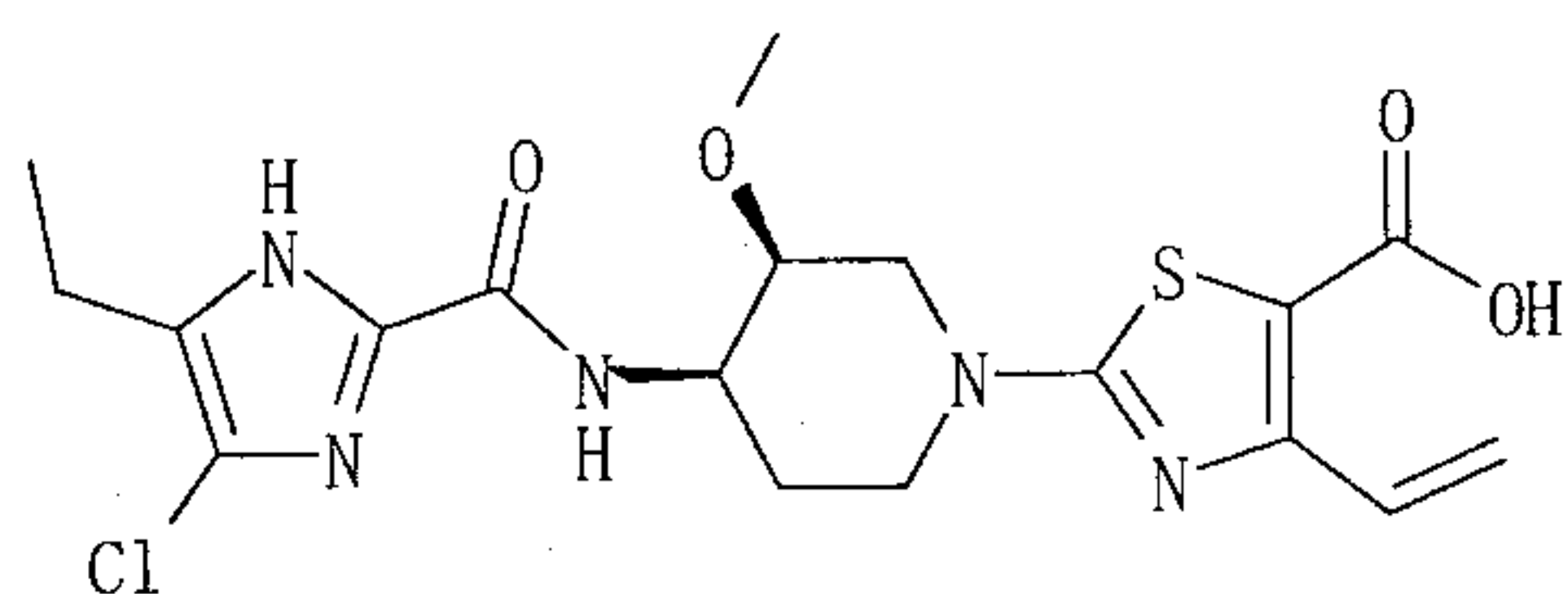
¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 1.14 (3H, t, J = 7.56 Hz), 1.63-1.72 (1H, m), 1.80-1.93 (1H, m), 2.55 (2H, q, J = 7.56 Hz), 3.23-3.37 (2H, m), 3.34 (3H, s), 3.57 (1H, br s), 3.91-4.04 (1H, m), 4.16-4.34 (2H, m), 4.55-4.62 (2H, m), 7.66 (1H, d, J = 8.54 Hz), 13.37 (1H, br s).

mass spectrum (ESI): m/z 444 (M+H)⁺.

(Example 28) cis(±)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-vinyl-1,3-thiazole-5-carboxylic acid

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(Exemplified Compound No. 28)



[0224]

(28a) Ethyl cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-formyl-1,3-thiazole-5-carboxylate

Ethyl cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(hydroxymethyl)-1,3-thiazole-5-carboxylate obtained by the method described in Example (27b) (0.17 g, 0.36 mmol) was dissolved in dichloromethane (8 mL). The Dess-Martin reagent (0.2 g, 0.48 mmol) was added, and the mixture was stirred at room temperature for 45 minutes. Saturated aqueous sodium bicarbonate solution was added to the reaction solution, followed by extraction with dichloromethane. The organic layer was washed with saturated aqueous sodium thiosulfate solution, saturated aqueous sodium bicarbonate solution and brine, and dried over anhydrous sodium sulfate. Following concentration under reduced pressure, the residue was purified by silica gel column chromatography (elution solvent: hexane/ethyl acetate = 5/1, 1/1, 1/3) to obtain 0.16 g of the title compound as a pale yellow solid (92%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.26 (6H, t, J = 7.67 Hz), 1.38 (3H, t, J = 7.20 Hz), 1.77-1.86 (1H, m), 1.98-2.10 (1H, m), 2.69 (2H, q, J = 7.67 Hz), 3.12-3.20

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(1H, m), 3.23-3.33 (1H, m), 3.42 (3H, s), 3.53 (1H, br s), 4.02-4.10 (1H, m), 4.22-4.31 (1H, m), 4.33-4.41 (2H, m), 4.55-4.67 (1H, m), 7.46 (1H, d, J = 8.54 Hz), 10.50 (1H, s), 11.04 (1H, br s).

(28b) Ethyl cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-vinyl-1,3-thiazole-5-carboxylate

Methyltriphenylphosphonium bromide (0.19 g, 0.53 mmol) was suspended in THF (4 mL), followed by cooling to -78°C. An n-butyllithium/1.58 M hexane solution (0.34 mL, 0.54 mmol) was added dropwise, followed by stirring for 25 minutes. Ethyl cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-formyl-1,3-thiazole-5-carboxylate obtained in Example (28a) (74 mg, 0.16 mmol) was added, and the mixture was heated to room temperature and stirred for one hour. Brine was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. Following concentration under reduced pressure, the residue was purified by silica gel column chromatography (elution solvent: hexane/ethyl acetate = 4/1, 3/1, 1/1) to obtain 15 mg of the title compound as a pale yellow solid (21%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.27 (5H, t, J = 7.64 Hz), 1.34 (3H, t, J = 7.07 Hz), 1.75-1.84 (1H, m), 1.99-2.10 (1H, m), 2.70 (2H, q, J = 7.64 Hz), 3.07-3.14 (1H, m), 3.18-3.29 (1H, m), 3.43 (3H, s), 3.51 (1H, br s),

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3.96-4.07 (1H, m), 4.22-4.32 (3H, m), 4.58-4.68 (1H, m), 5.54 (1H, dd, J = 10.73, 2.44 Hz), 6.24 (1H, dd, J = 17.32, 2.44 Hz), 7.44-7.52 (2H, m), 11.15 (1H, br s).

(28c) cis(±)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-vinyl-1,3-thiazole-5-carboxylic acid

The same operation as in Example (1i) was performed using ethyl cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-vinyl-1,3-thiazole-5-carboxylate obtained in Example (28b) (15 mg, 0.033 mmol) and a 2 N aqueous lithium hydroxide solution (0.5 mL), to obtain 10 mg of the title compound as a white solid (72%).

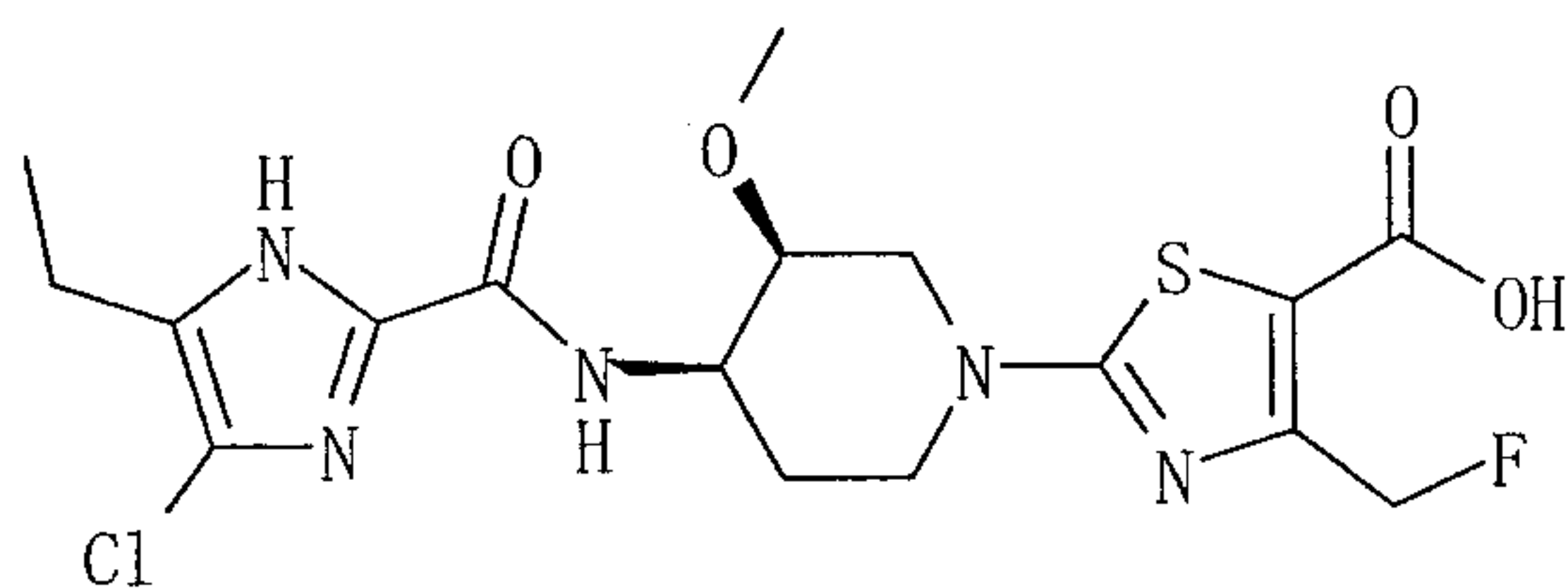
¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 1.14 (3H, t, J = 7.56 Hz), 1.64-1.74 (1H, m), 1.81-1.94 (1H, m), 2.55 (19H, q, J = 7.56 Hz), 3.28-3.36 (3H, m), 3.35 (3H, s), 3.57 (1H, br s), 3.87-4.02 (1H, m), 4.17-4.26 (1H, m), 4.30-4.44 (1H, m), 5.52 (1H, dd, J = 10.61, 2.68 Hz), 6.14 (1H, dd, J = 17.32, 2.68 Hz), 7.38 (1H, dd, J = 17.32, 10.61 Hz), 7.66 (1H, d, J = 8.29 Hz), 12.74 (1H, br s), 13.37 (1H, br s).

mass spectrum (ESI): m/z 440 (M+H)⁺.

(Example 29) cis(±)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(fluoromethyl)-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 29)

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[0225]

(29a) Ethyl cis(±)-2-(4-((4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl)amino)-3-methoxypiperidin-1-yl)-4-(fluoromethyl)-1,3-thiazole-5-carboxylate

Ethyl cis(±)-2-(4-((4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl)amino)-3-methoxypiperidin-1-yl)-4-(hydroxymethyl)-1,3-thiazole-5-carboxylate obtained by the method described in Example (27b) (0.14 g, 0.30 mmol) was dissolved in dichloromethane (5 mL). A solution of DAST (0.05 mL, 0.38 mmol) in dichloromethane (2 mL) was added dropwise at -40°C . The mixture was stirred at that temperature for 30 minutes. Brine was added to the reaction solution, followed by extraction with dichloromethane. The organic layer was washed with brine and dried over anhydrous sodium sulfate. Following concentration under reduced pressure, the residue was purified by silica gel column chromatography (elution solvent: hexane/ethyl acetate = 4/1, 3/1, 1/1) to obtain 83 mg of the title compound as a colorless oily substance (59%).

^1H NMR spectrum (400 MHz, CDCl_3) δ ppm: 1.27 (3H, t, $J = 7.62$ Hz), 1.34 (3H, t, $J = 7.19$ Hz), 1.72-1.85 (1H, m), 1.99-2.12 (1H, m), 2.70 (2H, q, $J = 7.62$ Hz), 3.08-3.16 (1H, m), 3.19-3.29 (1H, m), 3.43 (3H, s), 3.52 (1H, br s),

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3.97-4.07 (1H, m), 4.22-4.34 (3H, m), 4.55-4.65 (1H, m), 5.55 (1H, dd, J = 13.66, 11.22 Hz), 5.67 (1H, dd, J = 13.66, 11.22 Hz), 7.54 (1H, d, J = 9.02 Hz), 11.72 (1H, br s).

(29b) cis(±)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(fluoromethyl)-1,3-thiazole-5-carboxylic acid

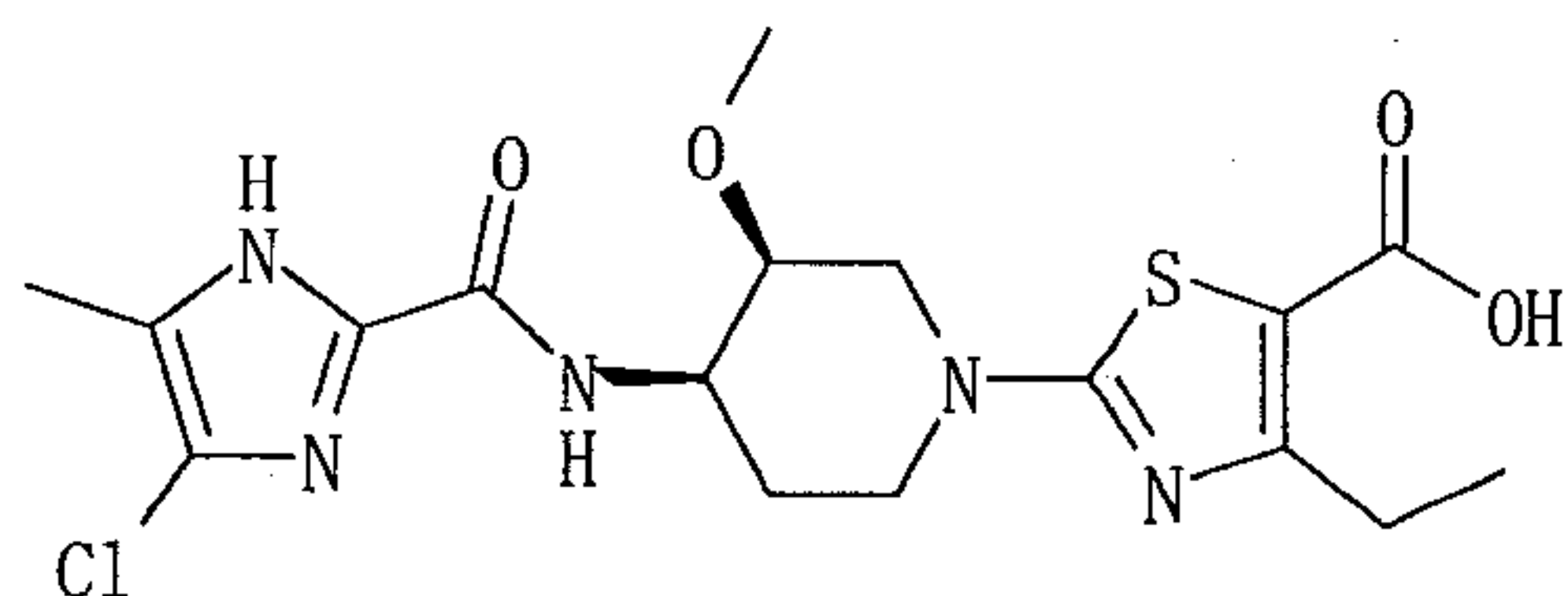
The same operation as in Example (1i) was performed using ethyl cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(fluoromethyl)-1,3-thiazole-5-carboxylate obtained in Example (29a) (80 mg, 0.17 mmol) and a 2 N aqueous lithium hydroxide solution (2 mL), to obtain 52 mg of the title compound as a pale red solid (69%).

¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 1.14 (3H, t, J = 7.57 Hz), 1.65-1.73 (1H, m), 1.80-1.94 (1H, m), 2.55 (2H, q, J = 7.57 Hz), 3.28-3.36 (2H, m), 3.34 (3H, s), 3.58 (1H, br s), 3.88-4.01 (1H, m), 4.17-4.34 (2H, m), 5.43-5.59 (2H, m), 7.67 (1H, d, J = 8.30 Hz), 12.93-13.07 (1H, m), 13.37 (1H, br s).

mass spectrum (ESI): m/z 446 (M+H)⁺.

(Example 30) cis(±)-2-(4-{[(4-Chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-ethyl-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 30)



[0226]

(30a) Methyl cis($\pm$)-2-(4-{[(4-chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-ethyl-1,3-thiazole-5-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis($\pm$)-4-{[(4-chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate obtained by the method described in Example (8a) (0.27 g, 0.72 mmol), a 4 N hydrochloric acid/ethyl acetate solution (5 ml), diisopropylethylamine (0.5 mL, 2.87 mmol) and methyl 2-bromo-4-ethyl-1,3-thiazole-5-carboxylate obtained by the method described in Example (22c) (0.24 g, 0.96 mmol), to obtain 0.22 g of the title compound as a yellow solid (68%).

^1H NMR spectrum (400 MHz, CDCl_3) δ ppm: 1.23 (3H, t, J = 7.57 Hz), 1.76-1.85 (1H, m), 1.96-2.09 (1H, m), 2.30 (3H, s), 2.86-3.10 (3H, m), 3.17-3.27 (1H, m), 3.43 (3H, s), 3.51 (1H, br s), 3.79 (3H, s), 3.91-4.00 (1H, m), 4.20-4.30 (1H, m), 4.56-4.66 (1H, m), 7.41 (1H, d, J = 8.71 Hz), 10.43 (1H, br s).

(30b) cis($\pm$)-2-(4-{[(4-Chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-ethyl-1,3-thiazole-5-carboxylic acid

The same operation as in Example (1i) was performed using methyl cis($\pm$)-2-(4-{[(4-chloro-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-ethyl-1,3-thiazole-5-carboxylate obtained in Example (30a) (0.22 g, 0.49 mmol) and a 2 N aqueous lithium

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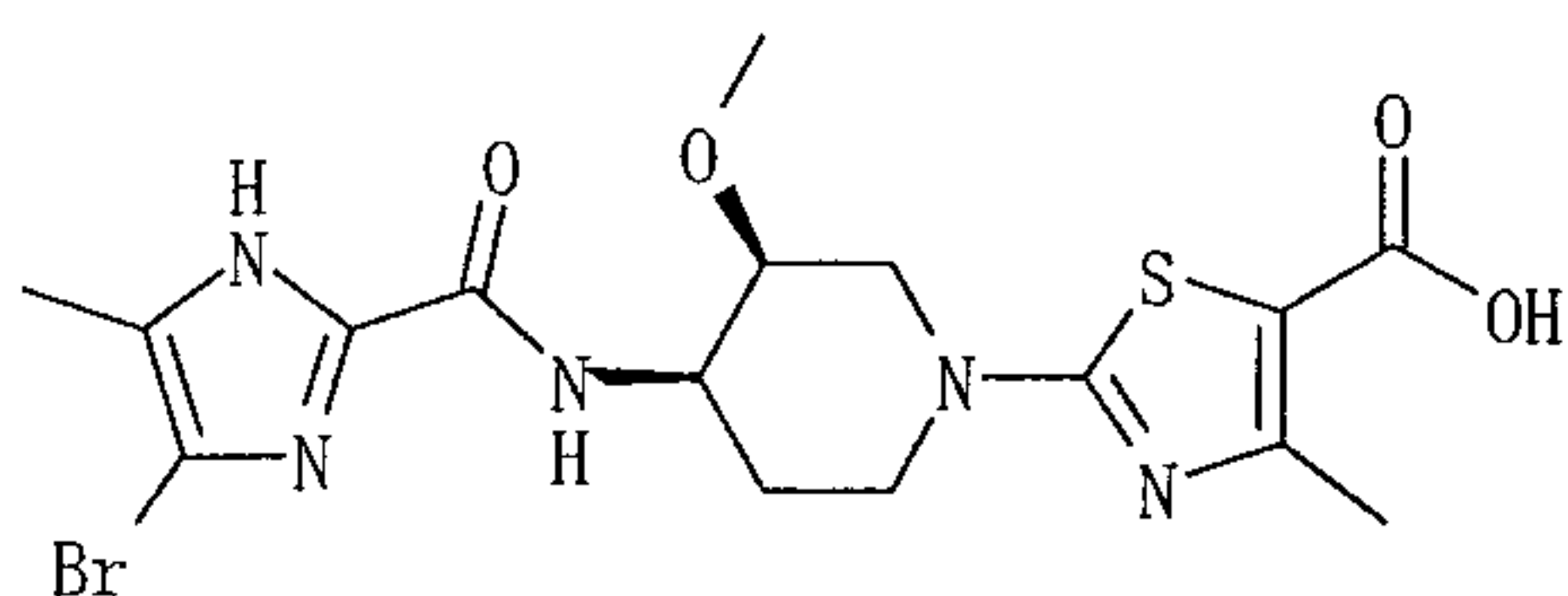
hydroxide solution (3.5 mL), to obtain 0.20 g of the title compound as a white solid (94%).

^1H NMR spectrum (400 MHz, DMSO- d_6) δ ppm: 1.13 (3H, t, J = 7.57 Hz), 1.63-1.72 (1H, m), 1.79-1.92 (1H, m), 2.16 (3H, s), 2.75-2.95 (2H, m), 3.24-3.32 (2H, m), 3.34 (3H, s), 3.56 (1H, br s), 3.81-3.96 (1H, m), 4.14-4.24 (1H, m), 4.27-4.40 (1H, m), 7.65 (1H, d, J = 8.25 Hz), 12.40 (1H, br s).

mass spectrum (ESI): m/z 428 ($M+H$) $^+$.

(Example 31) cis($\pm$)-2-(4-{[(4-Bromo-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 31)



[0227]

(31a) Ethyl 4-bromo-5-methyl-1H-imidazole-2-carboxylate

The same operation as in Example (1c) was performed using ethyl 5-methyl-1H-imidazole-2-carboxylate obtained by the method described in Example (5a) (0.30 g, 1.95 mmol) and NBS (0.35 g, 1.96 mmol), to obtain 0.43 g of the title compound as a white solid (94%).

^1H NMR spectrum (400 MHz, CDCl_3) δ ppm: 1.41 (3H, t, J = 7.15 Hz), 2.32 (3H, s), 4.42 (2H, q, J = 7.15 Hz), 10.53-11.21 (1H, m).

(31b) 4-Bromo-5-methyl-1H-imidazole-2-carboxylic acid

The same operation as in Example (1d) was performed

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using ethyl 4-bromo-5-methyl-1H-imidazole-2-carboxylate obtained in Example (31a) (0.43 g, 1.82 mmol) and a 3 N aqueous lithium hydroxide solution (3 mL), to obtain 0.37 g of the title compound as a white solid (99%).

¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 2.08 (3H, s).

(31c) tert-Butyl cis(±)-4-{[(4-bromo-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate

The same operation as in Example (1g) was performed using tert-butyl cis(±)-4-amino-3-methoxypiperidine-1-carboxylate obtained by the method described in Example (1e) (0.88 g, 3.82 mmol), 4-bromo-5-methyl-1H-imidazole-2-carboxylic acid obtained in Example (31b) (0.37 g, 1.80 mmol), WSC hydrochloride (1.03 g, 5.37 mmol) and HOBt (0.25 g, 1.81 mmol), to obtain 0.63 g of the title compound as a white solid (83%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.47 (9H, s), 1.61-1.70 (1H, m), 1.77-1.92 (1H, m), 2.28 (3H, s), 2.67-2.92 (2H, m), 3.33-3.47 (1H, m), 3.41 (3H, s), 3.97-4.27 (2H, m), 4.35-4.58 (1H, m), 7.43-7.51 (1H, m), 11.17 (1H, brs).

(31d) Ethyl cis(±)-2-(4-{[(4-bromo-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis(±)-4-{[(4-bromo-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate obtained in Example (31c) (0.2 g, 0.48 mmol),

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a 4 N hydrochloric acid/ethyl acetate solution (5 ml), diisopropylethylamine (0.34 mL, 1.95 mmol) and ethyl 2-bromo-4-methyl-1,3-thiazole-5-carboxylate (0.16 g, 0.62 mmol), to obtain 0.19 g of the title compound as an orange solid (82%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.33 (3H, t, J = 7.11 Hz), 1.75-1.84 (1H, m), 1.96-2.09 (1H, m), 2.29 (3H, s), 2.54 (3H, s), 3.07-3.13 (1H, m), 3.15-3.25 (1H, m), 3.42 (3H, s), 3.51 (1H, br s), 3.95-4.04 (1H, m), 4.20-4.30 (3H, m), 4.47-4.56 (1H, m), 7.45 (1H, d, J = 8.71 Hz), 10.73 (1H, br s).

(31e) cis(±)-2-(4-{[(4-Bromo-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid

The same operation as in Example (1i) was performed using ethyl cis(±)-2-(4-{[(4-bromo-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate obtained in Example (31d) (0.19 g, 0.39 mmol) and 2 N lithium hydroxide (4 mL), to obtain 0.11 g of the title compound as a white solid (61%).

¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 1.63-1.73 (1H, m), 1.82-1.90 (1H, m), 2.15 (3H, s), 2.41 (3H, s), 3.20-3.32 (2H, m), 3.33 (3H, s), 3.56 (1H, brs), 3.87-3.99 (1H, m), 4.14-4.32 (2H, m), 7.66 (1H, d, J = 8.25 Hz), 12.41 (1H, br s).

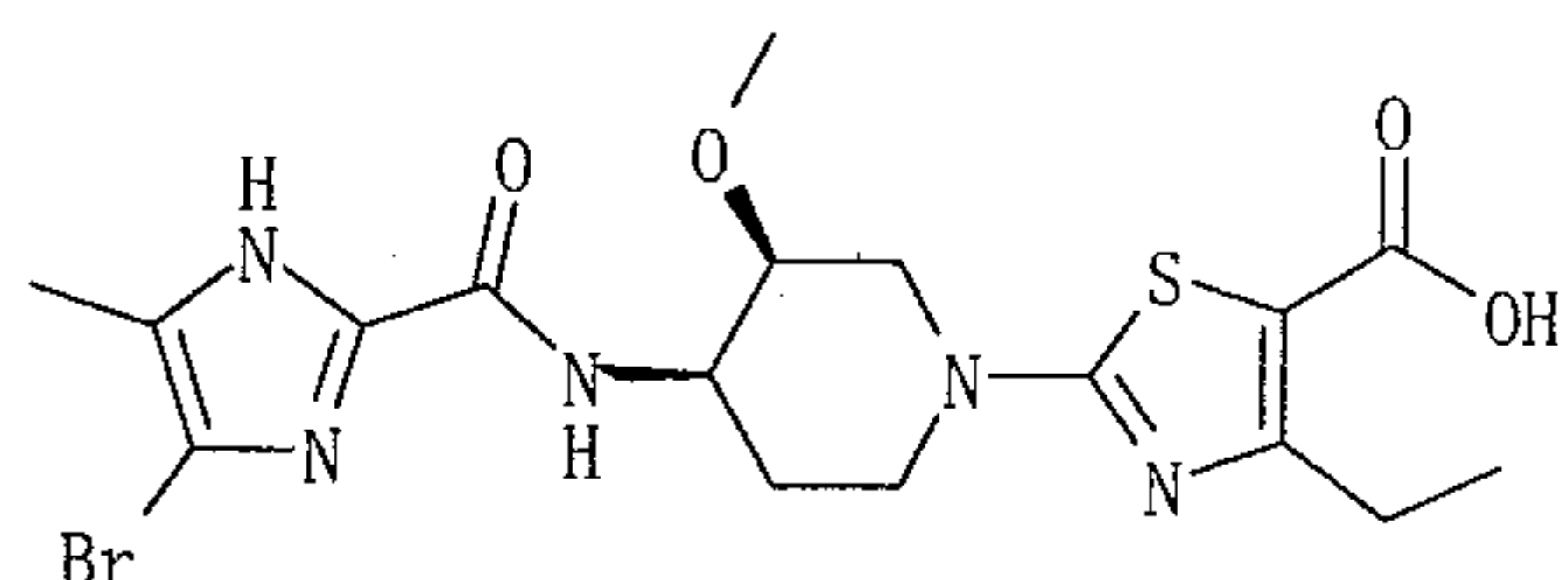
mass spectrum (ESI): m/z 459 (M+H)⁺.

(Example 32) cis(±)-2-(4-{[(4-Bromo-5-methyl-1H-imidazol-

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2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-ethyl-
1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 32)



[0228]

(32a) Methyl cis(±)-2-(4-{[(4-bromo-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-ethyl-1,3-thiazole-5-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis(±)-4-{[(4-bromo-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1--carboxylate obtained by the method described in Example (31c) (0.2 g, 0.48 mmol), a 4 N hydrochloric acid/ethyl acetate solution (5 ml), diisopropylethylamine (0.34 mL, 1.95 mmol) and methyl 2-bromo-4-ethyl-1,3-thiazole-5-carboxylate obtained by the method described in Example (22c) (0.16 g, 0.63 mmol), to obtain 0.17 g of the title compound as a yellow solid (71%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.23 (3H, t, J = 7.34 Hz), 1.75-1.85 (1H, m), 1.96-2.09 (1H, m), 2.30 (3H, s), 2.85-2.96 (1H, m), 2.99-3.10 (2H, m), 3.18-3.25 (1H, m), 3.42 (3H, s), 3.51 (1H, br s), 3.79 (3H, s), 3.91-4.00 (1H, m), 4.20-4.30 (1H, m), 4.56-4.66 (1H, m), 7.44 (1H, d, J = 9.17 Hz), 10.54 (1H, br s).

(32b) cis(±)-2-(4-{[(4-Bromo-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-ethyl-1,3-

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thiazole-5-carboxylic acid

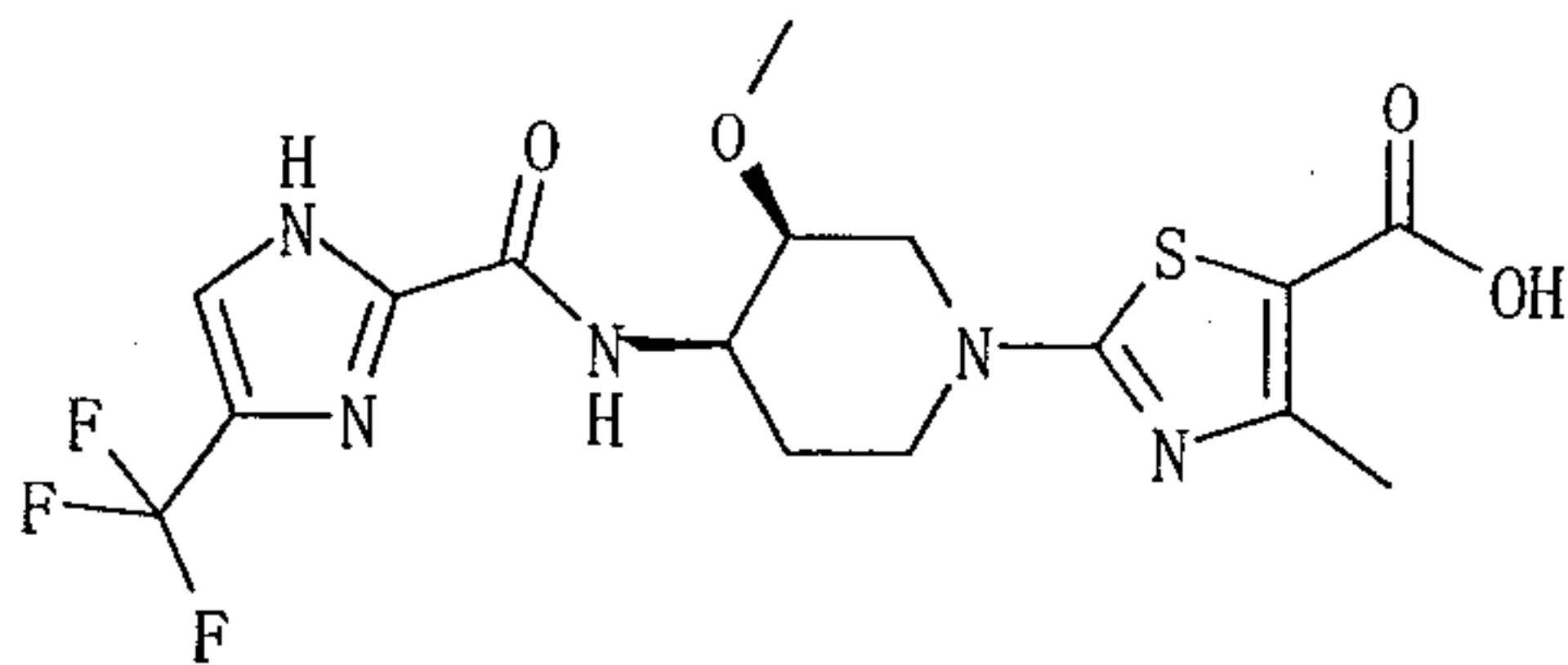
The same operation as in Example (1i) was performed using methyl cis($\pm$)-2-(4-{[(4-bromo-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-ethyl-1,3-thiazole-5-carboxylate obtained in Example (32a) (0.17 g, 0.34 mmol) and a 2 N aqueous lithium hydroxide solution (4 mL), to obtain 0.15 g of the title compound as a white solid (91%).

^1H NMR spectrum (400 MHz, DMSO- d_6) δ ppm: 1.13 (3H, t, J = 7.57 Hz), 1.63-1.72 (1H, m), 1.80-1.92 (1H, m), 2.15 (3H, s), 2.74-2.96 (2H, m), 3.23-3.32 (2H, m), 3.34 (3H, s), 3.56 (1H, br s), 3.81-3.93 (1H, m), 4.14-4.24 (1H, m), 4.27-4.41 (1H, m), 7.65 (1H, d, J = 8.25 Hz), 12.40 (1H, br s).

mass spectrum (ESI): m/z 473 ($M+H$) $^+$.

(Example 33) cis($\pm$)-2-(4-{[(4-Trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 33)



[0229]

(33a) 2-(Dimethoxymethyl)-4-(trifluoromethyl)-1H-imidazole

Sodium acetate (1.33 g, 16.2 mmol) was added to a solution of 3,3-dibromo-1,1,1-trifluoropropan-2-one (2.0

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g, 7.41 mmol) in water (10 ml), and the mixture was heated under reflux for 40 minutes. Following cooling to room temperature, dimethoxyacetaldehyde/60% aqueous solution (1.3 ml, 8.64 mmol), 28% aqueous ammonia solution (2 ml) and methanol (4 ml) were added, and the mixture was stirred for 19 hours. The reaction solution was extracted with ethyl acetate. Then, the organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure, to obtain 1.41 g of the title compound as a pale yellow oily substance (90%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 3.41 (6H, s), 5.49 (1H, s), 7.36 (1H, s), 9.60 (1H, br s).

(33b) 4-(Trifluoromethyl)-1H-imidazole-2-carbaldehyde

2 N sulfuric acid (20 ml) was added to 2-(dimethoxymethyl)-4-(trifluoromethyl)-1H-imidazole obtained in Example (33a) (720 mg, 3.43 mmol), and the mixture was stirred at 90°C for one hour. The reaction solution was neutralized with a 1 N aqueous sodium hydroxide solution, followed by extraction with ethyl acetate. Then, the organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure, to obtain 0.376 g of the title compound as a white solid (67%).

¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 8.02-8.08 (1H, m), 8.20 (1H, s), 9.71 (1H, s).

(33c) 4-(Trifluoromethyl)-1H-imidazole-2-carboxylic acid

Sodium dihydrogenphosphate dihydrate (720 mg, 4.62

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mmol), 2-methyl-2-butene (1.2 ml, 11.4 mmol) and sodium chlorite (420 mg, 4.64 mmol) were added under ice-cooling to a solution of 4-(trifluoromethyl)-1H-imidazole-2-carbaldehyde obtained in Example (33b) (375 mg, 2.29 mmol) in t-butyl alcohol (12 ml)/distilled water (5 ml), followed by stirring for 1.5 hours. The reaction solution was concentrated under reduced pressure, and then the residue was purified by reverse phase silica gel column chromatography (elution solvent: distilled water) to obtain 0.402 g of the title compound as a white solid (98%).

¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 7.41 (1H, s).

(33d) tert-Butyl cis(±)-4-{[(4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate

The same operation as in Example (1g) was performed using tert-butyl cis(±)-4-amino-3-methoxypiperidine-1-carboxylate obtained by the method described in Example (1e) (0.90 g, 3.91 mmol), 4-(trifluoromethyl)-1H-imidazole-2-carboxylic acid obtained in Example (33c) (0.40 g, 2.22 mmol), WSC hydrochloride (1.25 g, 6.52 mmol) and HOBT (0.30 g, 2.22 mmol), to obtain 0.67 g of the title compound as a white foamy substance (77%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.48 (9H, s), 1.66-1.73 (1H, m), 1.86-1.89 (1H, m), 2.83-2.90 (1H, m), 3.35-3.43 (2H, m), 3.44 (3H, s), 4.04-4.21 (2H, m), 4.43-4.50 (1H, m), 7.49 (1H, s), 7.63-7.65 (1H, m), 11.46 (1H, s).

