

PCT REQUEST

Original (for SUBMISSION)

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared Using	JPO-PAS 0322
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	Japan Patent Office (RO/JP)
0-7	Applicant's or agent's file reference	P05-55
I	Title of Invention	THIAZOLE COMPOUND AND USE THEREOF
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IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
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V	DESIGNATIONS	
V-1	The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.	
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	17 May 2004 (17.05.2004)
VI-1-2	Number	2004-146834
VI-1-3	Country	JP
VI-2	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1
VII-1	International Searching Authority Chosen	Japan Patent Office (ISA/JP)

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VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	7	✓
IX-2	Description	81	✓
IX-3	Claims	5	✓
IX-4	Abstract	1	✓
IX-5	Drawings	0	✓
IX-7	TOTAL	94	
	Accompanying Items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	-	✓
IX-11	Copy of general power of attorney	-	✓
IX-17	PCT-SAFE physical media	-	-
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	Japanese	
X-1	Signature of applicant, agent or common representative	/100065215/	
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X-1-2	Name of signatory		
X-1-3	Capacity		

PCT REQUESTOriginal (for **SUBMISSION**)**FOR RECEIVING OFFICE USE ONLY**

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/JP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	
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DESCRIPTION

THIAZOLE COMPOUND AND USE THEREOF

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TECHNICAL FIELD

The present invention relates to a novel thiazole compound. The present invention further relates to a pharmaceutical composition comprising the thiazole compound.

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BACKGROUND ART

Researchers have recently discovered that cyclic adenosine 3',5'-monophosphate (cAMP), which acts as an intracellular second messenger, controls the activity of inflammatory cells, such as lymphocytes, neutrophils, eosinophiles, mast cells, etc. It is known that cAMP is degraded to 5'-AMP, which does not act as a messenger, by the action of phosphodiesterase (PDE), and that PDE adjusts the intracellular cAMP concentration. Since PDE has such a close relationship with the intracellular cAMP concentration, controlling PDE activity is believed to be effective against diseases for which therapeutic effects are expected to be exhibited by controlling the increase or decrease of the cAMP concentration (Non-Patent Documents 1 and 2).

Eleven types of PDE isozymes (PDEs 1 to 11) are known, and their in vivo distributions are known to vary among different tissues (Non-Patent Documents 3 and 4). Reportedly, inhibitors specific to PDE4 suppress the functions of inflammatory cells, and are believed to be useful against conjunctivitis, asthma and like inflammatory allergic diseases, and multiple sclerosis, articular rheumatism and like autoimmune diseases (Non-Patent Documents 5 to 14).

Theophylline has been hitherto used as a PDE inhibitor for treating asthma. However, theophylline is known to nonspecifically inhibit various PDE isozymes, and thus inhibits not only PDE4 but also PDE3 and other isozymes. The inhibition of

- [Non-Patent Document 13] Clin. Exp. Immunol. 108: 415-419, 1997
[Non-Patent Document 14] J. Immunol. 159: 6253-6259, 1997
[Non-Patent Document 15] Physiol. Rev. 76: 725-748, 1995
[Non-Patent Document 16] J. Clin. Pathol. 54: 577-589, 2001
5 [Non-Patent Document 17] Curr. Drug Targets Inflamm. Allergy 1:
377-392, 2002
[Non-Patent Document 18] Curr. Opin. Pharmacol. 3: 449-455, 2003
[Non-Patent Document 19] J. Infus. Nurs. 26: 319-325, 2003

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DISCLOSURE OF THE INVENTION

[Problems to be Solved by the Invention]

An object of the present invention is to solve the above problems of the prior art. Specifically, an object of the present invention is to provide a novel thiazole compound that
15 has specific inhibitory activity against PDE4, and a pharmaceutical composition comprising the compound. Another object of the present invention is to provide a PDE4 inhibitor that exhibits specific inhibitory activity against PDE4. A further object of the present invention is to provide a
20 preventive or therapeutic agent for atopic dermatitis, and a method for treating atopic dermatitis.

[Means for Solving the problems]

The present inventors searched for a new compound that
25 has PDE4 inhibitory activity, and found that a thiazole compound with a new structure has strong PDE4 inhibitory activity that is highly specific and dissociated from HARBS binding activity. The inventors further found that the thiazole compound exhibits preventive or therapeutic effects against atopic dermatitis
30 because of its PDE4 inhibitory activity.

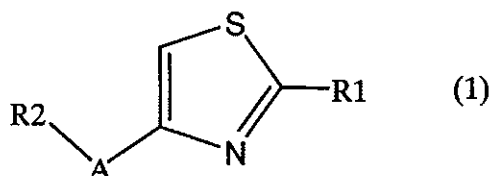
The inventors further found that the thiazole compound also exhibits TNF- α production inhibitory activity and IL-4 production inhibitory activity. In chronic inflammatory diseases, such as autoimmune diseases and allergic diseases, cytokines
35 produced by immunocompetent cells are known as important

inflammation mediators. Among such cytokines, tumor necrosis factor (TNF)- α and interleukin (IL)-4 are believed to play important roles (Non-Patent Documents 16 to 19). Accordingly, compounds with TNF- α production inhibitory activity or IL-4 production inhibitory activity are clinically useful.

The present invention was accomplished by conducting further research based on the above findings.

The present invention provides the following thiazole compounds.

1. A compound represented by Formula (1), an optical isomer thereof, or a salt thereof:



- wherein R1 is a di-C₁₋₆ alkoxyphenyl group;
R2 is any one of the following groups (a) to (t):
(a) a phenyl group in which the phenyl ring may be substituted with one or more members selected from the group consisting of (a-1) hydroxy groups, (a-2) halogen atoms, (a-3) unsubstituted or halogen-substituted C₁₋₆ alkyl groups, (a-4) unsubstituted or halogen-substituted C₁₋₆ alkoxy groups, (a-5) C₁₋₆ alkoxy-C₁₋₆ alkoxy groups, (a-6) amino-C₁₋₆ alkoxy groups which may be substituted with a C₁₋₆ alkyl group or groups, (a-7) methylenedioxy groups, (a-8) carboxyl groups, (a-9) phenoxy groups, (a-10) C₁₋₆ alkoxy carbonyl groups, (a-11) C₁₋₆ alkanoyloxy groups, (a-12) C₁₋₆ alkanoyl groups, (a-13) cyano groups, (a-14) nitro groups, (a-15) C₁₋₆ alkyl carbamoyl groups, (a-16) aminosulfonyl groups, (a-17) amino groups which may be substituted with a C₁₋₆ alkyl group or groups, (a-18) C₁₋₆ alkanoylamino groups, (a-19) C₁₋₆ alkylthio groups, (a-20) phenyl groups, (a-21) pyrazolyl groups, (a-22) imidazolyl groups, (a-23) triazolyl groups, (a-24) morpholino groups, (a-25) pyrrolidinyl

- groups, (a-26) piperazinylcarbonyl groups which may be substituted with a C₁₋₆ alkyl group or groups, and (a-27) phenyl-C₁₋₆ alkoxy groups;
- (b) a naphthyl group;
- 5 (c) a pyridyl group in which the pyridine ring may be substituted with one or more members selected from the group consisting of (c-1) hydroxy groups, (c-2) C₁₋₆ alkyl groups, (c-3) C₁₋₆ alkoxy groups, (c-4) phenyl-C₁₋₆ alkoxy groups, and (c-5) C₁₋₆ alkoxy carbonyl groups;
- 10 (d) a furyl group in which the furan ring may be substituted with a C₁₋₆ alkyl group or groups;
- (e) a thienyl group in which the thiophene ring may be substituted with one or more members selected from the group consisting of (e-1) halogen atoms, (e-2) C₁₋₆ alkyl groups, and
- 15 (e-3) C₁₋₆ alkoxy groups;
- (f) an isoxazolyl group in which the isoxazolyl ring may be substituted with a C₁₋₆ alkyl group or groups;
- (g) a thiazolyl group in which the thiazole ring may be substituted with one or more members selected from the group
- 20 consisting of (g-1) C₁₋₆ alkyl groups, and (g-2) phenyl groups which may be substituted with a C₁₋₆ alkoxy group or groups;
- (h) a pyrrolyl group in which the pyrrole ring may be substituted with a C₁₋₆ alkyl group or groups;
- (i) an imidazolyl group in which the imidazole ring may be
- 25 substituted with a C₁₋₆ alkyl group or groups;
- (j) a tetrazolyl group;
- (k) a pyrazinyl group;
- (l) a thienothienyl group;
- (m) a benzothienyl group;
- 30 (n) an indolyl group in which the indole ring may be substituted with a C₁₋₆ alkoxy group or groups;
- (o) a benzimidazolyl group in which the benzimidazole ring may be substituted with a C₁₋₆ alkyl group or groups;
- (p) an indazolyl group;
- 35 (q) a quinolyl group;

(r) a 1,2,3,4-tetrahydroquinolyl group in which the 1,2,3,4-tetrahydroquinoline ring may be substituted with an oxo group or groups;

(s) a quinoxalinyl group; and

5 (t) a 1,3-benzodioxolyl group; and

A is any one of the following groups (i) to (vi):

(i) -CO-B- wherein B is a C₁₋₆ alkylene group;

(ii) -CO-Ba- wherein Ba is a C₂₋₆ alkenylene group;

(iii) -CH(OH)-B- wherein B is as defined above;

10 (iv) -COCH(COOR₃)-Bb- wherein R₃ is a C₁₋₆ alkyl group and Bb is a C₁₋₆ alkylene group; and

(v) -Bc- wherein Bc is a C₂₋₆ alkylene group.

2. A compound according to Item 1, wherein, in Formula (1), R₁ is a 3,4-di-C₁₋₆ alkoxyphenyl group; an optical isomer
15 thereof; or a salt thereof.

3. A compound according to Item 1, wherein, in Formula (1), R₁ is a 3,4-dimethoxyphenyl group or a 3,4-diethoxyphenyl group; an optical isomer thereof; or a salt thereof.

4. A compound according to any one of Items 1 to 3,
20 wherein, in Formula (1), R₂ is (a) a phenyl group in which the phenyl ring may be substituted with one or more members selected from the group consisting of (a-1) hydroxy groups, (a-2) halogen atoms, (a-3) unsubstituted or halogen-substituted C₁₋₆ alkyl groups, (a-4) unsubstituted or halogen-substituted C₁₋₆ alkoxy groups, (a-5) C₁₋₆ alkoxy-C₁₋₆ alkoxy groups, (a-6) amino-C₁₋₆
25 alkoxy groups which may be substituted with a C₁₋₆ alkyl group or groups, (a-7) methylenedioxy groups, (a-8) carboxyl groups, (a-9) phenoxy groups, (a-10) C₁₋₆ alkoxy-carbonyl groups, (a-11) C₁₋₆ alkanoyloxy groups, (a-12) C₁₋₆ alkanoyl groups, (a-13) cyano groups, (a-14) nitro groups, (a-15) C₁₋₆ alkylcarbamoyl groups, (a-16) aminosulfonyl groups, (a-17) amino groups which may be
30 substituted with a C₁₋₆ alkyl group or groups, (a-18) C₁₋₆ alkanoylamino groups, (a-19) C₁₋₆ alkylthio groups, (a-20) phenyl groups, (a-21) pyrazolyl groups, (a-22) imidazolyl groups, (a-23) triazolyl groups, (a-24) morpholino groups, (a-25) pyrrolidinyl
35

groups, (a-26) piperazinylcarbonyl groups which may be substituted with a C₁₋₆ alkyl group or groups, and (a-27) phenyl-C₁₋₆ alkoxy groups;

5 (c) a pyridyl group in which the pyridine ring may be substituted with one or more members selected from the group consisting of (c-1) hydroxy groups, (c-2) C₁₋₆ alkyl groups, (c-3) C₁₋₆ alkoxy groups, (c-4) phenyl-C₁₋₆ alkoxy groups, and (c-5) C₁₋₆ alkoxy carbonyl groups;

10 (d) a furyl group in which the furan ring may be substituted with a C₁₋₆ alkyl group or groups;

(e) a thienyl group in which the thiophene ring may be substituted with one or more members selected from the group consisting of (e-1) halogen atoms, (e-2) C₁₋₆ alkyl groups, and (e-3) C₁₋₆ alkoxy groups;

15 (g) a thiazolyl group in which the thiazole ring may be substituted with one or more members selected from the group consisting of (g-1) C₁₋₆ alkyl groups, and (g-2) phenyl groups which may be substituted with a C₁₋₆ alkoxy group or groups;

20 (h) a pyrrolyl group in which the pyrrole ring may be substituted with a C₁₋₆ alkyl group or groups; or

(i) an imidazolyl group in which the imidazole ring may be substituted with a C₁₋₆ alkyl group or groups; an optical isomer thereof; or a salt thereof.