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(33e) Ethyl cis($\pm$)-2-(4-{[(4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis($\pm$)-4-{[(4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate obtained in Example (33d) (0.2 g, 0.51 mmol), a 4 N hydrochloric acid/ethyl acetate solution (6 ml), diisopropylethylamine (0.35 mL, 2.01 mmol) and ethyl 2-bromo-4-methyl-1,3-thiazole-5-carboxylate (0.13 g, 0.52 mmol), to obtain 0.19 g of the title compound as a yellow solid (79%).

^1H NMR spectrum (400 MHz, CDCl_3) δ ppm: 1.33 (3H, t, J = 7.11 Hz), 1.82-1.83 (1H, m), 2.01-2.13 (1H, m), 2.54 (3H, s), 3.10-3.14 (1H, m), 3.19-3.27 (1H, m), 3.45 (3H, s), 3.54 (1H, br s), 3.99-4.03 (1H, m), 4.21-4.32 (3H, m), 4.53-4.56 (1H, m), 7.50 (1H, s), 7.63 (1H, d, J = 8.71 Hz), 11.10 (1H, s).

(33f) cis($\pm$)-2-(4-{[(4-Trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid

The same operation as in Example (1i) was performed using ethyl cis($\pm$)-2-(4-{[(4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate obtained in Example (33e) (65.2 mg, 0.14 mmol) and a 2 N aqueous lithium hydroxide solution (2 mL), to obtain 41.6 mg of the title compound as a white solid (68%).

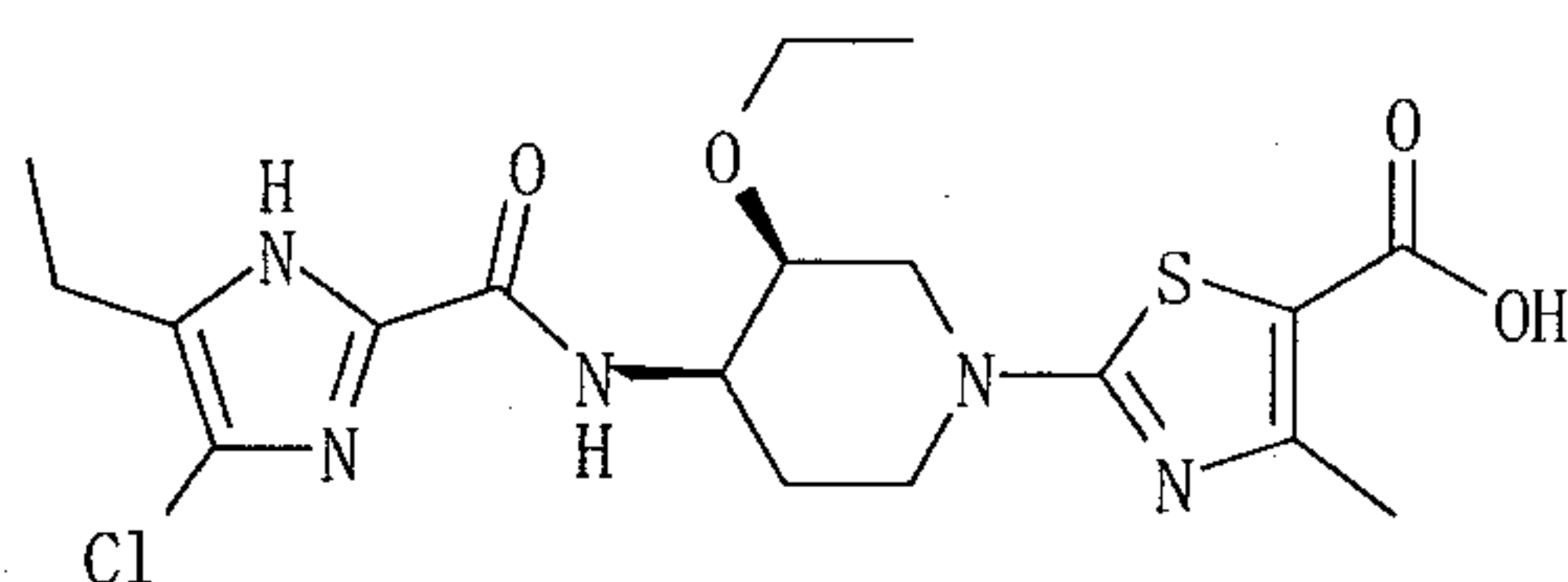
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^1H NMR spectrum (400 MHz, DMSO- d_6) δ ppm: 1.68-1.71 (1H, m), 1.88-1.94 (1H, m), 2.41 (3H, s), 3.26-3.29 (2H, m), 3.34 (3H, s), 3.60 (1H, br s), 3.92-3.95 (1H, m), 4.21-4.29 (2H, m), 7.90 (1H, d, $J = 8.71$ Hz), 7.97 (1H, s), 12.40 (1H, br s).

mass spectrum (ESI): m/z 434 ($M+H$) $^+$.

(Example 34) cis($\pm$)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 34)



[0230]

(34a) tert-Butyl cis($\pm$)-4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidine-1-carboxylate

The same operation as in Example (1g) was performed using tert-butyl cis($\pm$)-4-amino-3-ethoxypiperidine-1-carboxylate obtained by the method described in Example (112d) (0.48 g, 1.96 mmol), 4-chloro-5-ethyl-1H-imidazole-2-carboxylic acid obtained by the method described in Example (1d) (0.31 g, 1.51 mmol), WSC hydrochloride (0.88 g, 4.59 mmol) and HOBt (0.21 g, 1.51 mmol), to obtain 0.59 g of the title compound as a white foamy substance (91%).

^1H NMR spectrum (400 MHz, CDCl_3) δ ppm: 1.14-1.26 (6H, m), 1.47 (9H, s), 1.62-1.67 (1H, m), 1.91-2.00 (1H, m), 2.68

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(2H, q, $J = 7.64$ Hz), 2.79-2.82 (2H, m), 3.36-3.43 (2H, m), 3.75 (1H, br s), 4.06-4.46 (3H, m), 7.50 (1H, br s), 11.14 (1H, br s).

(34b) Ethyl cis($\pm$)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis($\pm$)-4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidine-1-carboxylate obtained in Example (34a) (0.29 g, 0.71 mmol), a 4 N hydrochloric acid/ethyl acetate solution (6 ml), diisopropylethylamine (0.5 mL, 2.87 mmol) and ethyl 2-bromo-4-methyl-1,3-thiazole-5-carboxylate (0.18 g, 0.71 mmol), to obtain 0.24 g of the title compound as a yellow foamy substance (71%).

^1H NMR spectrum (400 MHz, CDCl_3) δ ppm: 1.16 (3H, t, $J = 6.88$ Hz), 1.25-1.27 (3H, m), 1.33 (3H, t, $J = 7.11$ Hz), 1.75-1.80 (1H, m), 2.04-2.10 (1H, m), 2.54 (3H, s), 2.69 (2H, q, $J = 7.64$ Hz), 3.15-3.19 (2H, m), 3.41-3.45 (1H, m), 3.60 (1H, br s), 3.72-3.76 (1H, m), 4.01-4.04 (1H, m), 4.20-4.30 (3H, m), 4.40-4.43 (1H, m), 7.45 (1H, d, $J = 8.71$ Hz), 10.87 (1H, s).

(34c) cis($\pm$)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid

The same operation as in Example (1i) was performed using ethyl cis($\pm$)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-4-methyl-

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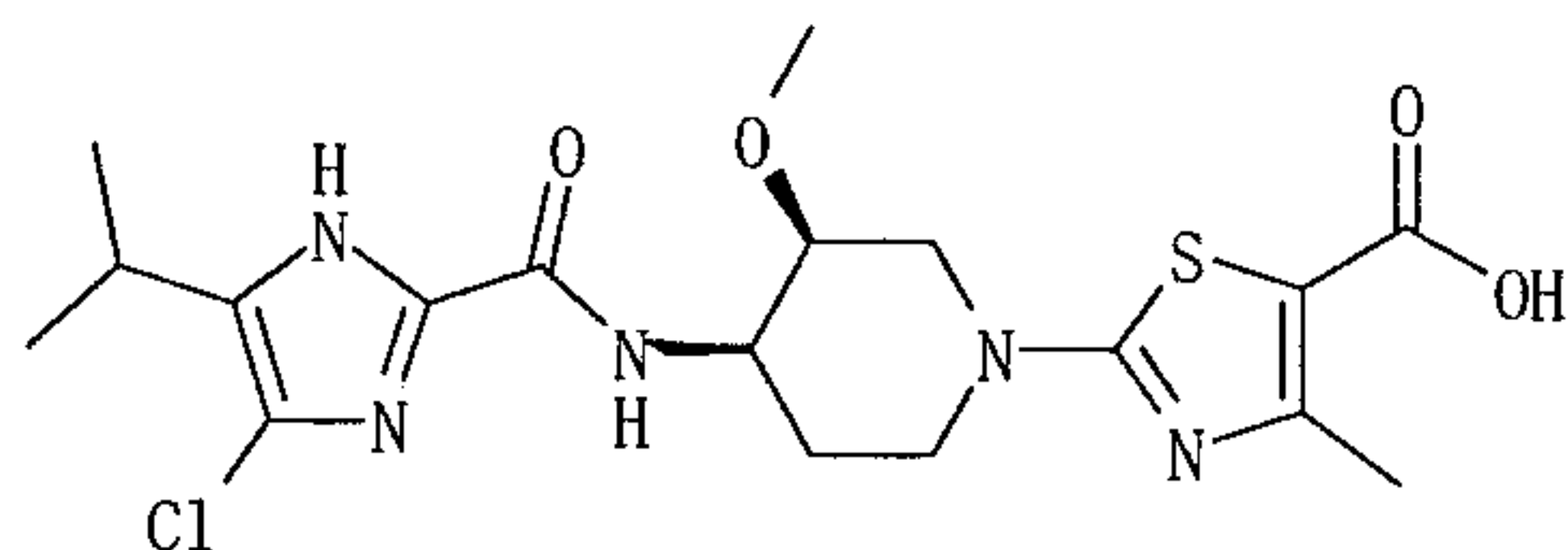
1,3-thiazole-5-carboxylate obtained in Example (34b) (0.23 g, 0.49 mmol) and a 2 N aqueous lithium hydroxide solution (3.5 mL), to obtain 0.20 g of the title compound as a white solid (91%).

¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 1.05 (3H, t, J = 6.88 Hz), 1.14 (3H, t, J = 7.57 Hz), 1.65-1.68 (1H, m), 1.83-1.89 (1H, m), 2.40 (3H, s), 2.55 (14H, q, J = 7.64 Hz), 3.23-3.31 (2H, m), 3.41-3.45 (1H, m), 3.59-3.67 (2H, m), 3.93-3.96 (1H, m), 4.14-4.19 (2H, m), 7.63 (1H, d, J = 8.25 Hz), 12.39 (1H, s).

mass spectrum (ESI): m/z 442 (M+H)⁺.

(Example 35) cis(±)-2-[4-({[4-Chloro-5-(propan-2-yl)-1H-imidazol-2-yl]carbonyl}amino)-3-methoxypiperidin-1-yl]-4-methyl-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 35)



[0231]

(35a) 1-Bromo-3-methylbutan-2-one

The compound was synthesized according to the method described in the following document.

[0232]

Heterocycles, 57, 2002, 357-360

(35b) 2-(3-Methyl-2-oxobutyl)-1H-isoindole-1,3(2H)-dione

The same operation as in Example (15b) was performed using 1-bromo-3-methylbutan-2-one obtained in Example (35a) (3.94 g, 23.9 mmol) and potassium phthalimide (4.4

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g, 23.8 mmol), to obtain 4.08 g of the title compound as a white solid (74%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.09 (6H, d, J = 6.88 Hz), 2.81-2.91 (1H, m), 4.64 (2H, s), 7.90-7.92 (4H, m), 11.35 (1H, br s).

(35c) 1-Amino-3-methylbutan-2-one hydrochloride

The same operation as in Example (15c) was performed using 2-(3-methyl-2-oxobutyl)-1H-isoindole-1,3(2H)-dione obtained in Example (35b) (4.08 g, 17.6 mmol) and 6 N hydrochloric acid (40 mL), to obtain the title compound as a white solid. The resulting compound was used for the next reaction without purification.

[0233]

(35d) Ethyl 5-(propan-2-yl)-1H-imidazole-2-carboxylate

The same operation as in Example (1b) was performed using 1-amino-3-methylbutan-2-one hydrochloride obtained in Example (35c) (about 17.6 mmol) and ethyl imino(methylthio)acetate tetrafluoroborate obtained according to a method known in the literature (J. Med. Chem., 38, 1995, 2196-2201) (about 22 mmol), to obtain 1.83 g of the title compound as a yellow solid (57%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.30 (6H, d, J = 6.88 Hz), 1.41 (3H, t, J = 7.14 Hz), 3.00-3.04 (1H, m), 4.43 (2H, q, J = 7.14 Hz), 6.96 (1H, s), 10.27 (1H, br s).

(35e) Ethyl 4-chloro-5-(propan-2-yl)-1H-imidazole-2-carboxylate

The same operation as in Example (1c) was performed using ethyl 5-(propan-2-yl)-1H-imidazole-2-carboxylate

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obtained in Example (35d) (0.82 g, 4.50 mmol) and NCS (0.60 g, 4.51 mmol), to obtain 0.75 g of the title compound as a white solid (77%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.31 (6H, d, J = 7.34 Hz), 1.41 (3H, t, J = 7.14 Hz), 3.11-3.21 (1H, m), 4.42 (2H, q, J = 7.14 Hz), 10.15 (1H, br s).

(35f) 4-Chloro-5-(propan-2-yl)-1H-imidazole-2-carboxylic acid

The same operation as in Example (1d) was performed using ethyl 4-chloro-5-(propan-2-yl)-1H-imidazole-2-carboxylate obtained in Example (35e) (0.40 g, 1.85 mmol) and a 3 N aqueous lithium hydroxide solution (4 mL), to obtain 0.31 g of the title compound as a white solid (88%).

¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 1.19 (6H, d, J = 6.88 Hz), 2.90-3.00 (1H, m).

(35g) tert-Butyl cis(±)-4-([4-chloro-5-(propan-2-yl)-1H-imidazol-2-yl]carbonyl)amino)-3-methoxypiperidine-1-carboxylate

The same operation as in Example (1g) was performed using tert-butyl cis(±)-4-amino-3-methoxypiperidine-1-carboxylate obtained by the method described in Example (1e) (0.50 g, 2.17 mmol), 4-chloro-5-(propan-2-yl)-1H-imidazole-2-carboxylic acid obtained in Example (35f) (0.30 g, 1.59 mmol), WSC hydrochloride (0.92 g, 4.80 mmol) and HOBt (0.22 g, 1.63 mmol), to obtain 0.60 g of the title compound as a white foamy substance (94%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.30 (6H, d, J =

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6.88 Hz), 1.47 (9H, s), 1.61-1.64 (1H, m), 1.83-1.85 (1H, m), 2.76-2.79 (2H, m), 3.10-3.23 (1H, m), 3.32-3.35 (1H, m), 3.41 (3H, s), 4.03-4.20 (2H, m), 4.35-4.58 (1H, m), 7.49 (1H, br s), 10.91 (1H, brs).

(35h) Ethyl cis(±)-2-[4-({[4-chloro-5-(propan-2-yl)-1H-imidazol-2-yl]carbonyl}amino)-3-methoxypiperidin-1-yl]-4-methyl-1,3-thiazole-5-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis(±)-4-({[4-chloro-5-(propan-2-yl)-1H-imidazol-2-yl]carbonyl}amino)-3-methoxypiperidine-1-carboxylate obtained in Example (35g) (0.31 g, 0.77 mmol), a 4 N hydrochloric acid/ ethyl acetate solution (6 mL), diisopropylethylamine (0.54 mL, 3.10 mmol) and ethyl 2-bromo-4-methyl-1,3-thiazole-5-carboxylate (0.22 g, 0.88 mmol), to obtain 0.25 g of the title compound as a yellow foamy substance (67%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.24-1.35 (9H, m), 1.77-1.81 (1H, m), 2.00-2.06 (1H, m), 2.54 (3H, s), 3.08-3.25 (3H, m), 3.43 (3H, s), 3.50 (1H, br s), 3.98-4.02 (1H, m), 4.24-4.29 (3H, m), 4.50-4.53 (1H, m), 7.45 (1H, d, J = 8.71 Hz), 10.56 (1H, br s).

(35i) cis(±)-2-[4-({[4-Chloro-5-(propan-2-yl)-1H-imidazol-2-yl]carbonyl}amino)-3-methoxypiperidin-1-yl]-4-methyl-1,3-thiazole-5-carboxylic acid

The same operation as in Example (1i) was performed using ethyl cis(±)-2-[4-({[4-chloro-5-(propan-2-yl)-1H-imidazol-2-yl]carbonyl}amino)-3-methoxypiperidin-1-yl]-4-methyl-1,3-thiazole-5-carboxylate obtained in Example

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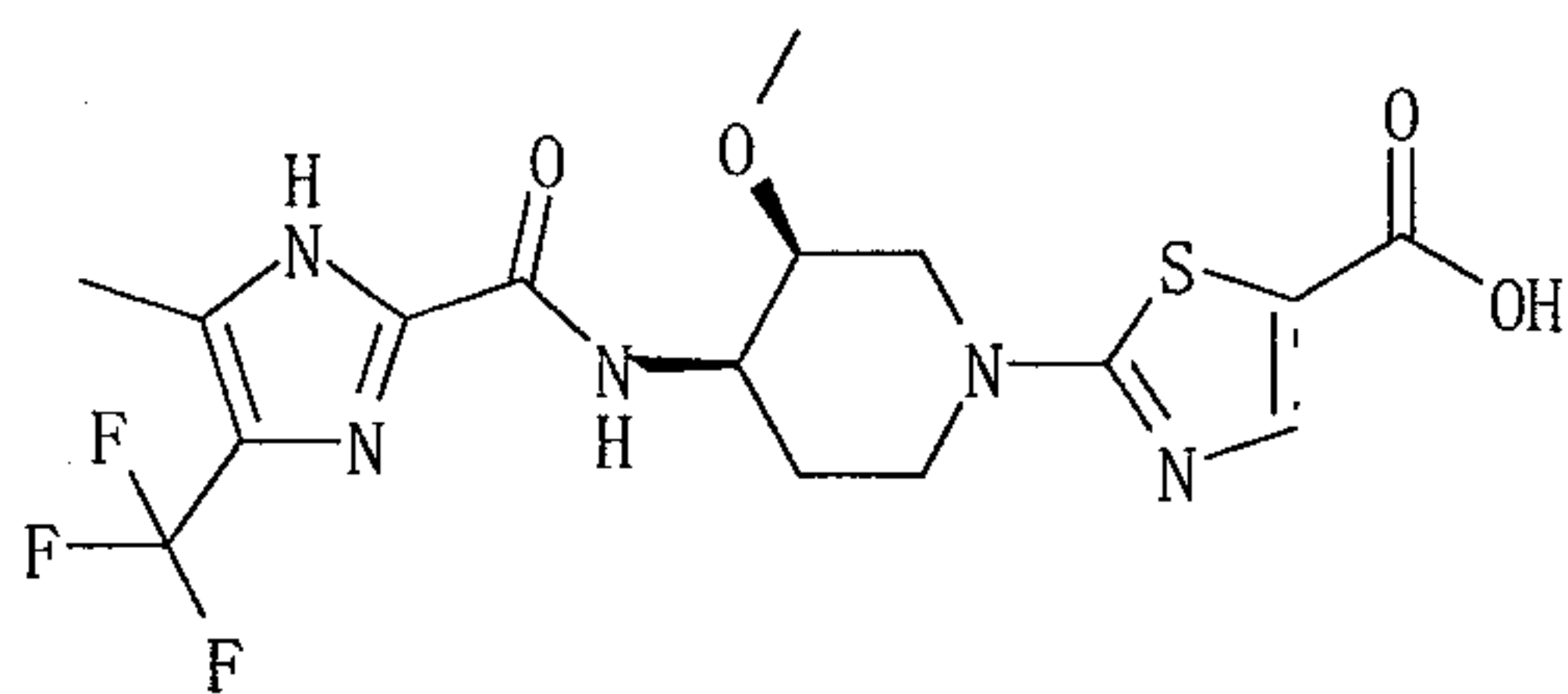
(35h) (0.24 g, 0.51 mmol) and a 2 N aqueous lithium hydroxide solution (3 mL), to obtain 204 mg of the title compound as a white solid (91%).

^1H NMR spectrum (400 MHz, DMSO- d_6) δ ppm: 1.22 (6H, d, J = 7.34 Hz), 1.65-1.69 (1H, m), 1.83-1.88 (1H, m), 2.41 (3H, s), 2.99-3.06 (1H, m), 3.23-3.30 (2H, m), 3.34 (3H, s), 3.55 (1H, br s), 3.91-3.93 (1H, m), 4.20-4.24 (2H, m), 7.65 (1H, d, J = 8.25 Hz), 12.39 (1H, br s).

mass spectrum (ESI): m/z 442 ($M+H$) $^+$.

(Example 36) *cis*($\pm$)-2-(4-{[(5-Methyl-4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 36)



[0234]

(36a) 2,2,2-Trifluoro-1-(2-methyl-1,3-dithian-2-yl)ethanone

2-Methyl-1,3-dithiane (1.50 g, 11.2 mmol) was dissolved in THF (50 mL), followed by cooling to -20°C . Then, *n*-butyllithium (1.58 M solution in hexane, 7 mL, 11.1 mmol) was added dropwise and the mixture was stirred for two hours. Ethyl trifluoroacetate (1.4 mL, 11.8 mmol) was added, and the mixture was heated to room temperature and stirred for 20 hours. Aqueous ammonium chloride solution was added to the reaction solution,

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followed by extraction with ethyl acetate. Then, the organic layer was washed with brine and dried over anhydrous sodium sulfate. Following concentration under reduced pressure, the residue was purified by silica gel column chromatography (elution solvent: hexane/ethyl acetate = 100/0, 95/5, 85/15) to obtain 1.09 g of the title compound as a pale yellow solid (42%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.58 (3H, s), 1.82-1.98 (1H, m), 2.05-2.16 (1H, m), 2.65-2.77 (2H, m), 2.91-3.09 (2H, m).

(36b) 2-(Dimethoxymethyl)-5-methyl-4-(trifluoromethyl)-1H-imidazole

NCS (870 mg, 6.51 mmol) and silver nitrate (1.48 g, 8.71 mmol) were dissolved in acetonitrile (40 mL) and distilled water (10 mL). 2,2,2-Trifluoro-1-(2-methyl-1,3-dithian-2-yl)ethanone obtained in Example (36a) (500 mg, 2.17 mmol) was added, and the mixture was stirred for 40 minutes. Thereafter, dimethoxyacetaldehyde (5.76 M aqueous solution, 0.4 mL, 23.0 mmol) and 28% aqueous ammonia (2 mL) were added, and the mixture was stirred at room temperature for 18 hours. The reaction solution was filtered through celite and then concentrated under reduced pressure. The resulting compound was used for the next reaction without purification.

[0235]

(36c) 5-Methyl-4-(trifluoromethyl)-1H-imidazole-2-carbaldehyde

The same operation as in Example (33b) was performed

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using 2-(dimethoxymethyl)-5-methyl-4-(trifluoromethyl)-1H-imidazole obtained in Example (36b) (about 2.17 mmol) and 2 N sulfuric acid (15 mL), to obtain 30.5 mg of the title compound as a white solid (7.9%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 2.52 (3H, s), 9.69 (1H, s), 10.47 (1H, br s).

(36d) 5-Methyl-4-(trifluoromethyl)-1H-imidazole-2-carboxylic acid

The same operation as in Example (33c) was performed using 5-methyl-4-(trifluoromethyl)-1H-imidazole-2-carbaldehyde obtained in Example (36c) (90 mg, 0.51 mmol), sodium chlorite (95 mg, 1.05 mmol), sodium dihydrogenphosphate (154 mg, 0.99 mmol) and 2-methyl-2-butene (0.3 mL, 2.84 mmol), to obtain 117 mg of the title compound as a white solid (100%).

mass spectrum (ESI): m/z 195 (M+H)⁺.

(36e) tert-Butyl cis(±)-4-{[(5-methyl-4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate

The same operation as in Example (1g) was performed using tert-butyl cis(±)-4-amino-3-methoxypiperidine-1-carboxylate obtained by the method described in Example (1e) (0.22 g, 0.96 mmol), 5-methyl-4-(trifluoromethyl)-1H-imidazole-2-carboxylic acid obtained in Example (36d) (0.10 g, 0.51 mmol), WSC hydrochloride (0.30 g, 1.57 mmol) and HOBt (70 mg, 0.52 mmol), to obtain 0.17 g of the title compound as a white foamy substance (83%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.48 (9H, s),

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1.65-1.68 (1H, m), 1.89-1.99 (1H, m), 2.44 (3H, d, J = 1.38 Hz), 2.79-2.83 (1H, m), 3.34-3.42 (2H, m), 3.43 (3H, s), 4.14-4.17 (2H, m), 4.42-4.51 (1H, m), 7.50-7.52 (1H, m), 10.61 (1H, br s).

(36f) Ethyl cis(±)-2-(4-{[(5-methyl-4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis(±)-4-{[(5-methyl-4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate obtained in Example (36e) (53 mg, 0.13 mmol), a 4 N hydrochloric acid/ethyl acetate solution (3 mL), diisopropylethylamine (0.1 mL, 0.57 mmol) and ethyl 2-bromo-1,3-thiazole-5-carboxylate (50 µL, 0.40 mmol), to obtain 60 mg of the title compound as a colorless oily substance (100%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.34 (3H, t, J = 7.11 Hz), 1.82-1.84 (1H, m), 2.04-2.11 (1H, m), 2.45 (3H, s), 3.14 (1H, d, J = 14.21 Hz), 3.23-3.28 (1H, m), 3.44 (3H, s), 3.54 (1H, br s), 3.98-4.02 (1H, m), 4.24-4.32 (3H, m), 4.57 (1H, d, J = 14.21 Hz), 7.53 (1H, d, J = 8.25 Hz), 7.84 (1H, s), 10.88 (1H, br s).

(36g) cis(±)-2-(4-{[(5-Methyl-4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid

Ethyl cis(±)-2-(4-{[(5-methyl-4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate obtained in Example (36f) (30

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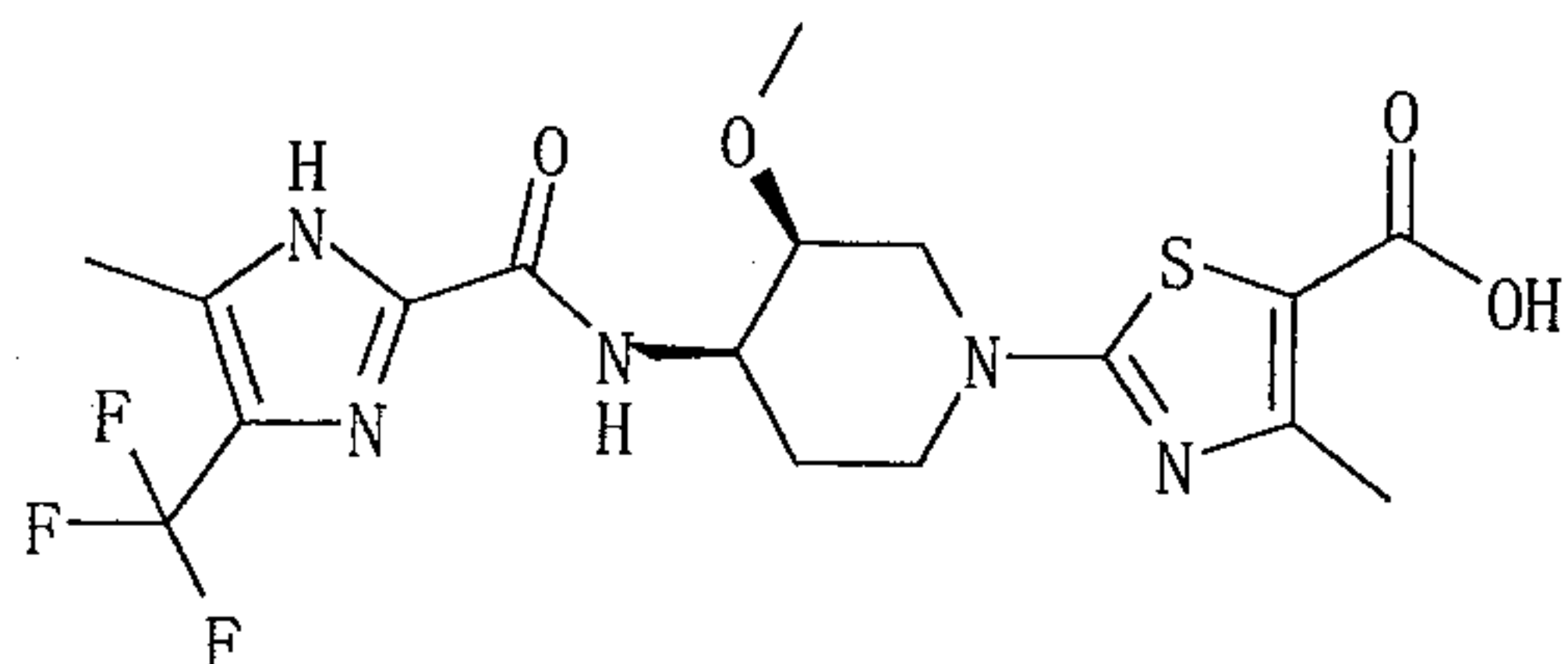
mg, 0.065 mmol) was dissolved in methanol (1 mL). A 1 N aqueous sodium hydroxide solution (1 mL) was added, and the mixture was stirred at room temperature for 1.5 hours. The reaction solution was neutralized with 1 N hydrochloric acid, and the residue was purified by reverse phase silica gel column chromatography (elution solvent: distilled water, methanol/distilled water = 20/80, 60/40) to obtain 9.1 mg of the title compound as a white solid (32%).

¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 1.70-1.71 (1H, m), 1.88-1.94 (1H, m), 2.33 (3H, s), 3.30-3.32 (2H, m), 3.33 (3H, s), 3.60 (1H, br s), 3.91-3.94 (1H, m), 4.22-4.24 (1H, m), 4.32-4.36 (1H, m), 7.74 (1H, s), 7.77 (1H, d, J = 8.25 Hz).

mass spectrum (ESI): m/z 434 (M+H)⁺.

(Example 37) cis(±)-2-(4-{[(5-Methyl-4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 37)



[0236]

(37a) Ethyl cis(±)-2-(4-{[(5-methyl-4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate

The same operation as in Example (1h) was performed

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using tert-butyl cis($\pm$)-4-{[(5-methyl-4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate obtained by the method described in Example (36e) (52 mg, 0.13 mmol), a 4 N hydrochloric acid/ethyl acetate solution (3 mL), diisopropylethylamine (0.11 mL, 0.63 mmol) and ethyl 2-bromo-4-methyl-1,3-thiazole-5-carboxylate (53 mg, 0.21 mmol), to obtain 48 mg of the title compound as a colorless oily substance (80%).

^1H NMR spectrum (400 MHz, CDCl_3) δ ppm: 1.33 (3H, t, J = 7.11 Hz), 1.79-1.83 (1H, m), 2.05-2.09 (1H, m), 2.45 (3H, s), 2.54 (3H, s), 3.11 (1H, d, J = 13.75 Hz), 3.17-3.26 (1H, m), 3.44 (3H, s), 3.51 (1H, br s), 3.99-4.02 (1H, m), 4.25-4.27 (3H, m), 4.51-4.55 (1H, m), 7.54 (1H, d, J = 8.71 Hz), 10.92 (1H, br s).

(37b) cis($\pm$)-2-(4-{[(5-Methyl-4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid

The same operation as in Example (36g) was performed using ethyl cis($\pm$)-2-(4-{[(5-methyl-4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate obtained in Example (37a) (48.3 mg, 0.10 mmol) and a 1 N aqueous sodium hydroxide solution (1 mL), to obtain 22.3 mg of the title compound as a white solid (49%).

^1H NMR spectrum (400 MHz, $\text{DMSO}-d_6$) δ ppm: 1.67-1.70 (1H, m), 1.88-1.90 (1H, m), 2.33 (3H, s), 2.41 (3H, s), 3.16-3.32 (2H, m), 3.34 (3H, s), 3.59 (1H, br s), 3.91 (1H, s), 4.23-4.27 (2H, m), 7.76 (1H, d, J = 8.25 Hz), 12.39 (1H,

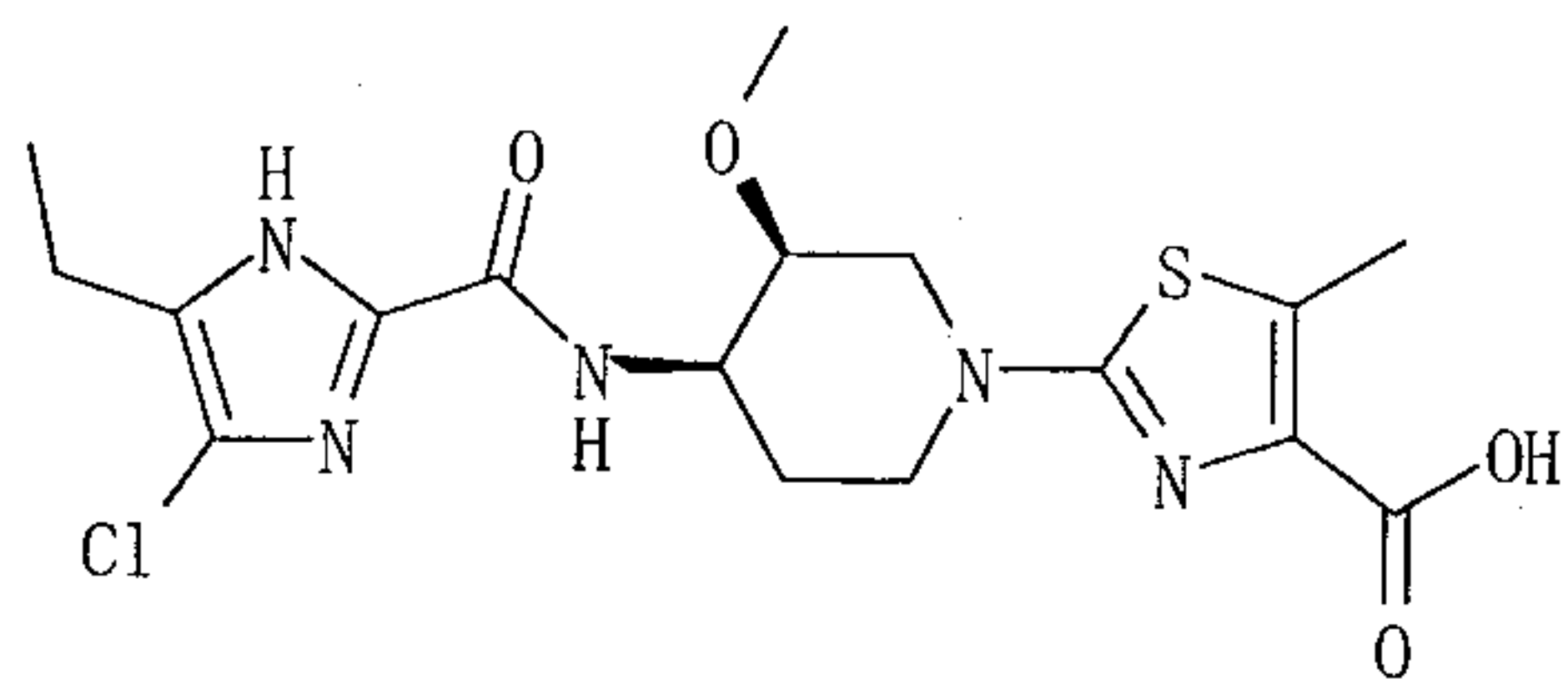
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br s).

mass spectrum (ESI): m/z 448 $(M+H)^+$.

(Example 38) cis($\pm$)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-methyl-1,3-thiazole-4-carboxylic acid

(Exemplified Compound No. 38)



[0237]

(38a) Ethyl 2-chloro-5-methyl-1,3-thiazole-4-carboxylate

The compound was synthesized according to the method described in the following document.

[0238]

WO 2006/087543 A1

(38b) Ethyl cis($\pm$)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-methyl-1,3-thiazole-4-carboxylate

tert-Butyl cis($\pm$)-4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate obtained by the method described in Example (1g) (80 mg, 0.21 mmol) was dissolved in methanol (1 mL). A 4 N hydrochloric acid/ethyl acetate solution (3 mL) was added, and the mixture was stirred at room temperature for one hour. Following concentration under reduced pressure, the residue was dissolved in DMF (2 mL).

Diisopropylethylamine (0.16 mL, 0.92 mmol) and ethyl 2-

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chloro-5-methyl-1,3-thiazole-4-carboxylate obtained in Example (38a) (70 mg, 0.34 mmol) were added, and the mixture was stirred using a microwave reactor at 160°C for three hours. Dilute hydrochloric acid was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with water, saturated aqueous sodium bicarbonate solution and brine, and dried over anhydrous sodium sulfate. Following concentration under reduced pressure, the residue was purified by silica gel column chromatography (elution solvent: hexane/ethyl acetate = 4/1, 1/1, ethyl acetate) to obtain 15.3 mg of the title compound as a pale yellow solid (16%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.26 (3H, t, J = 7.60 Hz), 1.37 (3H, t, J = 7.11 Hz), 1.76-1.78 (1H, m), 2.03-2.07 (1H, m), 2.59 (3H, s), 2.69 (2H, q, J = 7.60 Hz), 3.06 (1H, dd, J = 14.21, 1.38 Hz), 3.12-3.16 (1H, m), 3.43 (3H, s), 3.49 (1H, br s), 3.91-3.94 (1H, m), 4.19-4.28 (1H, m), 4.30-4.40 (3H, m), 7.49 (1H, d, J = 8.71 Hz), 11.19 (1H, br s).

(38c) cis(±)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-methyl-1,3-thiazole-4-carboxylic acid

The same operation as in Example (1i) was performed using ethyl cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-methyl-1,3-thiazole-4-carboxylate obtained in Example (38b) (15.3 mg, 0.034 mmol) and a 2 N aqueous lithium hydroxide

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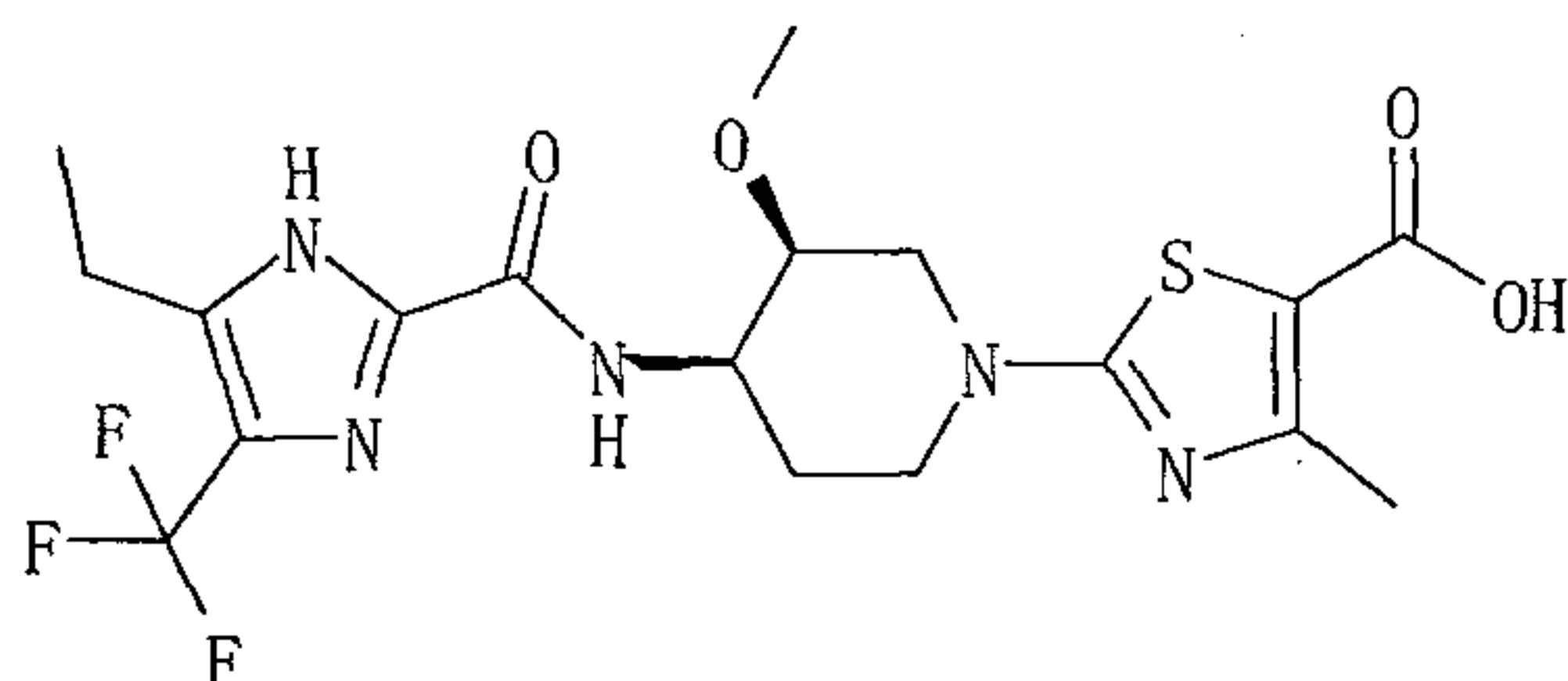
solution (1 mL), to obtain 5.7 mg of the title compound as a pale yellow solid (40%).

^1H NMR spectrum (400 MHz, DMSO-d_6) δ ppm: 1.14 (3H, t, $J = 7.34$ Hz), 1.64-1.67 (1H, m), 1.83-1.89 (1H, m), 2.46-2.52 (3H, m), 2.53-2.59 (2H, m), 3.15-3.52 (3H, m), 3.79-3.82 (1H, m), 4.13-4.17 (2H, m), 7.62 (1H, d, $J = 8.25$ Hz).

mass spectrum (ESI): m/z 428 ($\text{M}+\text{H}$) $^+$.

(Example 39) cis($\pm$)-2-(4-{[(5-Ethyl-4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 39)



[0239]

(39a) 2-Ethyl-1,3-dithiane

The compound was synthesized according to the method described in the following document.

[0240]

Tetrahedron, 52, 6, 1996, 2125-2154.

(39b) 2,2,2-Trifluoro-1-(2-ethyl-1,3-dithian-2-yl)ethanone

The same operation as in Example (36a) was performed using 2-ethyl-1,3-dithiane obtained in Example (39a) (3.51 g, 23.7 mmol), *n*-butyllithium (1.58 M solution in hexane, 18 mL, 28.3 mmol) and ethyl trifluoroacetate (4

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mL, 33.6 mmol), to obtain 2.02 g of the title compound as a pale yellow oily substance (35%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.14 (3H, t, J = 7.57 Hz), 1.76-1.95 (2H, m), 1.96-2.12 (2H, m), 2.69-2.74 (2H, m), 2.89-2.96 (1H, m), 2.99-3.07 (1H, m).

(39c) 2-(Dimethoxymethyl)-5-ethyl-4-(trifluoromethyl)-1H-imidazole

The same operation as in Example (36b) was performed using NCS (1.35 g, 10.1 mmol), silver nitrate (2.45 g, 14.4 mmol), 2,2,2-trifluoro-1-(2-ethyl-1,3-dithian-2-yl)ethanone obtained in Example (39b) (1.0 g, 4.09 mmol), dimethoxyacetaldehyde (5.76 M aqueous solution, 1.0 mL, 5.76 mmol) and 28% aqueous ammonia (4 mL). The resulting compound was used for the next reaction without purification.

[0241]

(39d) 5-Ethyl-4-(trifluoromethyl)-1H-imidazole-2-carbaldehyde

The same operation as in Example (33b) was performed using 2-(dimethoxymethyl)-5-ethyl-4-(trifluoromethyl)-1H-imidazole obtained in Example (39c) (about 4.09 mmol) and 2 N sulfuric acid (30 mL), to obtain 228.3 mg of the title compound as a white solid (29%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.33 (3H, t, J = 7.79 Hz), 2.87-2.93 (2H, m), 9.69 (1H, s).

(39e) 5-Ethyl-4-(trifluoromethyl)-1H-imidazole-2-carboxylic acid

The same operation as in Example (33c) was performed

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using 5-ethyl-4-(trifluoromethyl)-1H-imidazole-2-carbaldehyde obtained in Example (39d) (110 mg, 0.57 mmol), sodium chlorite (108 mg, 1.19 mmol), sodium dihydrogenphosphate (178 mg, 1.14 mmol) and 2-methyl-2-butene (0.3 mL, 2.84 mmol), to obtain 117.5 mg of the title compound as a white solid (99%).

mass spectrum (ESI): m/z 209 (M+H)⁺.

(39f) tert-Butyl cis(±)-4-{[(5-ethyl-4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate

The same operation as in Example (1g) was performed using tert-butyl cis(±)-4-amino-3-methoxypiperidine-1-carboxylate obtained by the method described in Example (1e) (0.26 g, 1.13 mmol), 5-ethyl-4-(trifluoromethyl)-1H-imidazole-2-carboxylic acid obtained in Example (39e) (117.5 mg, 0.56 mmol), WSC hydrochloride (0.38 g, 1.98 mmol) and HOBt (76 mg, 0.56 mmol), to obtain 0.19 g of the title compound as a white foamy substance (79%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.29 (3H, t, J = 7.79 Hz), 1.48 (9H, s), 1.64-1.68 (1H, m), 1.87-1.90 (1H, m), 2.81 (4H, m), 3.34-3.42 (1H, m), 3.43 (3H, s), 4.05-4.22 (2H, m), 4.42-4.49 (1H, m), 7.57 (1H, brs), 11.18 (1H, br s).

(39g) Ethyl cis(±)-2-(4-{[(5-ethyl-4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis(±)-4-{[(5-ethyl-4-trifluoromethyl-

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1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate obtained in Example (39f) (67.2 mg, 0.16 mmol), a 4 N hydrochloric acid/ethyl acetate solution (3 mL), diisopropylethylamine (0.1 mL, 0.57 mmol) and ethyl 2-bromo-4-methyl-1,3-thiazole-5-carboxylate (50 mg, 0.20 mmol), to obtain 65.3 mg of the title compound as a yellow oily substance (84%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.24-1.35 (6H, m), 1.79-1.82 (1H, m), 2.03-2.09 (1H, m), 2.54 (3H, s), 2.84 (2H, q, J = 7.64 Hz), 3.09-3.13 (1H, m), 3.19-3.22 (1H, m), 3.44 (3H, s), 3.53 (1H, br s), 3.99-4.02 (1H, m), 4.24-4.28 (3H, m), 4.53 (1H, d, J = 14.21 Hz), 7.52 (1H, d, J = 8.71 Hz), 10.62 (1H, br s).

(39h) cis(±)-2-(4-{[(5-Ethyl-4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid

The same operation as in Example (36g) was performed using ethyl cis(±)-2-(4-{[(5-ethyl-4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate obtained in Example (39g) (65 mg, 0.13 mmol) and a 1 N aqueous sodium hydroxide solution (2 mL), to obtain 9.4 mg of the title compound as a white solid (15%).

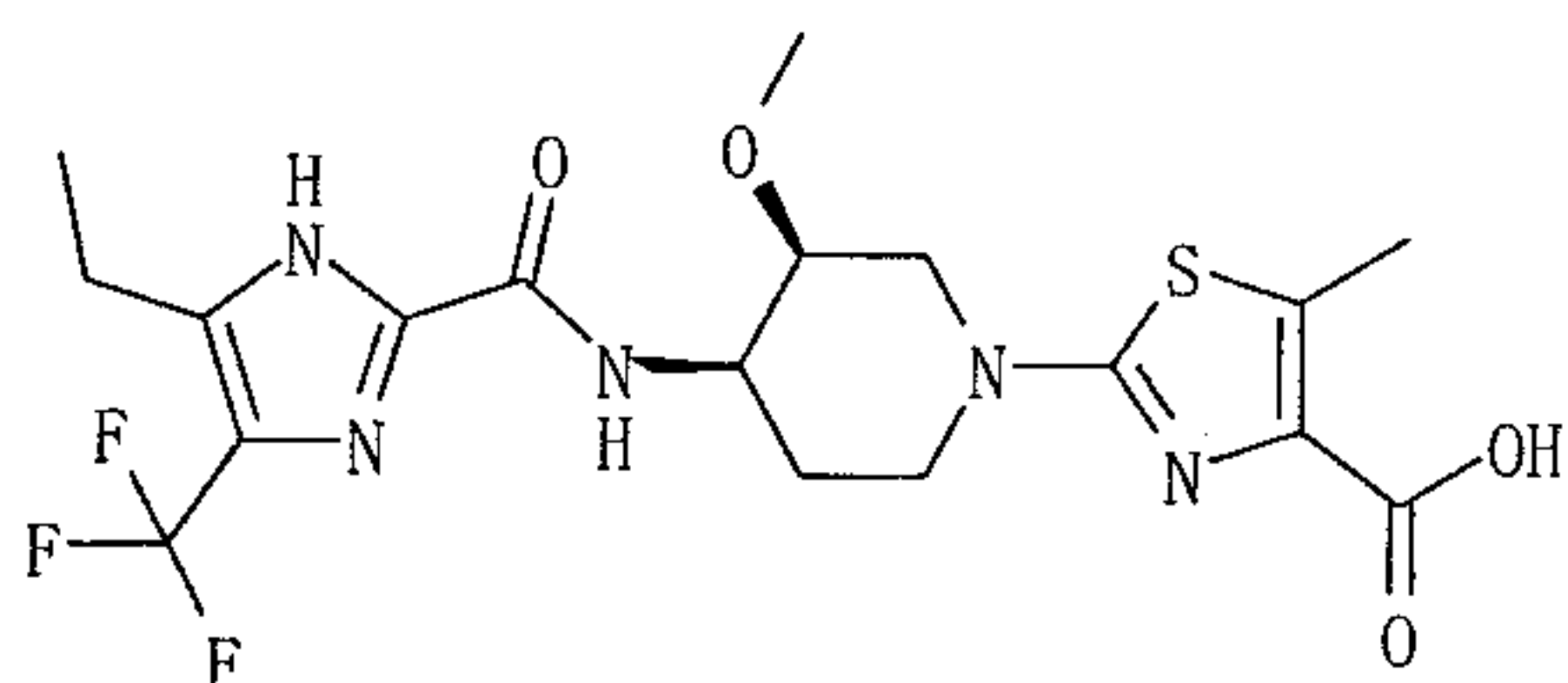
¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 1.16 (3H, t, J = 7.56 Hz), 1.66-1.69 (1H, m), 1.87-1.90 (1H, m), 2.39 (3H, s), 2.68-2.72 (3H, m), 3.34 (3H, s), 3.57 (1H, br s), 3.87-3.90 (1H, m), 4.20-4.23 (1H, m), 7.75 (1H, d, J = 8.29 Hz).

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mass spectrum (ESI): m/z 462 ($M+H$)⁺.

(Example 40) *cis*(±)-2-(4-{[(5-Ethyl-4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-methyl-1,3-thiazole-4-carboxylic acid

(Exemplified Compound No. 40)



[0242]

(40a) *tert*-Butyl *cis*(±)-4-{[(benzyloxy)carbonyl]amino}-3-methoxypiperidine-1-carboxylate

tert-Butyl *cis*(±)-4-amino-3-methoxypiperidine-1-carboxylate obtained by the method described in Example (1e) (3.0 g, 13.0 mmol) was dissolved in THF (60 mL), followed by cooling to 0°C. Thereafter, aqueous sodium carbonate solution (30 mL) and benzyl chloroformate (2.8 mL, 19.6 mmol) were added, and the mixture was stirred for one hour. Ethyl acetate was added to the reaction solution, and the organic layer was washed with brine and dried over anhydrous sodium sulfate. Following concentration under reduced pressure, the residue was purified by silica gel column chromatography (elution solvent: hexane/ethyl acetate = 90/10, 50/50) to obtain 4.29 g of the title compound as a pale yellow solid (90%).

(40b) Benzyl *cis*(±)-(3-methoxypiperidin-4-yl)-carbamate

tert-Butyl *cis*(±)-4-{[(benzyloxy)carbonyl]amino}-3-methoxypiperidine-1-carboxylate obtained in Example (40a)

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(4.28 g, 11.7 mmol) was dissolved in methanol (20 mL). A 4 N hydrochloric acid/ethyl acetate solution (60 mL) was added, and the mixture was stirred at room temperature for 40 minutes. The reaction solution was concentrated under reduced pressure and then saturated aqueous sodium bicarbonate solution was added, followed by extraction with THF. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting compound was used for the next reaction without purification.

[0243]

(40c) Ethyl 2-bromo-5-methyl-1,3-thiazole-4-carboxylate

The same operation as in Example (22c) was performed using ethyl 2-amino-5-methyl-1,3-thiazole-4-carboxylate (synthesized according to the method described in WO 2006/087543 A1, 0.5 g, 2.68 mmol), copper bromide (0.62 g, 2.70 mmol) and tert-butyl nitrite (0.35 mL, 2.94 mmol), to obtain 0.53 g of the title compound as a pale yellow oily substance (80%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.41 (3H, t, J = 7.14 Hz), 2.73 (3H, s), 4.41 (2H, q, J = 7.14 Hz).

(40d) Ethyl cis(±)-2-(4-{[(benzyloxy)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-methyl-1,3-thiazole-4-carboxylate

The same operation as in Example (38b) was performed using benzyl cis(±)-(3-methoxypiperidin-4-yl)-carbamate obtained in Example (40b) (0.2 g, 0.76 mmol), diisopropylethylamine (0.25 mL, 1.44 mmol) and ethyl 2-

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bromo-5-methyl-1,3-thiazole-4-carboxylate obtained in Example (40c) (0.2 g, 0.80 mmol), to obtain 157.6 mg of the title compound as a yellow oily substance (48%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.36 (3H, t, J = 7.20 Hz), 1.74-1.83 (1H, m), 1.84-1.97 (1H, m), 2.58 (3H, s), 3.03-3.21 (2H, m), 3.39 (3H, s), 3.44 (1H, br s), 3.83-3.86 (2H, m), 4.26-4.39 (3H, m), 5.11 (2H, s), 7.32-7.36 (5H, m).

(40e) Ethyl cis(±)-2-(4-amino-3-methoxypiperidin-1-yl)-5-methyl-1,3-thiazole-4-carboxylate

Ethyl cis(±)-2-(4-{[(benzyloxy)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-methyl-1,3-thiazole-4-carboxylate obtained in Example (40d) (75 mg, 0.17 mmol) was dissolved in ethanol (3 mL). A 10% palladium-carbon catalyst (40 mg) was added, and the mixture was stirred in a hydrogen atmosphere for 21 hours. The reaction solution was filtered through celite and then concentrated under reduced pressure to obtain 44.9 mg of the title compound as a colorless oily substance. The resulting compound was used for the next reaction without purification.

[0244]

(40f) Ethyl cis(±)-2-(4-{[(5-ethyl-4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-methyl-1,3-thiazole-4-carboxylate

The same operation as in Example (1g) was performed using ethyl cis(±)-2-(4-amino-3-methoxypiperidin-1-yl)-5-methyl-1,3-thiazole-4-carboxylate obtained in Example

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(40e) (44.9 mg, 0.15 mmol), 5-ethyl-4-(trifluoromethyl)-1H-imidazole-2-carboxylic acid obtained by the method described in Example (39e) (29 mg, 0.14 mmol), WSC hydrochloride (80 mg, 0.42 mmol) and HOBt (20 mg, 0.15 mmol), to obtain 29.2 mg of the title compound as a colorless oily substance (43%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.29 (3H, t, J = 7.56 Hz), 1.38 (3H, t, J = 7.19 Hz), 1.78-1.80 (1H, m), 2.07-2.11 (1H, m), 2.60 (3H, s), 2.84 (2H, q, J = 7.56 Hz), 3.02-3.09 (1H, m), 3.12-3.17 (1H, m), 3.45 (3H, s), 3.52 (1H, br s), 3.92-3.96 (1H, m), 4.22-4.25 (1H, m), 4.30-4.41 (3H, m), 7.63 (1H, d, J = 8.78 Hz), 11.69 (1H, br s).

(40g) cis(±)-2-(4-{[(5-Ethyl-4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-methyl-1,3-thiazole-4-carboxylic acid

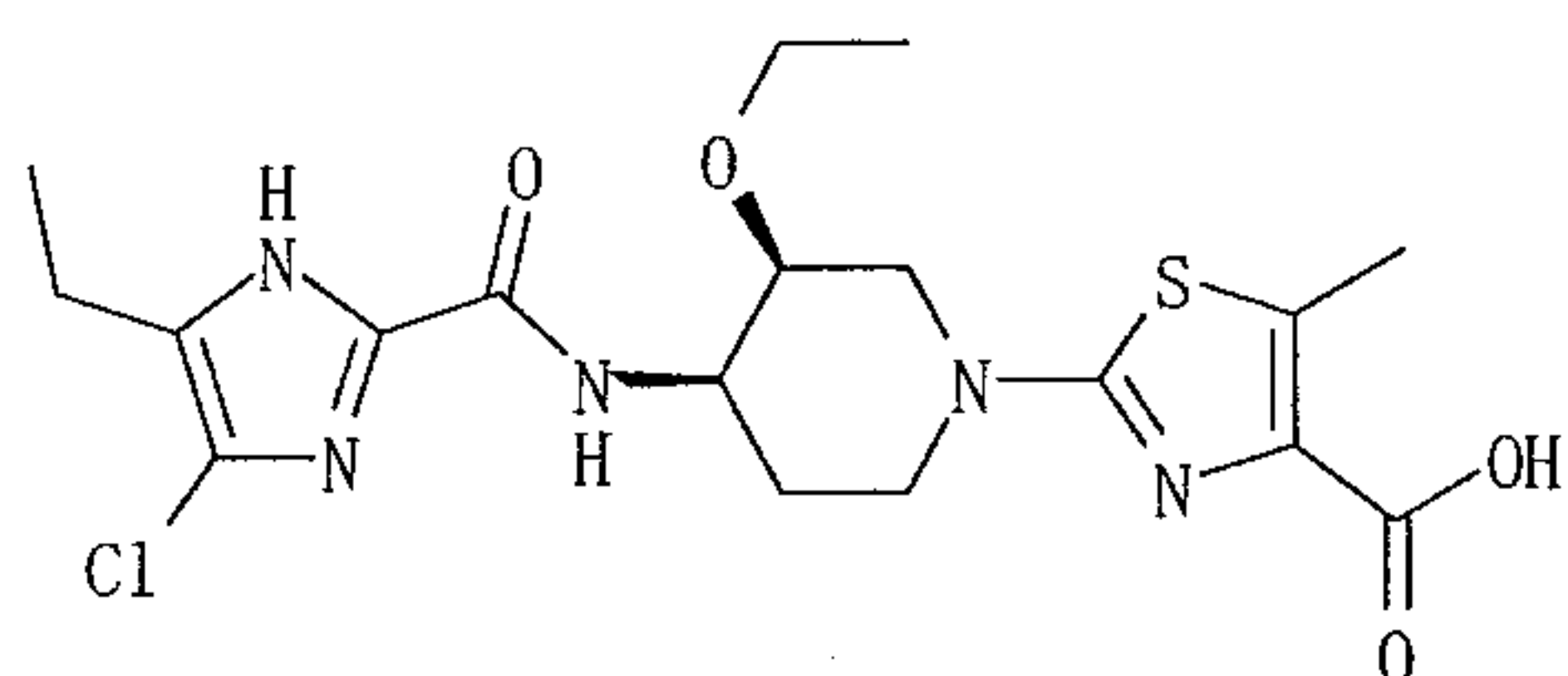
Ethyl cis(±)-2-(4-{[(5-ethyl-4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-methyl-1,3-thiazole-4-carboxylate obtained in Example (40f) (29.2 mg, 0.060 mmol) was dissolved in methanol (1 mL). The solution was subjected to the same operation as in Example (36g) using a 1 N aqueous sodium hydroxide solution (1.5 mL), to obtain 24.0 mg of the title compound as a white solid (87%).

¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 1.16 (3H, t, J = 7.57 Hz), 1.65-1.68 (1H, m), 1.86-1.91 (1H, m), 2.50 (3H, s), 2.70 (2H, q, J = 7.57 Hz), 3.16-3.21 (2H, m), 3.34 (3H, s), 3.56 (1H, br s), 3.79-3.83 (1H, m), 4.17-

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4.22 (2H, m), 7.74 (1H, d, $J = 8.25$ Hz), 12.43 (1H, br s).
mass spectrum (ESI): m/z 462 ($M+H$)⁺.

(Example 41) cis($\pm$)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-5-methyl-1,3-thiazole-4-carboxylic acid
(Exemplified Compound No. 41)



[0245]

(41a) Ethyl cis($\pm$)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-5-methyl-1,3-thiazole-4-carboxylate

The same operation as in Example (38b) was performed using tert-butyl cis($\pm$)-4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidine-1-carboxylate obtained by the method described in Example (34a) (142 mg, 0.35 mmol), diisopropylethylamine (0.3 mL, 1.72 mmol), a 4 N hydrochloric acid/ethyl acetate solution (4 mL) and ethyl 2-bromo-5-methyl-1,3-thiazole-4-carboxylate obtained in Example (40c) (102 mg, 0.41 mmol), to obtain 59.3 mg of the title compound as a yellow oil substance (36%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.17 (3H, t, $J = 7.11$ Hz), 1.26 (3H, t, $J = 7.57$ Hz), 1.38 (3H, t, $J = 7.11$ Hz), 1.69-1.77 (1H, m), 2.05-2.17 (1H, m), 2.60 (3H, s), 2.69 (2H, q, $J = 7.57$ Hz), 3.07-3.17 (2H, m), 3.42-

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3.45 (1H, m), 3.59 (1H, br s), 3.71-3.78 (1H, m), 3.95-3.98 (1H, m), 4.20-4.25 (2H, m), 4.30-4.40 (2H, m), 7.53 (1H, d, $J = 8.71$ Hz), 11.66 (1H, br s).

(41b) cis($\pm$)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-5-methyl-1,3-thiazole-4-carboxylic acid

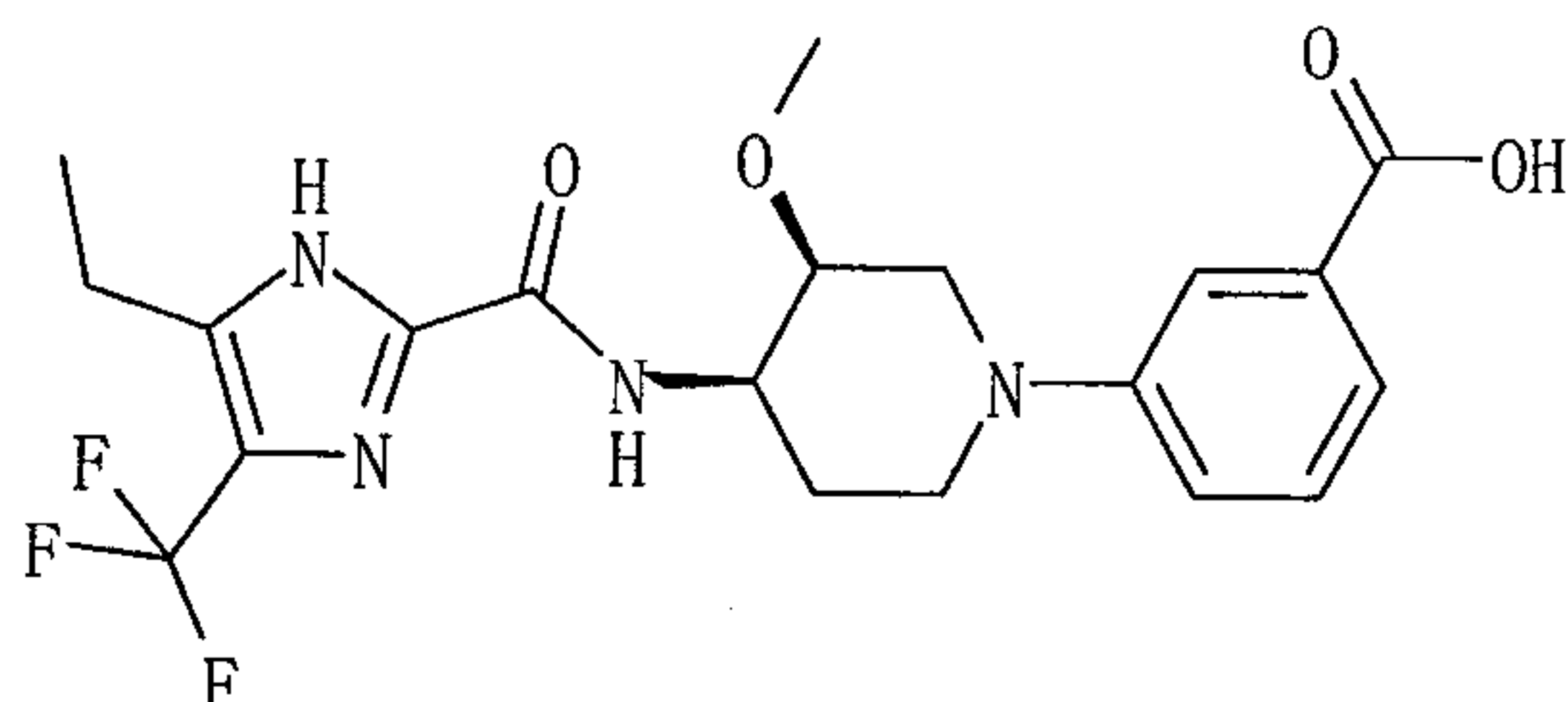
The same operation as in Example (1i) was performed using ethyl cis($\pm$)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-5-methyl-1,3-thiazole-4-carboxylate obtained in Example (41a) (59.3 mg, 0.13 mmol) and a 2 N aqueous lithium hydroxide solution (3 mL), to obtain 51.5 mg of the title compound as a pale yellow solid (92%).

^1H NMR spectrum (400 MHz, DMSO- d_6) δ ppm: 1.05 (3H, t, $J = 6.88$ Hz), 1.14 (3H, t, $J = 7.34$ Hz), 1.64-1.66 (1H, m), 1.85-1.88 (1H, m), 2.52-2.55 (5H, m), 3.19-3.40 (6H, m), 3.60-3.67 (2H, m), 3.82-3.85 (1H, m), 4.00-4.03 (1H, m), 4.14-4.16 (1H, m), 7.62 (1H, d, $J = 8.25$ Hz).

mass spectrum (ESI): m/z 442 ($M+H$) $^+$.

(Example 42) cis($\pm$)-3-(4-{[(5-Ethyl-4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)benzoic acid

(Exemplified Compound No. 42)



[0246]

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(42a) Methyl cis($\pm$)-3-(4-{[(benzyloxy)carbonyl]amino}-3-methoxypiperidin-1-yl)benzoate

Benzyl cis($\pm$)-4-(3-methoxypiperidin-4-yl)-carbamate obtained by the method described in Example (40b) (0.5 g, 1.89 mmol) was dissolved in dioxane (20 ml) and DMF (6 mL). Methyl 3-bromobenzoate (0.35 g, 1.63 mmol), palladium acetate (39 mg, 0.17 mmol), BINAP (214 mg, 0.34 mmol) and cesium carbonate (1.35 g, 4.14 mmol) were added, and the mixture was stirred at 100°C for 17 hours. Aqueous ammonium chloride solution was added to the reaction solution, followed by extraction with ethyl acetate. Then, the organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Thereafter, the residue was purified by silica gel column chromatography (elution solvent: hexane/ethyl acetate = 90/10, 80/20, 0/100) to obtain 250.9 mg of the title compound as a yellow oily substance (39%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.85-1.89 (1H, m), 2.01-2.13 (1H, m), 2.88-2.92 (2H, m), 3.41 (3H, s), 3.51 (1H, br s), 3.60-3.71 (1H, m), 3.85-3.89 (2H, m), 3.90 (3H, s), 5.12 (2H, s), 5.26-5.30 (1H, m), 7.12 (1H, dd, J = 8.02, 2.52 Hz), 7.25-7.40 (6H, m), 7.48-7.52 (1H, m), 7.59-7.63 (1H, m).

(42b) cis($\pm$)-3-(4-{[(Benzyloxy)carbonyl]amino}-3-methoxypiperidin-1-yl)benzoic acid

Methyl cis($\pm$)-3-(4-{[(benzyloxy)carbonyl]amino}-3-methoxypiperidin-1-yl)benzoate obtained in Example (42a)

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(250 mg, 0.63 mmol) was dissolved in methanol (5 mL). A 1 N aqueous sodium hydroxide solution (4 mL) was added, and the mixture was stirred at 70°C for one hour. The reaction solution was neutralized with 1 N hydrochloric acid, followed by extraction with ethyl acetate. Then, the organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting compound was used for the next reaction without purification.

[0247]

(42c) tert-Butyl cis($\pm$)-3-(4-
{[(benzyloxy)carbonyl]amino}-3-methoxypiperidin-1-
yl)benzoate

cis($\pm$)-3-(4-{[(Benzyloxy)carbonyl]amino}-3-methoxypiperidin-1-yl)benzoic acid obtained in Example (42b) (200 mg, about 0.52 mmol) was dissolved in THF (0.5 mL) and toluene (5 mL). N,N-Dimethylformamide di-tert-butylacetal (1 mL) was added, and the mixture was stirred at 90°C for 50 minutes. Ethyl acetate was added to the reaction solution, which was then washed with a 1 N aqueous sodium hydroxide solution and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Thereafter, the residue was purified by silica gel column chromatography (elution solvent: hexane/ethyl acetate = 75/25, 70/30) to obtain 117.7 mg of the title compound as a colorless oily substance (51%).

^1H NMR spectrum (400 MHz, CDCl_3) δ ppm: 1.58 (9H, s), 1.87-1.88 (1H, m), 1.94-2.05 (1H, m), 2.86-2.90 (2H, m),

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3.42 (3H, s), 3.51 (1H, br s), 3.58-3.62 (1H, m), 3.84-3.88 (2H, m), 5.12 (2H, s), 5.28 (1H, d, J = 8.25 Hz), 7.06-7.11 (1H, m), 7.25-7.40 (6H, m), 7.46 (1H, d, J = 7.79 Hz), 7.56 (1H, s).

(42d) tert-Butyl cis(±)-3-(4-amino-3-methoxypiperidin-1-yl)benzoate

The same operation as in Example (40e) was performed using tert-butyl cis(±)-3-(4-[[(benzyloxy)carbonyl]amino]-3-methoxypiperidin-1-yl)benzoate obtained in Example (42c) (115 mg, 0.26 mmol) and a 10% palladium-carbon catalyst (40 mg), to obtain the title compound. The resulting compound was used for the next reaction without purification.

[0248]

(42e) tert-Butyl cis(±)-3-(4-[[(5-ethyl-4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino]-3-methoxypiperidin-1-yl)benzoate

The same operation as in Example (1g) was performed using tert-butyl cis(±)-3-(4-amino-3-methoxypiperidin-1-yl)benzoate obtained in Example (42d) (about 0.26 mmol), 5-ethyl-4-(trifluoromethyl)-1H-imidazole-2-carboxylic acid obtained by the method described in Example (39e) (50 mg, 0.24 mmol), WSC hydrochloride (137 mg, 0.71 mmol) and HOBT (32 mg, 0.24 mmol), to obtain 79.7 mg of the title compound as a white solid (67%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.30 (3H, t, J = 7.57 Hz), 1.59 (9H, s), 1.86-1.89 (1H, m), 2.14-2.19 (1H, m), 2.86-2.92 (4H, m), 3.46 (3H, s), 3.57 (1H, br s),

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3.65-3.74 (1H, m), 3.95-3.99 (1H, m), 4.20-4.27 (1H, m), 7.12 (1H, dd, $J = 8.25, 2.29$ Hz), 7.26-7.32 (1H, m), 7.48 (1H, d, $J = 7.79$ Hz), 7.59-7.62 (2H, m), 11.27 (1H, s).

(42f) cis($\pm$)-3-(4-{[(5-Ethyl-4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)benzoic acid

tert-Butyl cis($\pm$)-3-(4-{[(5-ethyl-4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)benzoate obtained in Example (42e) (78 mg, 0.16 mmol) was dissolved in dichloromethane (3 ml). Trifluoroacetic acid (0.75 ml) was added, followed by stirring for five hours. The reaction solution was concentrated under reduced pressure, and the residue was purified by reverse phase silica gel column chromatography (elution solvent: distilled water, acetonitrile) to obtain 60.1 mg of the title compound as a white solid (87%).