5. A compound according to any one of Items 1 to 3,
25 wherein, in Formula (1), R₂ is (a) a phenyl group in which the phenyl ring may be substituted with one or more members selected from the group consisting of (a-1) hydroxy groups, (a-2) halogen atoms, (a-3) unsubstituted or halogen-substituted C₁₋₆ alkyl groups, (a-4) unsubstituted or halogen-substituted C₁₋₆ alkoxy groups, (a-5) C₁₋₆ alkoxy-C₁₋₆ alkoxy groups, (a-6) amino-C₁₋₆
30 alkoxy groups which may be substituted with a C₁₋₆ alkyl group or groups, (a-7) methylenedioxy groups, (a-8) carboxyl groups, (a-9) phenoxy groups, (a-10) C₁₋₆ alkoxy carbonyl groups, (a-11) C₁₋₆ alkanoyloxy groups, (a-12) C₁₋₆ alkanoyl groups, (a-13) cyano
35 groups, (a-14) nitro groups, (a-15) C₁₋₆ alkyl carbamoyl groups,

(a-16) aminosulfonyl groups, (a-17) amino groups which may be substituted with a C₁₋₆ alkyl group or groups, (a-18) C₁₋₆ alkanoylamino groups, (a-19) C₁₋₆ alkylthio groups, (a-20) phenyl groups, (a-21) pyrazolyl groups, (a-22) imidazolyl groups, (a-23) triazolyl groups, (a-24) morpholino groups, (a-25) pyrrolidinyl groups, (a-26) piperazinylcarbonyl groups which may be substituted with a C₁₋₆ alkyl group or groups, and (a-27) phenyl-C₁₋₆ alkoxy groups;

(c) a pyridyl group in which the pyridine ring may be substituted with one or more members selected from the group consisting of (c-1) hydroxy groups, (c-2) C₁₋₆ alkyl groups, (c-3) C₁₋₆ alkoxy groups, (c-4) phenyl-C₁₋₆ alkoxy groups, and (c-5) C₁₋₆ alkoxy carbonyl groups; or

(g) a thiazolyl group in which the thiazole ring may be substituted with one or more members selected from the group consisting of (g-1) C₁₋₆ alkyl groups, and (g-2) phenyl groups which may be substituted with a C₁₋₆ alkoxy group or groups; an optical isomer thereof; or a salt thereof.

6. A compound according to any one of Items 1 to 5, wherein, in Formula (1), A is (i) -CO-B- wherein B is a methylene group, an ethylene group or a trimethylene group; (ii) -CO-Ba- wherein Ba is a vinylidene group; (iii) -CH(OH)-B- wherein B is a methylene group or an ethylene group; (iv) -COCH(COOR₃)-Bb- wherein R₃ is a methyl group, an ethyl group or a tert-butyl group and Bb is a methylene group or an ethylene group; or (v) -Bc- wherein Bc is an ethylene group, a trimethylene group or a tetramethylene group; an optical isomer thereof; or a salt thereof.

7. A compound according to any one of Items 1 to 5, wherein, in Formula (1), A is (i) -CO-B- wherein B is an ethylene group; (iii) -CH(OH)-B- wherein B is an ethylene group; (iv) -COCH(COOR₃)-Bb- wherein R₃ is a methyl group and Bb is a methylene group; or (v) -Bc- wherein Bc is a trimethylene group; an optical isomer thereof; or a salt thereof.

8. A compound according to Item 1, wherein, in Formula

(1), R1 is a 3,4-di-C₁₋₆ alkoxyphenyl group;

- R2 is (a) a phenyl group in which the phenyl ring may be substituted with one or more members selected from the group consisting of (a-1) hydroxy groups, (a-2) halogen atoms, (a-3) unsubstituted or halogen-substituted C₁₋₆ alkyl groups, (a-4) unsubstituted or halogen-substituted C₁₋₆ alkoxy groups, (a-5) C₁₋₆ alkoxy-C₁₋₆ alkoxy groups, (a-6) amino-C₁₋₆ alkoxy groups which may be substituted with a C₁₋₆ alkyl group or groups, (a-7) methylenedioxy groups, (a-8) carboxyl groups, (a-9) phenoxy groups, (a-10) C₁₋₆ alkoxy carbonyl groups, (a-11) C₁₋₆ alkanoyloxy groups, (a-12) C₁₋₆ alkanoyl groups, (a-13) cyano groups, (a-14) nitro groups, (a-15) C₁₋₆ alkyl carbamoyl groups, (a-16) aminosulfonyl groups, (a-17) amino groups which may be substituted with a C₁₋₆ alkyl group or groups, (a-18) C₁₋₆ alkanoylamino groups, (a-19) C₁₋₆ alkylthio groups, (a-20) phenyl groups, (a-21) pyrazolyl groups, (a-22) imidazolyl groups, (a-23) triazolyl groups, (a-24) morpholino groups, (a-25) pyrrolidinyl groups, (a-26) piperazinyl carbonyl groups which may be substituted with a C₁₋₆ alkyl group or groups, and (a-27) phenyl-C₁₋₆ alkoxy groups;
- (c) a pyridyl group in which the pyridine ring may be substituted with one or more members selected from the group consisting of (c-1) hydroxy groups, (c-2) C₁₋₆ alkyl groups, (c-3) C₁₋₆ alkoxy groups, (c-4) phenyl-C₁₋₆ alkoxy groups, and (c-5) C₁₋₆ alkoxy carbonyl groups;
- (d) a furyl group in which the furan ring may be substituted with a C₁₋₆ alkyl group or groups;
- (e) a thienyl group in which the thiophene ring may be substituted with one or more members selected from the group consisting of (e-1) halogen atoms, (e-2) C₁₋₆ alkyl groups, and (e-3) C₁₋₆ alkoxy groups;
- (g) a thiazolyl group in which the thiazole ring may be substituted with one or more members selected from the group consisting of (g-1) C₁₋₆ alkyl groups, and (g-2) phenyl groups which may be substituted with a C₁₋₆ alkoxy group or groups;

(h) a pyrrolyl group in which the pyrrole ring may be substituted with one or more C₁₋₆ alkyl groups;

(i) an imidazolyl group in which the imidazole ring may be substituted with a C₁₋₆ alkyl group or groups; and

5 A is (i) -CO-B- wherein B is as defined above;

(ii) -CO-Ba wherein Ba is as defined above; (iii) -CH(OH)-B-

wherein B is as defined above; (iv) -COCH(COOR₃)-Bb- wherein R₃

and Bb are as defined above; or (v) -Bc- wherein Bc is as defined above; an optical isomer thereof; or a salt thereof.

10 9. A compound according to Item 1, wherein, in Formula (1), R₁ is a 3,4-di-C₁₋₆ alkoxyphenyl group;

R₂ is (a) a phenyl group in which the phenyl ring may be substituted with one or more members selected from the group consisting of (a-1) hydroxy groups, (a-2) halogen atoms, (a-3) unsubstituted or halogen-substituted C₁₋₆ alkyl groups, (a-4) unsubstituted or halogen-substituted C₁₋₆ alkoxy groups, (a-5) C₁₋₆ alkoxy-C₁₋₆ alkoxy groups, (a-6) amino-C₁₋₆ alkoxy groups which may be substituted with a C₁₋₆ alkyl group or groups, (a-7) methylenedioxy groups, (a-8) carboxyl groups, (a-9) phenoxy groups, (a-10) C₁₋₆ alkoxycarbonyl groups, (a-11) C₁₋₆ alkanoyloxy groups, (a-12) C₁₋₆ alkanoyl groups, (a-13) cyano groups, (a-14) nitro groups, (a-15) C₁₋₆ alkylcarbamoyl groups, (a-16) aminosulfonyl groups, (a-17) amino groups which may be substituted with a C₁₋₆ alkyl group or groups, (a-18) C₁₋₆ alkanoylamino groups, (a-19) C₁₋₆ alkylthio groups, (a-20) phenyl groups, (a-21) pyrazolyl groups, (a-22) imidazolyl groups, (a-23) triazolyl groups, (a-24) morpholino groups, (a-25) pyrrolidinyl groups, (a-26) piperazinylcarbonyl groups which may be substituted with a C₁₋₆ alkyl group or groups, and (a-27) phenyl-C₁₋₆ alkoxy groups;

(c) a pyridyl group in which the pyridine ring may be substituted with one or more members selected from the group consisting of (c-1) hydroxy groups, (c-2) C₁₋₆ alkyl groups, (c-3) C₁₋₆ alkoxy groups, (c-4) phenyl-C₁₋₆ alkoxy groups, and (c-5) C₁₋₆ alkoxycarbonyl groups;

- (d) a furyl group in which the furan ring may be substituted with a C₁₋₆ alkyl group or groups;
- (e) a thienyl group in which the thiophene ring may be substituted with one or more members selected from the group consisting of (e-1) halogen atoms, (e-2) C₁₋₆ alkyl groups, and (e-3) C₁₋₆ alkoxy groups;
- (g) a thiazolyl group in which the thiazole ring may be substituted with one or more members selected from the group consisting of (g-1) C₁₋₆ alkyl groups, and (g-2) phenyl groups which may be substituted with a C₁₋₆ alkoxy group or groups;
- (h) a pyrrolyl group in which the pyrrole ring may be substituted with a C₁₋₆ alkyl group or groups; or
- (i) an imidazolyl group in which the imidazole ring may be substituted with a C₁₋₆ alkyl group or groups; and

15 A is (i) -CO-B- wherein B is a methylene group, an ethylene group or a trimethylene group; (ii) -CO-Ba- wherein Ba is a vinylidene group; (iii) -CH(OH)-B- wherein B is a methylene group or an ethylene group; (iv) -COCH(COOR₃)-Bb- wherein R₃ is a methyl group, an ethyl group or a tert-butyl group and Bb is a methylene group or an ethylene group; or (v) -Bc- wherein Bc is an ethylene group, a trimethylene group or a tetramethylene group; an optical isomer thereof; or a salt thereof.

10. A compound according to Item 1, wherein, in Formula (1), R₁ is a 3,4-di-C₁₋₆ alkoxyphenyl group;

25 R₂ is (a) a phenyl group in which the phenyl ring may be substituted with one or more members selected from the group consisting of (a-1) hydroxy groups, (a-2) halogen atoms, (a-3) unsubstituted or halogen-substituted C₁₋₆ alkyl groups, (a-4) unsubstituted or halogen-substituted C₁₋₆ alkoxy groups, (a-5) C₁₋₆ alkoxy-C₁₋₆ alkoxy groups, (a-6) amino-C₁₋₆ alkoxy groups which may be substituted with a C₁₋₆ alkyl group or groups, (a-7) methylenedioxy groups, (a-8) carboxyl groups, (a-9) phenoxy groups, (a-10) C₁₋₆ alkoxycarbonyl groups, (a-11) C₁₋₆ alkanoyloxy groups, (a-12) C₁₋₆ alkanoyl groups, (a-13) cyano groups, (a-14) nitro groups, (a-15) C₁₋₆ alkylcarbamoyl groups, (a-16)

- aminosulfonyl groups, (a-17) amino groups which may be substituted with a C₁₋₆ alkyl group or groups, (a-18) C₁₋₆ alkanoylamino groups, (a-19) C₁₋₆ alkylthio groups, (a-20) phenyl groups, (a-21) pyrazolyl groups, (a-22) imidazolyl groups, (a-23) triazolyl groups, (a-24) morpholino groups, (a-25) pyrrolidinyl groups, (a-26) piperazinylcarbonyl groups which may be substituted with a C₁₋₆ alkyl group or groups, and (a-27) phenyl-C₁₋₆ alkoxy groups;
- (c) a pyridyl group in which the pyridine ring may be substituted with one or more members selected from the group consisting of (c-1) hydroxy groups, (c-2) C₁₋₆ alkyl groups, (c-3) C₁₋₆ alkoxy groups, (c-4) phenyl-C₁₋₆ alkoxy groups, and (c-5) C₁₋₆ alkoxycarbonyl groups; or
- (g) a thiazolyl group in which the thiazole ring may be substituted with one or more members selected from the group consisting of (g-1) C₁₋₆ alkyl groups, and (g-2) phenyl groups which may be substituted with a C₁₋₆ alkoxy group or groups; and
- A is (i) -CO-B- wherein B is an ethylene group;
- (iii) -CH(OH)-B- wherein B is an ethylene group;
- (iv) -COCH(COOR₃)-B_b- wherein R₃ is a methyl group and B_b is a methylene group; or (v) -B_c- wherein B_c is a trimethylene group.

The present invention further provide the following uses of the above thiazole compounds:

11. A pharmaceutical composition comprising a compound according to any one of Items 1 to 10, an optical isomer thereof, or a salt thereof.
12. A phosphodiesterase 4 inhibitor comprising as an active ingredient a compound according to any one of Items 1 to 10, an optical isomer thereof, or a salt thereof.
13. An IFN- α production inhibitor comprising as an active ingredient a compound according to any one of Items 1 to 10, an optical isomer thereof, or a salt thereof.
14. An IL-4 production inhibitor comprising as an active ingredient a compound according to any one of Items 1 to

10, an optical isomer thereof, or a salt thereof.

15 15. A preventive or therapeutic agent for atopic dermatitis, comprising as an active ingredient a compound according to any one of Items 1 to 10, an optical isomer thereof, or a salt thereof.

16. A method for treating atopic dermatitis, comprising the step of administering to a human or non-human mammal an effective amount of a compound according to any one of Items 1 to 10, an optical isomer thereof, or a salt thereof.

10 17. Use of a compound according to any one of Items 1 to 10, an optical isomer thereof, or a salt thereof, for producing a preventive or therapeutic agent for atopic dermatitis.

15 18. Use of a compound according to any one of Items 1 to 10, an optical isomer thereof, or a salt thereof, for producing a phosphodiesterase 4 inhibitor.

19. Use of a compound according to any one of Items 1 to 10, an optical isomer thereof, or a salt thereof, for producing an IFN- α production inhibitor.

20 20. Use of a compound according to any one of Items 1 to 10, an optical isomer thereof, or a salt thereof, for producing an IL-4 production inhibitor.

BEST MODE FOR CARRYING OUT THE INVENTION

25 The present invention is described below in further detail.

(I) Compound represented by Formula (1)

In Formula (1), R1 represents a di-C₁₋₆ alkoxyphenyl group, i.e., a phenyl group substituted with two C₁₋₆ straight- or branched-chain alkoxy groups. Specific examples include 2,3-
30 dimethoxyphenyl, 2,4-dimethoxyphenyl, 2,5-dimethoxyphenyl, 2,6-dimethoxyphenyl, 3,4-dimethoxyphenyl, 3,5-dimethoxyphenyl, 2,3-diethoxyphenyl, 2,4-diethoxyphenyl, 2,5-diethoxyphenyl, 2,6-diethoxyphenyl, 3,4-diethoxyphenyl, 3,5-diethoxyphenyl, 2,3-dipropoxyphenyl, 2,4-dipropoxyphenyl, 2,5-dipropoxyphenyl, 2,6-
35 dipropoxyphenyl, 3,4-dipropoxyphenyl, 3,5-dipropoxyphenyl, 2,3-

diisopropoxyphenyl, 2,4-diisopropoxyphenyl, 2,5-diisopropoxyphenyl, 2,6-diisopropoxyphenyl, 3,4-diisopropoxyphenyl, 3,5-diisopropoxyphenyl, 2,3-dibutoxyphenyl, 2,4-dibutoxyphenyl, 2,5-dibutoxyphenyl, 2,6-dibutoxyphenyl, 3,4-dibutoxyphenyl, 3,5-dibutoxyphenyl, 2,3-dipentoxyphenyl, 2,4-dipentoxyphenyl, 2,5-dipentoxyphenyl, 2,6-dipentoxyphenyl, 3,4-dipentoxyphenyl, 3,5-dipentoxyphenyl, 2,3-dihexyloxyphenyl, 2,4-dihexyloxyphenyl, 2,5-dihexyloxyphenyl, 2,6-dihexyloxyphenyl, 3,4-dihexyloxyphenyl, 3,5-dihexyloxyphenyl and the like. R1 in
10 Formula (1) is preferably a 3,4-di-C₁₋₆ alkoxyphenyl group, more preferably a 3,4-di-C₁₋₃ alkoxyphenyl group, and especially preferably a 3,4-dimethoxyphenyl group or a 3,4-diethoxyphenyl group.

In Formula (1), R2 represents (a) a phenyl group, (b) a
15 naphthyl group, (c) a pyridyl group, (d) a furyl group, (e) a thienyl group, (f) an isoxazolyl group, (g) a thiazolyl group, (h) a pyrrolyl group, (i) an imidazolyl group, (j) a tetrazolyl group, (k) a pyrazinyl group, (l) a thienothienyl group, (m) a benzothienyl group, (n) an indolyl group, (o) a benzimidazolyl
20 group, (p) an imidazolyl group, (q) a quinolyl group, (r) a 3,4-dihydrocarbostyryl group, (s) a quinoxaliny group, or (t) a 1,3-benzodioxolyl group.

When R2 is (a) a phenyl group, the phenyl ring of the phenyl group may be substituted with one or more members selected
25 from the group consisting of (a-1) hydroxy groups, (a-2) halogen atoms, (a-3) unsubstituted or halogen-unsubstituted C₁₋₆ alkyl groups, (a-4) unsubstituted or halogen-substituted C₁₋₆ alkoxy groups, (a-5) C₁₋₆ alkoxy-C₁₋₆ alkoxy groups, (a-6) amino-C₁₋₆ alkoxy groups which may be substituted with a C₁₋₆ alkyl group or
30 groups, (a-7) methylenedioxy groups, (a-8) carboxyl groups, (a-9) phenoxy groups, (a-10) C₁₋₆ alkoxy-carbonyl groups, (a-11) C₁₋₆ alkanoyloxy groups, (a-12) C₁₋₆ alkanoyl groups, (a-13) cyano groups, (a-14) nitro groups, (a-15) C₁₋₆ alkylcarbamoyl groups, (a-16) aminosulfonyl groups, (a-17) amino groups which may be
35 substituted with a C₁₋₆ alkyl group or groups, (a-18) C₁₋₆

alkanoylamino groups, (a-19) C₁₋₆ alkylthio groups, (a-20) phenyl groups, (a-21) pyrazolyl groups, (a-22) imidazolyl groups, (a-23) triazolyl groups, (a-24) morpholino groups, (a-25) pyrrolidinyl groups, and (a-26) piperazinylcarbonyl groups which may be

- 5 substituted with a C₁₋₆ alkyl group or groups. When R₂ is a substituted phenyl group, the number of substituents is not limited, and may be, for example, 1 to 5, and preferably 1 to 3.

- When R₂ is (c) a pyridyl group, the pyridine ring of the pyridyl group may be substituted with one or more members
10 selected from the group consisting of (c-1) hydroxy groups, (c-2) C₁₋₆ alkyl groups, (c-3) C₁₋₆ alkoxy groups, and (c-4) phenyl-C₁₋₆ alkoxy groups. When R₂ is a substituted pyridyl group, the number of substituents is not limited, and may be, for example, 1 to 4, and preferably 1 to 3.

- 15 When R₂ is (d) a furyl group, the furan ring of the furyl group may be substituted with a C₁₋₆ alkyl group or groups. When R₂ is a substituted furyl group, the number of substituents is not limited, and may be, for example, 1 to 3, and preferably 1 or 2.

- 20 When R₂ is (e) a thienyl group, the thiophene ring of the thienyl group may be substituted with one or more members selected from the group consisting of (e-1) halogen atoms, (e-2) C₁₋₆ alkyl groups, and (e-3) C₁₋₆ alkoxy groups. When R₂ is a substituted thienyl group, the number of substituents is not
25 limited, and may be, for example, 1 to 3, and preferably 1 or 2.

- When R₂ is (f) an isooxazolyl group, the isooxazolyl ring of the isooxazolyl group may be substituted with a C₁₋₆ alkyl group or groups. When R₂ is a substituted isooxazolyl group, the number of substituents is not limited, and may be, for example, 1
30 or 2.

- When R₂ is (g) a thiazolyl group, the thiazole ring of the thiazolyl group may be substituted with one or more members selected from the group consisting of (g-1) C₁₋₆ alkyl groups and (g-2) phenyl groups which may be substituted with a C₁₋₆ alkoxy
35 group or groups. When R₂ is a substituted thiazolyl group, the

number of substituents is not limited, and may be, for example, 1 to 2.

When R2 is (h) a pyrrolyl group, the pyrrole ring of the pyrrolyl group may be substituted with a C₁₋₆ alkyl group or groups. When R2 is a substituted pyrrolyl group, the number of substituents is not limited, and may be, for example, 1 to 4, and preferably 1 or 2.

When R2 is (i) an imidazolyl group, the imidazole ring of the imidazolyl group may be substituted with a C₁₋₆ alkyl group or groups. When R2 is a substituted imidazolyl group, the number of substituents is not limited, and may be, for example, 1 to 3, and preferably 1 or 2.

When R2 is (o) a benzimidazolyl group, the benzimidazole ring of the benzimidazolyl group may be substituted with a C₁₋₆ alkyl group or groups. When R2 is a substituted benzimidazolyl group, the number of substituents is not limited, and may be, for example, 1 to 5, and preferably 1 to 3.

When R2 is (n) an indolyl group, the indole ring of the indolyl group may be substituted with a C₁₋₆ alkyl group or groups. When R2 is a substituted indolyl group, the number of substituents is not limited, and may be, for example, 1 to 6, and preferably 1 to 3.

When R2 is (r) a 1,2,3,4-tetrahydroquinolyl group, the 1,2,3,4-tetrahydroquinoline ring of the 1,2,3,4-tetrahydroquinolyl group may be substituted with an oxo group or groups. When R2 is an oxo-substituted 1,2,3,4-tetrahydroquinolyl group, the number of oxo groups is not limited, and may be, for example, 1 to 3, and preferably 1 or 2.

The terms used in the description of the groups represented by R2 in Formula (1) are defined as follows.

Halogen atoms include fluorine atoms, chlorine atoms, bromine atoms, iodine atoms and the like.

C₁₋₆ alkyl groups are straight- or branched-chain alkyl groups with 1 to 6 carbon atoms. Examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, n-

pentyl, neopentyl, n-hexyl, isohexyl, 3-methylpentyl, etc.

Unsubstituted or halogen-substituted C₁₋₆ alkyl groups are straight- or branched-chain alkyl groups with 1 to 6 carbon atoms as defined above, or such alkyl groups substituted with 1
5 to 7 halogen atoms. Examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, n-pentyl, neopentyl, n-hexyl, isohexyl, 3-methylpentyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, bromomethyl, dibromomethyl, dichlorofluoromethyl,
10 2,2,2-trifluoroethyl, pentafluoroethyl, 2-chloroethyl, 3,3,3-trifluoropropyl, heptafluoropropyl, heptafluoroisopropyl, 3-chloropropyl, 2-chloropropyl, 3-bromopropyl, 4,4,4-trifluorobutyl, 4,4,4,3,3-pentafluorobutyl, 4-chlorobutyl, 4-bromobutyl, 2-chlorobutyl, 5,5,5-trifluoropentyl, 5-chloropentyl, 6,6,6-
15 trifluorohexyl, 6-chlorohexyl, etc.

C₁₋₆ alkoxy groups are groups composed of a C₁₋₆ alkyl group as defined above and oxygen. Examples include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, sec-butoxy, n-pentoxy, neopentoxy, n-hexyloxy, isohexyloxy, 3-
20 methylpentoxy, etc.

Unsubstituted or halogen-substituted C₁₋₆ alkoxy groups are C₁₋₆ alkoxy groups as defined above, or such alkoxy groups substituted with 1 to 7 halogen atoms. Examples include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, sec-butoxy, n-pentoxy, neopentoxy, n-hexyloxy, isohexyloxy, 3-
25 methylpentoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy, trichloromethoxy, bromomethoxy, dibromomethoxy, dichlorofluoromethoxy, 2,2,2-trifluoroethoxy, pentafluoroethoxy, 2-chloroethoxy, 3,3,3-trifluoropropoxy, heptafluoropropoxy, heptafluoroisopropoxy, 3-chloropropoxy, 2-
30 chloropropoxy, 3-bromopropoxy, 4,4,4-trifluorobutoxy, 4,4,4,3,3-pentafluorobutoxy, 4-chlorobutoxy, 4-bromobutoxy, 2-chlorobutoxy, 5,5,5-trifluoropentoxy, 5-chloropentoxy, 6,6,6-trifluorohexyloxy, 6-chlorohexyloxy, etc.

35 C₁₋₆ alkoxy-C₁₋₆ alkoxy groups are C₁₋₆ alkoxy groups

substituted with 1 to 7 C₁₋₆ alkoxy groups as defined above.

Examples include methoxymethoxy, 2-methoxyethoxy, 3-methoxypropoxy, 4-methoxybutoxy, 5-methoxypentoxy, 6-methoxyhexyloxy, ethoxymethoxy, 1-ethoxyethoxy, 2-ethoxyethoxy,
5 3-ethoxypropoxy, 2-isopropoxyethoxy, tert-butoxymethoxy, 2-(tert-butoxy)ethoxy, 3-(tert-butoxy)propoxy, 6-(tert-butoxy)hexyloxy, 4-(tert-butoxy)butoxy, etc.