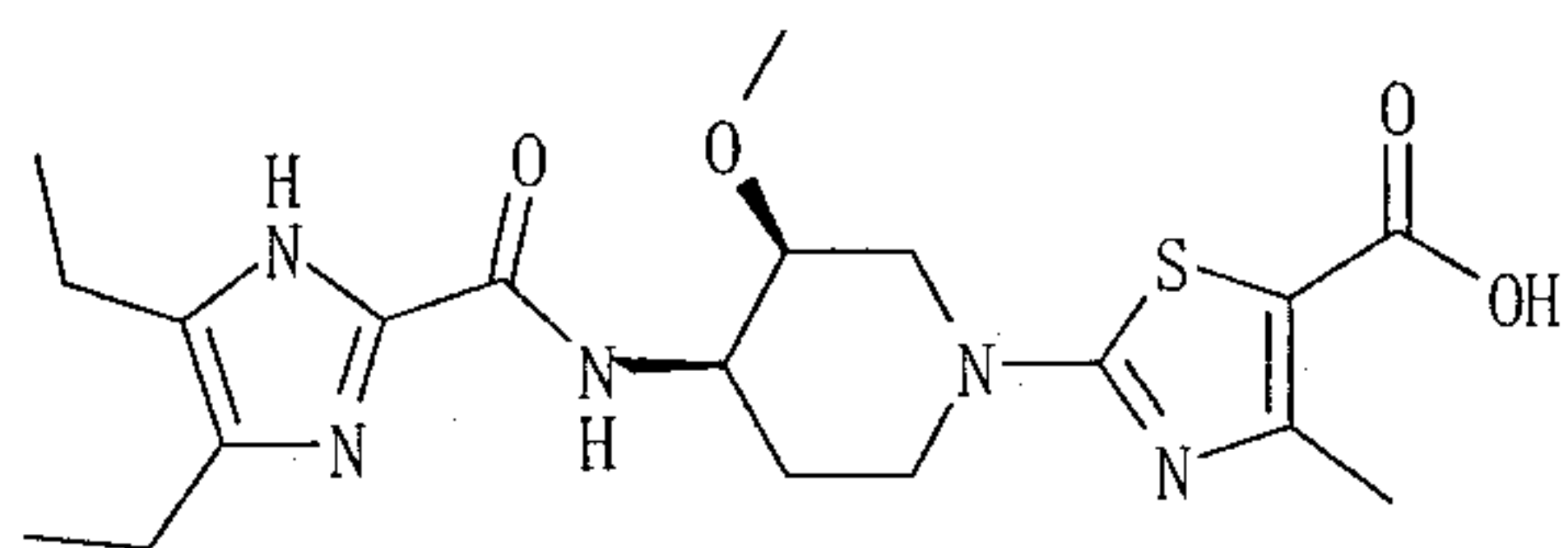
^1H NMR spectrum (400 MHz, DMSO- d_6) δ ppm: 1.16 (3H, t, $J = 7.57$ Hz), 1.71-1.75 (1H, m), 1.95-2.01 (1H, m), 2.70 (2H, q, $J = 7.57$ Hz), 2.93-2.97 (2H, m), 3.33 (3H, s), 3.58 (1H, br s), 3.63-3.66 (1H, m), 3.96-3.99 (1H, m), 4.14-4.18 (1H, m), 7.23-7.24 (1H, m), 7.30-7.32 (2H, m), 7.46-7.46 (1H, m), 7.68 (1H, d, $J = 8.71$ Hz).

mass spectrum (ESI): m/z 441 ($M+H$) $^+$.

(Example 43) cis($\pm$)-2-(4-{[(4,5-Diethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 43)

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[0249]

(43a) 4,5-Diethyl-2-(dimethoxymethyl)-1H-imidazole

The same operation as in Example (36b) was performed using hexane-3,4-dione (1.0 g, 8.76 mmol), dimethoxyacetaldehyde (5.76 M aqueous solution, 1.75 mL, 10.1 mmol) and 28% aqueous ammonia (2.5 mL). The resulting compound was used for the next reaction without purification.

[0250]

(43b) 4,5-Diethyl-1H-imidazole-2-carbaldehyde

The same operation as in Example (33b) was performed using 4,5-diethyl-2-(dimethoxymethyl)-1H-imidazole obtained in Example (43a) (about 8.12 mmol) and 2 N sulfuric acid (40 mL), to obtain 352 mg of the title compound as a white solid (28%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.26-1.28 (6H, m), 2.61 (2H, q, J = 7.64 Hz), 2.69 (2H, q, J = 7.64 Hz), 9.59 (1H, s), 10.05 (1H, br s).

(43c) 4,5-Diethyl-1H-imidazole-2-carboxylic acid

The same operation as in Example (33c) was performed using 4,5-diethyl-1H-imidazole-2-carbaldehyde obtained in Example (43b) (352 mg, 2.31 mmol), sodium chlorite (420 mg, 4.64 mmol), sodium dihydrogenphosphate (725 mg, 4.64 mmol) and 2-methyl-2-butene (1 mL, 9.45 mmol), to obtain 36.7 mg of the title compound as a white solid (9.4%).

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mass spectrum (ESI): m/z 169 ($M+H$)⁺.

(43d) tert-Butyl cis(±)-4-{[(4,5-diethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate

The same operation as in Example (1g) was performed using tert-butyl cis(±)-4-amino-3-methoxypiperidine-1-carboxylate obtained by the method described in Example (1e) (120 mg, 0.52 mmol), 4,5-diethyl-1H-imidazole-2-carboxylic acid obtained in Example (43c) (36.7 mg, 0.22 mmol), WSC hydrochloride (145 mg, 0.76 mmol) and HOBt (35 mg, 0.26 mmol), to obtain 55.0 mg of the title compound as a white foamy substance (66%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.20-1.32 (6H, m), 1.48 (9H, s), 1.60-1.65 (1H, m), 1.85-1.88 (1H, m), 2.54 (2H, q, J = 7.64 Hz), 2.62 (2H, q, J = 7.49 Hz), 2.79-2.81 (2H, m), 3.42 (3H, s), 3.90-4.19 (2H, m), 4.40-4.49 (1H, m), 7.49 (1H, br s), 10.71 (1H, br s).

(43e) Ethyl cis(±)-2-(4-{[(4,5-diethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis(±)-4-{[(4,5-diethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate obtained in Example (43d) (55.0 mg, 0.14 mmol), a 4 N hydrochloric acid/ethyl acetate solution (3 mL), diisopropylethylamine (0.15 mL, 0.86 mmol) and ethyl 2-bromo-4-methyl-1,3-thiazole-5-carboxylate (43 mg, 0.17 mmol), to obtain 50.0 mg of the title compound as a yellow oily substance (77%).

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¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.15-1.26 (6H, m), 1.33 (3H, t, J = 7.11 Hz), 1.76-1.85 (1H, m), 2.03-2.09 (1H, m), 2.49-2.54 (4H, m), 2.63 (2H, q, J = 7.64 Hz), 3.06-3.13 (1H, m), 3.19-3.23 (1H, m), 3.43 (3H, s), 3.53 (1H, br s), 3.96-4.05 (1H, m), 4.20-4.31 (3H, m), 4.48-4.52 (1H, m), 7.51 (1H, d, J = 8.71 Hz), 10.70 (1H, br s).

(43f) cis(±)-2-(4-{[(4,5-Diethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid

The same operation as in Example (1i) was performed using ethyl cis(±)-2-(4-{[(4,5-diethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate obtained in Example (43e) (50 mg, 0.11 mmol) and a 2 N aqueous lithium hydroxide solution (2 mL), to obtain 47 mg of the title compound as a white solid (100%).

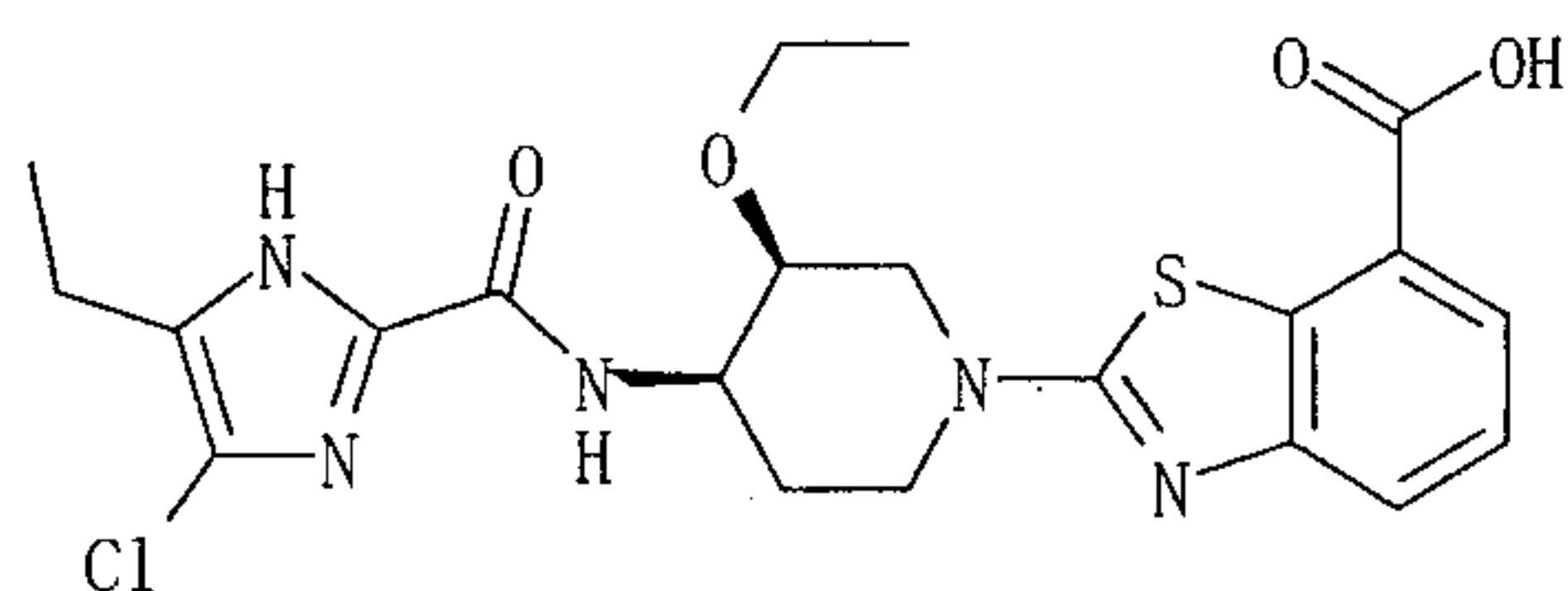
¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 1.10-1.11 (6H, m), 1.64-1.66 (1H, m), 1.79-1.81 (1H, m), 2.35 (3H, s), 2.45-2.50 (4H, m), 3.11-3.15 (2H, m), 3.34 (3H, s), 3.51 (1H, br s), 3.82-3.85 (1H, m), 4.16-4.19 (2H, m), 7.43 (1H, d, J = 8.71 Hz).

mass spectrum (ESI): m/z 422 (M+H)⁺.

(Example 44) cis(±)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylic acid

(Exemplified Compound No. 44)

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[0251]

(44a) Ethyl cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis(±)-4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidine-1-carboxylate obtained by the method described in Example (34a) (126.4 mg, 0.32 mmol), a 4 N hydrochloric acid/ethyl acetate solution (5 mL), diisopropylethylamine (0.22 mL, 1.26 mmol) and ethyl 2-bromo-1,3-benzothiazole-7-carboxylate obtained by the method described in Example (1f) (115 mg, 0.40 mmol), to obtain 127.4 mg of the title compound as a yellow oily substance (80%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.14 (3H, t, J = 7.48 Hz), 1.27 (3H, t, J = 7.79 Hz), 1.44 (3H, t, J = 7.15 Hz), 1.81-1.84 (1H, m), 2.10-2.16 (1H, m), 2.70 (2H, q, J = 7.48 Hz), 3.26-3.31 (2H, m), 3.43-3.50 (1H, m), 3.65 (1H, brs), 3.76-3.84 (1H, m), 4.25-4.31 (2H, m), 4.45 (2H, q, J = 7.15 Hz), 4.48-4.55 (1H, m), 7.35-7.37 (1H, m), 7.47 (1H, d, J = 8.71 Hz), 7.69 (1H, d, J = 7.34 Hz), 7.79 (1H, d, J = 6.88 Hz), 10.79 (1H, brs).

(44b) cis(±)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylic acid

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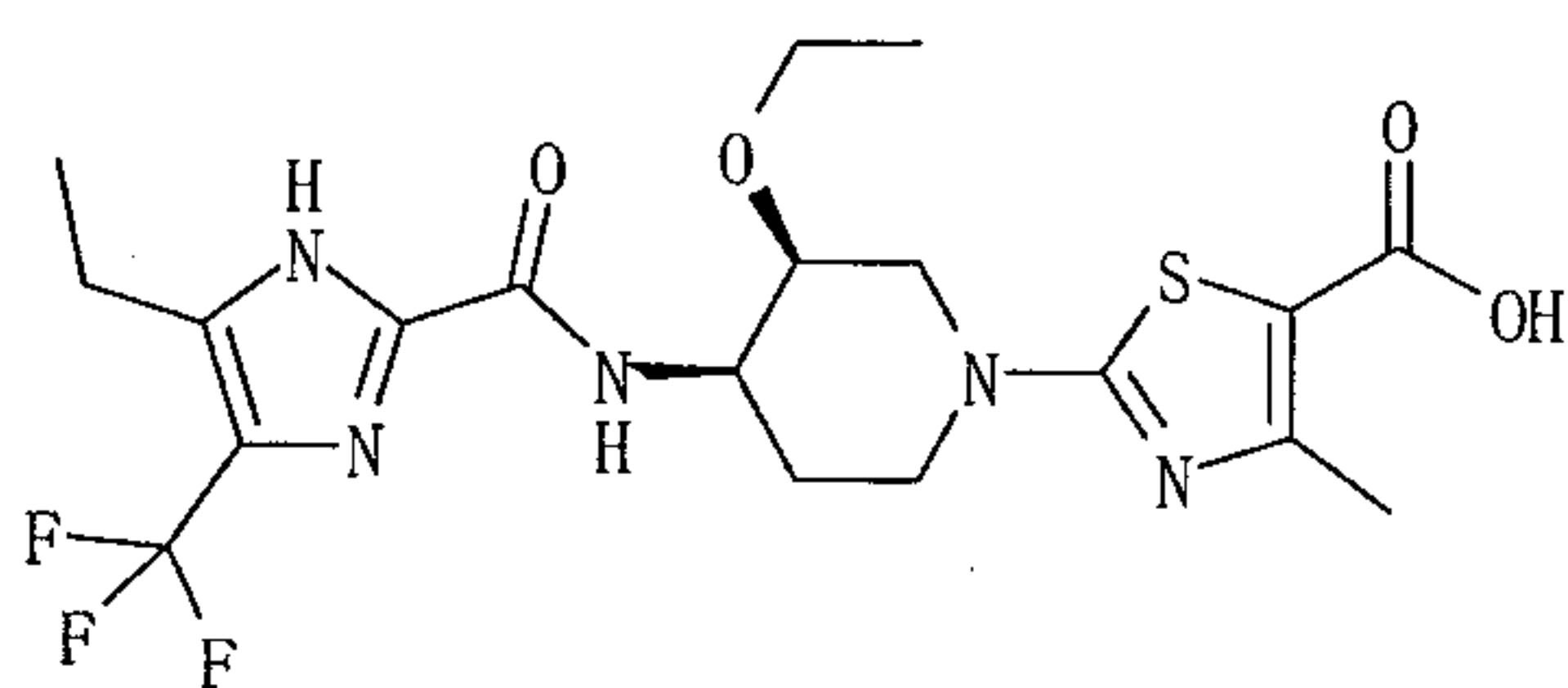
The same operation as in Example (1i) was performed using ethyl cis($\pm$)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylate obtained in Example (44a) (125 mg, 0.25 mmol) and a 2 N aqueous lithium hydroxide solution (2 mL), to obtain 104.6 mg of the title compound as a pale yellow solid (90%).

^1H NMR spectrum (400 MHz, DMSO- d_6) δ ppm: 1.03 (3H, t, J = 6.88 Hz), 1.14 (3H, t, J = 7.53 Hz), 1.71-1.73 (1H, m), 1.89-1.95 (1H, m), 2.55 (2H, q, J = 7.53 Hz), 3.25-3.51 (3H, m), 3.64-3.72 (3H, m), 4.16-4.28 (2H, m), 7.38-7.40 (1H, m), 7.64-7.66 (3H, m).

mass spectrum (ESI): m/z 478 ($M+H$) $^+$.

(Example 45) cis($\pm$)-2-(4-{[(5-Ethyl-4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 45)



[0252]

(45a) tert-Butyl cis($\pm$)-4-{[(5-ethyl-4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidine-1-carboxylate

The same operation as in Example (1g) was performed using tert-butyl cis($\pm$)-4-amino-3-ethoxypiperidine-1-carboxylate obtained in Example (112d) (178 mg, 0.73

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mmol), 5-ethyl-4-(trifluoromethyl)-1H-imidazole-2-carboxylic acid obtained by the method described in Example (39e) (100 mg, 0.48 mmol), WSC hydrochloride (280 mg, 1.46 mmol) and HOBt (66 mg, 0.49 mmol), to obtain 173.5 mg of the title compound as a white foamy substance (91%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.28 (3H, t, J = 7.57 Hz), 1.47 (9H, s), 1.63-1.66 (1H, m), 1.88-1.91 (1H, m), 2.73-2.86 (4H, m), 3.39-3.44 (2H, m), 3.77 (1H, br s), 4.19-4.37 (3H, m), 7.59 (1H, br s), 11.07 (1H, br s).

(45b) Ethyl cis(±)-2-(4-{[(5-ethyl-4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis(±)-4-{[(5-ethyl-4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidine-1-carboxylate obtained in Example (45a) (170 mg, 0.39 mmol), a 4 N hydrochloric acid/ethyl acetate solution (6 ml), diisopropylethylamine (0.27 mL, 1.55 mmol) and ethyl 2-bromo-4-methyl-1,3-thiazole-5-carboxylate (0.13 g, 0.52 mmol), to obtain 179.5 mg of the title compound as a yellow foamy substance (91%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.17 (3H, t, J = 6.88 Hz), 1.24-1.35 (6H, m), 1.78-1.81 (1H, m), 2.05-2.15 (1H, m), 2.54 (3H, s), 2.84 (2H, q, J = 7.49 Hz), 3.15-3.19 (2H, m), 3.42-3.46 (1H, m), 3.61 (1H, br s), 3.73-3.81 (1H, m), 4.02-4.05 (1H, m), 4.21-4.30 (3H, m), 4.42-4.45 (1H, m), 7.57 (1H, d, J = 8.71 Hz), 10.83 (1H, br s).

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(45c) cis($\pm$)-2-(4-{[(5-Ethyl-4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid

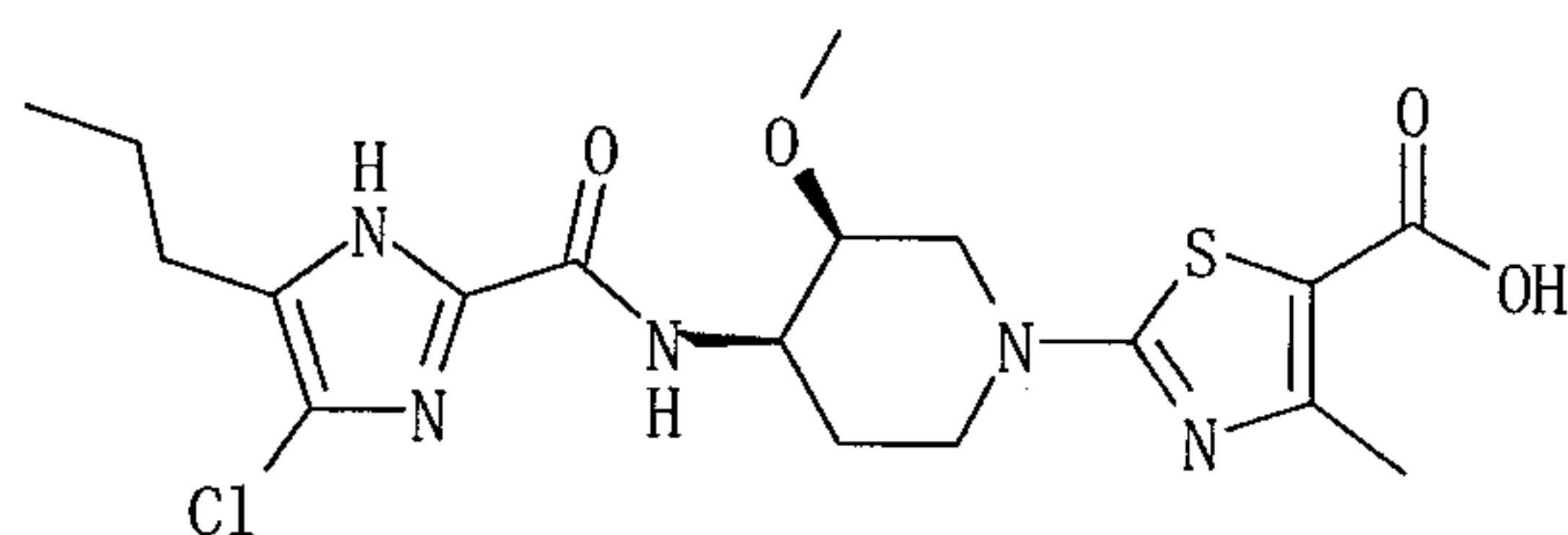
The same operation as in Example (36g) was performed using ethyl cis($\pm$)-2-(4-{[(5-ethyl-4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate obtained in Example (45b) (178 mg, 0.35 mmol) and a 1 N aqueous sodium hydroxide solution (3 mL), to obtain 19.6 mg of the title compound as a white solid (12%).

^1H NMR spectrum (400 MHz, DMSO- d_6) δ ppm: 1.05 (3H, t, J = 6.88 Hz), 1.16 (3H, t, J = 7.53 Hz), 1.68-1.70 (1H, m), 1.85-1.89 (1H, m), 2.40 (3H, s), 2.70 (2H, q, J = 7.53 Hz), 3.24-3.31 (2H, m), 3.41-3.45 (1H, m), 3.62-3.65 (2H, m), 3.96 (1H, br s), 4.19-4.21 (2H, m), 7.74 (1H, d, J = 8.71 Hz), 12.40 (1H, br s).

mass spectrum (ESI): m/z 476 ($M+H$) $^+$.

(Example 46) cis($\pm$)-2-(4-{[(4-Chloro-5-propyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 46)



[0253]

(46a) 1-Amino-pentan-2-one hydrochloride

The compound was synthesized according to the method described in the following document.

[0254]

Eur. J. Med. Chem., 1987, 22, 283-292

(46b) Ethyl 5-propyl-1H-imidazole-2-carboxylate

The same operation as in Example (1b) was performed using 1-amino-pentan-2-one hydrochloride obtained in Example (46a) (about 16.8 mmol) and ethyl imino(methylthio)acetate tetrafluoroborate obtained according to a method known in the literature (J. Med. Chem., 38, 1995, 2196-2201) (about 22.4 mmol), to obtain 2.61 g of the title compound as a brown foamy substance (86%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 0.97 (3H, t, J = 7.45 Hz), 1.42 (3H, t, J = 7.14 Hz), 1.59-1.74 (2H, m), 2.64 (2H, t, J = 7.45 Hz), 4.42 (2H, q, J = 7.14 Hz), 6.96 (1H, s), 10.13 (1H, br s).

(46c) Ethyl 4-chloro-5-propyl-1H-imidazole-2-carboxylate

The same operation as in Example (1c) was performed using ethyl 5-propyl-1H-imidazole-2-carboxylate obtained in Example (46b) (1.01 g, 5.54 mmol) and NCS (0.74 g, 5.50 mmol), to obtain 876 mg of the title compound as a white solid (73%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 0.97 (3H, t, J = 7.34 Hz), 1.42 (3H, t, J = 7.07 Hz), 1.66-1.70 (2H, m), 2.62-2.68 (2H, m), 4.42 (2H, q, J = 7.07 Hz), 10.23 (1H, br s).

(46d) 4-Chloro-5-propyl-1H-imidazole-2-carboxylic acid

The same operation as in Example (1d) was performed using ethyl 4-chloro-5-propyl-1H-imidazole-2-carboxylate

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obtained in Example (46c) (0.40 g, 1.85 mmol) and a 3 N aqueous lithium hydroxide solution (8 mL), to obtain 0.32 g of the title compound as a white solid (100%).

(46e) tert-Butyl cis(±)-4-{[(4-chloro-5-propyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate

The same operation as in Example (1g) was performed using tert-butyl cis(±)-4-amino-3-methoxypiperidine-1-carboxylate obtained by the method described in Example (1e) (0.39 g, 1.69 mmol), 4-chloro-5-propyl-1H-imidazole-2-carboxylic acid obtained in Example (46d) (0.16 g, 0.85 mmol), WSC hydrochloride (0.50 g, 2.58 mmol) and HOBt (0.12 g, 0.87 mmol), to obtain 0.32 g of the title compound as a white foamy substance (94%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 0.96 (3H, t, J = 7.34 Hz), 1.47 (9H, s), 1.62-1.72 (3H, m), 1.83-1.85 (1H, m), 2.63 (2H, t, J = 7.34 Hz), 2.73-2.78 (2H, m), 3.32-3.38 (1H, m), 3.41 (3H, s), 4.03-4.51 (3H, m), 7.41-7.50 (1H, m), 10.88 (1H, brs).

(46f) Ethyl cis(±)-2-(4-{[(4-chloro-5-propyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis(±)-4-{[(4-chloro-5-propyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate obtained in Example (46e) (160 mg, 0.40 mmol), a 4 N hydrochloric acid/ethyl acetate solution (6 mL), diisopropylethylamine (0.28 mL, 1.61 mmol) and ethyl 2-

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bromo-4-methyl-1,3-thiazole-5-carboxylate (145 mg, 0.58 mmol), to obtain 118.9 mg of the title compound as a yellow solid (63%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 0.96 (3H, t, J = 7.34 Hz), 1.33 (3H, t, J = 7.11 Hz), 1.65-1.69 (2H, m), 1.77-1.81 (1H, m), 2.00-2.06 (1H, m), 2.54 (3H, s), 2.64 (2H, t, J = 7.34 Hz), 3.08-3.12 (1H, m), 3.16-3.25 (1H, m), 3.43 (3H, s), 3.50 (1H, br s), 3.98-4.02 (1H, m), 4.24-4.27 (3H, m), 4.50-4.53 (1H, m), 7.45 (1H, d, J = 8.71 Hz), 10.71 (1H, br s).

(46g) cis(±)-2-(4-{[(4-Chloro-5-propyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid

The same operation as in Example (1i) was performed using ethyl cis(±)-2-(4-{[(4-chloro-5-propyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate obtained in Example (46f) (115 mg, 0.24 mmol) and a 2 N aqueous lithium hydroxide solution (3 mL), to obtain 104.6 mg of the title compound as a white solid (97%).

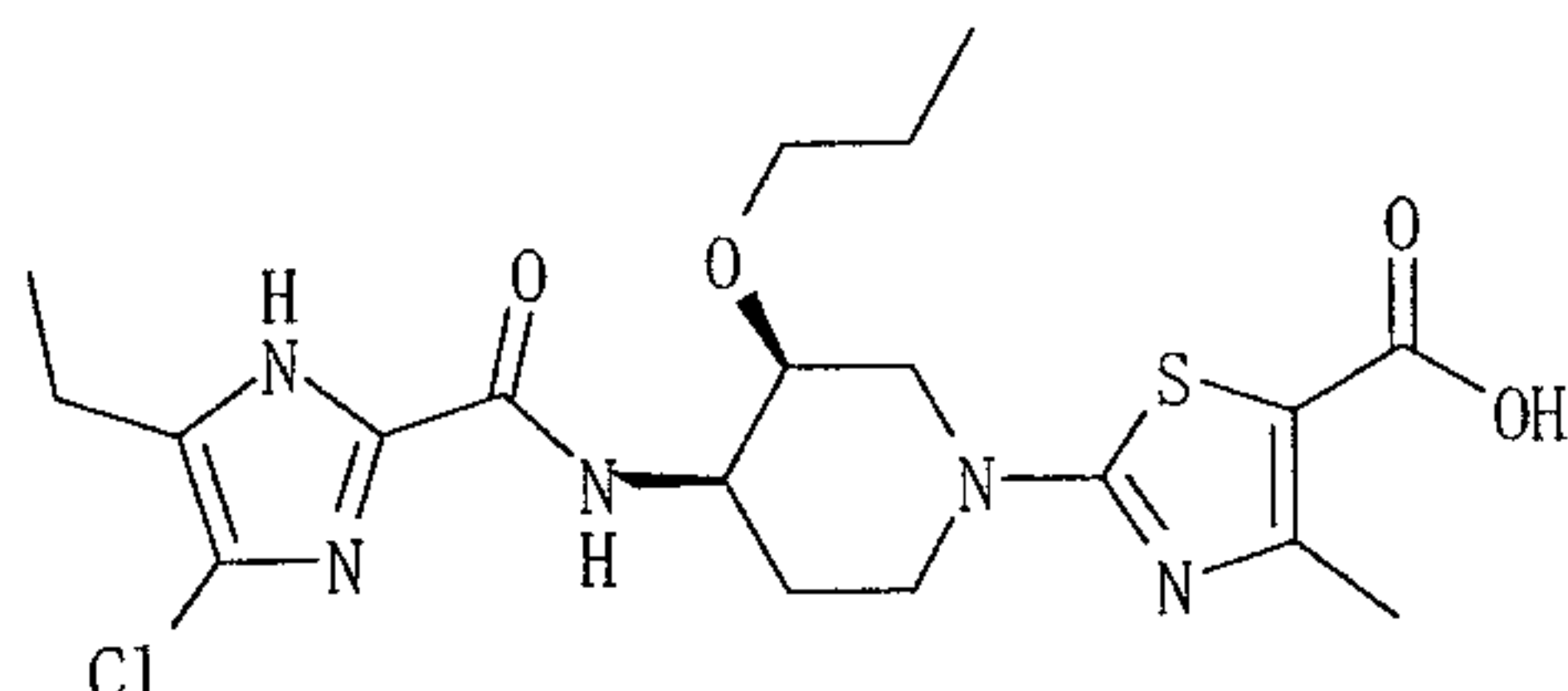
¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 0.84 (3H, t, J = 7.34 Hz), 1.56-1.60 (2H, m), 1.65-1.69 (1H, m), 1.80-1.99 (1H, m), 2.41 (3H, s), 2.50-2.53 (2H, m), 3.26-3.33 (2H, m), 3.34 (3H, s), 3.56 (1H, br s), 3.91-3.94 (1H, m), 4.20-4.23 (2H, m), 7.66 (1H, d, J = 8.25 Hz), 12.40 (1H, br s).

mass spectrum (ESI): m/z 442 (M+H)⁺.

(Example 47) cis(±)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-

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2-yl)carbonyl]amino}-3-propoxypiperidin-1-yl)-4-methyl-
1,3-thiazole-5-carboxylic acid
(Exemplified Compound No. 47)



[0255]

(47a) tert-Butyl cis(±)-4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-propoxypiperidine-1-carboxylate

The same operation as in Example (1g) was performed using tert-butyl cis(±)-4-amino-3-propoxypiperidine-1-carboxylate obtained by the method described in Example (113d) (125.5 mg, 0.49 mmol), 4-chloro-5-ethyl-1H-imidazole-2-carboxylic acid obtained by the method described in Example (1d) (74 mg, 0.42 mmol), WSC hydrochloride (235 mg, 1.23 mmol) and HOBT (56 mg, 0.41 mmol), to obtain 145.6 mg of the title compound as a white foamy substance (83%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.25-1.27 (6H, m), 1.47 (9H, s), 1.62-1.69 (1H, m), 1.86-1.88 (1H, m), 2.68 (3H, q, J = 7.49 Hz), 2.77-2.81 (1H, m), 3.24-3.30 (1H, m), 3.40-3.49 (1H, m), 3.60-3.71 (1H, m), 4.08-4.51 (3H, m), 7.48 (1H, br s), 11.25 (1H, brs).

(47b) Ethyl cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-propoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate

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The same operation as in Example (1h) was performed using tert-butyl cis($\pm$)-4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-propoxypiperidine-1-carboxylate obtained in Example (47a) (100 mg, 0.71 mmol), a 4 N hydrochloric acid/ethyl acetate solution (5 ml), diisopropylethylamine (0.2 mL, 1.15 mmol) and ethyl 2-bromo-4-methyl-1,3-thiazole-5-carboxylate (82 mg, 0.33 mmol), to obtain 92.0 mg of the title compound as a yellow foamy substance (79%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 0.87 (3H, t, J = 7.34 Hz), 1.27 (5H, t, J = 7.60 Hz), 1.33 (3H, t, J = 7.34 Hz), 1.49-1.61 (2H, m), 1.77-1.79 (1H, m), 2.01-2.13 (1H, m), 2.54 (3H, s), 2.69 (2H, q, J = 7.60 Hz), 3.09-3.13 (1H, m), 3.19-3.22 (1H, m), 3.31-3.34 (1H, m), 3.62-3.67 (2H, m), 3.99-4.02 (1H, m), 4.20-4.30 (3H, m), 4.44-4.47 (1H, m), 7.49 (1H, d, J = 8.71 Hz), 11.19 (1H, br s).

(47c) cis($\pm$)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-propoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid

The same operation as in Example (1i) was performed using ethyl cis($\pm$)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-propoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate obtained in Example (47b) (90 mg, 0.19 mmol) and a 2 N aqueous lithium hydroxide solution (3 mL), to obtain 28.2 mg of the title compound as a pale red solid (33%).

¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 0.81 (3H, t, J = 7.57 Hz), 1.14 (3H, t, J = 7.57 Hz), 1.42-1.46 (2H, m),

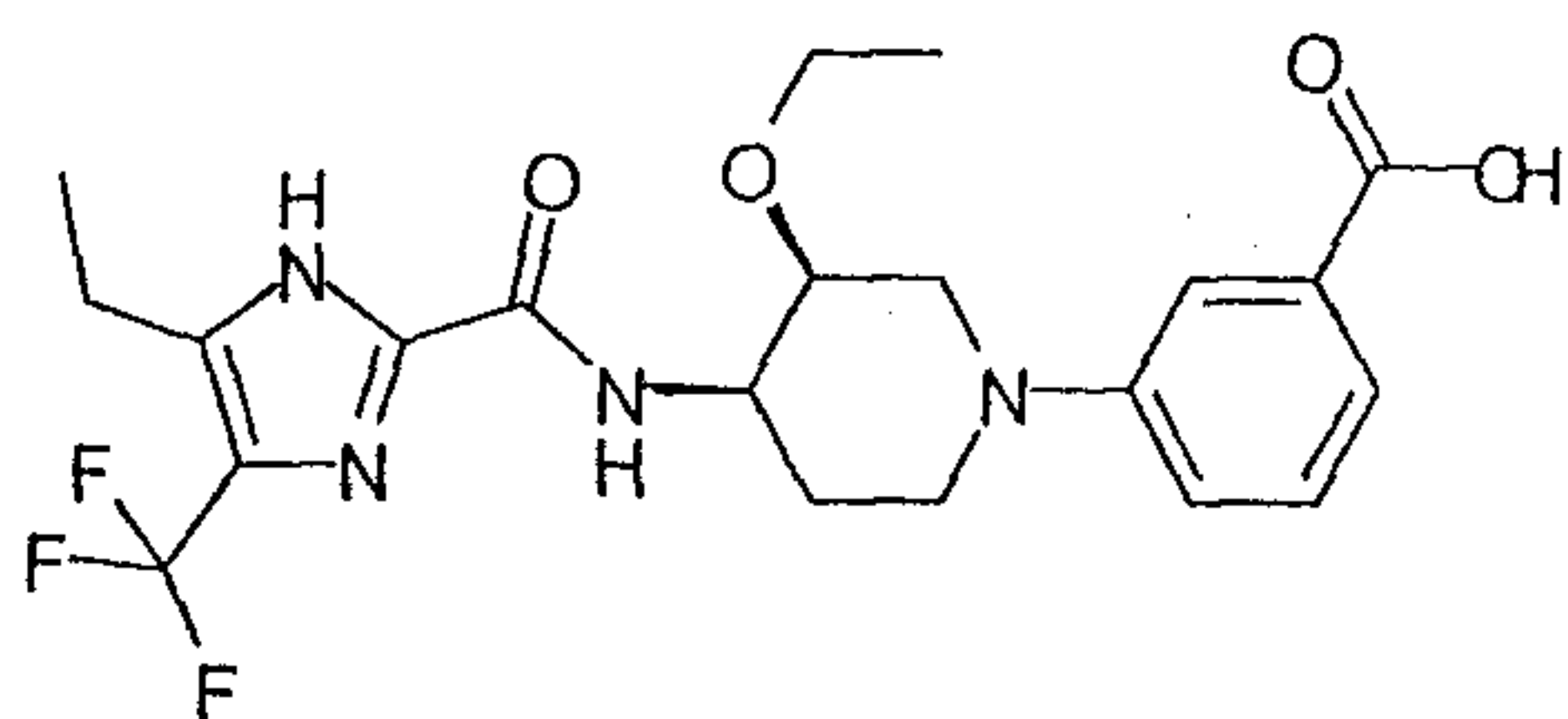
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1.67-1.68 (1H, m), 1.83-1.89 (1H, m), 2.40 (3H, s), 2.51-2.59 (2H, m), 3.23-3.35 (3H, m), 3.54-3.57 (1H, m), 3.64 (1H, brs), 3.91-3.93 (1H, m), 4.17-4.19 (2H, m), 7.63 (1H, d, $J = 8.25$ Hz), 12.39 (1H, br s).

mass spectrum (ESI): m/z 456 ($M+H$)⁺.

(Example 48) cis(±)-3-(4-{[(5-Ethyl-4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)benzoic acid

(Exemplified Compound No. 48)



[0256]

(48a) tert-Butyl cis(±)-4-{[(benzyloxy)carbonyl]amino}-3-ethoxypiperidine-1-carboxylate

The same operation as in Example (40a) was performed using tert-butyl cis(±)-4-amino-3-ethoxypiperidine-1-carboxylate obtained by the method described in Example (112d) (0.5 g, 2.05 mmol) and benzyl chloroformate (0.5 mL, 3.50 mmol), to obtain 0.73 g of the title compound as a colorless oily substance (93%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.15-1.16 (3H, m), 1.45 (9H, s), 1.61-1.77 (2H, m), 2.73-2.75 (2H, m), 3.32-3.45 (2H, m), 3.71-3.74 (2H, m), 4.09-4.28 (2H, m), 5.10 (2H, s), 5.23 (1H, br s), 7.32-7.38 (5H, m).