Amino-C₁₋₆ alkoxy groups which may be substituted with a C₁₋₆ alkyl group or groups are aminoalkoxy groups in which the
10 alkoxy moiety is a C₁₋₆ straight- or branched-chain alkoxy group and in which 1 to 2 C₁₋₆ alkyl groups may be substituted on the nitrogen atom. Examples of such aminoalkoxy groups include aminomethoxy, 2-aminoethoxy, 1-aminoethoxy, 3-aminopropoxy, 4-aminobutoxy, 5-aminopentyloxy, 6-aminohexyloxy, 1,1-dimethyl-2-
15 aminoethoxy, 2-methyl-3-aminopropoxy, methylaminomethoxy, 1-ethylaminoethoxy, 2-propylaminoethoxy, 3-isopropylaminopropoxy, 4-isopropylaminobutoxy, 4-butylaminobutoxy, 4-tert-butylaminobutoxy, 5-pentylaminopentyloxy, 6-hexylaminohexyloxy, dimethylaminomethoxy, 2-diethylaminoethoxy, 2-dimethylaminoethoxy,
20 (N-ethyl-N-propylamino)methoxy, 2-(N-methyl-N-hexylamino)ethoxy, etc.

C₁₋₆ alkoxycarbonyl groups include, for example, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl,
25 pentyloxycarbonyl, hexyloxycarbonyl, and other C₁₋₆ straight- or branched-chain alkoxycarbonyl groups.

C₁₋₆ alkanoyloxy groups include, for example, formyloxy, acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, pentanoyloxy, tert-butylcarbonyloxy, hexanoyloxy, and other C₁₋₆ straight- or
30 branched-chain alkanoyloxy groups.

C₁₋₆ alkanoyl groups include, for example, formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, tert-butylcarbonyl, hexanoyl, and other C₁₋₆ straight- or branched-chain alkanoyl groups.

35 C₁₋₆ alkylcarbamoyl groups include, for example,

methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, butylcarbamoyl, tert-butylcarbamoyl, pentylcarbamoyl, hexylcarbamoyl, and other C₁₋₆ straight- or branched-chain alkylcarbamoyl groups.

5 Amino groups which may be substituted with a C₁₋₆ alkyl group or groups include, for example, amino, methylamino, ethylamino, propylamino, isopropylamino, butylamino, tert-butylamino, pentylamino, hexylamino, dimethylamino, diethylamino, dipropylamino, dibutylamino, dipentylamino, dihexylamino, N-
10 methyl-N-ethylamino, N-ethyl-N-propylamino, N-methyl-N-butylamino, N-methyl-N-hexylamino, and other amino groups which may have 1 or 2 C₁₋₆ straight- or branched-chain alkyl groups as substituents.

 C₁₋₆ alkanoylamino groups include, for example, formylamino, acetylamino, propionylamino, butyrylamino,
15 isobutyrylamino, pentanoylamino, tert-butylcarbonylamino, hexanoylamino, and other C₁₋₆ straight- or branched-chain alkanoylamino groups.

 C₁₋₆ alkylthio groups include, for example, methylthio, ethylthio, propylthio, isopropylthio, butylthio, tert-butylthio,
20 pentylthio, hexylthio, and other C₁₋₆ straight- or branched-chain alkylthio groups.

 Piperazinylcarbonyl groups which may be substituted with a C₁₋₆ alkyl group or groups include, for example, piperazinylcarbonyl, methylpiperazinylcarbonyl,
25 ethylpiperazinylcarbonyl, propylpiperazinylcarbonyl, isopropylpiperazinylcarbonyl, isopropylpiperazinylcarbonyl, butylpiperazinylcarbonyl, tert-butylpiperazinylcarbonyl, pentylpiperazinylcarbonyl, hexylpiperazinylcarbonyl, and other
30 piperazinylcarbonyl groups which may have a C₁₋₆ straight- or branched-chain alkyl group or groups as substituents.

 Phenyl-C₁₋₆ alkoxy groups include, for example, benzyloxy, phenethyloxy, 3-phenylpropoxy, 4-phenylbutoxy, 5-phenylpentoxy, 6-phenylhexyloxy, etc.

 R₂ in Formula (1) is preferably (a) a phenyl group, (c)
35 a pyridyl group, (d) a furyl group, (e) a thienyl group, (g) a

thiazolyl group, (h) a pyrrolyl group or (i) an imidazolyl group, and more preferably (a) a phenyl group, (c) a pyridyl group or (g) a thiazolyl group.

In Formula (1), A is (i) -CO-B- wherein B is a C₁₋₆ alkylene group, (ii) -CO-Ba- wherein Ba is a C₂₋₆ alkenylene group, (iii) -CH(OH)-B- wherein B is as defined above, (iv) -COCH(COOR₃)-Bb- wherein R₃ is a C₁₋₆ alkyl group and Bb is a C₁₋₆ alkylene group, or (v) -Bc- wherein Bc is a C₂₋₆ alkylene group. In A in Formula (1), B, Ba or Bb is bound to the thiazole ring.

The terms used in the description of the groups represented by A in Formula (1) are defined as follows.

C₁₋₆ alkylene groups include, for example, methylene, ethylene, trimethylene, 2-methyltrimethylene, 2,2-dimethyltrimethylene, 1-methyltrimethylene, methylmethylene, ethylmethylene, tetramethylene, pentamethylene, hexamethylene and other C₁₋₆ straight- or branched-chain alkylene groups.

C₂₋₆ alkylene groups include, for example, ethylene, trimethylene, 2-methyltrimethylene, 2,2-dimethyltrimethylene, 1-methyltrimethylene, methylmethylene, ethylmethylene, tetramethylene, pentamethylene, hexamethylene and other C₁₋₆ straight- or branched-chain alkylene groups.

C₂₋₆ alkenylene groups include, for example, vinylidene, propylene, butenylene and other C₁₋₆ straight- or branched-chain alkenylene groups.

The term "C₁₋₆ alkyl group" used in the description of A in Formula (1) has the same definition as used in the description of R₂.

A in Formula (1) is preferably (i) -CO-B- wherein B is a methylene group, an ethylene group or a trimethylene group; (ii) -CO-Ba- wherein Ba is a vinylidene group; (iii) -CH(OH)-B- wherein B is a methylene group or an ethylene group, (iv) -COCH(COOR₃)-Bb- wherein R₃ is a methyl group, an ethyl group or a tert-butyl group and Bb is a methylene group or a ethylene group; or (v) -Bc- wherein Bc is an ethylene group, a

trimethylene group or a tetramethylene group; and more preferably,
(i) -CO-B- wherein B is an ethylene group, (iii) -CH(OH)-B-
wherein B is an ethylene group, (iv) -COCH(COOR3)-Bb- wherein R3
is a methyl group and Bb is a methylene group, or (v) -Bc-

5 wherein Bc is a trimethylene group.

The compound represented by Formula (1) encompasses
within its scope the following Compounds (1-1) to (1-3):

Compound (1-1)

A compound in which R1 is a 3,4-di-C₁₋₆ alkoxyphenyl
10 group, and preferably a 3,4-dimethoxyphenyl group or a 3,4-
diethoxyphenyl group;

R2 is (a) a phenyl group, (c) a pyridyl group, (d) a
furyl group, (e) a thienyl group, (g) a thiazolyl group, (h) a
pyrrolyl group or (i) an imidazolyl group; and

15 A is (i) -CO-B-, (ii) -CO-Ba-, (iii) -CH(OH)-B-,
(iv) -COCH(COOR3)-Bb- or (v) -Bc-.

Compound (1-2)

A compound in which R1 is a 3,4-di-C₁₋₆ alkoxyphenyl
group, and preferably a 3,4-dimethoxyphenyl group or a 3,4-
20 diethoxyphenyl group;

R2 is (a) a phenyl group, (c) a pyridyl group, (d) a
furyl group, (e) a thienyl group, (g) a thiazolyl group, (h) a
pyrrolyl group or (i) an imidazolyl group; and

A is (i) -CO-B- wherein B is a methylene group, an
25 ethylene group or a trimethylene group, (ii) -CO-Ba- wherein Ba
is a vinylidene group, (iii) -CH(OH)-B- wherein B is a methylene
group or an ethylene group, (iv) -COCH(COOR3)-Bb- wherein R3 is a
methyl group, an ethyl group or a tert-butyl group, and Bb is a
methylene group or an ethylene group, or (v) -Bc- wherein Bc is
30 an ethylene group, a trimethylene group or a tetramethylene group.

Compound (1-3)

A compound in which R1 is a 3,4-di-C₁₋₆ alkoxyphenyl
group, and preferably a 3,4-dimethoxyphenyl group or a 3,4-
diethoxyphenyl group;

35 R2 is (a) a phenyl group, (c) a pyridyl group or (g) a

thiazolyl group; and

A is (i) -CO-B- wherein B is ethylene, (iii) -CH(OH)-B- wherein B is ethylene, (iv) -COCH(COOR₃)-Bb- wherein R₃ is a methyl group and Bb is a methylene group, or (v) -Bc- wherein Bc is a trimethylene group.

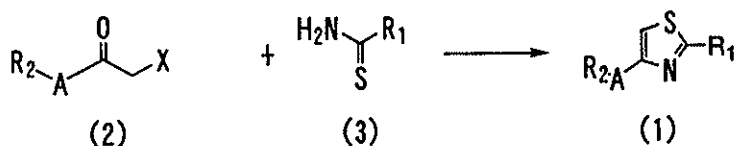
Some of the compounds represented by Formula (1) have optical isomers. Some of the compounds represented by Formula (1) and optical isomers thereof form acid addition salts or salts with bases. The present invention encompasses optical isomers of the compounds represented by Formula (1), as well as salts of the compounds represented by Formula (1) and optical isomers thereof.

Production process for the compound of Formula (1)

The compound of Formula (1), optical isomers thereof, and salts thereof can be prepared by various synthetic processes selected according to the basic skeleton, types of substituents, etc. Typical production processes for the compound of Formula (1) are described below.

<Process 1>

In Process 1, the compound of Formula (1) is produced by reacting the compound of Formula (2) with the compound of Formula (3).



wherein R₁, R₂ and A are as defined above; and X is a halogen atom.

A suitable ratio of the compound of Formula (3) to the compound of Formula (2) is usually 0.5 to 5 mol, and preferably 0.5 to 3 mol, of the compound of Formula (3) per mol of the compound of Formula (2).

The reaction of the compound of Formula (2) with the compound of Formula (3) is usually carried out in a suitable

solvent. A wide variety of known solvents can be used as long as they do not hinder the reaction. Examples of usable solvents include dimethylformamide (DMF), dimethylsulfoxide (DMSO), acetonitrile and other aprotic polar solvents; acetone, methyl
5 ethyl ketone and other ketone solvents; benzene, toluene, xylene, tetralin, liquid paraffin and other hydrocarbon solvents; methanol, ethanol, isopropanol, n-butanol, tert-butanol and other alcohol solvents; tetrahydrofuran (THF), dioxane, dipropyl ether, diethyl ether, dimethoxyethane, diglyme and other ether solvents;
10 ethyl acetate, methyl acetate and other ester solvents; mixtures thereof; etc. Such solvents may contain water.

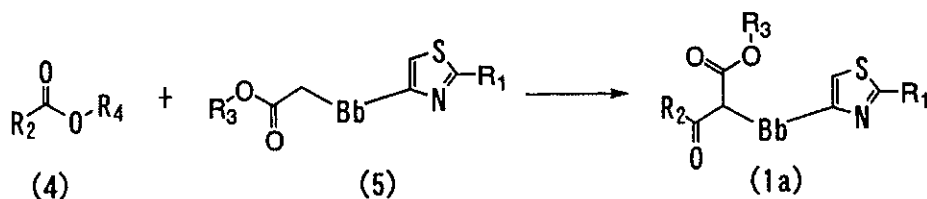
The reaction of the compound of Formula (2) with the compound of Formula (3) is usually performed by continuing stirring at -20 to 200°C, and preferably at 0 to 150°C, for 30
15 minutes to 60 hours, and preferably for 1 to 30 hours.

The compound of Formula (3) used as a starting material is a known compound. Formula (2) encompasses novel compounds. Production processes for the compounds are described hereinafter.

The reaction mixture obtained by the above reaction is,
20 for example, cooled and subjected to an isolation procedure, such as filtration, concentration, extraction and/or the like, to separate a crude reaction product, which is further subjected, as required, to a conventional purification procedure, such as column chromatography, recrystallization and/or the like, to
25 thereby isolate and purify the compound of Formula (1).

<Process 2>

In Process 2, the compound of Formula (4) is reacted with the compound of Formula (5) in the presence of a basic compound, to produce the compound of Formula (1) wherein A
30 is $-\text{COCH}(\text{COOR}_3)-\text{Bb}-$ (hereinafter referred to as "Compound (1a)").



wherein R1, R2, R3 and Bb are as defined above; and R4 is a C₁₋₆ alkyl group.

5 The ratio of the compound of Formula (5) to the compound of Formula (4) is usually 0.5 to 5 mol, and preferably 0.5 to 3 mol, of the compound of Formula (5) per mol of the compound of Formula (4).