(48b) Benzyl cis(±)-(3-ethoxypiperidin-4-yl)-carbamate

The same operation as in Example (40b) was performed

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using tert-butyl cis($\pm$)-4-{[(benzyloxy)carbonyl]amino}-3-ethoxypiperidine-1-carboxylate obtained in Example (48a) (0.72 g, 1.90 mmol) and a 4 N hydrochloric acid/ethyl acetate solution (15 mL), to obtain the title compound. The resulting compound was used for the next reaction without purification.

[0257]

(48c) Methyl cis($\pm$)-3-(4-{[(benzyloxy)carbonyl]amino}-3-ethoxypiperidin-1-yl)benzoate

The same operation as in Example (42a) was performed using benzyl cis($\pm$)-(3-ethoxypiperidin-4-yl)-carbamate obtained in Example (48b) (about 1.90 mmol), palladium acetate (46 mg, 0.20 mmol), BINAP (240 mg, 0.39 mmol) and cesium carbonate (1.36 g, 4.17 mmol), to obtain 0.22 g of the title compound as a yellow oily substance (30%).

^1H NMR spectrum (400 MHz, CDCl_3) δ ppm: 1.15 (3H, t, J = 7.11 Hz), 1.83-1.87 (1H, m), 2.00-2.03 (1H, m), 2.92-2.95 (2H, m), 3.43-3.46 (1H, m), 3.59-3.72 (3H, m), 3.82-3.84 (2H, m), 3.90 (3H, s), 5.12 (2H, s), 5.21-5.29 (1H, m), 7.10 (1H, dd, J = 8.25, 1.83 Hz), 7.25-7.40 (6H, m), 7.46-7.51 (1H, m), 7.56-7.59 (1H, m).

(48d) tert-Butyl cis($\pm$)-3-(4-
{[(benzyloxy)carbonyl]amino}-3-ethoxypiperidin-1-yl)benzoate

The same operation as in Example (42b) was performed using methyl cis($\pm$)-3-(4-{[(benzyloxy)carbonyl]amino}-3-ethoxypiperidin-1-yl)benzoate obtained in Example (48c) (220 mg, 0.53 mmol) and a 1 N aqueous sodium hydroxide

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solution (4 mL). The resulting compound was used for the next reaction without purification.

[0258]

The same operation as in Example (42c) was performed using cis(±)-3-(4-{{(benzyloxy)carbonyl}amino}-3-ethoxypiperidin-1-yl)benzoic acid obtained by the above operation and N,N-dimethylformamide di-tert-butylacetal (1 mL), to obtain 102.2 mg of the title compound as a yellow oily substance (42%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.16 (3H, t, J = 6.88 Hz), 1.58 (9H, s), 1.83-1.87 (1H, m), 1.99-2.03 (1H, m), 2.90-2.93 (2H, m), 3.43-3.47 (1H, m), 3.56-3.60 (2H, m), 3.67-3.71 (1H, m), 3.79-3.82 (2H, m), 5.12 (2H, s), 5.25 (1H, d, J = 8.25 Hz), 7.04-7.10 (1H, m), 7.23-7.40 (6H, m), 7.43-7.45 (1H, m), 7.53-7.56 (1H, m).

(48e) tert-Butyl cis(±)-3-(4-amino-3-ethoxypiperidin-1-yl)benzoate

The same operation as in Example (40e) was performed using tert-butyl cis(±)-3-(4-{{(benzyloxy)carbonyl}amino}-3-ethoxypiperidin-1-yl)benzoate obtained in Example (48d) (100 mg, 0.22 mmol) and a 10% palladium-carbon catalyst (40 mg) to obtain the title compound. The resulting compound was used for the next reaction without purification.

[0259]

(48f) tert-Butyl cis(±)-3-(4-{{(5-Ethyl-4-trifluoromethyl-1H-imidazol-2-yl)carbonyl}amino}-3-ethoxypiperidin-1-yl)benzoate

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The same operation as in Example (1g) was performed using tert-butyl cis($\pm$)-3-(4-amino-3-ethoxypiperidin-1-yl)benzoate obtained in Example (48e) (about 0.22 mmol), 5-ethyl-4-(trifluoromethyl)-1H-imidazole-2-carboxylic acid obtained by the method described in Example (39e) (40 mg, 0.19 mmol), WSC hydrochloride (120 mg, 0.63 mmol) and HOBT (40 mg, 0.30 mmol), to obtain 81.0 mg of the title compound (83%).

^1H NMR spectrum (400 MHz, CDCl_3) δ ppm: 1.22 (3H, t, J = 6.88 Hz), 1.30 (3H, t, J = 7.53 Hz), 1.59 (9H, s), 1.85-1.89 (1H, m), 2.15-2.21 (1H, m), 2.85 (2H, q, J = 7.53 Hz), 2.93-2.97 (2H, m), 3.45-3.53 (1H, m), 3.70-3.74 (3H, m), 3.91-3.94 (1H, m), 4.18-4.25 (1H, m), 7.10 (1H, dd, J = 8.25, 2.75 Hz), 7.27-7.30 (1H, m), 7.46 (1H, d, J = 7.34 Hz), 7.58 (1H, s), 7.66 (1H, d, J = 8.71 Hz), 11.43 (1H, brs).

(48g) cis($\pm$)-3-(4-{[(5-Ethyl-4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)benzoic acid

The same operation as in Example (42f) was performed using tert-butyl cis($\pm$)-3-(4-{[(5-ethyl-4-trifluoromethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)benzoate obtained in Example (48f) (80 mg, 0.16 mmol) and trifluoroacetic acid (1 ml), to obtain 61.1 mg of the title compound (86%).

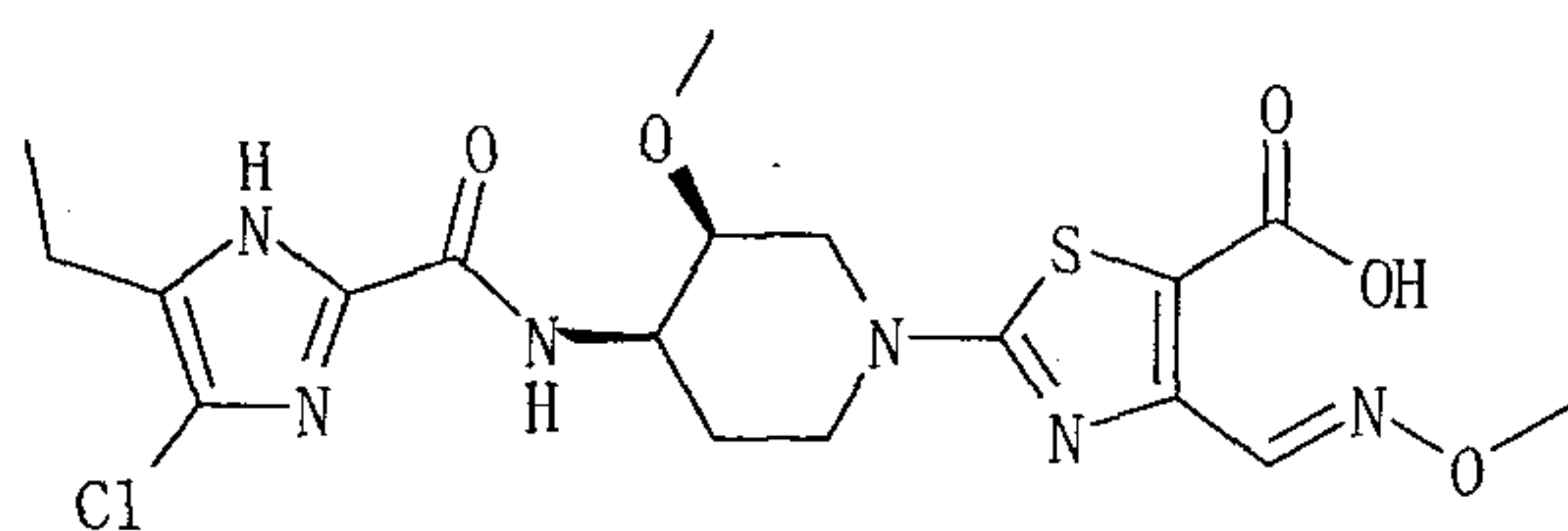
^1H NMR spectrum (400 MHz, $\text{DMSO}-d_6$) δ ppm: 1.04 (3H, t, J = 7.11 Hz), 1.16 (3H, t, J = 7.49 Hz), 1.72-1.74 (1H, m), 1.93-2.00 (1H, m), 2.70 (2H, q, J = 7.49 Hz), 2.96-2.99

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(2H, m), 3.41-3.48 (1H, m), 3.58-3.66 (3H, m), 3.92-3.95 (1H, m), 4.13-4.17 (1H, m), 7.19-7.24 (1H, m), 7.30-7.31 (2H, m), 7.45 (1H, s), 7.68 (1H, d, $J = 8.25$ Hz).

mass spectrum (ESI): m/z 455 ($M+H$)⁺.

(Example 49) *cis*(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(methoxyimino)methyl-1,3-thiazole-5-carboxylic acid
(Exemplified Compound No. 49)



[0260]

(49a) Ethyl *cis*(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(methoxyimino)methyl-1,3-thiazole-5-carboxylate

Ethyl *cis*(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-formyl-1,3-thiazole-5-carboxylate obtained by the method described in Example (28a) (100 mg, 0.21 mmol) was dissolved in pyridine (3 mL). Methoxyamine hydrochloride (28 mg, 0.34 mmol) was added, and the mixture was stirred at 60°C for two hours. The reaction solution was concentrated under reduced pressure, diluted with ethyl acetate, washed with 1 N hydrochloric acid and brine, and dried over anhydrous sodium sulfate. Following concentration under reduced pressure, the residue was purified by silica gel column chromatography (elution solvent: hexane/ethyl acetate = 4/1, ethyl acetate) to obtain 107 mg of the title

compound (100%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.27 (5H, t, J = 7.60 Hz), 1.35 (3H, t, J = 7.11 Hz), 1.76-1.83 (1H, m), 2.04-2.09 (3H, m), 2.69 (2H, q, J = 7.60 Hz), 3.17-3.27 (2H, m), 3.43 (3H, s), 3.52 (1H, brs), 4.03 (3H, s), 4.10-4.19 (1H, m), 4.21-4.35 (3H, m), 4.44-4.48 (1H, m), 7.47 (1H, d, J = 8.71 Hz), 8.82 (1H, s), 11.15 (1H, br s).

(49b) cis(±)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(methoxyimino)methyl-1,3-thiazole-5-carboxylic acid

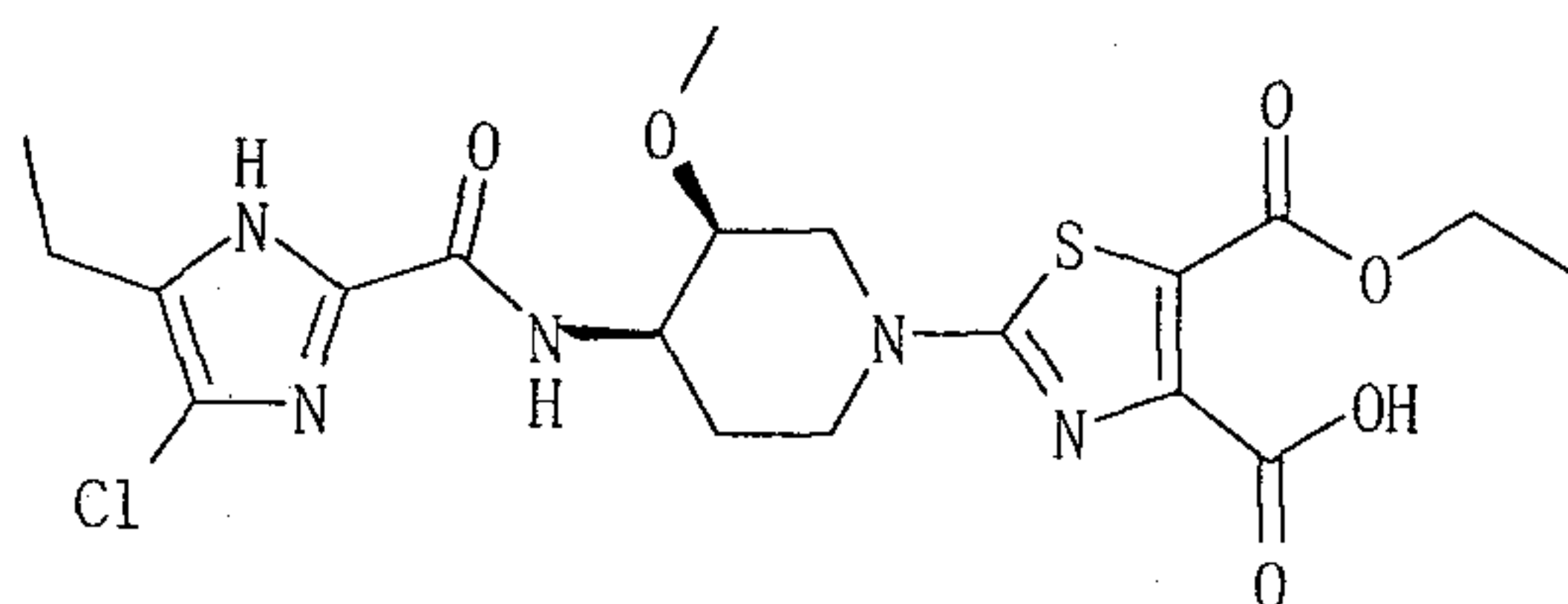
The same operation as in Example (1i) was performed using ethyl cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(methoxyimino)methyl-1,3-thiazole-5-carboxylate obtained in Example (49a) (107 mg, 0.21 mmol) and a 2 N aqueous lithium hydroxide solution (2.5 mL), to obtain 82.3 mg of the title compound as a pale yellow solid (83%).

¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 1.14 (3H, t, J = 7.60 Hz), 1.68-1.70 (1H, m), 1.83-1.93 (1H, m), 2.55 (2H, q, J = 7.60 Hz), 3.29-3.31 (2H, m), 3.35 (3H, s), 3.58 (1H, br s), 3.91 (3H, s), 3.97-4.11 (1H, m), 4.21-4.23 (2H, m), 7.69 (1H, d, J = 8.25 Hz), 8.68 (1H, s).

mass spectrum (ESI): m/z 471 (M+H)⁺.

(Example 50) cis(±)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-(ethoxycarbonyl)-1,3-thiazole-4-carboxylic acid

(Exemplified Compound No. 50)



[0261]

(50a) cis(±)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-(ethoxycarbonyl)-1,3-thiazole-4-carboxylic acid

The same operation as in Example (33c) was performed using ethyl cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-formyl-1,3-thiazole-5-carboxylate obtained by the method described in Example (28a) (400 mg, 0.85 mmol), sodium chlorite (158 mg, 1.75 mmol), sodium dihydrogenphosphate (410 mg, 2.63 mmol) and 2-methyl-2-butene (0.55 mL, 5.20 mmol), to obtain 439 mg of the title compound (100%).

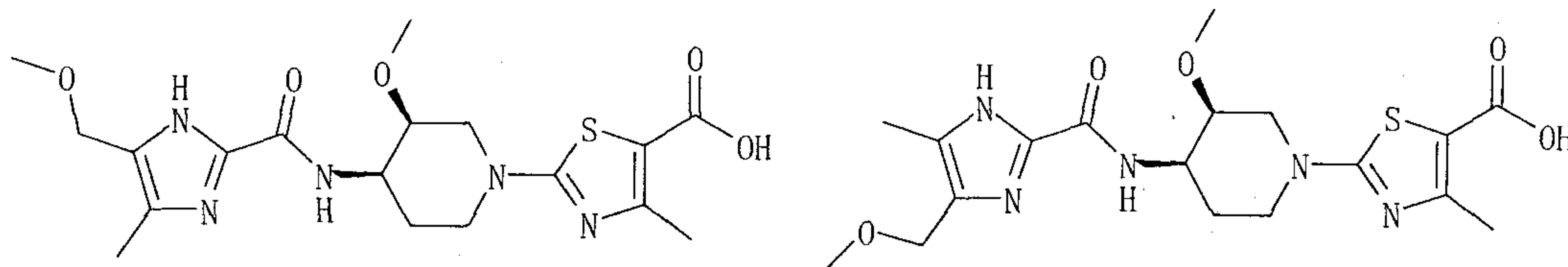
¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 1.14 (3H, t, J = 7.57 Hz), 1.22 (3H, t, J = 7.11 Hz), 1.62-1.70 (1H, m), 1.84-1.90 (1H, m), 2.51-2.58 (2H, m), 3.33 (3H, s), 3.34-3.40 (2H, m), 3.57 (1H, br s), 3.96-4.03 (1H, m), 4.14-4.36 (4H, m), 7.69 (1H, d, J = 8.71 Hz).

mass spectrum (ESI): m/z 486 (M+H)⁺

(Example 51) cis(±)-2-(4-{[(4-Methoxymethyl-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid and cis(±)-2-(4-{[(5-methoxymethyl-4-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid

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(Exemplified Compound No. 51)



[0262]

(51a) 4-([tert-Butyl(dimethyl)silyl]oxy)methyl-5-methyl-1H-imidazole

4-(Hydroxymethyl)-5-methyl-1H-imidazole (4 g, 26.9 mmol) was dissolved in DMF (80 mL). Triethylamine (13.5 mL, 96.9 mmol) and tert-butyl(dimethyl)silyl chloride (4.68 g, 31.0 mmol) were added, followed by stirring for three hours. Ethyl acetate was added to the reaction solution, and the organic layer was washed with brine and dried over anhydrous sodium sulfate. Following concentration under reduced pressure, the residue was purified by silica gel column chromatography (elution solvent: hexane/ethyl acetate = 4/1, dichloromethane/methanol = 92/8) to obtain 4.67 g of the title compound (77%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 0.08 (6H, s), 0.91 (9H, s), 2.23 (3H, s), 4.67 (2H, s), 7.48 (1H, s).

(51b) 4-([tert-Butyl(dimethyl)silyl]oxy)methyl-5-methyl-1-([2-(trimethylsilyl)ethoxy]methyl)-1H-imidazole and 5-([tert-butyl(dimethyl)silyl]oxy)methyl-4-methyl-1-([2-(trimethylsilyl)ethoxy]methyl)-1H-imidazole

4-([tert-Butyl(dimethyl)silyl]oxy)methyl-5-methyl-1H-imidazole obtained in Example (51a) obtained in

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Example (51a) (4.67 g, 20.6 mmol) was dissolved in THF (120 mL), followed by cooling to 0°C. Then, sodium hydride (1.5 g, 34.4 mmol) and [2-(trimethylsilyl)ethoxy]methyl chloride (5 mL, 28.3 mmol) were added, and the mixture was heated to room temperature and stirred for four hours. Brine was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. Following concentration under reduced pressure, the residue was purified by silica gel column chromatography (elution solvent: hexane/ethyl acetate = 9/1, 4/6) to obtain 2.57 g of the title compound as a yellow oily substance and as an about 3:2 mixture (35%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: -0.04 (9H, s), -0.02 (6x3/5H, s), 0.00-0.01 (2H, m), 0.07 (6x2/5H, s), 0.87 (9x3/5H, s), 0.89 (9x2/5H, s), 2.19 (3x3/5H, s), 2.26 (3x2/5H, s), 3.41-3.52 (2H, m), 4.63 (2x2/5H, s), 4.66 (2x3/5H, s), 5.15 (2x2/5H, s), 5.29 (2x3/5H, s), 7.40 (1x2/5H, s), 7.43 (1x3/5H, s).

(51c) Ethyl 4-([tert-butyl(dimethyl)silyl]oxy)methyl)-5-methyl-1-([2-(trimethylsilyl)ethoxy]methyl)-1H-imidazole-2-carboxylate and ethyl 5-([tert-butyl(dimethyl)silyl]oxy)methyl)-4-methyl-1-([2-(trimethylsilyl)ethoxy]methyl)-1H-imidazole-2-carboxylate

The same operation as in Example (4b) was performed using the mixture of 4-([tert-butyl(dimethyl)silyl]oxy)methyl)-5-methyl-1-([2-

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(trimethylsilyl)ethoxy)methyl}-1H-imidazole and 5-([tert-butyl(dimethyl)silyl]oxy)methyl)-4-methyl-1-([2-(trimethylsilyl)ethoxy)methyl]-1H-imidazole obtained in Example (51b) (2.57 g, 7.21 mmol), n-butyllithium (1.57 M solution in hexane, 5.5 mL, 8.64 mmol) and ethyl chloroformate (0.8 mL, 8.37 mmol), to obtain 1.95 g of the title compound as a yellow oily substance and as an about 1:1 mixture (63%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: -0.03 (9H, s), 0.02-0.04 (2H, m), 0.08 (6x1/2H, s), 0.08 (6x1/2H, s), 0.89 (9x1/2H, s), 0.90 (9x1/2H, s), 1.36-1.44 (3H, m), 2.27 (3x1/2H, s), 2.38 (3x1/2H, s), 3.50-3.64 (2H, m), 4.34-4.48 (2H, m), 4.73 (2H, s), 5.80 (2x1/2H, s), 5.92 (2x1/2H, s).

(51d) Ethyl 4-(hydroxymethyl)-5-methyl-1-([2-(trimethylsilyl)ethoxy)methyl]-1H-imidazole-2-carboxylate and ethyl 5-([tert-butyl(dimethyl)silyl]oxy)methyl)-4-methyl-1-([2-(trimethylsilyl)ethoxy)methyl]-1H-imidazole-2-carboxylate

The mixture of ethyl 4-([tert-butyl(dimethyl)silyl]oxy)methyl)-5-methyl-1-([2-(trimethylsilyl)ethoxy)methyl]-1H-imidazole-2-carboxylate and ethyl 5-([tert-butyl(dimethyl)silyl]oxy)methyl)-4-methyl-1-([2-(trimethylsilyl)ethoxy)methyl]-1H-imidazole-2-carboxylate obtained in Example (51c) (1.95 g, 4.54 mmol) was dissolved in THF (40 mL). Tetrabutylammonium fluoride (1.0 M solution in THF, 5 mL) was added, followed by stirring for one hour. Ethyl acetate was added to the reaction solution, and the organic layer was

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washed with brine and dried over anhydrous sodium sulfate. Following concentration under reduced pressure, the residue was purified by silica gel column chromatography (elution solvent: hexane/ethyl acetate = 4/1, 4/6, ethyl acetate) to obtain 517.4 mg of the title compound (36%) and 421.9 mg of the title compound (30%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: -0.02 (9H, s), 0.89-0.94 (2H, m), 1.43 (3H, t, J = 7.07 Hz), 2.32 (3H, s), 2.93 (1H, t, J = 6.08 Hz), 3.59-3.62 (2H, m), 4.43 (2H, q, J = 7.07 Hz), 4.64 (2H, d, J = 6.08 Hz), 5.96 (2H, s).

-0.03 (9H, s), 0.85-0.97 (3H, m), 1.43 (3H, t, J = 7.03 Hz), 2.36 (3H, s), 3.53-3.64 (2H, m), 4.43 (2H, q, J = 7.03 Hz), 4.60-4.65 (2H, m), 5.81 (2H, s).

(51e) Ethyl 4 (or 5)-(methoxymethyl)-5 (or 4)-methyl-1-
{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazole-2-
carboxylate

Ethyl 4 (or 5)-(hydroxymethyl)-5 (or 4)-methyl-1-
{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazole-2-
carboxylate obtained in Example (51d) (515 mg, 1.64 mmol)
was dissolved in DMF (12 mL), followed by cooling to 0°C.
Then, sodium hydride (1.5 g, 34.4 mmol) and iodomethane
(0.3 mL, 4.82 mmol) were added, and the mixture was
stirred for two hours. Brine was added to the reaction
solution, followed by extraction with ethyl acetate. The
organic layer was washed with brine and dried over
anhydrous sodium sulfate. Following concentration under
reduced pressure, the residue was purified by silica gel

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column chromatography (elution solvent: hexane/ethyl acetate = 1/1, ethyl acetate) to obtain 285.3 mg of the title compound as a yellow oily substance (53%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: -0.03 (9H, s), 0.85-0.95 (2H, m), 1.42 (3H, t, J = 7.14 Hz), 2.30 (3H, s), 3.33 (3H, s), 3.53-3.59 (2H, m), 4.42 (2H, q, J = 7.14 Hz), 4.52 (2H, s), 5.88 (2H, s).

(51f) Ethyl 4-(methoxymethyl)-5-methyl-1H-imidazole-2-carboxylate

Ethyl 4 (or 5)-(methoxymethyl)-5 (or 4)-methyl-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-imidazole-2-carboxylate obtained in Example (51e) (285 mg, 0.87 mmol) was dissolved in methanol (2 mL). A 4 N hydrochloric acid/ethyl acetate solution (5 mL) was added, and the mixture was stirred at 50°C for one hour. The reaction solution was concentrated under reduced pressure, and ethyl acetate was added, and the organic layer was washed with saturated aqueous sodium bicarbonate solution, and dried over anhydrous sodium sulfate. Following concentration under reduced pressure, the residue was purified by silica gel column chromatography (elution solvent: hexane/ethyl acetate = 4/1, 1/1, ethyl acetate) to obtain 145.6 mg of the title compound (53%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.40 (3H, t, J = 7.11 Hz), 2.36 (3H, s), 3.37 (3H, s), 4.35-4.52 (4H, m), 10.64 (1H, br s).

(51g) 4-(Methoxymethyl)-5-methyl-1H-imidazole-2-carboxylic acid

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The same operation as in Example (1d) was performed using ethyl 4-(methoxymethyl)-5-methyl-1H-imidazole-2-carboxylate obtained in Example (51f) (145.6 mg, 0.73 mmol) and a 2 N aqueous lithium hydroxide solution (2 mL), to obtain 109.9 mg of the title compound as a white solid (88%).

mass spectrum (ESI): m/z 171 (M+H)⁺.

(51h) tert-Butyl cis(±)-3-methoxy-4-{[(4-methoxymethyl-5-methyl-1H-imidazol-2-yl)carbonyl]amino}piperidine-1-carboxylate and tert-butyl cis(±)-3-methoxy-4-{[(5-methoxymethyl-4-methyl-1H-imidazol-2-yl)carbonyl]amino}piperidine-1-carboxylate

The same operation as in Example (1g) was performed using tert-butyl cis(±)-4-amino-3-methoxypiperidine-1-carboxylate obtained by the method described in Example (1e) (320 mg, 1.39 mmol), 4-(methoxymethyl)-5-methyl-1H-imidazole-2-carboxylic acid obtained in Example (51g) (109.9 mg, 0.65 mmol), WSC hydrochloride (0.38 g, 1.98 mmol) and HOBt (85 mg, 0.63 mmol), to obtain 283.1 mg of the title compound (100%).

mass spectrum (ESI): m/z 383 (M+H)⁺.

(51i) Ethyl cis(±)-2-(4-{[(4-methoxymethyl-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate and ethyl cis(±)-2-(4-{[(5-methoxymethyl-4-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate

The same operation as in Example (1h) was performed

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using the mixture of tert-butyl cis($\pm$)-3-methoxy-4-{[(4-methoxymethyl-5-methyl-1H-imidazol-2-yl)carbonyl]amino}piperidine-1-carboxylate and tert-butyl cis($\pm$)-3-methoxy-4-{[(5-methoxymethyl-4-methyl-1H-imidazol-2-yl)carbonyl]amino}piperidine-1-carboxylate obtained in Example (51h) (283 mg, 0.65 mmol), a 4 N hydrochloric acid/ethyl acetate solution (6 mL), diisopropylethylamine (0.8 mL, 4.60 mmol) and ethyl 2-bromo-4-methyl-1,3-thiazole-5-carboxylate (258 mg, 1.03 mmol), to obtain 278.9 mg of the title compound as a yellow foamy substance (96%).

^1H NMR spectrum (400 MHz, CDCl_3) δ ppm: 1.26-1.36 (3H, m), 1.78-1.81 (1H, m), 2.02-2.06 (1H, m), 2.33 (3H, s), 2.54 (3H, s), 3.33-3.36 (1H, m), 3.41-3.45 (6H, m), 3.52 (1H, br s), 3.96-4.04 (1H, m), 4.23-4.29 (3H, m), 4.36-4.39 (2H, m), 4.43-4.55 (2H, m), 7.45-7.56 (1H, m), 10.48-10.59 (1H, m).

(51j) cis($\pm$)-2-(4-{[(4-Methoxymethyl-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid and cis($\pm$)-2-(4-{[(5-methoxymethyl-4-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid

The same operation as in Example (1i) was performed using the mixture of ethyl cis($\pm$)-2-(4-{[(4-methoxymethyl-5-methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate and ethyl cis($\pm$)-2-(4-{[(5-methoxymethyl-4-

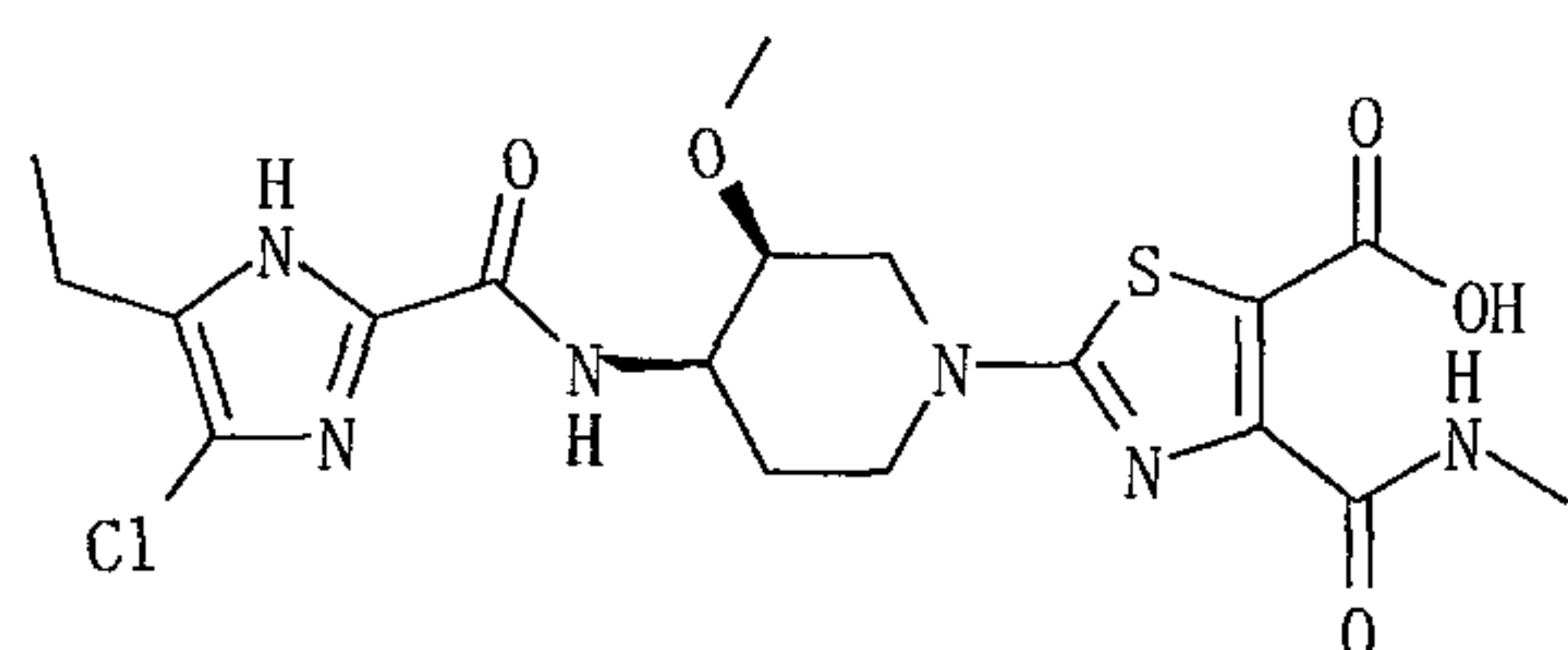
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methyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate obtained in Example (51i) (278 mg, 0.62 mmol) and a 2 N aqueous lithium hydroxide solution (4.5 mL), to obtain 191.4 mg of the title compound as a white solid and as an about 3:1 tautomer mixture (73%).

¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 1.62-1.67 (1H, m), 1.78-1.84 (1H, m), 2.13-2.22 (3H, m), 2.34 (3H, s), 3.06-3.11 (2H, m), 3.17-3.22 (3H, m), 3.34 (3H, s), 3.51 (1H, br s), 3.76-3.85 (1H, m), 4.13-4.16 (2H, m), 4.24 (2x3/4H, s), 4.32 (2x1/4H, s), 7.50-7.55 (1H, m).

mass spectrum (ESI): m/z 424 (M+H)⁺.

(Example 52) cis(±)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(methylcarbamoyl)-1,3-thiazole-5-carboxylic acid
(Exemplified Compound No. 52)



[0263]

(52a) Ethyl cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(methylcarbamoyl)-1,3-thiazole-5-carboxylate

The same operation as in Example (1g) was performed using cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-(ethoxycarbonyl)-1,3-thiazole-4-carboxylic acid obtained

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by the method described in Example (50a) (100 mg, 0.21 mmol), methylamine hydrochloride (35 mg, 0.52 mmol), WSC hydrochloride (120 mg, 0.63 mmol) and HOBT (28 mg, 0.21 mmol), to obtain 84.2 mg of the title compound as a white solid (82%).

¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 1.14 (3H, t, J = 7.60 Hz), 1.21 (3H, t, J = 7.11 Hz), 1.67-1.69 (1H, m), 1.82-1.88 (1H, m), 2.55 (2H, q, J = 7.60 Hz), 2.69 (3H, d, J = 4.58 Hz), 3.32-3.33 (2H, m), 3.33 (3H, s), 3.57 (1H, br s), 3.97-4.24 (4H, m), 7.67 (1H, d, J = 8.71 Hz), 8.32 (1H, q, J = 4.58 Hz).

(52b) cis(±)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(methylcarbamoyl)-1,3-thiazole-5-carboxylic acid

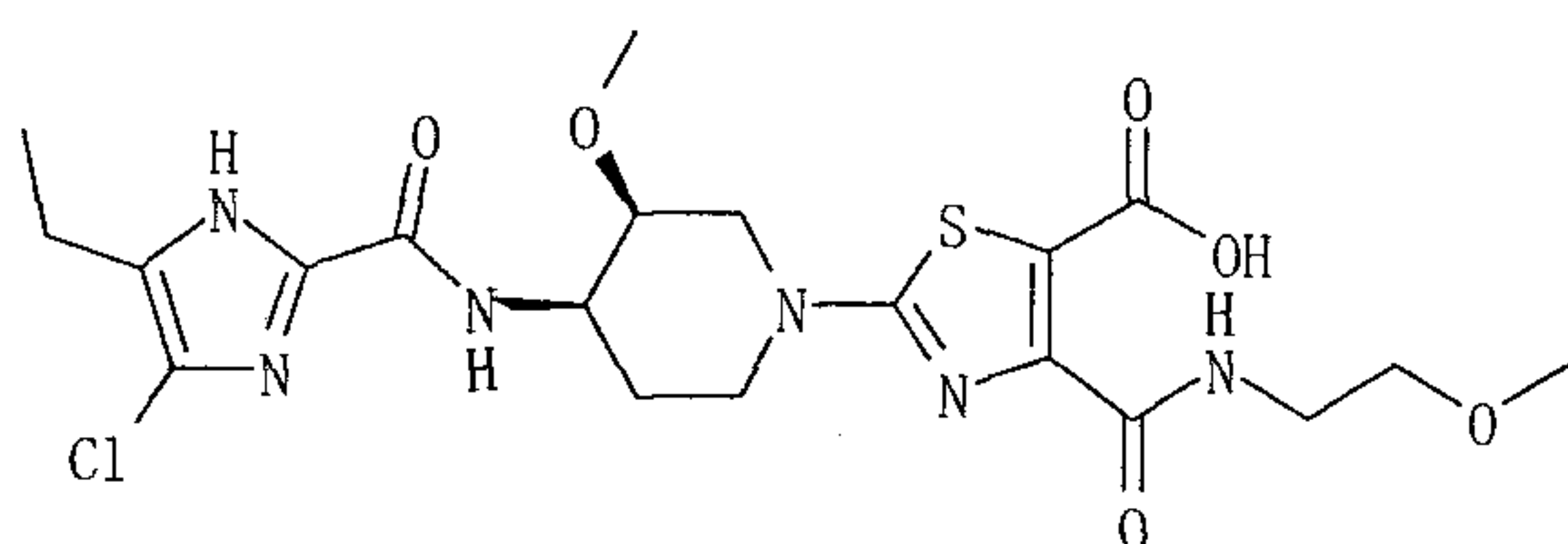
The same operation as in Example (1i) was performed using ethyl cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(methylcarbamoyl)-1,3-thiazole-5-carboxylate obtained in Example (52a) (82 mg, 0.16 mmol) and a 2 N aqueous lithium hydroxide solution (3 mL), to obtain 66.7 mg of the title compound as a pale yellow solid (86%). This compound is estimated to be an about 6:1 rotamer mixture according to NMR and HPLC.

¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 1.14 (3H, t, J = 7.11 Hz), 1.64-1.75 (1H, m), 1.83-1.96 (1H, m), 2.52-2.59 (2H, m), 2.75-2.91 (2H, m), 3.35 (3H, s), 3.36-3.42 (2H, m), 3.59 (1H, br s), 4.05-4.28 (3H, m), 7.65-7.73 (1H, m), 9.33-9.42 (1H, m).

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mass spectrum (ESI): m/z 471 ($M+H$)⁺.

(Example 53) *cis*(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-[(methoxyethyl)carbamoyl]-1,3-thiazole-5-carboxylic acid
(Exemplified Compound No. 53)



[0264]

(53a) Ethyl *cis*(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-[(methoxyethyl)carbamoyl]-1,3-thiazole-5-carboxylate

The same operation as in Example (1g) was performed using *cis*(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-(ethoxycarbonyl)-1,3-thiazole-4-carboxylic acid obtained by the method described in Example (50a) (120 mg, 0.25 mmol), methoxyethylamine (45 μ L, 0.52 mmol), WSC hydrochloride (120 mg, 0.63 mmol) and HOBt (35 mg, 0.26 mmol), to obtain 117.9 mg of the title compound as a white solid (88%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.26 (3H, t, J = 7.53 Hz), 1.34 (3H, t, J = 7.11 Hz), 1.79-1.81 (1H, m), 1.93-2.25 (1H, m), 2.69 (2H, q, J = 7.53 Hz), 3.12-3.15 (1H, m), 3.22-3.25 (1H, m), 3.39 (3H, s), 3.43 (3H, s), 3.52 (1H, br s), 3.60-3.64 (4H, m), 4.02-4.05 (1H, m), 4.22-4.34 (3H, m), 4.54-4.57 (1H, m), 7.47 (1H, d, J =

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8.71 Hz), 8.46 (1H, br s), 11.30 (1H, br s).

(53b) cis(±)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-[(methoxyethyl)carbamoyl]-1,3-thiazole-5-carboxylic acid

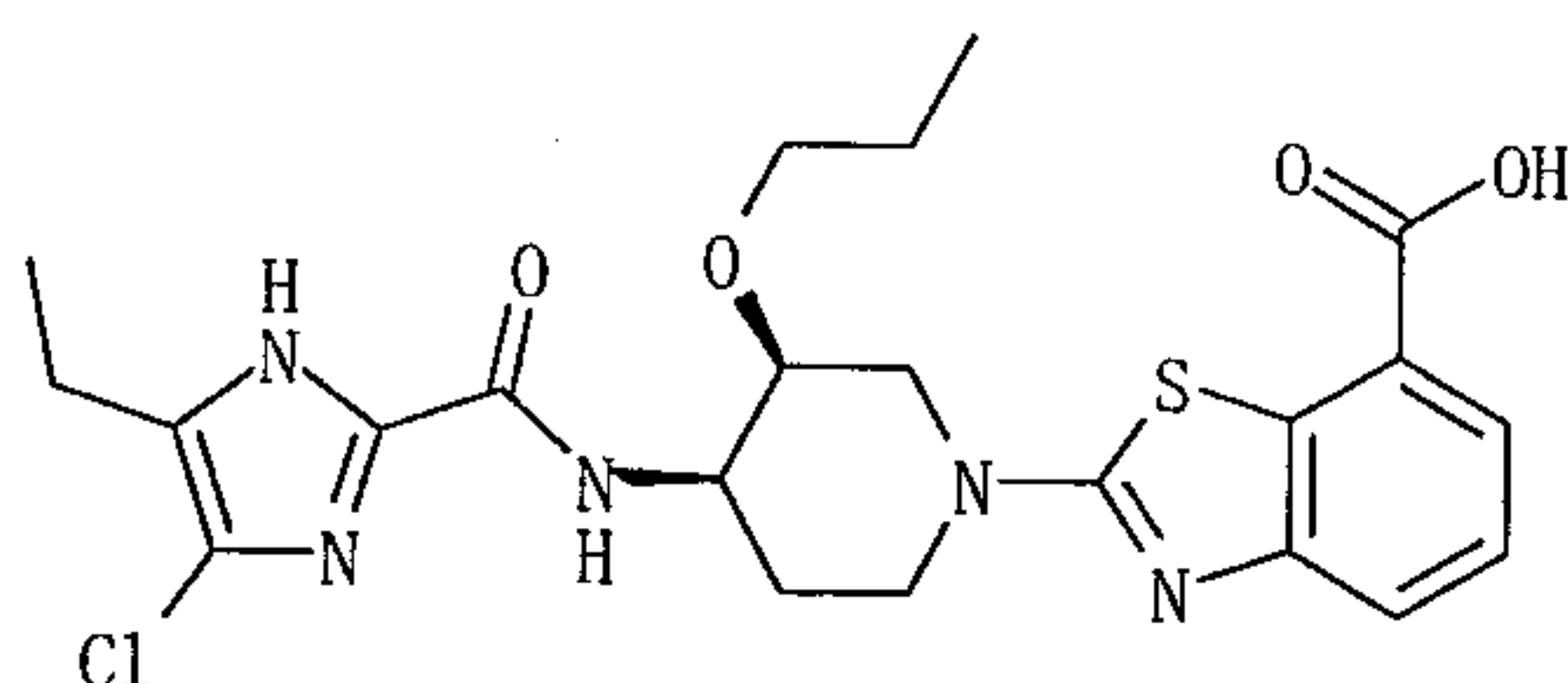
The same operation as in Example (1i) was performed using ethyl cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-[(methoxyethyl)carbamoyl]-1,3-thiazole-5-carboxylate obtained in Example (53a) (115 mg, 0.21 mmol) and a 2 N aqueous lithium hydroxide solution (2.5 mL), to obtain 60.9 mg of the title compound as a pale yellow solid (56%).

¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 1.14 (3H, t, J = 7.57 Hz), 1.66-1.75 (1H, m), 1.83-1.96 (1H, m), 2.52-2.60 (2H, m), 3.26 (3H, s), 3.30-3.40 (4H, m), 3.36 (3H, s), 3.49-3.51 (4H, m), 3.59 (1H, br s), 4.22-4.24 (1H, m), 7.70 (1H, d, J = 8.25 Hz), 9.36 (1H, br s).

mass spectrum (ESI): m/z 516 (M+H)⁺.

(Example 54) cis(±)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-propoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylic acid

(Exemplified Compound No. 54)



[0265]

(54a) Ethyl cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-

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2-yl)carbonyl]amino}-3-propoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis($\pm$)-4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-propoxypiperidine-1-carboxylate obtained by the method described in Example (47a) (208.6 mg, 0.50 mmol), a 4 N hydrochloric acid/ethyl acetate solution (5 mL), diisopropylethylamine (0.35 mL, 2.01 mmol) and ethyl 2-bromo-1,3-benzothiazole-7-carboxylate obtained by the method described in Example (1f) (200 mg, 0.70 mmol), to obtain 199.6 mg of the title compound as a yellow oily substance (76%).

^1H NMR spectrum (400 MHz, CDCl_3) δ ppm: 0.82 (3H, t, J = 7.34 Hz), 1.27 (3H, t, J = 7.57 Hz), 1.44 (3H, t, J = 7.11 Hz), 1.51-1.57 (2H, m), 1.82-1.85 (1H, m), 2.11-2.17 (1H, m), 2.70 (2H, q, J = 7.64 Hz), 3.24-3.38 (3H, m), 3.64 (1H, br s), 3.67-3.75 (1H, m), 4.23-4.33 (2H, m), 4.45 (2H, q, J = 7.18 Hz), 4.53-4.56 (1H, m), 7.35-7.37 (1H, m), 7.49 (1H, d, J = 8.71 Hz), 7.69 (1H, d, J = 7.79 Hz), 7.79 (1H, d, J = 7.79 Hz), 10.83 (1H, br s).

(54b) cis($\pm$)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-propoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylic acid

The same operation as in Example (1i) was performed using ethyl cis($\pm$)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-propoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylate obtained in Example (54a) (198 mg, 0.38 mmol) and a 2 N aqueous lithium hydroxide

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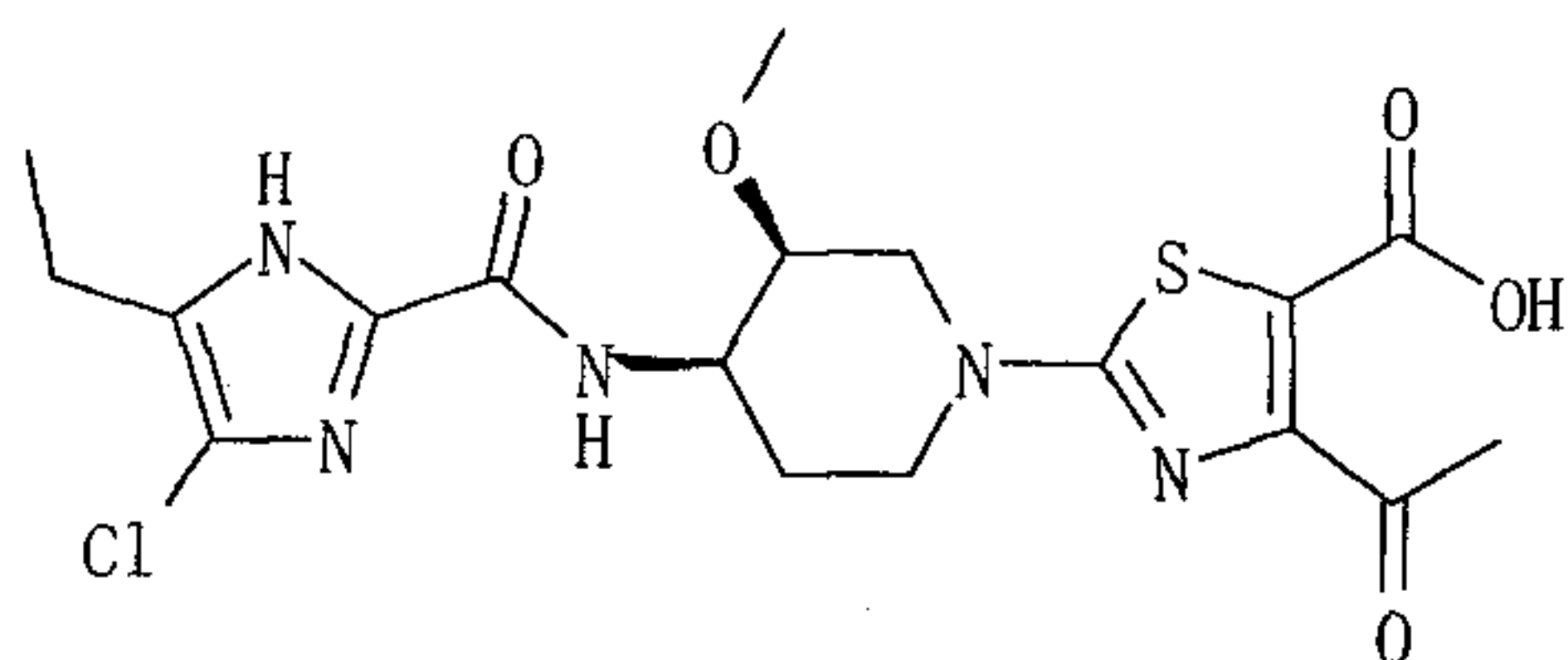
solution (4 mL), to obtain 162.5 mg of the title compound as a pale yellow solid (87%).

^1H NMR spectrum (400 MHz, DMSO-d_6) δ ppm: 0.76 (3H, t, $J = 7.34$ Hz), 1.14 (3H, t, $J = 7.57$ Hz), 1.40-1.43 (2H, m), 1.71-1.73 (1H, m), 1.89-1.95 (1H, m), 2.52-2.59 (2H, m), 3.35-3.40 (3H, m), 3.58-3.68 (2H, m), 4.19-4.26 (3H, m), 7.35-7.37 (1H, m), 7.61-7.65 (3H, m).

mass spectrum (ESI): m/z 493 ($\text{M}+\text{H}$) $^+$.

(Example 55) cis($\pm$)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-acetyl-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 55)



[0266]

(55a) Methyl 4-acetyl-2-chloro-1,3-thiazole-5-carboxylate

The compound was synthesized according to the method described in the following document.

[0267]

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(55b) Methyl cis($\pm$)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-acetyl-1,3-thiazole-5-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis($\pm$)-4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-

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carboxylate obtained by the method described in Example (1g) (142 mg, 0.37 mmol), a 4 N hydrochloric acid/ethyl acetate solution (6 mL), diisopropylethylamine (0.25 mL, 1.44 mmol) and methyl 4-acetyl-2-chloro-1,3-thiazole-5-carboxylate obtained in Example (55a) (110 mg, 0.50 mmol), to obtain 165.5 mg of the title compound as a yellow foamy substance (96%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.27 (3H, t, J = 7.60 Hz), 1.80-1.82 (1H, m), 2.01-2.05 (1H, m), 2.55 (3H, s), 2.69 (2H, q, J = 7.60 Hz), 3.11-3.14 (1H, m), 3.23-3.26 (1H, m), 3.43 (3H, s), 3.52 (1H, br s), 3.81 (3H, s), 3.96-3.99 (1H, m), 4.25-4.27 (1H, m), 4.53-4.57 (1H, m), 7.45 (1H, d, J = 9.17 Hz), 10.82 (1H, br s).

(55c) cis(±)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-acetyl-1,3-thiazole-5-carboxylic acid

The same operation as in Example (1i) was performed using methyl cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-acetyl-1,3-thiazole-5-carboxylate obtained in Example (55b) (165 mg, 0.35 mmol) and a 2 N aqueous lithium hydroxide solution (3 mL), to obtain 141.9 mg of the title compound as a yellow solid (89%).

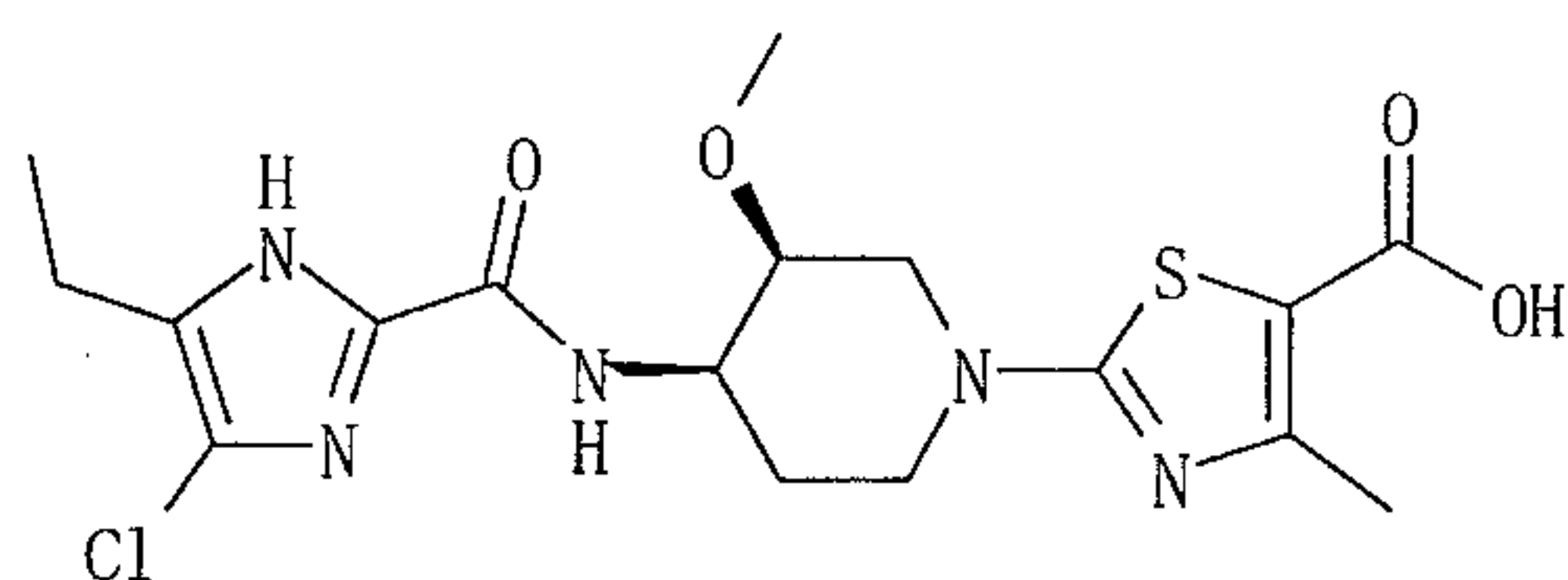
¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 1.14 (3H, t, J = 7.53 Hz), 1.68-1.71 (1H, m), 1.85-1.89 (1H, m), 2.49 (3H, s), 2.55 (2H, q, J = 7.53 Hz), 3.34 (3H, s), 3.36-3.39 (2H, m), 3.58 (1H, br s), 3.90-3.92 (1H, m), 4.22-4.25 (2H, m), 7.67 (1H, d, J = 8.25 Hz).

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mass spectrum (ESI): m/z 456 (M+H)⁺.

(Example 56) 2-[(3S,4R)-4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl]-4-methyl-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 56)



[0268]

(56a) tert-Butyl (3S,4R)-4-amino-3-methoxypiperidine-1-carboxylate

The compound was synthesized according to the method described in the following document.

[0269]

WO 2006/087543 A1

(56b) tert-Butyl (3S,4R)-4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate

The same operation as in Example (1g) was performed using tert-butyl (3S,4R)-4-amino-3-methoxypiperidine-1-carboxylate obtained in Example (56a) (224.4 mg, 0.96 mmol), 4-chloro-5-ethyl-1H-imidazole-2-carboxylic acid synthesized by the method described in Example (1d) (140 mg, 0.80 mmol), WSC hydrochloride (440 mg, 2.29 mmol) and HOBT (110 mg, 0.81 mmol), to obtain 222.4 mg of the title compound as a white solid (72%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.26 (3H, t, J = 7.57 Hz), 1.47 (9H, s), 1.61-1.69 (1H, m), 1.79-1.91 (1H,

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m), 2.68 (2H, q, J = 7.57 Hz), 2.72-2.89 (1H, m), 3.32-3.39 (2H, m), 3.41 (3H, s), 4.19-4.35 (3H, m), 7.45 (1H, br s), 10.90 (1H, br s).

(56c) Ethyl 2-[(3S,4R)-4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl]-4-methyl-1,3-thiazole-5-carboxylate

The same operation as in Example (1h) was performed using tert-butyl (3S,4R)-4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate obtained in Example (56b) (210 mg, 0.54 mmol), a 4 N hydrochloric acid/ethyl acetate solution (6 mL), diisopropylethylamine (0.4 mL, 2.87 mmol) and ethyl 2-bromo-4-methyl-1,3-thiazole-5-carboxylate (203 mg, 0.81 mmol), to obtain 228.4 mg of the title compound as a pale yellow foamy substance (92%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.27 (5H, t, J = 7.60 Hz), 1.33 (3H, t, J = 7.11 Hz), 1.78-1.80 (1H, m), 2.01-2.07 (1H, m), 2.54 (3H, s), 2.70 (2H, q, J = 7.60 Hz), 3.08-3.11 (1H, m), 3.15-3.24 (1H, m), 3.42 (3H, s), 3.51 (1H, br s), 4.00-4.03 (1H, m), 4.21-4.32 (3H, m), 4.50-4.53 (1H, m), 7.51 (1H, d, J = 8.71 Hz), 11.39 (1H, br s).

(56d) 2-[(3S,4R)-4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl]-4-methyl-1,3-thiazole-5-carboxylic acid

The same operation as in Example (1i) was performed using ethyl 2-[(3S,4R)-4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl]-4-methyl-

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1,3-thiazole-5-carboxylate obtained in Example (56c) (225 mg, 0.49 mmol) and a 2 N aqueous lithium hydroxide solution (3.5 mL), to obtain 156.7 mg of the title compound as a pale red solid (74%).

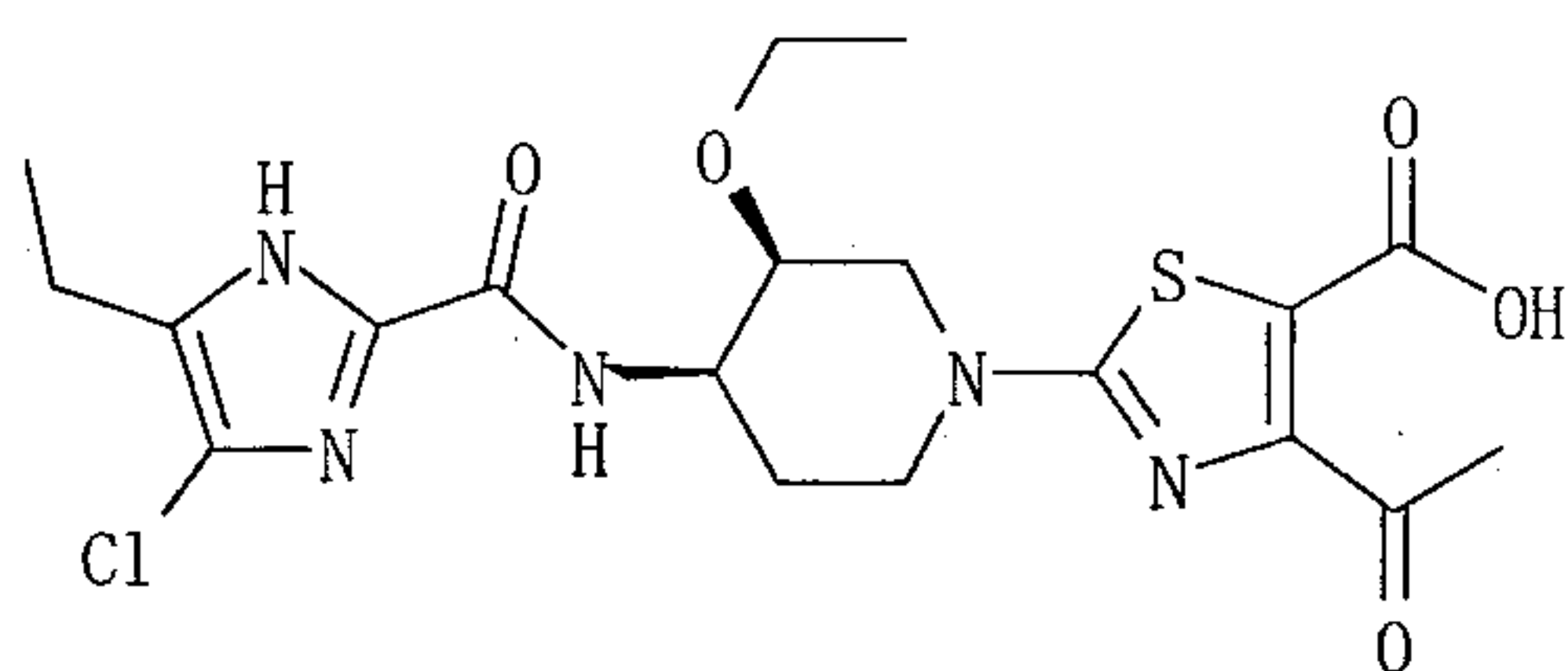
^1H NMR spectrum (400 MHz, DMSO- d_6) δ ppm: 1.14 (3H, t, J = 7.60 Hz), 1.65-1.69 (1H, m), 1.82-1.88 (1H, m), 2.41 (3H, s), 2.55 (2H, q, J = 7.60 Hz), 3.23-3.33 (2H, m), 3.34 (3H, s), 3.56 (1H, br s), 3.91-3.94 (1H, m), 4.20-4.23 (2H, m), 7.66 (1H, d, J = 8.25 Hz), 12.40 (1H, br s).

mass spectrum (FAB): m/z 428 ($M+H$) $^+$.

$[\alpha]_D^{24}$: +38.1 (c = 0.1185, THF/ H_2O = 5/1)

(Example 57) cis($\pm$)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-4-acetyl-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 57)



[0270]

(57a) Methyl cis($\pm$)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-4-acetyl-1,3-thiazole-5-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis($\pm$)-4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidine-1-carboxylate obtained by the method described in Example (34a) (200 mg, 0.50 mmol), a 4 N hydrochloric acid/ethyl

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acetate solution (3 mL), diisopropylethylamine (0.35 mL, 2.01 mmol) and methyl 4-acetyl-2-chloro-1,3-thiazole-5-carboxylate obtained by the method described in Example (55a) (100 mg, 0.46 mmol), to obtain 192.5 mg of the title compound as a yellow foamy substance (87%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.17 (3H, t, J = 6.88 Hz), 1.27 (3H, t, J = 7.57 Hz), 1.78-1.81 (1H, m), 2.05-2.09 (1H, m), 2.55 (3H, s), 2.69 (2H, q, J = 7.64 Hz), 3.13-3.17 (1H, m), 3.21-3.28 (1H, m), 3.44 (1H, m), 3.62 (1H, br s), 3.72-3.76 (1H, m), 3.81 (3H, s), 3.99-4.02 (1H, m), 4.23-4.27 (1H, m), 4.43-4.47 (1H, m), 7.44 (1H, d, J = 8.71 Hz), 10.74 (1H, br s).

(57b) cis(±)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-4-acetyl-1,3-thiazole-5-carboxylic acid

The same operation as in Example (1i) was performed using methyl cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-4-acetyl-1,3-thiazole-5-carboxylate obtained in Example (57a) (190 mg, 0.39 mmol) and a 2 N aqueous lithium hydroxide solution (3.5 mL), to obtain 154.3 mg of the title compound as a yellow solid (86%).

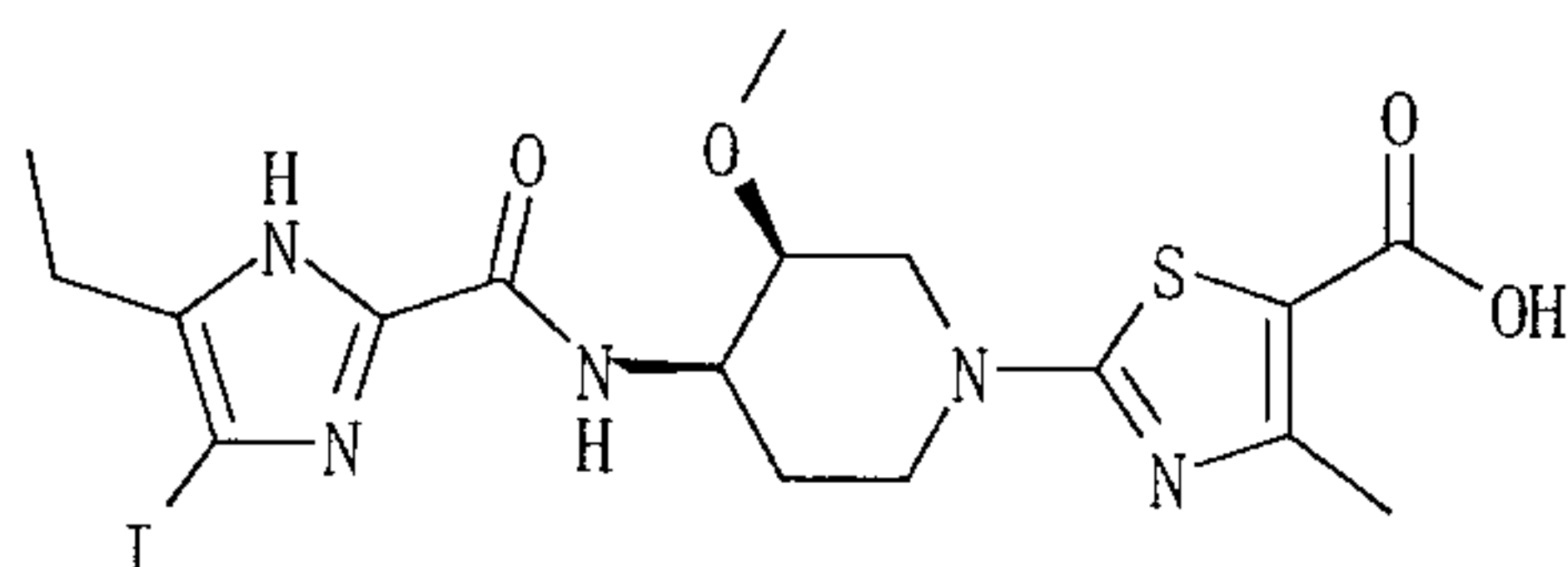
¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 1.05 (3H, t, J = 6.88 Hz), 1.14 (3H, t, J = 7.57 Hz), 1.67-1.70 (1H, m), 1.84-1.91 (1H, m), 2.48 (3H, s), 2.52-2.58 (2H, m), 3.30-3.48 (3H, m), 3.63-3.65 (2H, m), 3.96 (1H, br s), 4.18-4.22 (2H, m), 7.66 (1H, d, J = 8.71 Hz).

mass spectrum (ESI): m/z 470 (M+H)⁺.

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(Example 58) cis($\pm$)-2-(4-{[(5-Ethyl-4-iodo-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 58)



[0271]

(58a) Ethyl 5-ethyl-4-iodo-1H-imidazole-2-carboxylate

The same operation as in Example (1c) was performed using ethyl 5-ethyl-1H-imidazole-2-carboxylate obtained by the method described in Example (1b) (0.20 g, 1.19 mmol) and NIS (0.29 g, 1.31 mmol), to obtain 0.35 g of the title compound as a pale yellow solid (100%).

^1H NMR spectrum (400 MHz, CDCl_3) δ ppm: 1.27 (3H, t, J = 7.60 Hz), 1.41 (3H, t, J = 7.14 Hz), 2.68 (2H, q, J = 7.60 Hz), 4.43 (2H, q, J = 7.14 Hz), 10.44 (1H, br s).

(58b) 5-Ethyl-4-iodo-1H-imidazole-2-carboxylic acid

The same operation as in Example (1d) was performed using ethyl 5-ethyl-4-iodo-1H-imidazole-2-carboxylate obtained in Example (58a) (230 mg, 0.78 mmol) and a 3 N aqueous lithium hydroxide solution (2.5 mL), to obtain 187.7 mg of the title compound as a white solid (90%).
mass spectrum (ESI): m/z 267 ($\text{M}+\text{H}$) $^+$.

(58c) tert-Butyl cis($\pm$)-4-{[(5-ethyl-4-iodo-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate

The same operation as in Example (1g) was performed using tert-butyl cis($\pm$)-4-amino-3-methoxypiperidine-1-

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carboxylate obtained by the method described in Example (1e) (130 mg, 0.56 mmol), 5-ethyl-4-iodo-1H-imidazole-2-carboxylic acid obtained in Example (58b) (95 mg, 0.36 mmol), WSC hydrochloride (220 mg, 1.15 mmol) and HOBt (46 mg, 0.34 mmol), to obtain 146.2 mg of the title compound as a white solid (86%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.24 (5H, t, J = 7.57 Hz), 1.48 (9H, s), 1.58-1.73 (1H, m), 1.86-1.87 (1H, m), 2.51-2.81 (4H, m), 3.39-3.42 (4H, m), 3.93-4.52 (3H, m), 7.51-7.61 (1H, m), 11.77 (1H, br s).

(58d) Ethyl cis(±)-2-(4-{[(5-ethyl-4-iodo-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis(±)-4-{[(5-ethyl-4-iodo-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate obtained in Example (58c) (145 mg, 0.30 mmol), a 4 N hydrochloric acid/ethyl acetate solution (4 ml), diisopropylethylamine (0.21 mL, 1.21 mmol) and ethyl 2-bromo-4-methyl-1,3-thiazole-5-carboxylate (113 mg, 0.45 mmol), to obtain 133 mg of the title compound (80%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.25 (3H, t, J = 7.69 Hz), 1.33 (3H, t, J = 7.16 Hz), 1.75-1.83 (1H, m), 2.03-2.08 (1H, m), 2.54 (3H, s), 2.67 (2H, q, J = 7.69 Hz), 3.06-3.10 (1H, m), 3.17-3.20 (1H, m), 3.42 (3H, s), 3.51 (1H, br s), 4.00-4.03 (1H, m), 4.22-4.31 (3H, m), 4.50-4.53 (1H, m), 7.58 (1H, d, J = 9.16 Hz), 11.69 (1H, br s).

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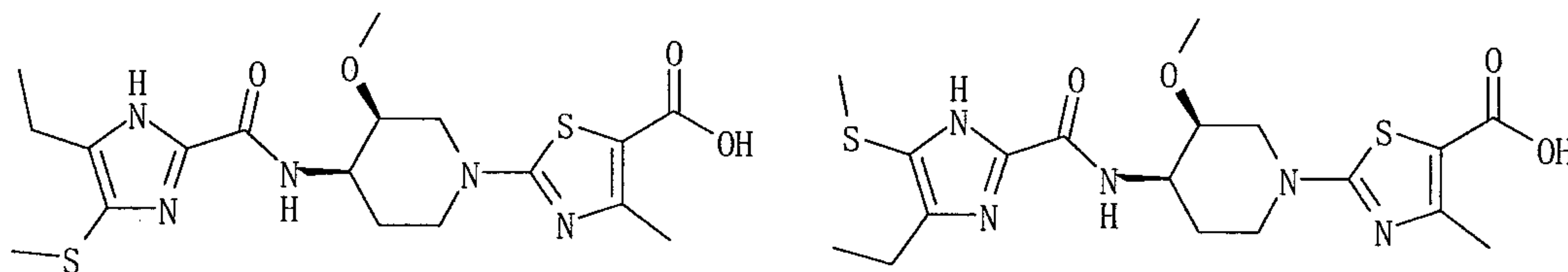
(58e) cis($\pm$)-2-(4-{[(5-Ethyl-4-iodo-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid

The same operation as in Example (1i) was performed using ethyl cis($\pm$)-2-(4-{[(5-ethyl-4-iodo-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate obtained in Example (58d) (130 mg, 0.24 mmol) and 2 N lithium hydroxide (3 mL), to obtain 40.7 mg of the title compound as a pale red solid (32%).
¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 1.11 (3H, t, J = 7.45 Hz), 1.67-1.68 (1H, m), 1.84-1.88 (1H, m), 2.41 (3H, s), 2.43-2.53 (2H, m), 3.30-3.37 (5H, m), 3.56 (1H, s), 3.90-3.92 (1H, m), 4.21-4.24 (2H, m), 7.63 (1H, d, J = 8.59 Hz), 12.40 (1H, br s).

mass spectrum (ESI): m/z 520 (M+H)⁺.

(Example 59) cis($\pm$)-2-[(4-{[(5-Ethyl-4-(methylsulfanyl)-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid and cis($\pm$)-2-[(4-{[(4-ethyl-5-(methylsulfanyl)-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 59)



[0272]

(59a) Ethyl 5-ethyl-4-(methylsulfanyl)-1H-imidazole-2-carboxylate and ethyl 4-ethyl-5-(methylsulfanyl)-1H-

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imidazole-2-carboxylate

Ethyl 5-ethyl-4-iodo-1H-imidazole-2-carboxylate obtained by the method described in Example (58a) (171 mg, 0.58 mmol) was dissolved in N-methyl-pyrrolidone (2 mL). Copper chloride (84 mg, 0.81 mmol) and sodium methylmercaptan (131 mg, 1.78 mmol) were added, and the mixture was stirred at 140°C for 1.5 hours. A 28% aqueous ammonia solution was added to the reaction solution, followed by extraction with ethyl acetate. Then, the organic layer was washed with brine and dried over anhydrous sodium sulfate. Following concentration under reduced pressure, the residue was purified by silica gel column chromatography (elution solvent: hexane/ethyl acetate = 4/1, 1/1) to obtain 62.1 mg of the title compound as an about 2:1 mixture (50%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.12-1.31 (3H, m), 1.36-1.43 (3H, m), 2.34 (3x1/3H, s), 2.43 (3x2/3H, s), 2.73-2.80 (2H, m), 4.38-4.46 (2H, m), 10.17-10.28 (1H, m).

(59b) 5-Ethyl-4-(methysulfanyl)-1H-imidazole-2-carboxylic acid and 4-ethyl-5-(methysulfanyl)-1H-imidazole-2-carboxylic acid

The same operation as in Example (1d) was performed using the mixture of ethyl 5-ethyl-4-(methysulfanyl)-1H-imidazole-2-carboxylate and ethyl 4-ethyl-5-(methysulfanyl)-1H-imidazole-2-carboxylate obtained in Example (59a) (62.1 mg, 0.29 mmol) and a 3 N aqueous lithium hydroxide solution (3 mL), to obtain 43.9 mg of the title compound as a white solid (81%).

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mass spectrum (ESI): m/z 187 ($M+H$)⁺.

(59c) tert-Butyl cis(±)-4-({[(5-ethyl-4-(methylsulfanyl)-1H-imidazol-2-yl]carbonyl}amino)-3-methoxypiperidine-1-carboxylate and tert-butyl cis(±)-4-({[(4-ethyl-5-(methylsulfanyl)-1H-imidazol-2-yl]carbonyl}amino)-3-methoxypiperidine-1-carboxylate

The same operation as in Example (1g) was performed using tert-butyl cis(±)-4-amino-3-methoxypiperidine-1-carboxylate obtained by the method described in Example (1e) (120 mg, 0.52 mmol), the mixture of 5-ethyl-4-(methylsulfanyl)-1H-imidazole-2-carboxylic acid and 4-ethyl-5-(methylsulfanyl)-1H-imidazole-2-carboxylic acid obtained in Example (59b) (42 mg, 0.20 mmol), WSC hydrochloride (120 mg, 0.63 mmol) and HOBT (25 mg, 0.19 mmol), to obtain 81.7 mg of the title compound as a colorless oily substance and as an about 4:1 mixture.

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.23-1.29 (3H, m), 1.48 (9H, s), 1.63-1.71 (1H, m), 1.80-1.93 (1H, m), 2.32 (3x1/5H, s), 2.38 (3x4/5H, s), 2.65-2.81 (2H, m), 3.27-3.46 (4H, m), 4.04-4.14 (2H, m), 4.42-4.48 (1H, m), 7.55-7.66 (1H, m), 11.47-11.69 (1H, m).

(59d) Ethyl cis(±)-2-[(4-({[(5-ethyl-4-(methylsulfanyl)-1H-imidazol-2-yl]carbonyl}amino)-3-methoxypiperidin-1-yl]-4-methyl-1,3-thiazole-5-carboxylate and ethyl cis(±)-2-[(4-({[(4-ethyl-5-(methylsulfanyl)-1H-imidazol-2-yl]carbonyl}amino)-3-methoxypiperidin-1-yl]-4-methyl-1,3-thiazole-5-carboxylate

The same operation as in Example (1h) was performed

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using the mixture of tert-butyl cis($\pm$)-4-({[(5-ethyl-4-(methylsulfanyl)-1H-imidazol-2-yl)carbonyl]amino)-3-methoxypiperidine-1-carboxylate and tert-butyl cis($\pm$)-4-({[(4-ethyl-5-(methylsulfanyl)-1H-imidazol-2-yl)carbonyl]amino)-3-methoxypiperidine-1-carboxylate obtained in Example (59c) (about 0.20 mmol), a 4 N hydrochloric acid/ethyl acetate solution (2 ml), diisopropylethylamine (0.2 mL, 1.15 mmol) and ethyl 2-bromo-4-methyl-1,3-thiazole-5-carboxylate (60 mg, 0.24 mmol), to obtain 83.3 mg of the title compound as a yellow oily substance and as an about 4:1 mixture (91%).

^1H NMR spectrum (400 MHz, CDCl_3) δ ppm: 1.23-1.28 (3H, m), 1.31-1.36 (3H, m), 1.80-1.81 (1H, m), 2.01-2.10 (1H, m), 2.32 (3x1/5H, s), 2.38 (3x4/5H, s), 2.54 (3H, s), 2.68 (2x1/5H, q, $J = 7.64$ Hz), 2.77 (2x4/5H, q, $J = 7.64$ Hz), 3.10-3.13 (1H, m), 3.21-3.24 (1H, m), 3.42 (3x4/5H, s), 3.44 (3x1/5H, s), 3.50-3.55 (1H, m), 3.96-4.06 (1H, m), 4.22-4.30 (3H, m), 4.48-4.56 (1H, m), 7.56-7.63 (1H, m), 10.96 (1x1/5H, s), 11.14 (1x4/5H, s).

(59e) cis($\pm$)-2-[(4-({[(5-Ethyl-4-(methylsulfanyl)-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid and cis($\pm$)-2-[(4-({[(4-ethyl-5-(methylsulfanyl)-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid

The same operation as in Example (1i) was performed using the mixture of ethyl cis($\pm$)-2-[(4-({[(5-ethyl-4-(methylsulfanyl)-1H-imidazol-2-yl)carbonyl]amino}-3-

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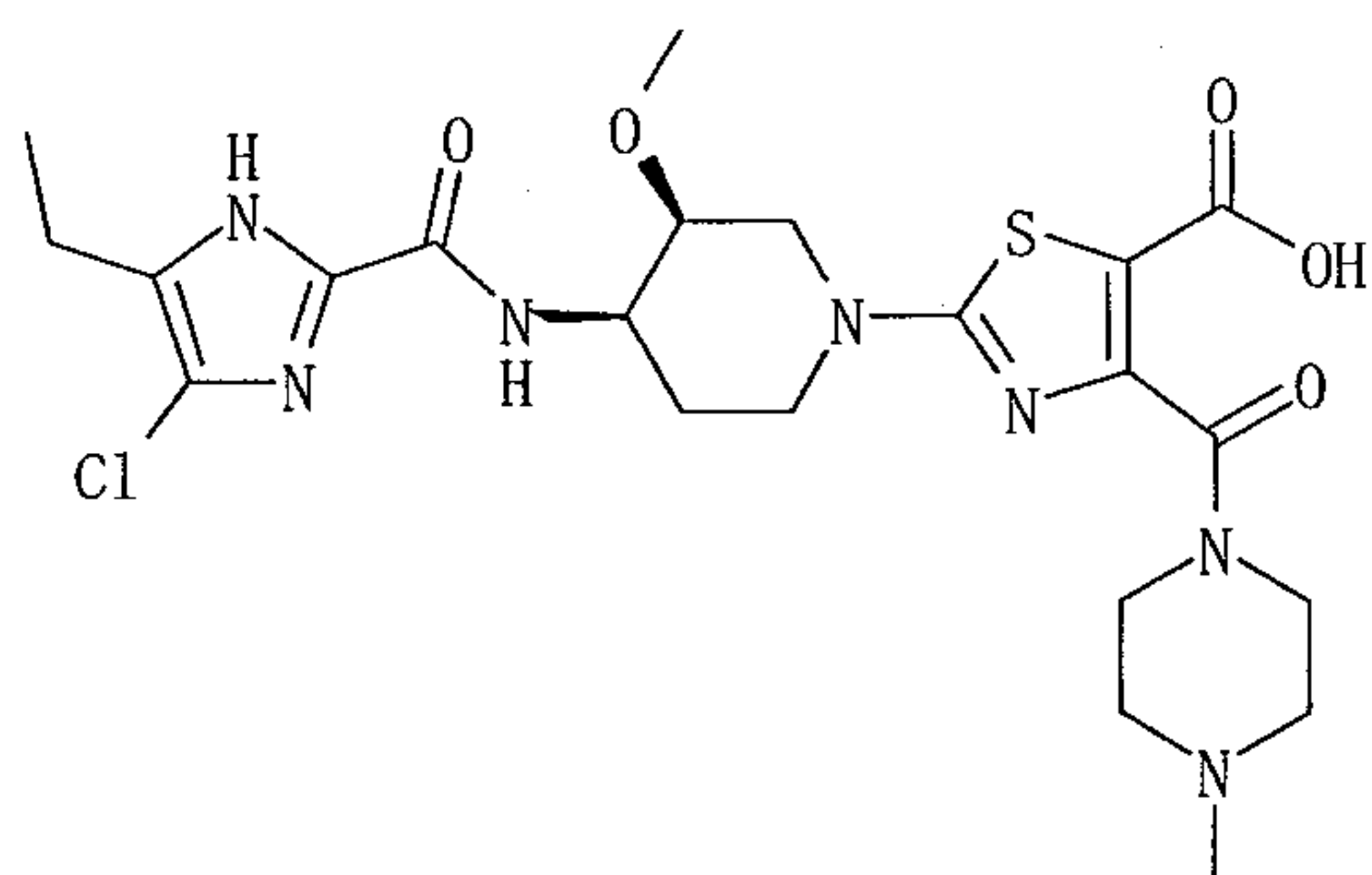
methoxypiperidin-1-yl]-4-methyl-1,3-thiazole-5-carboxylate and ethyl cis($\pm$)-2-[(4-{[(4-ethyl-5-(methylsulfanyl)-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl]-4-methyl-1,3-thiazole-5-carboxylate obtained in Example (59d) (83.3 mg, 0.18 mmol) and 2 N lithium hydroxide (2 mL), to obtain 40.6 mg of the title compound as an about 4:1 mixture (32%).

^1H NMR spectrum (400 MHz, DMSO- d_6) δ ppm: 1.13 (3H, m), 1.68-1.70 (1H, m), 1.83-1.84 (1H, m), 2.28 (3x4/5H, s), 2.31 (3x1/5H, s), 2.41 (3H, s), 2.59-2.63 (2H, m), 3.32-3.33 (2H, m), 3.35 (3H, s), 3.53-3.59 (1H, m), 3.87-3.99 (1H, m), 4.15-4.32 (2H, m), 7.56-7.64 (1H, m), 12.38-12.40 (1H, m).

mass spectrum (ESI): m/z 440 ($M+H$) $^+$.

(Example 60) cis($\pm$)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-[(4-methylpiperazin-1-yl)carbonyl]-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 60)



[0273]

(60a) Ethyl cis($\pm$)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-[(4-

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methylpiperazin-1-yl)carbonyl]-1,3-thiazole-5-carboxylate

The same operation as in Example (1g) was performed using cis($\pm$)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-(ethoxycarbonyl)-1,3-thiazole-4-carboxylic acid obtained by the method described in Example (50a) (65 mg, 0.13 mmol), 4-methyl-piperazine (35 μ L, 0.27 mmol), WSC hydrochloride (80 mg, 0.42 mmol) and HOBt (18 mg, 0.13 mmol), to obtain 52.1 mg of the title compound as a white solid (69%).

^1H NMR spectrum (400 MHz, CDCl_3) δ ppm: 1.26 (3H, t, J = 7.68 Hz), 1.31 (3H, t, J = 7.16 Hz), 1.67-1.82 (1H, m), 2.02-2.06 (1H, m), 2.33 (3H, s), 2.33-2.42 (2H, m), 2.46-2.55 (2H, m), 2.69 (2H, q, J = 7.68 Hz), 3.10-3.13 (1H, m), 3.23-3.25 (1H, m), 3.29-3.34 (2H, m), 3.42 (3H, s), 3.52 (1H, br s), 3.78-3.84 (2H, m), 3.95-3.97 (1H, m), 4.23-4.27 (3H, m), 4.56-4.58 (1H, m), 7.47 (1H, d, J = 9.16 Hz), 11.21 (1H, br s).

(60b) cis($\pm$)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-[(4-methylpiperazin-1-yl)carbonyl]-1,3-thiazole-5-carboxylic acid

The same operation as in Example (1i) was performed using ethyl cis($\pm$)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-[(4-methylpiperazin-1-yl)carbonyl]-1,3-thiazole-5-carboxylate obtained in Example (60a) (52.1 mg, 0.092 mmol) and a 2 N aqueous lithium hydroxide solution (1 mL), to obtain 42.3

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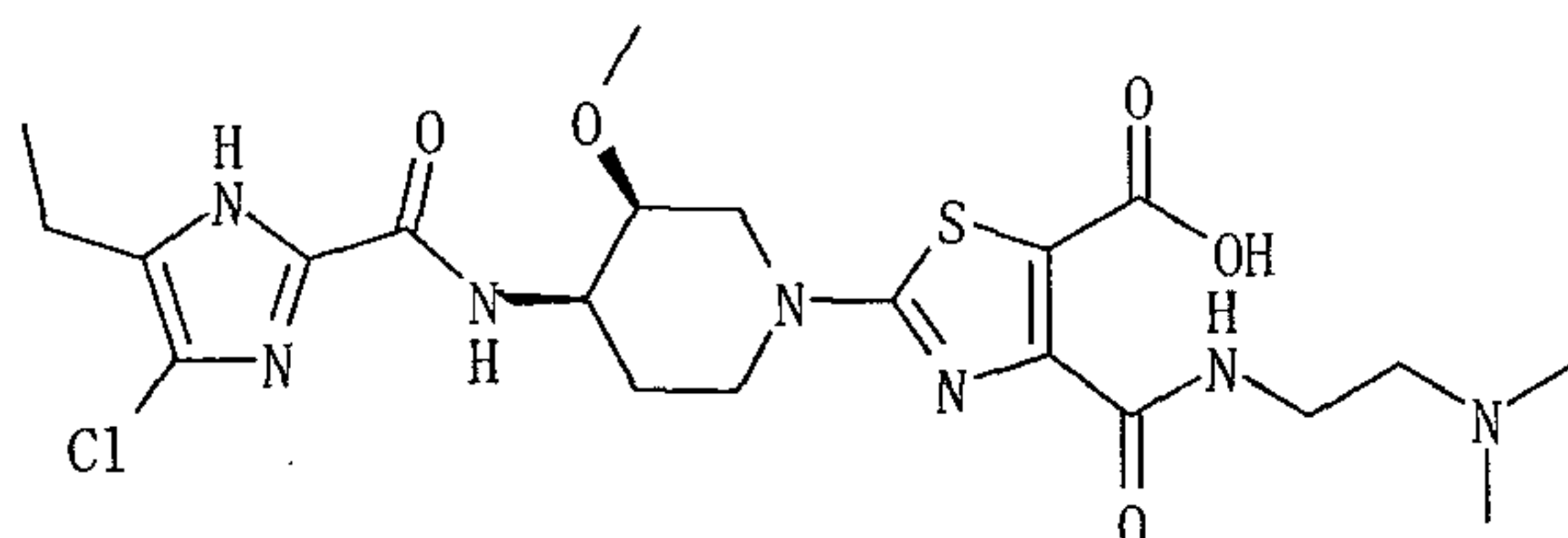
mg of the title compound as a pale yellow solid (85%).

^1H NMR spectrum (400 MHz, DMSO-d_6) δ ppm: 1.14 (3H, t, $J = 7.55$ Hz), 1.67-1.69 (1H, m), 1.83-1.90 (1H, m), 2.23 (3H, s), 2.38-2.49 (4H, m), 2.55 (2H, q, $J = 7.55$ Hz), 3.15-3.23 (2H, m), 3.28-3.33 (5H, m), 3.48-3.64 (3H, m), 3.83-3.85 (1H, m), 4.19-4.30 (2H, m), 7.67 (1H, d, $J = 8.59$ Hz).

mass spectrum (ESI): m/z 541 ($\text{M}+\text{H}$) $^+$.

(Example 61) cis($\pm$)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[2-(dimethylamino)ethyl]carbamoyl}-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 61)



[0274]

(61a) Ethyl cis($\pm$)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[2-(dimethylamino)ethyl]carbamoyl}-1,3-thiazole-5-carboxylate

The same operation as in Example (1g) was performed using cis($\pm$)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-(ethoxycarbonyl)-1,3-thiazole-4-carboxylic acid obtained by the method described in Example (50a) (65 mg, 0.13 mmol), N,N -dimethylethylenediamine (35 μL , 0.27 mmol),

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WSC hydrochloride (80 mg, 0.42 mmol) and HOBT (18 mg, 0.13 mmol), to obtain 61.5 mg of the title compound as a white solid (83%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.26 (3H, t, J = 7.68 Hz), 1.33 (3H, t, J = 7.16 Hz), 1.78-1.81 (1H, m), 1.98-2.09 (1H, m), 2.27 (6H, s), 2.53 (2H, t, J = 6.30 Hz), 2.69 (2H, q, J = 7.68 Hz), 3.11-3.14 (1H, m), 3.22-3.24 (1H, m), 3.43 (3H, s), 3.48-3.55 (3H, m), 3.96-4.06 (1H, m), 4.26-4.30 (3H, m), 4.51-4.62 (1H, m), 7.48 (1H, d, J = 9.16 Hz), 8.11-8.16 (1H, m).

(61b) cis(±)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[2-(dimethylamino)ethyl]carbamoyl}-1,3-thiazole-5-carboxylic acid

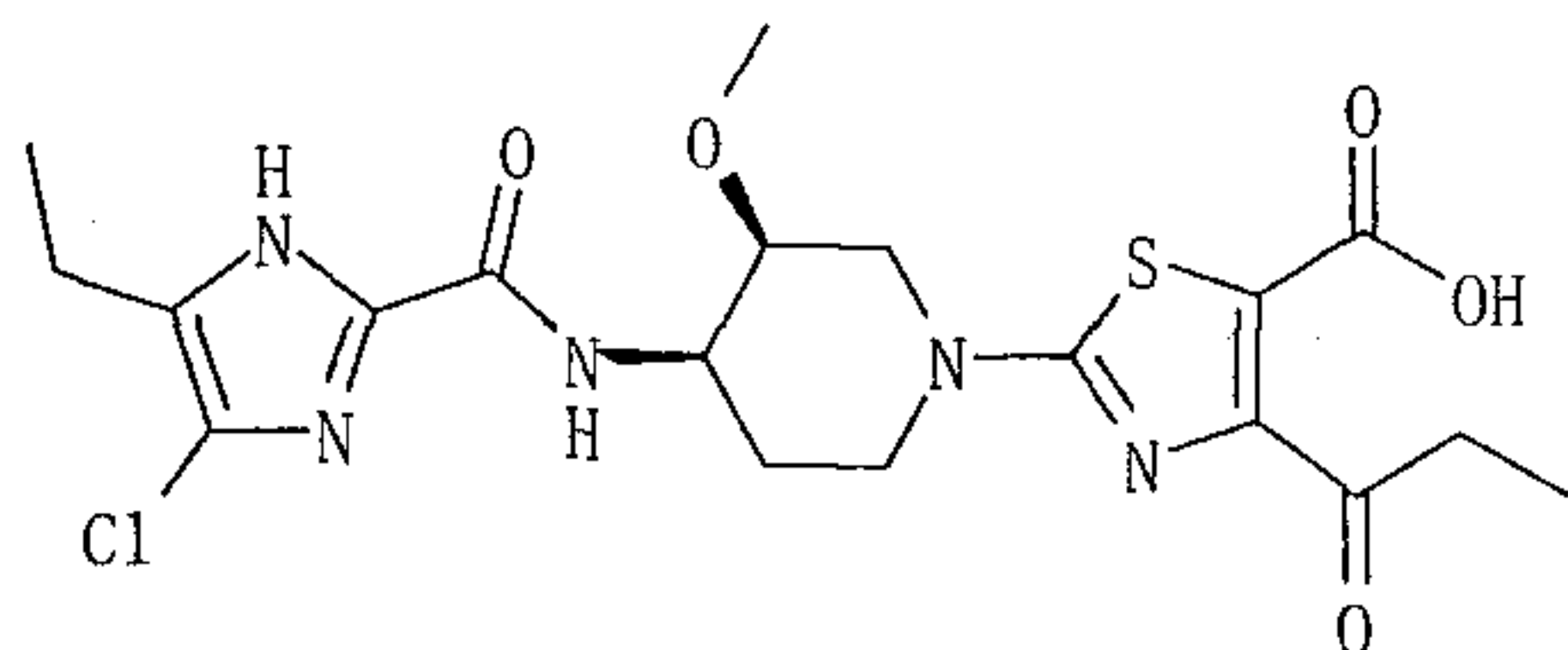
The same operation as in Example (1i) was performed using ethyl cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[2-(dimethylamino)ethyl]carbamoyl}-1,3-thiazole-5-carboxylate obtained in Example (61a) (61.5 mg, 0.11 mmol) and a 2 N aqueous lithium hydroxide solution (1 mL), to obtain 51.4 mg of the title compound as a pale yellow solid (88%).

¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 1.14 (3H, t, J = 7.68 Hz), 1.67-1.69 (1H, m), 1.84-1.89 (1H, m), 2.34 (6H, s), 2.55 (3H, q, J = 7.68 Hz), 2.61-2.67 (2H, m), 3.24-3.34 (2H, m), 3.35 (3H, s), 3.37-3.43 (1H, m), 3.56 (1H, br s), 3.97-3.99 (1H, m), 4.18-4.22 (2H, m), 4.28-4.30 (1H, m), 7.66 (1H, d, J = 8.59 Hz).

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mass spectrum (ESI): m/z 529 ($M+H$)⁺.

(Example 62) *cis*(±)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-propanoyl-1,3-thiazole-5-carboxylic acid
(Exemplified Compound No. 62)



[0275]

(62a) Ethyl 2-amino-4-({[tert-butyl(dimethyl)silyl]oxy}methyl)-1,3-thiazole-5-carboxylate

The compound was synthesized according to the method described in the following document.

[0276]

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(62b) Ethyl 2-[bis(tert-butoxycarbonyl)amino]-4-({[tert-butyl(dimethyl)silyl]oxy}methyl)-1,3-thiazole-5-carboxylate

Ethyl 2-amino-4-({[tert-butyl(dimethyl)silyl]oxy}methyl)-1,3-thiazole-5-carboxylate obtained in Example (62a) (2.0 g, 6.32 mmol) was dissolved in THF (50 mL). Di-tert-butyl dicarboxylate (4.1 g, 18.8 mmol), triethylamine (2 mL, 14.3 mmol) and DMAP (150 mg, 1.23 mmol) were added, followed by stirring for 4.5 hours. Ethyl acetate was added to the reaction solution, and the organic layer was washed with 1 N hydrochloric acid and brine, and dried

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over anhydrous sodium sulfate. Following concentration under reduced pressure, the residue was purified by silica gel column chromatography (elution solvent: hexane/ethyl acetate = 97/3, 95/5) to obtain 2.87 g of the title compound as a white solid (88%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 0.08 (6H, s), 0.89 (9H, s), 1.34 (3H, t, J = 7.19 Hz), 1.57 (18H, s), 4.30 (2H, q, J = 7.19 Hz), 5.01 (2H, s).

(62c) Ethyl 2-[bis(tert-butoxycarbonyl)amino]-4-(hydroxymethyl)-1,3-thiazole-5-carboxylate

Ethyl 2-[bis(tert-butoxycarbonyl)amino]-4-([tert-butyl(dimethyl)silyl]oxy)methyl)-1,3-thiazole-5-carboxylate obtained in Example (62b) (2.87 g, 5.55 mmol) was dissolved in THF (60 mL). TBAF (1 M solution in THF, 9.3 mL) and acetic acid (0.48 mL, 8.39 mmol) were added, followed by stirring for 15 hours. Ethyl acetate was added to the reaction solution, and the organic layer was washed with saturated aqueous sodium bicarbonate solution and brine, and dried over anhydrous sodium sulfate. Following concentration under reduced pressure, the residue was purified by silica gel column chromatography (elution solvent: hexane/ethyl acetate = 90/10, 70/30) to obtain 1.83 g of the title compound as a white solid (82%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.35 (3H, t, J = 7.15 Hz), 1.58 (18H, s), 3.84 (1H, t, J = 6.54 Hz), 4.33 (2H, q, J = 7.15 Hz), 4.86 (2H, d, J = 6.54 Hz).

(62d) Ethyl 2-[bis(tert-butoxycarbonyl)amino]-4-formyl-

1,3-thiazole-5-carboxylate

The same operation as in Example (28a) was performed using ethyl 2-[bis(tert-butoxycarbonyl)amino]-4-(hydroxymethyl)-1,3-thiazole-5-carboxylate obtained in Example (62c) (1 g, 2.48 mmol) and the Dess-Martin reagent (1.28 g, 3.02 mmol), to obtain 915.5 mg of the title compound as a yellow solid (92%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.39 (3H, t, J = 7.14 Hz), 1.59 (18H, s), 4.40 (2H, q, J = 7.14 Hz), 10.54 (1H, s).

(62e) Ethyl 2-[bis(tert-butoxycarbonyl)amino]-4-(1-hydroxypropyl)-1,3-thiazole-5-carboxylate

Ethyl 2-[bis(tert-butoxycarbonyl)amino]-4-formyl-1,3-thiazole-5-carboxylate obtained in Example (62d) (915.5 mg, 2.29 mmol) was dissolved in diethyl ether (30 mL), followed by cooling to -78°C. Then, tetrabutylammonium bromide (890 mg, 2.76 mmol) and ethylmagnesium bromide (1 M solution in THF, 2.8 mL) were added, and the mixture was stirred for one hour. Diethyl ether was added to the reaction solution, and the organic layer was washed with brine and dried over anhydrous sodium sulfate. Following concentration under reduced pressure, the residue was purified by silica gel column chromatography (elution solvent: hexane/ethyl acetate = 91/9, 85/15) to obtain 327.2 mg of the title compound (33%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 0.96 (3H, t, J = 7.35 Hz), 1.35 (3H, t, J = 7.16 Hz), 1.57 (18H, s), 1.75-

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1.89 (2H, m), 3.86 (1H, d, $J = 9.16$ Hz), 4.32 (2H, q, $J = 7.35$ Hz), 5.00-5.08 (1H, m).

(62f) Ethyl 2-[bis(tert-butoxycarbonyl)amino]-4-propanoyl-1,3-thiazole-5-carboxylate

The same operation as in Example (28a) was performed using ethyl 2-[bis(tert-butoxycarbonyl)amino]-4-(1-hydroxypropyl)-1,3-thiazole-5-carboxylate obtained in Example (62e) (327.2 mg, 0.76 mmol) and the Dess-Martin reagent (420 mg, 0.99 mmol), to obtain 270.5 mg of the title compound as a white solid (83%).

^1H NMR spectrum (400 MHz, CDCl_3) δ ppm: 1.18 (3H, t, $J = 7.26$ Hz), 1.33 (3H, t, $J = 7.14$ Hz), 1.57 (18H, s), 2.91 (2H, q, $J = 7.26$ Hz), 4.32 (2H, q, $J = 7.14$ Hz).

(62g) Ethyl 2-chloro-4-propanoyl-1,3-thiazole-5-carboxylate

Ethyl 2-[bis(tert-butoxycarbonyl)amino]-4-propanoyl-1,3-thiazole-5-carboxylate obtained in Example (62f) (270.5 mg, 0.63 mmol) was dissolved in methanol (2 mL). A 4 N hydrochloric acid/ethyl acetate solution (6 mL) was added, and the mixture was stirred at 50°C for 50 minutes. The reaction solution was washed with saturated aqueous sodium bicarbonate solution, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. The same operation as in Example (22c) was performed using the resulting crude product, copper chloride (96 mg, 0.71 mmol) and tert-butyl nitrite (86 μL , 0.72 mmol), to obtain 49.0 mg of the title compound as a colorless oily substance (31%).

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¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.21 (3H, t, J = 7.11 Hz), 1.35 (3H, t, J = 7.21 Hz), 2.98 (2H, q, J = 7.11 Hz), 4.36 (2H, q, J = 7.21 Hz).

(62h) Ethyl cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-propanoyl-1,3-thiazole-5-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis(±)-4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate obtained by the method described in Example (1g) (62 mg, 0.16 mmol), ethyl 2-chloro-4-propanoyl-1,3-thiazole-5-carboxylate obtained in Example (62g) (24 mg, 0.097 mmol), a 4 N hydrochloric acid/ethyl acetate solution (2 mL) and diisopropylethylamine (0.11 mL, 0.63 mmol), to obtain 20.2 mg of the title compound (42%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.19 (3H, t, J = 7.16 Hz), 1.25-1.34 (6H, m), 1.79-1.82 (1H, m), 2.02-2.05 (1H, m), 2.69 (2H, q, J = 7.64 Hz), 2.85-2.91 (2H, m), 3.11-3.12 (1H, m), 3.22-3.26 (1H, m), 3.42 (3H, s), 3.52 (1H, br s), 3.95-3.98 (1H, m), 4.22-4.28 (3H, m), 4.55-4.58 (1H, m), 7.48 (1H, d, J = 8.59 Hz), 11.17 (1H, br s).

(62i) cis(±)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-propanoyl-1,3-thiazole-5-carboxylic acid

The same operation as in Example (1i) was performed using ethyl cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-propanoyl-1,3-thiazole-5-carboxylate obtained in Example

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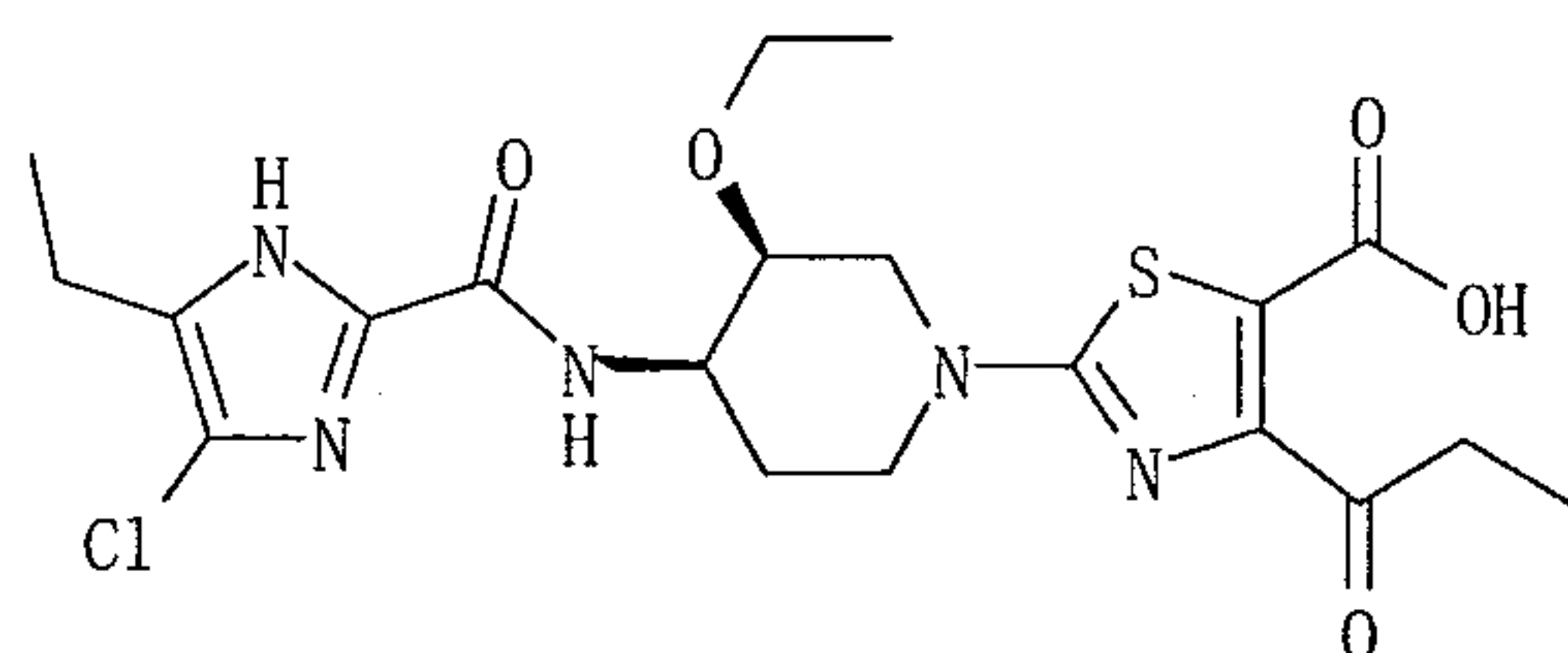
(62h) (20.2 mg, 0.041 mmol) and a 2 N aqueous lithium hydroxide solution (0.7 mL), to obtain 22.2 mg of the title compound as a yellow solid (100%).

¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 1.04 (3H, t, J = 7.11 Hz), 1.14 (3H, t, J = 7.26 Hz), 1.65-1.74 (1H, m), 1.83-1.92 (1H, m), 2.52-2.59 (2H, m), 2.84 (2H, q, J = 7.26 Hz), 3.33 (5H, m), 3.58 (1H, br s), 3.89-3.91 (1H, m), 4.19-4.28 (2H, m), 7.68 (1H, d, J = 8.71 Hz).

mass spectrum (ESI): m/z 470 (M+H)⁺.

(Example 63) cis(±)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-4-propanoyl-1,3-thiazole-5-carboxylic acid

(Exemplified Compound No. 63)



[0277]

(63a) Ethyl cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-4-propanoyl-1,3-thiazole-5-carboxylate

The same operation as in Example (1h) was performed using tert-butyl cis(±)-4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidine-1-carboxylate obtained by the method described in Example (34a) (66 mg, 0.16 mmol), ethyl 2-chloro-4-propanoyl-1,3-thiazole-5-carboxylate obtained in Example (62g) (24 mg, 0.097 mmol), a 4 N hydrochloric acid/ethyl acetate

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solution (2 mL) and diisopropylethylamine (0.11 mL, 0.63 mmol), to obtain 33.1 mg of the title compound (67%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.14-1.22 (6H, m), 1.23-1.39 (6H, m), 1.74-1.81 (1H, m), 2.06-2.10 (1H, m), 2.70 (2H, q, J = 7.49 Hz), 2.86-2.88 (2H, m), 3.12-3.15 (1H, m), 3.19-3.27 (1H, m), 3.42-3.45 (1H, m), 3.62 (1H, br s), 3.70-3.82 (1H, m), 3.93-4.06 (1H, m), 4.22-4.27 (3H, m), 4.44-4.47 (1H, m), 7.50 (1H, d, J = 8.71 Hz), 11.37 (1H, br s).

(63b) cis(±)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-4-propanoyl-1,3-thiazole-5-carboxylic acid

The same operation as in Example (1i) was performed using ethyl cis(±)-2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-4-propanoyl-1,3-thiazole-5-carboxylate obtained in Example (63a) (33.1 mg, 0.065 mmol) and a 2 N aqueous lithium hydroxide solution (0.8 mL), to obtain 26.4 mg of the title compound as a yellow solid (84%).

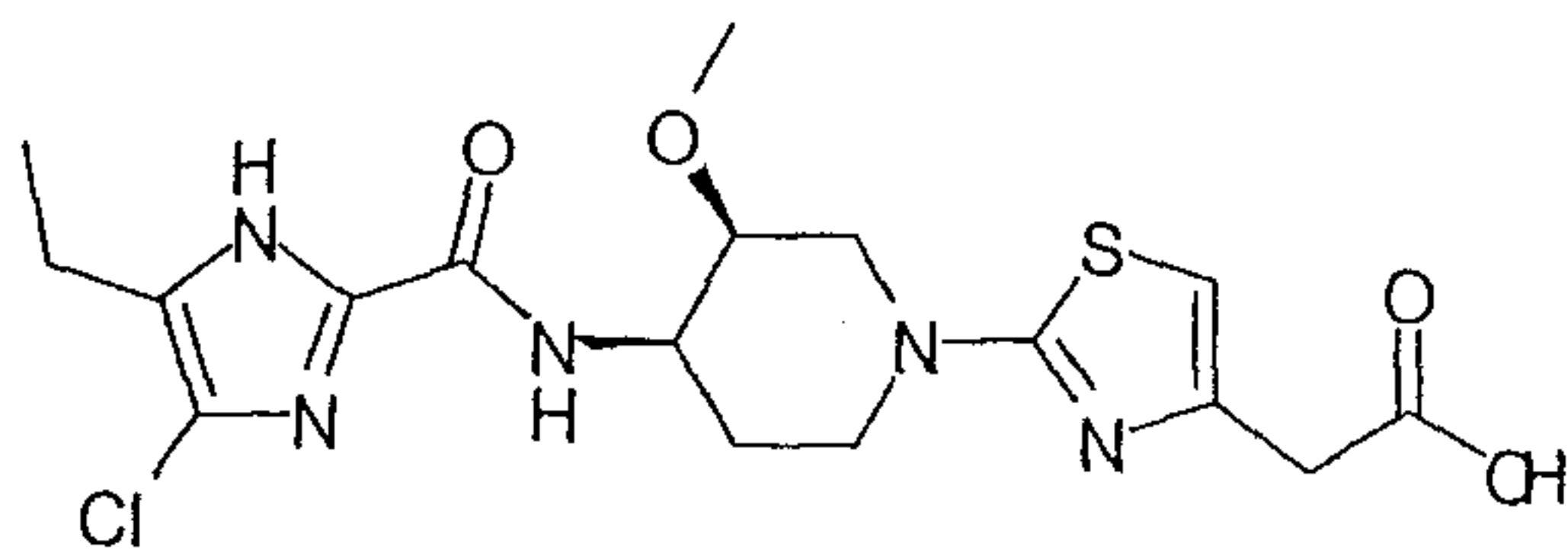
¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 1.04-1.06 (6H, m), 1.14 (3H, t, J = 7.45 Hz), 1.67-1.69 (1H, m), 1.86-1.88 (1H, m), 2.52-2.58 (2H, m), 2.83 (2H, q, J = 7.06 Hz), 3.29-3.47 (1H, m), 3.62-3.65 (2H, m), 3.94-3.96 (1H, m), 4.18-4.21 (2H, m), 7.65 (1H, d, J = 8.59 Hz).

mass spectrum (ESI): m/z 484 (M+H)⁺.

(Example 64) cis(±)-[2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazol-4-yl]acetic acid

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(Exemplified Compound No. 64)



[0278]

(64a) Benzyl cis($\pm$)-[1-(1H-imidazol-1-ylthiocarbonyl)-3-methoxypiperidin-4-yl]-carbamate

Benzyl cis($\pm$)-4-(3-methoxypiperidin-4-yl)-carbamate obtained by the method described in Example (40b) (735 mg, 1.37 mmol) was dissolved in THF (8 mL). 1,1'-Thiocarbonyldiimidazole (270 mg, 1.36 mmol) was added, and the mixture was stirred for 1.5 hours. 0.5 M hydrochloric acid was added to the reaction solution, followed by extraction with ethyl acetate and dichloromethane. The organic layer was dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The resulting compound was used for the next reaction without purification.