10 The reaction of the compound of Formula (4) with the compound of Formula (5) is usually carried out in a suitable solvent. A wide variety of known solvents can be used as long as they do not hinder the reaction. Examples of usable solvents include dimethylformamide (DMF), dimethylsulfoxide (DMSO), N-methylpyrrolidone (NMP) and other aprotic polar solvents; benzene, 15 toluene, xylene, tetralin, liquid paraffin and other hydrocarbon solvents; methanol, ethanol, isopropanol, n-butanol, tert-butanol and other alcohol solvents; tetrahydrofuran (THF), dioxane, dipropyl ether, diethyl ether, dimethoxyethane, diglyme and other ether solvents; mixtures thereof; etc. Such solvents may contain 20 water.

 The reaction of the compound of Formula (4) with the compound of Formula (5) is usually carried out by continuing stirring at 0 to 200°C, and preferably at room temperature to 150°C, for 30 minutes to 60 hours, and preferably 1 to 50 hours.

25 A wide variety of known basic compounds are usable, including, for example, alkali metals, metal hydrides, metal alkoxides, carbonates, hydrogencarbonates and other inorganic basic compounds; acetate and other organic basic compounds; etc.

 Examples of alkali metals include lithium, sodium, 30 potassium, etc. Examples of metal hydrides include sodium hydride, potassium hydride, etc. Examples of metal alkoxides include

sodium methoxide, sodium ethoxide, potassium tert-butoxide, sodium tert-butoxide, etc. Examples of carbonates include sodium carbonate, potassium carbonate, etc. Examples of hydrogencarbonates include sodium hydrogencarbonate, potassium hydrogencarbonate, etc. Inorganic basic compounds further include sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, sodium hexamethyldisilazide, n-butyl lithium, sec-butyl lithium, methyl lithium, etc.

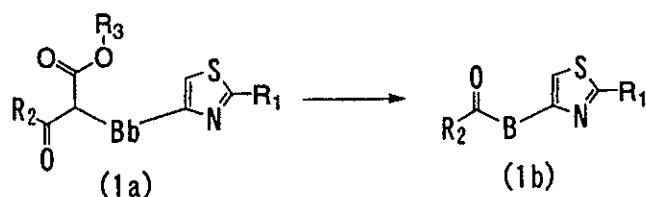
Examples of acetates include sodium acetate, potassium acetate, etc. Other examples of organic basic compounds include triethylamine, trimethylamine, diisopropylethylamine, pyridine, dimethylaniline, 1-methylpyrrolidine, N-methylmorpholine, 1,5-diazabicyclo-[4.3.0]nonene-5 (DBN), 1,8-diazabicyclo[5.4.0]undecene-7 (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO), 2-tert-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine (BEMP), etc.

Such a basic compound is used in an amount of usually 0.1 to 5 mol, and preferably 0.5 to 3 mol per mol of the compound of Formula (5).

The reaction mixture obtained by the above reaction is, for example, cooled and subjected to an isolation procedure, such as filtration, concentration, extraction and/or the like, to separate a crude reaction product, which is further subjected, as required, to a conventional purification procedure, such as column chromatography, recrystallization and/or the like, to thereby isolate and purify the Compound (1a).

<Process 3>

In Process 3, the compound of Formula (1) in which A is -COCH(COOR₃)-Bb- (Compound (1a)) is hydrolyzed and decarboxylated to produce the compound of Formula (1) in which A is -CO-B- (hereinafter referred to as "Compound (1b)").



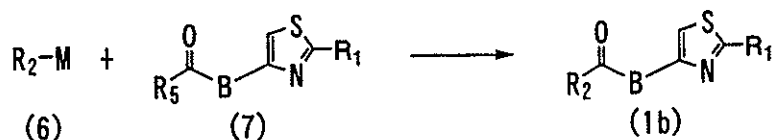
wherein R1, R2, R3, B and Bb are as defined as above.

The hydrolysis and decarboxylation of Compound (1a) is carried out under acidic conditions. For example, an acid is added to a suspension or solution of Compound (1a) in a suitable solvent, and the resulting mixture was stirred at 0 to 120°C. Usable solvents include water, alcohol solvents such as methanol, ethanol, isopropanol, ethylene glycol, etc., acetonitrile, acetone, toluene, DMF, DMSO, acetic acid, trifluoroacetic acid, mixtures thereof, etc. Usable acids include trifluoroacetic acid, acetic acid and other organic acids; hydrochloric acid, bromic acid, hydrobromic acid, sulfuric acid and other inorganic acids; etc. An organic acid such as trifluoroacetic acid, acetic acid or the like can also be used as a reaction solvent. The reaction temperature is usually 0 to 120°C, preferably room temperature to 100°C, and more preferably room temperature to 80°C. The reaction time is usually 30 minutes to 24 hours, preferably 30 minutes to 12 hours, and more preferably 1 to 8 hours.

The reaction mixture obtained by the above reaction is, for example, cooled and subjected to an isolation procedure, such as filtration, concentration, extraction and/or the like, to separate a crude reaction product, which is further subjected, as required, to a conventional purification procedure, such as column chromatography, recrystallization and/or the like, to thereby isolate and purify the Compound (1b).

<Process 4>

In Process 4, the compound of Formula (6) is reacted with the compound of Formula (7) to produce the compound of Formula (1) in which A is -CO-B- (hereinafter referred to as "Compound (1b)").



wherein R1, R2 and B are as defined above; R5 is a C₁₋₆ alkoxy group or CH₃ON(CH₃)-; M is a lithium atom or -MgX; and X is a halogen atom.

5 The ratio of the compound of Formula (7) to the compound of Formula (6) is usually 0.5 to 5 mol, and preferably 0.5 to 3 mol of the compound of Formula (7) per mol of the compound of Formula (6).

10 The reaction of the compound of Formula (6) with the compound of Formula (7) is usually performed in a suitable solvent, which can be selected from a wide variety of known solvents, as long as the solvent does not hinder the reaction. Examples of such solvents include benzene, toluene, xylene, tetralin, liquid paraffin and other hydrocarbon solvents; 15 tetrahydrofuran (THF), dioxane, dipropyl ether, diethyl ether, dimethoxyethane, diglyme and other ether solvents; mixtures thereof; etc.

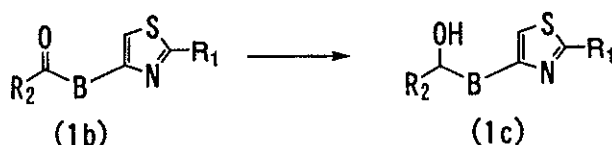
20 The reaction of the compound of Formula (6) with the compound of Formula (7) is usually performed by continuing stirring at -100 to 200°C, and preferably at -100 to 100°C, for 30 minutes to 60 hours, and preferably 1 to 50 hours.

25 The reaction mixture obtained by the above reaction is, for example, cooled and subjected to an isolation procedure, such as filtration, concentration, extraction and/or the like, to separate a crude reaction product, which is further subjected, as required, to a conventional purification procedure, such as column chromatography, recrystallization and/or the like, to thereby isolate and purify the Compound (1b).

<Process 5>

30 In Process 5, the compound of Formula (1b) is reacted in the presence of a reducing agent to produce the compound of Formula (1) in which A is -CH(OH)-B- (hereinafter referred to as

"Compound (1c)").



wherein R1, R2 and B are as defined above.

Examples of solvents usable in the above reaction
5 include water; methanol, ethanol, isopropanol, butanol, tert-
butanol, ethylene glycol and other lower alcohols; ethyl acetate,
methyl acetate and other ester solvents; diethyl ether,
tetrahydrofuran, dioxane, monoglyme, diglyme and other ethers;
benzene, toluene, xylene and other aromatic hydrocarbons;
10 dichloromethane, dichloroethane, chloroform, carbon tetrachloride
and other halogenated hydrocarbons; mixtures thereof; etc.

Examples of usable reducing agents include sodium
borohydride, lithium aluminium hydride, diisobutylaluminum
hydride and other hydride reducing agents, and mixtures of such
15 hydride reducing agents.

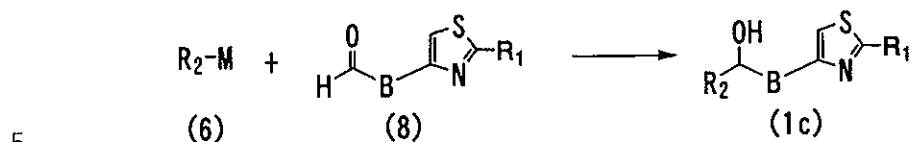
When a hydride reducing agent is used as a reducing
agent, a suitable reaction temperature is usually about -80 to
about 100°C, and preferably about -80 to about 70°C, and the
reaction is completed in about 30 minutes to about 100 hours. The
20 amount of the hydride reducing agent to be used is usually about
1 to about 20 mol, and preferably about 1 to about 6 mol per mol
of Compound (1b). In particular, when lithium aluminium hydride
is used as a reducing agent, it is preferred to use as a solvent
an ether, such as diethyl ether, tetrahydrofuran, dioxane,
25 monoglyme, diglyme or the like, or an aromatic hydrocarbon, such
as benzene, toluene, xylene or the like.

The reaction mixture obtained by the above reaction is,
for example, cooled and subjected to an isolation procedure, such
as filtration, concentration, extraction and/or the like, to
30 separate a crude reaction product, which is further subjected, as
required, to a conventional purification procedure, such as
column chromatography, recrystallization and/or the like, to

thereby isolate and purify the Compound (1c).

<Process 6>

In Process 6, the compound of Formula (6) is reacted with the compound of Formula (8) to produce Compound (1c).

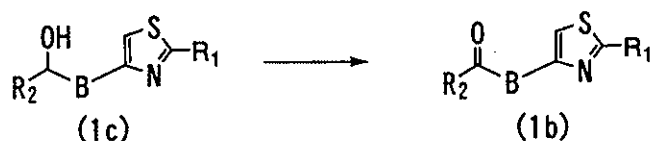


wherein R1, R2, B and M are as defined above.

The reaction in Process 6 is performed under the same reaction conditions as for the reaction in Process 4.

<Process 7>

10 In Process 7, Compound (1c) is reacted in a suitable solvent in the presence of an oxidizing agent to produce Compound (1b).



wherein R1, R2 and B are as defined above.

15 The solvent for use in Process 7 can be selected from a wide variety of known solvents, as long as it does not hinder the reaction. Examples of usable solvents include dimethylformamide (DMF), dimethyl sulfoxide (DMSO), N-methylpyrrolidone (NMP), acetonitrile and other aprotic polar solvents; benzene, toluene, 20 xylene, tetralin, liquid paraffin and other hydrocarbon solvents; ethyl acetate, methyl acetate and other ester solvents; tetrahydrofuran (THF), dioxane, dipropyl ether, diethyl ether, dimethoxyethane, diglyme and other ether solvents; dichloromethane, dichloroethane, chloroform, carbon tetrachloride 25 and other halogenated hydrocarbons; mixtures thereof; etc. Such solvents may contain water.

In Process 7, the oxidizing agent can selected from a wide variety of known oxidizing agents. Examples of usable oxidizing agents include dimethyl sulfoxide (DMSO)-sulfur

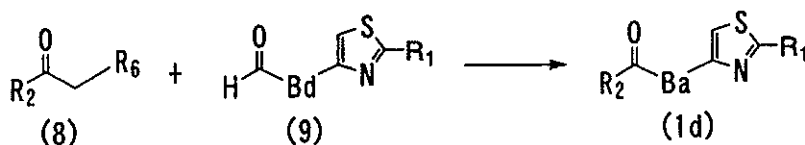
trioxide-pyridine, dimethyl sulfoxide (DMSO)-oxalyl chloride-triethylamine, pyridinium chlorochromate (PCC), chromic acid, manganese dioxide, etc.

The amount of oxidizing agent to be used is usually about 1 to about 20 mol, and preferably about 1 to about 6 mol per mol of Compound (1c).

The reaction mixture obtained by the above reaction is, for example, cooled and subjected to an isolation procedure, such as filtration, concentration, extraction and/or the like, to
10 separate a crude reaction product, which is further subjected, as required, to a conventional purification procedure, such as column chromatography, recrystallization and/or the like, to thereby isolate and purify the Compound (1b).

<Process 8>

15 In Process 8, the compound of Formula (8) is reacted with the compound of Formula (9) in the presence of a basic compound to produce the compound of Formula (1) in which A is -CO-Ba- (hereinafter referred to as "Compound (1d)").



20 wherein R1, R2 and Ba are as defined above; R6 is a hydrogen atom
or $-\text{PO}(\text{OR}7)_2$; Bd is $-(\text{CH}_2)_n-$; n is an integer from 0 to 4; and R7
is a C_{1-6} alkyl group.

The ratio of the compound of Formula (9) to the compound of Formula (8) is usually 0.5 to 5 mol, and preferably 0.5 to 3 mol of the compound of Formula (9) per mol of the compound of Formula (8).

The reaction of the compound of Formula (8) with the compound of Formula (9) is usually carried out in a suitable solvent. A wide variety of known solvents can be used as long as they do not hinder the reaction. Examples of usable solvents include dimethylformamide (DMF), dimethylsulfoxide (DMSO), N-methylpyrrolidone (NMP) and other aprotic polar solvents; benzene,

toluene, xylene, tetralin, liquid paraffin and other hydrocarbon solvents; methanol, ethanol, isopropanol, n-butanol, tert-butanol and other alcohol solvents; tetrahydrofuran (THF), dioxane, dipropyl ether, diethyl ether, dimethoxyethane, diglyme and other
5 ether solvents; mixtures thereof; etc. Such solvents may contain water.

The reaction of the compound of Formula (8) with the compound of Formula (9) is usually carried out by continuing stirring at 0 to 200°C, and preferably at room temperature to
10 150°C, for 30 minutes to 60 hours, and preferably 1 to 50 hours.

A wide variety of known basic compounds are usable, including, for example, alkali metals, metal hydrides, metal alkoxides, carbonates, hydrogencarbonates and other inorganic basic compounds; acetates and other organic basic compounds; etc.

15 Examples of alkali metals include lithium, sodium, potassium, etc. Examples of metal hydrides include sodium hydride, potassium hydride, etc. Examples of metal alkoxides include sodium methoxide, sodium ethoxide, potassium tert-butoxide, sodium tert-butoxide, etc. Examples of carbonates include sodium
20 carbonate, potassium carbonate, etc. Examples of hydrogencarbonates include sodium hydrogencarbonate, potassium hydrogencarbonate, etc. Inorganic basic compounds include, in addition to the above compounds, sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, sodium
25 hexamethyldisilazide, etc.

Examples of acetates include sodium acetate, potassium acetate, etc. Examples of organic basic compounds other than the above include triethylamine, trimethylamine, diisopropylethylamine, pyridine, dimethylaniline, 1-
30 methylpyrrolidine, N-methylmorpholine, 1,5-diazabicyclo[4.3.0]nonene-5 (DBN), 1,8-diazabicyclo[5.4.0]-undecene-7 (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO), 2-tert-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphospholine (BEMP), etc.

35 It is suitable to use such a basic compound in an

amount of 0.1 to 5 mol, preferably 0.5 to 3 mol per mol of the compound represented by Formula (8).

The reaction mixture obtained by the above reaction is, for example, cooled and subjected to an isolation procedure, such as filtration, concentration, extraction and/or the like, to separate a crude reaction product, which is further subjected, as required, to a conventional purification procedure, such as column chromatography, recrystallization and/or the like, to thereby isolate and purify the Compound (1d).

<Process 9>

In Process 9, Compound (1d) is reacted in the presence of a reducing agent to produce Compound (1b).



wherein R1, R2, Ba and B are as defined above.

Examples of reducing agents include hydrogen catalytic reducing agents, such as palladium-black, palladium-carbon, platinum oxide, platinum black, Raney nickel, etc.

When using a hydrogen catalytic reducing agent, it is usually suitable to perform the reaction in an hydrogen atmosphere at atmospheric normal pressure to about 20 atm, and preferably at atmospheric normal pressure to about 10 atm, or in the presence of a hydrogen donor, such as formic acid, ammonium formate, cyclohexene, hydrazine hydrate or the like, usually at about -30 to about 100°C, and preferably at about 0 to about 60°C.

The reaction is usually completed in about 1 to about 12 hours. A suitable amount of the hydrogen catalytic reducing agent to be used is usually about 0.1 to about 40 parts by weight, and preferably about 1 to about 20 parts by weight, per 100 parts by weight of Compound (1d).

Examples of solvents usable in the reaction in Process 9 include water; methanol, ethanol, isopropanol, n-butanol, tert-butanol, ethylene glycol and other lower alcohols; ethyl acetate,

methyl acetate and other ester solvents; dimethylformamide (DMF),
N-methylpyrrolidone (NMP) and other aprotic polar solvents;
diethyl ether, tetrahydrofuran, dioxane, monoglyme, diglyme and
other ethers; benzene, toluene, xylene and other aromatic
5 hydrocarbons; mixtures thereof; etc.

The reaction mixture obtained by the above reaction is,
for example, cooled and subjected to an isolation procedure, such
as filtration, concentration, extraction and/or the like, to
separate a crude reaction product, which is further subjected, as
10 required, to a conventional purification procedure, such as
column chromatography, recrystallization and/or the like, to
thereby isolate and purify the Compound (1b).

<Process 10>

In Process 10, Compound (1b) is subjected to a
15 reduction reaction to produce the compound of Formula (1e)
(hereinafter referred to as "Compound (1e)").



wherein R1, R2 and B are as defined above; and Bc is a C₂₋₆
alkylene group.

20 A wide variety of known reduction reactions can be
employed as the above reduction reaction. For example, the
reduction reaction can be performed by heating the compound in
the presence of hydrazine and a basic compound in a suitable
solvent.

25 Examples of usable solvents include water; methanol,
ethanol, isopropanol, butanol, tert-butanol, ethylene glycol,
diethylene glycol and other lower alcohols; dimethylformamide
(DMF), N-methylpyrrolidone (NMP) and other aprotic polar
solvents; diethyl ether, tetrahydrofuran, dioxane, monoglyme,
30 diglyme and other ethers; benzene, toluene, xylene and other
aromatic hydrocarbons; mixtures thereof; etc.

A wide variety of known basic compounds are usable,

which include, for example, metal hydrides, metal alkoxides, hydroxides, carbonates, hydrogencarbonates and other inorganic basic compounds, etc.

5 Examples of metal hydrides include sodium hydride, potassium hydride, etc. Examples of metal alkoxides include sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. Examples of hydroxides include sodium hydroxide, potassium hydroxide, etc. Examples of carbonates include sodium carbonate, potassium carbonate, etc. Examples of hydrogencarbonates include
10 sodium hydrogencarbonate, potassium hydrogencarbonate, etc. Inorganic basic compounds include, besides the above compounds, sodium amide and the like.

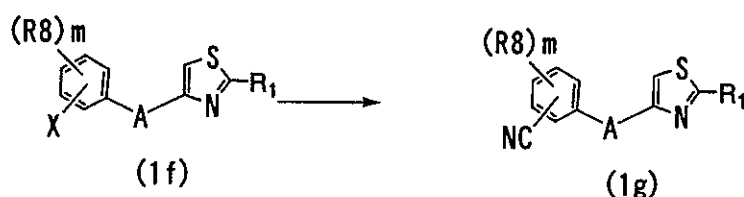
 It is usually suitable to use such a basic compound in an amount of 0.1 to 2 mol, preferably 0.1 to 1 mol, and more
15 preferably 0.1 to 0.5 mol per mol of Compound (1b).

 A suitable reaction temperature is usually about 50 to about 250°C, and preferably about 100 to about 200°C, and the reaction is completed usually in about 30 minutes to about 10 hours.

20 The reaction mixture thus obtained is, for example, cooled and subjected to an isolation procedure, such as filtration, concentration, extraction and/or the like, to separate a crude reaction product, which is further subjected, as required, to a conventional purification procedure, such as
25 column chromatography, recrystallization and/or the like, to thereby isolate and purify the Compound (1e).

<Process 11>

 In Process 11, a halogen atom in the compound of Formula (1f) (hereinafter referred to as "Compound (1f)") is
30 substituted by cyano to produce the compound of Formula (1g) (hereinafter referred to as "Compound (1g)").



wherein R₁, A and X are as defined above; R₈ is a hydroxy group, an unsubstituted or halogen-substituted C₁₋₆ alkyl group, an unsubstituted or halogen-substituted C₁₋₆ alkoxy group, a C₁₋₆ alkoxy-C₁₋₆ alkoxy group, a phenyl-C₁₋₆ alkoxy group, an amino-C₁₋₆ alkoxy group which may be substituted with a C₁₋₆ alkyl group, a methylenedioxy group, a carboxyl group, a phenoxy group, a C₁₋₆ alkoxy-carbonyl group, C₁₋₆ alkanoyloxy group, a C₁₋₆ alkanoyl group, a cyano group, a nitro group, a C₁₋₆ alkylcarbamoyl group, an aminosulfonyl group, an amino group which may be substituted with a C₁₋₆ alkyl group or groups, a C₁₋₆ alkanoylamino group, a C₁₋₆ alkylthio group, a phenyl group, a pyrazolyl group, an imidazolyl group, a triazolyl group, a morpholino group, a pyrrolidinyl group, or a piperazinylcarbonyl group which may be substituted with a C₁₋₆ alkyl group or groups; and m is an integer from 0 to 4.

A wide variety of known substitution reactions can be employed as the above substitution reaction. For example, the substitution reaction can be performed by heating the compound with a cyanide in the presence of a palladium catalyst in a suitable solvent.

Examples of palladium catalysts include tetrakis(triphenylphosphine) palladium and the like. A suitable amount of palladium catalyst is usually about 0.001 to about 0.4 mol, and preferably about 0.001 to about 0.2 mol per mol of Compound (1f).

Examples of cyanides include zinc (II) cyanide and the like. It is usually suitable to use such a cyanide in an amount of 0.1 to 5 mol, preferably 0.5 to 3 mol, and more preferably 0.5 to 1 mol per mol of Compound (1f).

The solvent can be selected from a wide variety of

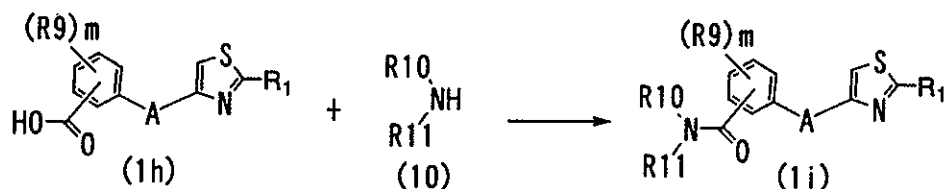
known solvents, as long as it does not hinder the reaction. Examples of usable solvents include dimethylformamide (DMF), dimethylsulfoxide (DMSO), acetonitrile and other aprotic polar solvents; acetone, methyl ethyl ketone and other ketone solvents; 5 benzene, toluene, xylene, tetralin, liquid paraffin and other hydrocarbon solvents; methanol, ethanol, isopropanol, n-butanol, tert-butanol and other alcohol solvents; tetrahydrofuran (THF), dioxane, dipropyl ether, diethyl ether, diglyme and other ether solvents; ethyl acetate, methyl acetate and other ester solvents; 10 mixtures thereof; etc. Such solvents may contain water.

The reaction of the Compound (1f) with a cyanide is usually carried out at -100 to 200°C, and preferably at -100 to 100°C, for 30 minutes to 60 hours, and preferably 1 to 50 hours.

The reaction mixture thus obtained is, for example, 15 cooled and subjected to an isolation procedure, such as filtration, concentration, extraction and/or the like, to separate a crude reaction product, which is further subjected, as required, to a conventional purification procedure, such as column chromatography, recrystallization and/or the like, to 20 thereby isolate and purify the Compound (1g).

<Process 12>

In Process 12, the carboxylic acid moiety of the compound of Formula (1h) (hereinafter referred to as "Compound (1h)") is subjected to an amide bond formation reaction with the 25 compound of Formula (10) (hereinafter referred to as "Compound 10") to produce the compound of Formula (1i) (hereinafter referred to as "Compound (1i)").



wherein R1, A and m are as defined above; R9 is a hydroxy group, 30 a halogen atom, an unsubstituted or halogen-substituted C₁₋₆ alkyl group, an unsubstituted or halogen-substituted C₁₋₆ alkoxy group, a C₁₋₆ alkoxy-C₁₋₆ alkoxy group, a phenyl-C₁₋₆ alkoxy group,

an amino-C₁₋₆ alkoxy group which may be substituted with a C₁₋₆ alkyl group or groups, a methylenedioxy group, a phenoxy group, a C₁₋₆ alkoxy carbonyl group, a C₁₋₆ alkanoyloxy group, a C₁₋₆ alkanoyl group, a cyano group, a nitro group, a C₁₋₆ alkyl carbamoyl group, an aminosulfonyl group, an amino group which may be substituted with a C₁₋₆ alkyl group, a C₁₋₆ alkanoylamino group, a C₁₋₆ alkylthio group, a phenyl group, a pyrazolyl group, an imidazolyl group, a triazolyl group, a morpholino group, a pyrrolidinyl group or a piperazinyl carbonyl group which may be substituted by a C₁₋₆ alkyl group or groups; m is an integer from 0 to 4; and R₁₀ and R₁₁ are independently each a hydrogen atom or a C₁₋₆ alkyl group, and may be bonded to each other via the adjacent nitrogen atom and a carbon atom or atoms or another nitrogen atom, to form a piperazine ring which may be substituted with a C₁₋₆ alkyl group or groups.