[0279]

(64b) Benzyl cis($\pm$)-(1-carbamothioyl-3-methoxypiperidin-4-yl)-carbamate

Benzyl cis($\pm$)-[1-(1H-imidazol-1-ylthiocarbonyl)-3-methoxypiperidin-4-yl]-carbamate obtained in Example (64a) (about 1.36 mmol) was dissolved in THF (2 mL). A 2 N ammonia/methanol solution (10 mL) was added, and the mixture was stirred for 42 hours. Brine was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was dried over anhydrous

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sodium sulfate and then concentrated under reduced pressure. The precipitated solid was collected by filtration to obtain 296.5 mg of the title compound as a white solid (67%).

mass spectrum (ESI): m/z 324 ($M+H$)⁺.

(64c) Ethyl cis(±)-[2-(4-{[(benzyloxy)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazol-4-yl]acetate

The same operation as in Example (22b) was performed using benzyl cis(±)-(1-carbamothioyl-3-methoxypiperidin-4-yl)-carbamate obtained in Example (64b) (97 mg, 0.30 mmol) and ethyl 4-chloro-acetoacetate (60 μ L, 0.44 mmol), to obtain 125.4 mg of the title compound as a colorless oily substance (96%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.26 (3H, t, J = 7.11 Hz), 1.78-1.80 (1H, m), 1.88-1.93 (1H, m), 3.01-3.04 (1H, m), 3.10-3.12 (1H, m), 3.38 (3H, s), 3.45 (1H, br s), 3.56 (2H, s), 3.81-3.84 (2H, m), 4.17 (2H, q, J = 7.11 Hz), 4.34-4.38 (1H, m), 5.11 (2H, s), 5.27 (1H, d, J = 9.16 Hz), 6.34 (1H, s), 7.32-7.36 (5H, m).

(64d) Ethyl cis(±)-[2-(4-amino-3-methoxypiperidin-1-yl)-1,3-thiazol-4-yl]acetate

Ethyl cis(±)-[2-(4-{[(benzyloxy)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazol-4-yl]acetate obtained in Example (64c) (124 mg, 0.29 mmol) was dissolved in ethanol (5 mL). A 10% palladium-carbon catalyst (75 mg) and ammonium formate (90 mg, 1.43 mmol) were added, and the mixture was heated under reflux for 15 hours. The reaction solution was filtered through celite. The

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filtrate was washed with saturated sodium bicarbonate, dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The resulting compound was used for the next reaction without purification.

[0280]

(64e) Ethyl cis(±)-[2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazol-4-yl]acetate

The same operation as in Example (1g) was performed using ethyl cis(±)-[2-(4-amino-3-methoxypiperidin-1-yl)-1,3-thiazol-4-yl]acetate obtained in Example (64d) (about 0.29 mmol), 4-chloro-5-ethyl-1H-imidazole-2-carboxylic acid obtained by the method described in Example (1d) (45 mg, 0.26 mmol), WSC hydrochloride (150 mg, 0.78 mmol) and HOBT (35 mg, 0.26 mmol), to obtain 42.6 mg of the title compound (36%).

¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.25-1.30 (6H, m), 1.86-1.88 (1H, m), 2.03-2.12 (1H, m), 2.69 (2H, q, J = 7.64 Hz), 3.03-3.06 (1H, m), 3.12-3.14 (1H, m), 3.41 (3H, s), 3.50 (1H, br s), 3.58 (2H, s), 3.89-3.92 (1H, m), 4.13-4.26 (3H, m), 4.43-4.45 (1H, m), 6.38 (1H, s), 7.56 (1H, d, J = 9.16 Hz), 11.81 (1H, br s).

(64f) cis(±)-[2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazol-4-yl]acetic acid

The same operation as in Example (1i) was performed using ethyl cis(±)-[2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-

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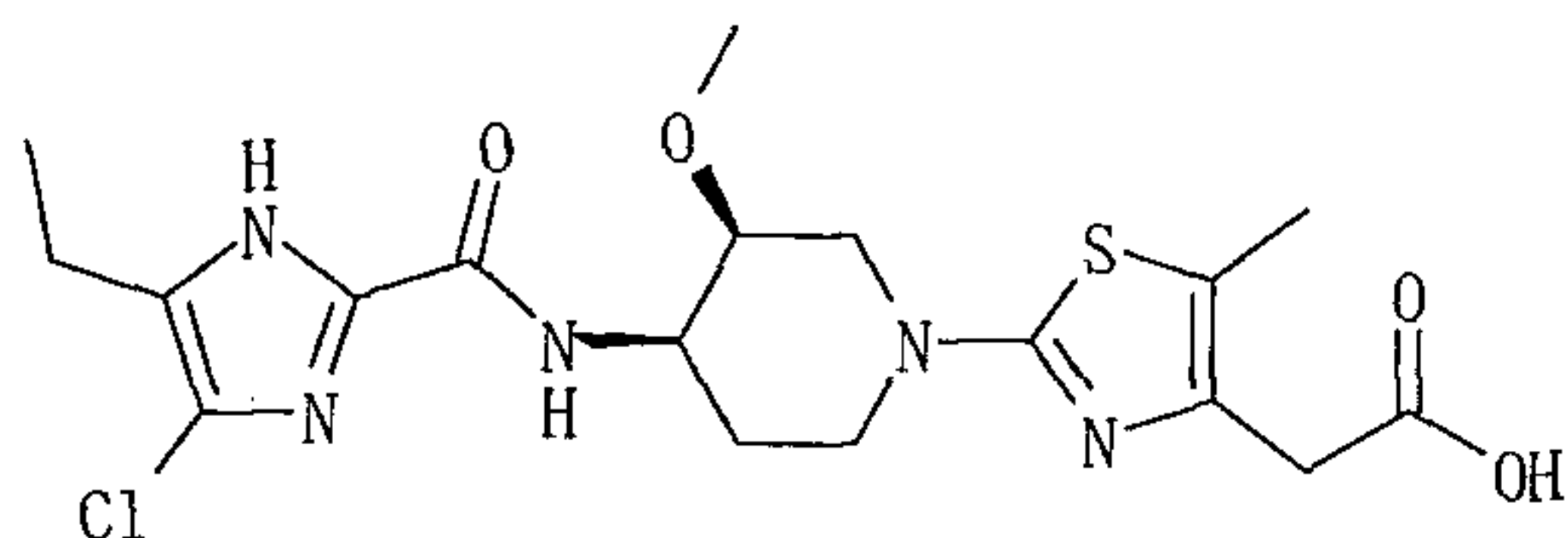
thiazol-4-yl]acetate obtained in Example (64e) (42.6 mg, 0.093 mmol) and a 2 N aqueous lithium hydroxide solution, (0.8 mL) to obtain 22.0 mg of the title compound as a red solid (55%).

¹H NMR spectrum (400 MHz, DMSO-d₆) δ ppm: 1.14 (3H, t, J = 7.55 Hz), 1.67-1.68 (1H, m), 1.87-1.89 (1H, m), 2.55 (2H, q, J = 7.55 Hz), 3.23-3.26 (2H, m), 3.33 (3H, s), 3.47-3.55 (4H, m), 3.79-3.82 (1H, m), 4.18-4.20 (2H, m), 6.55 (1H, s), 7.65 (1H, d, J = 8.59 Hz).

mass spectrum (ESI): m/z 428 (M+H)⁺.

(Example 65) cis(±)-[2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-methyl-1,3-thiazol-4-yl]acetic acid

(Exemplified Compound No. 65)



[0281]

(65a) Methyl 4-bromo-3-oxopentanoate

Methyl 3-oxopentanoate (1 g, 7.68 mmol) was dissolved in chloroform (30 mL). Bromine (0.4 mL, 7.80 mmol) was added under ice-cooling and the mixture was stirred for 40 minutes. The reaction solution was washed with saturated aqueous sodium bicarbonate solution, dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The resulting compound was used for the next reaction without purification.

[0282]

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(65b) cis($\pm$)-4-Chloro-5-ethyl-N-[1-(1H-imidazol-1-ylthiocarbonyl)-3-methoxypiperidin-4-yl]-1H-imidazole-2-carboxamide

tert-Butyl cis($\pm$)-4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate obtained by the method described in Example (1g) (130 mg, 0.34 mmol) was dissolved in methanol (1 mL). A 4 N hydrochloric acid/ethyl acetate solution (3 mL) was added, and the mixture was stirred for 15 minutes. The reaction solution was concentrated under reduced pressure, and then the same operation as in Example (64a) was performed using 1,1'-thiocarbonyldiimidazole (81 mg, 0.45 mmol), to obtain the title compound. The resulting compound was used for the next reaction without purification.

[0283]

(65c) cis($\pm$)-N-(1-Carbamothioyl-3-methoxypiperidin-4-yl)-4-chloro-5-ethyl-1H-imidazole-2-carboxamide

The same operation as in Example (64b) was performed using cis($\pm$)-4-chloro-5-ethyl-N-[1-(1H-imidazol-1-ylthiocarbonyl)-3-methoxypiperidin-4-yl]-1H-imidazole-2-carboxamide obtained in Example (65b) (about 0.34 mmol) and a 2 N ammonia/methanol solution (5 mL), to obtain 80.4 mg of the title compound as a white solid (69%).
mass spectrum (ESI): m/z 346 (M+H)⁺.

(65d) Methyl cis($\pm$)-[2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-methyl-1,3-thiazol-4-yl]acetate

The same operation as in Example (22b) was performed

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using cis($\pm$)-N-(1-carbamothioyl-3-methoxypiperidin-4-yl)-4-chloro-5-ethyl-1H-imidazole-2-carboxamide (40 mg, 0.12 mmol) obtained in Example (65c) and methyl 4-bromo-3-oxopentanoate obtained in Example (65a) (45 mg, 0.22 mmol), to obtain 44.5 mg of the title compound (84%).

^1H NMR spectrum (400 MHz, CDCl_3) δ ppm: 1.26 (3H, t, J = 7.68 Hz), 1.73-1.77 (1H, m), 2.03-2.06 (1H, m), 2.23 (3H, s), 2.69 (2H, q, J = 7.68 Hz), 2.97-3.00 (1H, m), 3.07-3.09 (1H, m), 3.41 (3H, s), 3.48 (1H, br s), 3.52 (2H, s), 3.69 (3H, s), 3.82-3.83 (1H, m), 4.19-4.21 (1H, m), 4.35-4.38 (1H, m), 7.54 (1H, d, J = 8.59 Hz), 11.75 (1H, br s).

(65e) cis($\pm$)-[2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-methyl-1,3-thiazol-4-yl]acetic acid

The same operation as in Example (1i) was performed using methyl cis($\pm$)-[2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-methyl-1,3-thiazol-4-yl]acetate obtained in Example (65d) (44.5 mg, 0.098 mmol) and a 2 N aqueous lithium hydroxide solution (0.8 mL), to obtain 35.6 mg of the title compound as a pale yellow solid (83%).

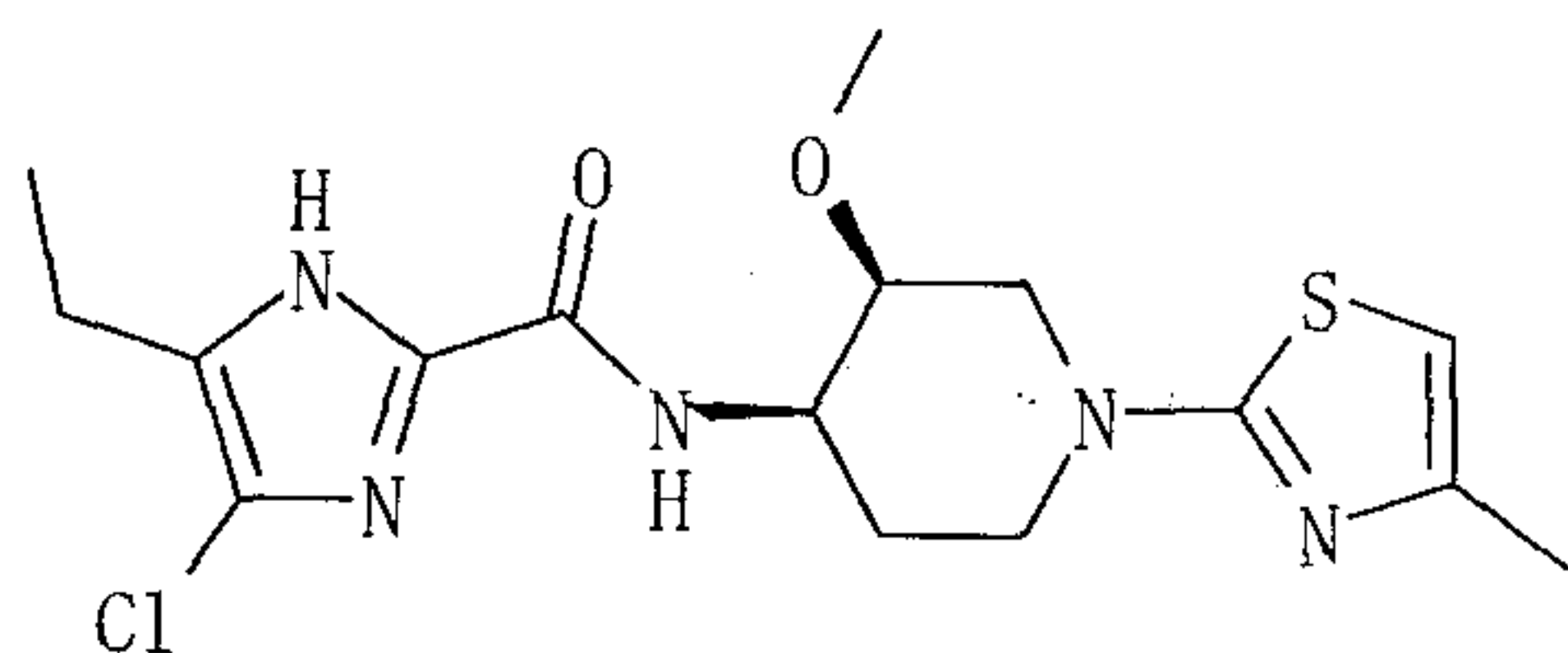
^1H NMR spectrum (400 MHz, $\text{DMSO}-d_6$) δ ppm: 1.14 (3H, t, J = 7.45 Hz), 1.63-1.65 (1H, m), 1.83-1.86 (1H, m), 2.17 (3H, s), 2.55 (2H, q, J = 7.45 Hz), 3.11-3.14 (2H, m), 3.30-3.35 (2H, m), 3.37 (3H, s), 3.51 (1H, br s), 3.71-3.74 (1H, m), 4.11-4.15 (2H, m), 7.60 (1H, d, J = 8.59 Hz).

mass spectrum (ESI): m/z 442 ($\text{M}+\text{H}$) $^+$.

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(Example 66) 4-Chloro-5-ethyl-N-[(3S,4R)-3-methoxy-1-(5-methyl-1,3-thiazol-2-yl)piperidin-4-yl]-1H-imidazole-2-carboxamide

(Exemplified Compound No. 66)



[0284]

(66a) 4-Chloro-5-ethyl-N-[(3S,4R)-3-methoxy-1-(5-methyl-1,3-thiazol-2-yl)piperidin-4-yl]-1H-imidazole-2-carboxamide

2-[(3S,4R)-4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl]-4-methyl-1,3-thiazole-5-carboxylic acid obtained by the method described in Example (56d) (15 mg, 0.035 mmol) was dissolved in THF (3 mL). 1 N hydrochloric acid (1 mL) was added, and the mixture was stirred at 60°C for 40 minutes. A 1 N aqueous sodium hydroxide solution was added to the reaction solution, followed by extraction with ethyl acetate. Then, the organic layer was washed with brine and dried over anhydrous sodium sulfate. Following concentration under reduced pressure, the residue was purified by silica gel column chromatography (elution solvent: hexane/ethyl acetate = 1/1, ethyl acetate) to obtain 13.5 mg of the title compound as a white solid (100%).

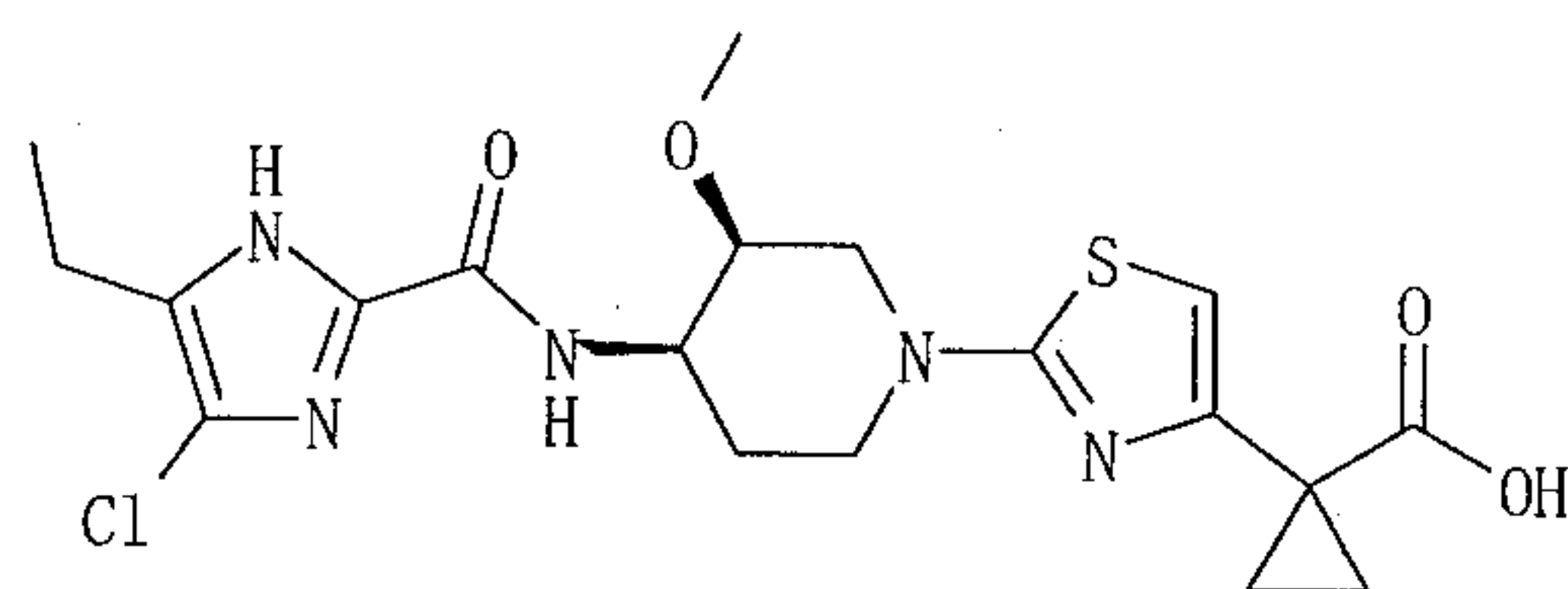
¹H NMR spectrum (400 MHz, CDCl₃) δ ppm: 1.27 (3H, t, J =

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7.55 Hz), 1.77-1.80 (1H, m), 2.06-2.11 (1H, m), 2.24 (3H, s), 2.69 (2H, q, $J = 7.55$ Hz), 3.04-3.15 (2H, m), 3.42 (3H, s), 3.51 (1H, br s), 3.92-3.95 (1H, m), 4.22-4.25 (1H, m), 4.39-4.40 (1H, m), 6.11 (1H, s), 7.56 (1H, d, $J = 8.59$ Hz), 11.70 (1H, br s).

(Example 67) cis($\pm$)-[2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazol-4-yl]cyclopropanecarboxylic acid

(Exemplified Compound No. 67)



[0285]

(67a) Ethyl cis($\pm$)-[2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazol-4-yl]cyclopropanecarboxylate

The same operation as in Example (22b) was performed using cis($\pm$)-N-(1-carbamothioyl-3-methoxypiperidin-4-yl)-4-chloro-5-ethyl-1H-imidazole-2-carboxamide obtained by the method described in Example (65c) (40 mg, 0.12 mmol) and ethyl 1-(bromoacetyl)cyclopropanecarboxylate obtained according to a method known in the literature

(Heterocycles, 63, 3, 2004, 699-706) (60 mg, 0.26 mmol), to obtain 23.5 mg of the title compound as a colorless oily substance (42%).

^1H NMR spectrum (400 MHz, CDCl_3) δ ppm: 1.12-1.31 (6H, m), 1.37-1.48 (2H, m), 1.53-1.63 (2H, m), 1.77-1.78 (1H, m),

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2.05-2.09 (1H, m), 2.69 (2H, q, $J = 7.64$ Hz), 3.00-3.02 (1H, m), 3.10-3.12 (1H, m), 3.41 (3H, s), 3.50 (1H, br s), 3.85-3.87 (1H, m), 4.10-4.25 (3H, m), 4.42-4.46 (1H, m), 6.68 (1H, s), 7.54 (1H, d, $J = 8.59$ Hz), 11.67 (1H, br s).

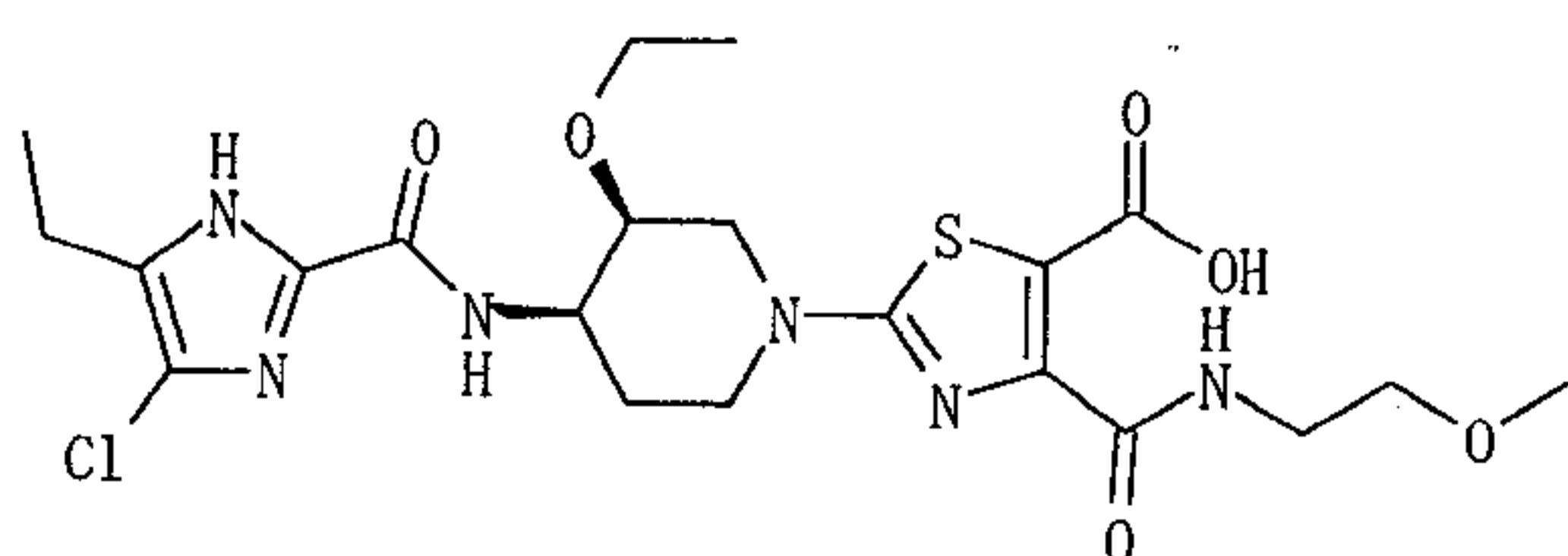
(67b) cis($\pm$)-[2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazol-4-yl]cyclopropanecarboxylic acid

The same operation as in Example (1i) was performed using ethyl cis($\pm$)-[2-(4-{[(4-chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazol-4-yl]cyclopropanecarboxylate obtained in Example (67a) (23.5 mg, 0.049 mmol) and a 2 N aqueous lithium hydroxide solution (0.8 mL), to obtain 14.3 mg of the title compound as a pale yellow solid (65%).

^1H NMR spectrum (400 MHz, DMSO- d_6) δ ppm: 1.14 (3H, t, $J = 7.53$ Hz), 1.25-1.30 (2H, m), 1.37-1.40 (2H, m), 1.64-1.67 (1H, m), 1.82-1.88 (1H, m), 2.55 (2H, q, $J = 7.53$ Hz), 3.14-3.21 (2H, m), 3.32 (3H, s), 3.52 (1H, br s), 3.72-3.76 (1H, m), 4.15-4.19 (2H, m), 6.73 (1H, s), 7.60 (1H, d, $J = 8.71$ Hz), 12.39 (1H, br s).

mass spectrum (ESI): m/z 454 ($M+H$) $^+$.

(Example 68) cis($\pm$)-2-(4-{[(4-Chloro-5-ethyl-1H-imidazol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-4-[(methoxyethyl)carbamoyl]-1,3-thiazole-5-carboxylic acid
(Exemplified Compound No. 68)



DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __4__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

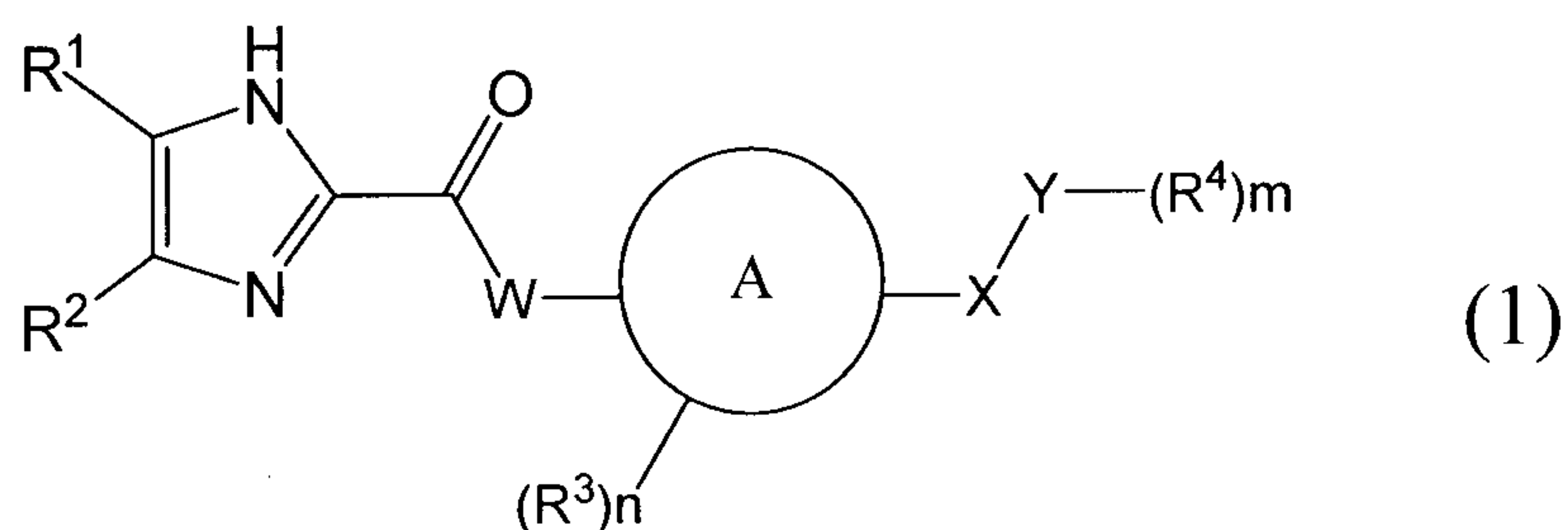
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The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A compound represented by the formula (1), a pharmacologically acceptable salt thereof, or a hydrate thereof:



wherein

R^1 and R^2 are each independently a hydrogen atom, a methyl group, an ethyl group, a propyl group, a 1-methylethyl group, a methoxymethyl group, a trifluoromethyl group, -S-methyl, a chlorine atom, a bromine atom, or an iodine atom;

W represents $-NR^5-$;

ring A represents an indan ring, a cyclohexene ring, an azetidine ring, a pyrrolidine ring, or a piperidine ring;

X represents a single bond, $-CH_2-$, or $-C(O)-$;

Y represents a single bond, a benzene ring group, a cyclopropane ring group, a pyrrolidine ring, an oxazole ring group, a benzoxazole ring group, a benzimidazole ring group, a thiazole ring group, a thiadiazole ring group, a thiophene ring group, a tetrazole ring group, a 1,4-dihydroquinoline ring group, a benzothiazole ring group, a pyrimidine ring group, a 5,6-dihydro-4H-pyrrolo[3,4-d][1,3]thiazole ring

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group, a 1,2-dihydropyridine ring group, or a pyridine ring group;

R^3 is a chlorine atom, an ethyl group, a methoxy group, an ethoxy group, a 2-fluoroethoxy group, a 2-difluoroethoxy group, a 1-methylethoxy group, a propoxy group, a 2-methylpropoxy group, a 2-difluoropropoxy group, a 3-fluoropropoxy group, -NH-2-methylpropyl, -NHCH(Et)₂, -NH-3-methylbutyl, -NH-butyl, -NH-pentyl, -NH-hexyl, -NH-benzyl, -NH-cyclobutyl, -NH-cyclopentyl, -NH-cyclopropylmethyl, or a butoxy group;

R^4 is a hydrogen atom, a halogen atom, a nitro group, a cyano group, an oxo group, a hydroxy group, a trifluoromethoxy group, an amino group, a carboxy group, a carbamoyl group, a mercapto group, a sulfamoyl group, a sulfo group, a formyl group, an ureido group, a hydroxyiminomethyl group, a (C₁-C₄) alkoxyiminomethyl group, an N-hydroxyformamide group, a (C₁-C₄) alkylhydrazino group, a hydrazinocarbonyl group, an N-hydroxyethanimidoyl group, a (C₁-C₄) alkyl group, a (C₂-C₄) alkenyl group, a (C₂-C₄) alkynyl group, a (C₁-C₄) alkoxy group, -CO(C₁-C₄) alkyl, -OC(O)(C₁-C₄) alkyl, -NH(C₁-C₄) alkyl, -N[di(C₁-C₄) alkyl], -NHC(O)(C₁-C₄) alkyl, -C(O)NH(C₁-C₄) alkyl, -C(O)N[di(C₁-C₄) alkyl], -C(O)NH(C₁-C₄) alkoxy, -NHC(O)NH(C₁-C₄) alkyl, -NHC(O)N[di(C₁-C₄) alkyl], -C(O)N[(C₁-C₄) alkyl][(C₁-C₄) alkoxy], -S(O)_a(C₁-C₄) alkyl (wherein a is 0, 1, or 2), -C(O)(C₁-C₄) alkoxy, -OC(O)(C₁-C₄) alkoxy, -NHC(O)(C₁-C₄) alkoxy, -S(O)₂NH(C₁-C₄) alkyl, -S(O)₂N[di(C₁-C₄) alkyl], -NHSO₂(C₁-C₄) alkyl, -C(O)NHSO₂(C₁-C₄) alkyl, -C(O)NHNH(C₁-C₄) alkyl, -C(O)NHN[di(C₁-C₄) alkyl], =CH(C₁-C₄) alkyl, =C[di(C₁-C₄)

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alkyl], =N(C₁-C₄) alkoxy, or =NN[di(C₁-C₄) alkyl], and R⁴ may be substituted with one or more R¹⁷ moiety/moieties;

R⁵ represents a hydrogen atom, a methyl group, an ethyl group, a 2-methoxyethyl group, a propyl group, a butyl group, a 1-methylethyl group, a 1,1-dimethylethyl group, a 1-methylpropyl group, or a 2-methylpropyl group;

n is an integer of 0, 1, 2, 3, or 4, wherein a plurality of R³ moieties are the same or different;

m is an integer of 0, 1, 2, 3, or 4, wherein a plurality of R⁴ moieties are the same or different; and

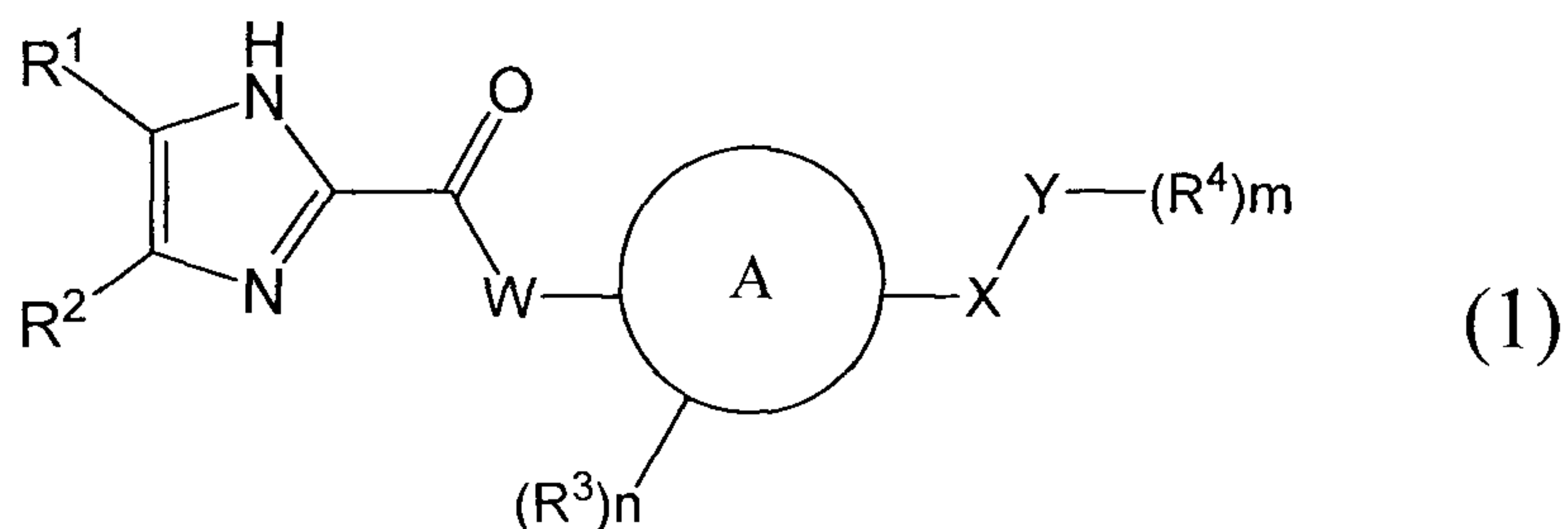
R¹⁷ is an azide group, a halogen atom, a nitro group, a cyano group, an oxo group, a hydroxy group, a trifluoromethoxy group, an amino group, a carboxy group, a carbamoyl group, a mercapto group, a sulfamoyl group, a (C₁-C₄) alkyl group, a (C₂-C₄) alkenyl group, a (C₂-C₄) alkynyl group, a (C₁-C₄) alkoxy group, a -CO(C₁-C₄) alkyl group, a -OC(O)(C₁-C₄) alkyl group, -OC(O)(C₁-C₄) alkoxy, a -NH(C₁-C₄) alkyl group, a -N[di(C₁-C₄) alkyl] group, a -NHC(O)(C₁-C₄) alkyl group, -C(O)NH(C₁-C₄) alkyl, -C(O)N[di(C₁-C₄) alkyl], -C(O)NH(C₁-C₄) alkoxy, -NHC(O)NH(C₁-C₄) alkyl, -NHC(O)N[di(C₁-C₄) alkyl], -C(O)N[(C₁-C₄) alkyl][(C₁-C₄) alkoxy], -S(O)_a(C₁-C₄) alkyl (wherein a is 0, 1, or 2), -C(O)(C₁-C₄) alkoxy, -S(O)₂NH(C₁-C₄) alkyl, -S(O)₂N[di(C₁-C₄) alkyl], -NHS(O)₂(C₁-C₄) alkyl, -NHC(O)(C₁-C₄) alkoxy, =CH(C₁-C₄) alkyl, =C[di(C₁-C₄) alkyl], =N(C₁-C₄) alkoxy, or =NN[di(C₁-C₄) alkyl].

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2. The compound, pharmacologically acceptable salt thereof, or hydrate thereof according to claim 1, wherein the ring A is an azetidine ring, a pyrrolidine ring, or a piperidine ring.

3. A pharmaceutical composition comprising a compound, pharmacologically acceptable salt thereof, or hydrate thereof as defined in claim 1 or claim 2, together with a pharmaceutically acceptable excipient or carrier.

4. Use of a compound represented by the formula (1), a pharmacologically acceptable salt thereof, or a hydrate thereof:



wherein

ring A represents an indan ring, a cyclohexane ring, a cyclohexene ring, an azetidine ring, a pyrrolidine ring, or a piperidine ring, and R^1 - R^4 , W, X, Y, n and m are as defined in claim 1 or claim 2, for producing a pharmaceutical agent for inhibiting bacterial DNA gyrase in a warm-blooded animal.

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5. Use of a compound, pharmacologically acceptable salt thereof, or hydrate thereof as defined in claim 4, for producing a pharmaceutical agent for producing an antibacterial effect in a warm-blooded animal.

6. Use of a compound, pharmacologically acceptable salt thereof, or hydrate thereof as defined in claim 4, for producing a pharmaceutical agent for treating bacterial infection in a warm-blooded animal.

7. Use of a compound, pharmacologically acceptable salt thereof, or hydrate thereof as defined in claim 4, for producing a pharmaceutical agent for treating or preventing infectious disease in a warm-blooded animal.