Conditions for known amide bond formation reactions can be employed in the amide formation reaction in Process 12. For example, the following reaction methods can be employed: (A) a mixed acid anhydride method, in which carboxylic acid (1h) is reacted with an alkyl halocarboxylate to form a mixed acid anhydride, which is then reacted with Compound (10); (B) an active ester method, in which carboxylic acid (1h) is converted to an activated ester, such as a phenyl ester, p-nitrophenyl ester, N-hydroxysuccinimide ester, 1-hydroxybenzotriazole ester or the like, or an activated amide with benzoxazoline-2-thione, and the activated ester or amide is reacted with Compound (10); (C) a carbodiimide method, in which carboxylic acid (1h) is subjected to a condensation reaction with Compound (10) in the presence of an activating agent, such as dicyclohexylcarbodiimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (WSC), carbonyldiimidazole or the like; (D) other methods, for example, a method in which carboxylic acid (1h) is converted to a carboxylic anhydride using a dehydrating agent such as acetic anhydride, and the carboxylic anhydride is then reacted with Compound (10), or a method in which an ester of carboxylic acid

(1h) with a lower alcohol is reacted with Compound (10) at a high pressure and a high temperature, a method in which an acid halide of carboxylic acid (1h), i.e., a carboxylic acid halide, is reacted with Compound (10); etc.

5 The mixed acid anhydride used in the mixed acid anhydride method (A) can be obtained by the known Schotten-Baumann reaction, and the obtained mixed acid anhydride is reacted with Compound (10), usually without being isolated, to thereby produce the Compound (1i). The Schotten-Baumann reaction
10 is performed in the presence of a basic compound. Usable basic compounds include compounds conventionally used in the Schotten-Baumann reaction, such as triethylamine, trimethylamine, pyridine, dimethylaniline, N-ethyldiisopropylamine, dimethylaminopyridine, N-methylmorpholine, 1,5-diazabicyclo[4.3.0]nonene-5 (DBN), 1,8-
15 diazabicyclo[5.4.0]undecene-7 (DBU), 1,4-diazabicyclo[2.2.2]-octane (DABCO) and other organic bases; sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate and other carbonates; sodium hydroxide, potassium hydroxide, calcium hydroxide and other metal
20 hydroxides; potassium hydride, sodium hydride, potassium, sodium, sodium amide, metal alkoxides such as sodium methoxide and sodium ethoxide, and other inorganic bases; etc. The reaction is usually performed at about -20 to about 100°C, and preferably at about 0 to about 50°C, usually for about 5 minutes to about 10 hours, and preferably for about 5 minutes to about 2 hours. The reaction of
25 the obtained mixed acid anhydride with Compound (10) is usually carried out at about -20 to about 150°C, and preferably at about 10 to about 50°C, usually for about 5 minutes to about 10 hours, and preferably for about 5 minutes to about 5 hours. Generally,
30 the mixed acid anhydride method is performed in a solvent. Solvents used for conventional mixed acid anhydride methods are usable. Examples of usable solvents include chloroform, dichloromethane, dichloroethane, carbon tetrachloride and other halogenated hydrocarbons; benzene, toluene, xylene and other
35 aromatic hydrocarbons; diethyl ether, diisopropyl ether,

tetrahydrofuran, dimethoxyethane and other ethers; methyl acetate, ethyl acetate, isopropyl acetate and other esters; N,N-dimethylacetamide, N,N-dimethylformamide, dimethylsulfoxide, hexamethylphosphoric triamide and other aprotic polar solvents; mixtures thereof; etc. Examples of alkyl halocarboxylates usable in the mixed acid anhydride method include methyl chloroformate, methyl bromoformate, ethyl chloroformate, ethyl bromoformate, isobutyl chloroformate, etc. In this method, Compound (1h), an alkyl halocarboxylate and Compound (10) are preferably used in equimolar amounts, but each of the alkyl halocarboxylate and Compound (1h) can also be used in an amount of about 1 to about 1.5 mol per mol of Compound (10).

Method (C), in which a condensation reaction is carried out in the presence of an activating agent, can be performed in a suitable solvent in the presence or absence of a basic compound. Solvents and basic compounds usable in this method include those mentioned hereinafter as solvents and basic compounds usable in the method in which a carboxylic acid halide is reacted with Compound (10) mentioned above as one of the other methods (D). A suitable amount of activating agent is at least 1 mol, and preferably 1 to 5 mol per mol of Compound (10). When using WSC as an activating agent, addition of 1-hydroxybenzotriazole to the reaction system enables the reaction to proceed advantageously. The reaction is usually performed at about -20 to about 180°C, and preferably at about 0 to about 150°C, and is usually completed in about 5 minutes to about 90 hours.

When the method in which a carboxylic acid halide is reacted with Compound (10), mentioned above as one of the other methods (D), is employed, the reaction is performed in the presence of a basic compound in a suitable solvent. Usable basic compounds include a wide variety of known basic compounds, such as those for use in the Schotten-Baumann reaction described above. Usable solvents include, in addition to those usable in the mixed acid anhydride method, methanol, ethanol, isopropanol, propanol, butanol, 3-methoxy-1-butanol, ethylcellosolve, methylcellosolve

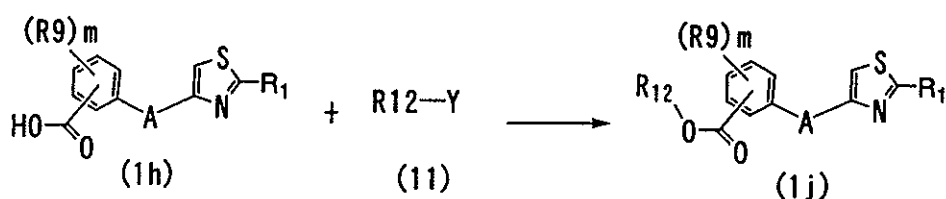
and other alcohols; acetonitrile; pyridine; acetone; water; etc. The ratio of the carboxylic acid halide to Compound (10) is not limited and can be suitably selected from a wide range. It is usually suitable to use, for example, at least about 1 mol, and preferably about 1 to about 5 mol of the carboxylic acid halide per mol of Compound (10). The reaction is usually performed at about -20 to about 180°C, and preferably at about 0 to about 150°C, and usually completed in about 5 minutes to about 50 hours.

The amide bond formation reaction in Process 12 can also be performed by reacting Compound (1h) with Compound (10) in the presence of a phosphorus compound serving as a condensing agent, such as triphenylphosphine, diphenylphosphinyl chloride, phenyl-N-phenylphosphoramidate chloridate, diethyl chlorophosphate, diethyl cyanophosphate, diphenylphosphoric azide, bis(2-oxo-3-oxazolidinyl)phosphinic chloride or the like.

The reaction is carried out in the presence of a solvent and a basic compound usable for the method in which a carboxylic acid halide is reacted with Compound (10), usually at about -20 to about 150°C, and preferably at about 0 to about 100°C, and is usually completed in about 5 minutes to about 30 hours. It is suitable to use each of the condensing agent and Compound (1h) in amounts of at least about 1 mol, and preferably about 1 to about 2 mol per mol of Compound (10).

<Process 13>

In Process 13, the carboxylic acid moiety of Compound (1h) is subjected to an ester bond formation reaction with the compound of Formula (11) (hereinafter referred to as "Compound (11)") to produce the compound of Formula (1j) (hereinafter referred to as "Compound 1j").



wherein R1, R9, A and m are as defined above; R12 is a C₁₋₆ alkyl

group; and Y is a hydroxy group or a halogen atom.

Conditions for known ester bond formation reactions can be employed. For example, when Y in Compound (11) is a hydroxy group, the ester bond formation reaction can be performed by heating Compound (1h) and Compound (11) in a suitable solvent in the presence of acid. Examples of usable solvents include chloroform, dichloromethane, dichloroethane, carbon tetrachloride and other halogenated hydrocarbons; benzene, toluene, xylene and other aromatic hydrocarbons; diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane and other ethers; methyl acetate, ethyl acetate, isopropyl acetate and other esters; N,N-dimethylacetamide, N,N-dimethylformamide, dimethylsulfoxide, hexamethylphosphoric triamide and other aprotic polar solvents; mixtures thereof; etc. Compound (11) can also be used as a solvent. Examples of usable acids include trifluoroacetic acid and other organic acids; hydrochloric acid, bromic acid, hydrobromic acid, sulfuric acid and other inorganic acids; etc. The reaction is usually performed at about 0 to about 150°C, and preferably at about room temperature to about 100°C, and is usually completed in about 0.5 to about 30 hours.

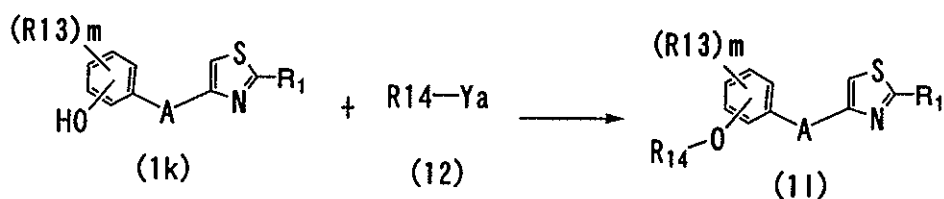
When Y in Compound (11) is a halogen atom, the reaction in Process 13 is performed by reacting Compound (11) with Compound (1h) in a suitable solvent in the presence of a basic compound. Examples of usable solvents include methanol, ethanol, isopropanol, butanol, tert-butanol, ethylene glycol, diethylene glycol and other lower alcohols; chloroform, dichloromethane, dichloroethane, carbon tetrachloride and other halogenated hydrocarbons; benzene, toluene, xylene and other aromatic hydrocarbons; diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane and other ethers; methyl acetate, ethyl acetate, isopropyl acetate and other esters; N,N-dimethylacetamide, N,N-dimethylformamide, dimethylsulfoxide, hexamethylphosphoric triamide and other aprotic polar solvents; mixtures thereof; etc.

Examples of usable basic compounds include

triethylamine, trimethylamine, pyridine, dimethylaniline, N-ethyl-diisopropylamine, dimethylaminopyridine, N-methylmorpholine, 1,5-diazabicyclo[4.3.0]nonene-5 (DBN), 1,8-diazabicyclo-[5.4.0]undecene-7 (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO) and other organic bases; sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate and other carbonates; sodium hydroxide, potassium hydroxide, calcium hydroxide and other metal hydroxides; potassium hydride, sodium hydride, potassium, sodium, sodium amide, metal alkoxides such as sodium methoxide and sodium ethoxide, and other inorganic bases; etc. A suitable ratio of Compound (1h) to Compound (11) is at least 1 mol, and preferably 1 to 5 mol of Compound (1h) per mol of Compound (11). The reaction is usually performed at about 0 to about -150°C, and preferably at about room temperature to about 100°C, and is usually completed in about 0.5 hours to about 30 hours.

<Process 14>

In Process 14, the compound of Formula (1k) (hereinafter referred to as "Compound (1k)") is alkylated with the compound of Formula (12) (hereinafter referred to as "Compound (12)") to produce the compound of Formula (11) (hereinafter referred to as "Compound 11").



wherein R1, A and m are as defined above; R13 is a halogen atom, an unsubstituted or halogen-substituted C₁₋₆ alkyl group, an unsubstituted or halogen-substituted C₁₋₆ alkoxy group, a C₁₋₆ alkoxy-C₁₋₆ alkoxy group, a phenyl-C₁₋₆ alkoxy group, an amino-C₁₋₆ alkoxy group which may be substituted with a C₁₋₆ alkyl group, a methylenedioxy group, a carboxyl group, a phenoxy group, a C₁₋₆ alkoxy-carbonyl group, a C₁₋₆ alkanoyloxy group, C₁₋₆ alkanoyl group, a cyano group, a nitro group, a C₁₋₆ alkylcarbamoyl group, an

aminosulfonyl group, an amino group which may be substituted with a C₁₋₆ alkyl group or groups, a C₁₋₆ alkanoylamino group, a C₁₋₆ alkylthio group, a phenyl group, a pyrazolyl group, an imidazolyl group, a triazolyl group, a morpholino group, a pyrrolidinyl group, or a piperazinylcarbonyl group which may be substituted with a C₁₋₆ alkyl group or groups; R₁₂ is a C₁₋₆ alkyl group; Y is a hydroxy group, a halogen atom or -OSO₂-R₁₃; R₁₃ is a C₁₋₆ alkyl group or a phenyl group in which the phenyl ring may be substituted with a C₁₋₆ alkyl group or groups, a halogen atom or atoms or a nitro group or groups; R₁₄ is a C₁₋₆ alkyl group or a C₁₋₆ alkoxy-C₁₋₆ alkoxy group; and Y_a is a halogen atom.

In Process 14, the alkylation reaction can be performed by reacting Compound (1k) with Compound (12), for example, in a suitable solvent in the presence of a basic compound. Examples of usable solvents include methanol, ethanol, isopropanol, butanol, tert-butanol, ethylene glycol, diethylene glycol and other lower alcohols; chloroform, dichloromethane, dichloroethane, carbon tetrachloride and other halogenated hydrocarbons; benzene, toluene, xylene and other aromatic hydrocarbons; diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane and other ethers; methyl acetate, ethyl acetate, isopropyl acetate and other esters; N,N-dimethylacetamide, N,N-dimethylformamide, dimethylsulfoxide, hexamethylphosphoric triamide and other aprotic polar solvents; mixtures thereof; etc.

Examples of basic compounds include triethylamine, trimethylamine, pyridine, dimethylaniline, N-ethyl-diisopropylamine, dimethylaminopyridine, N-methylmorpholine, 1,5-diazabicyclo[4.3.0]nonene-5 (DBN), 1,8-diazabicyclo[5.4.0]-undecene-7 (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO) and other organic bases; sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate and other carbonates; metal hydroxides such as sodium hydroxide, potassium hydroxide and calcium hydroxide; potassium hydride, sodium hydride, potassium, sodium, sodium amide, metal alkoxides such as sodium methoxide and sodium ethoxide, and other inorganic bases;

etc. A suitable ratio of Compound (12) to Compound (1k) is at least 1 mol, and preferably 1 to 5 mol of Compound (12) per mol of Compound (1k). The reaction is usually performed at about 0 to about 150°C, and preferably at about room temperature to about 100°C, and is usually completed in about 0.5 to about 30 hours.

Production process for compound of Formula (2)

The compound of Formula (2) (hereinafter referred to as "Compound (2)") for use as a starting material can be produced by, for example, the following Process 15 or 16.

<Process 15>

In Process 15, the compound represented by Formula (13) (hereinafter referred to as "Compound (13)") is halogenated to produce Compound (2).



wherein R₂, A and X are as defined above. The halogenation reaction of Compound (13) can be performed in a suitable solvent in the presence of a halogenating agent. Examples of usable halogenating agents include bromine, chlorine and other molecular halogens; iodine chloride; sulfonyl chloride; cupric bromide and other copper compounds; N-bromosuccinimide, N-chlorosuccinimide and other N-halogenated succinimides; etc. Examples of usable solvents include dichloromethane, dichloroethane, chloroform, carbon tetrachloride and other halogenated hydrocarbons; acetic acid; propionic acid and other fatty acids; carbon disulfide; etc. A suitable amount of halogenating agent is usually about 1 to about 10 mol, and preferably about 1 to about 5 mol per mol of Compound (13). The reaction is usually performed at about 0°C to about the boiling point of the solvent, and preferably at about 0 to about 100°C, and is usually completed in about 5 minutes to about 20 hours.

<Process 16>

In Process 16, the compound represented by Formula (14)

(hereinafter referred to as "Compound (14)") is halogenated in the presence of water under acidic conditions to produce Compound (2).



5 wherein R₂, A and X are as defined above. The halogenation reaction of Compound (14) is performed in a suitable solvent in the presence of a halogenating agent. Examples of usable halogenating agents include bromine, chlorine and other molecular halogens; iodine chloride; sulfonyl chloride; N-bromosuccinimide, 10 N-chlorosuccinimide and other N-halogenated succinimides; etc. Examples of usable solvents include hydrous acetonitrile. Examples of usable acids include hydrochloric acid, bromic acid, hydrobromic acid, sulfuric acid and other inorganic acids, and the like. A suitable amount of the halogenating agent is usually 15 about 1 to about 10 mol, and preferably about 1 to about 5 mol per mol of Compound (14). The reaction is usually performed at 0°C to the boiling temperature of the solvent, and preferably at about 0 to about 100°C, and is usually completed in about 5 minutes to about 20 hours.

20

(II) Medicinal effects and uses

The compounds represented by Formula (1), optical isomers thereof and salts thereof (hereinafter collectively referred to as "the compound of the present invention") exhibit 25 specific inhibitory activity against PDE4, and thus are useful as active ingredients of PDE4 inhibitors.

The compound of the present invention, based on its specific inhibitory activity against PDE4, can be used as an active ingredient of a pharmaceutical composition for use as a 30 preventive or therapeutic agent for various diseases. Examples of diseases on which preventive or therapeutic effects are exhibited based on the specific inhibitory activity against PDE4 include acute or chronic (in particular, inflammatory and allergen-

induced) respiratory tract diseases (e.g., bronchial asthma and chronic obstructive pulmonary diseases) of various origins; dermatoses (in particular, proliferative, inflammatory and allergic types) (e.g., psoriasis vulgaris, toxic and allergic contact eczemas, atopic dermatitis, alopecia areata and other proliferative, inflammatory and allergic dermatoses); diseases related to nervous dysfunctions, such as of learning, memory and cognition disorders, caused due to Alzheimer's disease, Parkinson's disease, etc.; diseases related to mental dysfunctions (e.g., manic-depressive psychosis, schizophrenia and anxiety syndrome); systemic or local joint diseases (e.g., knee osteoarthrosis and articular rheumatism); diffuse inflammation in the gastrointestinal region (e.g., Crohn's disease and ulcerative colitis); allergic and/or chronic diseases in the upper respiratory tract (pharyngeal cavity, nose) region and adjacent regions (paranasal sinus, eye) caused by improper immunological reactions (e.g., allergic rhinitis/sinusitis, chronic rhinitis/sinusitis and allergic conjunctivitis); and other diseases. Among these, for atopic dermatitis, the compound of the present invention exhibits particularly high preventive or therapeutic effects, and therefore can be suitably applied to prevent or treat this disease.

When the compound of the present invention is employed as a PDE 4 inhibitor or a preventive or therapeutic agent for diseases as mentioned above, the compound can be used as an oral preparation, an injection, an external preparation or like preparation.

When used as an oral preparation, the compound can be formulated into a powder, tablets, granules, capsules, a syrup, films, troches, a liquid or like forms. The oral preparation may contain a pharmaceutically acceptable base and/or carrier, and pharmaceutically acceptable additives, such as binders, disintegrators, lubricants, humectants, buffers, preservatives, flavors, etc., as required.

When used as an injection, the compound can be

formulated into an aqueous solution or suspension obtained by dissolving or suspending the compound in physiological saline, an aqueous glucose solution or the like.

When used as an external preparation, the compound can
5 be formulated into a liquid, oily preparation, lotion, liniment, milky lotion, suspension, cream, ointment or like forms. The external preparation may contain a carrier, a base and/or additives that are conventionally used in external preparations, as required. Examples of usable additives include water, oils,
10 surfactants, solubilizing components, emulsifiers, colorants (dyes, pigments), flavors, preservatives, antiseptics, thickeners, antioxidants, sequestering agents, pH modifiers, deodorizers, etc.

When the compound of the present invention is employed as a PDE4 inhibitor or a preventive or therapeutic agent for the
15 above diseases, the effective dosage amount and number of doses of the compound of the present invention vary depending on the type of the compound, the age and weight of the subject to be given the compound, the symptom, the purpose of use and other factors, and cannot generally be defined. For example, for an
20 adult per day, an amount corresponding 0.1 to 1000 mg of the compound of the present invention can be administered or applied in a single dose or in two or more divided doses.

Another aspect of the present invention provides a method for treating the above-mentioned diseases, the method
25 comprising the step of administering an effective amount of the compound of the present invention to a human or non-human mammal.

Further, the compound of the present invention has TNF- α production inhibitory activity and IL-4 production inhibitory activity, and thus is useful as an active ingredient in a TNF- α
30 production inhibitor or an IL-4 production inhibitor. The form, route of administration, dosage amount and the like of a TNF- α production inhibitor or an IL-4 production inhibitor comprising the compound of the present invention are the same as those of the above-mentioned PDE4 inhibitor and preventive or therapeutic
35 agent.

EXAMPLES

The following Examples are given to illustrate the present invention, and are not intended to limit the scope of the invention.

Reference Example 1 Production of ethyl 2-benzoyl-4-bromo-4-pentenoate

Sodium hydride (0.26 g, 6.0 mmol) was added under ice cooling to a solution (10 ml) of ethyl benzoylacetate (1.0 ml, 5.77 mmol) in DMF, followed by stirring for 30 minutes, and then 2,3-dibromopropene (0.63 ml, 5.77mmol) was added. The resulting mixture was stirred at room temperature for 1.5 hours, water was added to the reaction mixture, and extraction with ethyl acetate was performed three times. The organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: n-hexane/ethyl acetate=4/1). The solvent was distilled off under reduced pressure, to thereby obtain 1.55 g (yield: 86%) of ethyl 2-benzoyl-4-bromo-4-pentenoate as a colorless oil.

NMR δ ppm(CDCl₃); 8.06-8.04(2H, m), 7.63-7.60(1H, m), 7.52-7.49(2H, m), 5.71(1H, d, J=1.8Hz), 5.46(1H, d, J=1.8Hz), 4.81-4.79(2H, m), 4.16(2H, q, J=7.1Hz), 3.15-3.11(2H, m), 1.18(3H, t, J=7.1Hz)

Reference Example 2 Production of ethyl 2-benzoyl-5-bromo-4-oxopentanoate

N-bromosuccinimide (0.95 g, 5.3 mmol) and a drop of hydrobromic acid were added to a solution of ethyl 2-benzoyl-4-bromo-4-pentenoate (1.5 g, 4.82 mmol) in acetonitrile (16 ml) and water (4 ml), followed by stirring at room temperature for 3 hours and 40 minutes. The reaction mixture was diluted with diethyl ether, and a 5% aqueous sodium thiosulfate solution was added to separate the mixture into layers. The organic layer was washed twice with a saturated aqueous sodium hydrogencarbonate solution, washed with a saturated salt solution, and dried over

anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: n-hexane/ethyl acetate=4/1). The solvent was distilled off under reduced pressure, to thereby
5 obtain 0.91 g (yield: 58%) of ethyl 2-benzoyl-5-bromo-4-oxopentenoate as a colorless oil.

NMR δ ppm(CDCl₃); 8.03-8.01(2H, m), 7.63-7.59(1H, m), 7.51-7.48(2H, m), 4.93(1H, dd, J=6.4Hz, 7.5Hz), 4.15(2H, q, J=7.1Hz), 4.05(2H, dd, J=13.0Hz, 21.7Hz), 3.43(1H, dd, J=7.5Hz, 18.1Hz), 3.36(1H, dd, J=6.4Hz, 18.1Hz), 1.16(3H, t, J=7.1Hz)
10

Reference Example 3 Production of 4-chloromethyl-2-(3,4-diethoxyphenyl)thiazole

3,4-diethoxythiobenzamide (30.0 g, 133 mmol) was
15 suspended in ethanol (300 ml), and 1,3-dichloroacetone (12.8 ml, 135 mmol) was added, followed by heating under reflux for 4 hours. After cooling to room temperature, the solvent was distilled off under reduced pressure, and the residue was subjected to extraction with ethyl acetate. The organic layer was washed with
20 a saturated aqueous sodium hydrogencarbonate solution, and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: ethyl acetate/n-hexane=1/3). The solvent was distilled off under reduced pressure, and the
25 residue was recrystallized from an ethyl acetate/n-hexane mixed solvent, to thereby obtain 26.9 g (yield: 68%) of 4-chloromethyl-2-(3,4-diethoxyphenyl)thiazole as yellow prisms.

Melting point: 81.5-82.3°C

30 Reference Example 4 Production of 2-(3,4-diethoxyphenyl)thiazole-4-carboxaldehyde

N-methylmorpholine-N-oxide (16.5 g, 141 mmol) was added to a solution (200 ml) of 4-chloromethyl-2-(3,4-diethoxyphenyl)thiazole (13.99 g, 47 mmol) in acetonitrile,
35 followed by heating under reflux for 1.5 hours. After cooling to

room temperature, the solvent was distilled off under reduced pressure, and the residue was subjected to extraction with ethyl acetate. The organic layer was washed with a saturated salt solution, and dried over anhydrous sodium sulfate. The solvent
5 was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: ethyl acetate/n-hexane=1/2). The solvent was distilled off under reduced pressure, to thereby obtain 11.2 g (yield: 86%) of 2-(3,4-diethoxyphenyl)thiazole-4-carboxaldehyde as a yellow solid.
10 Melting point: 84.0-87.0°C

Reference Example 5 Production of 3-[2-(3,4-diethoxyphenyl)-thiazole-4-yl]propionic acid

Bromine (55 ml, 1.07 mol) was added dropwise under ice
15 cooling to a solution (1.2 l) of dimethyl acetyl succinate (200 g, 1.06 mol) in diethyl ether. The resulting mixture was stirred at room temperature overnight, and the solvent was distilled off under reduced pressure. Acetic acid (0.4 l) and concentrated hydrochloric acid (0.4 l) were added to the residue, and the
20 resulting mixture was stirred at room temperature for 4.5 hours and further at 80°C for 3.5 hours. The solvent was distilled off under reduced pressure, and 3,4-diethoxythiobenzamide (215.5 g, 0.96 mol), dimethoxyethane (0.8 l) and water (0.4 l) were added to the residue, followed by stirring at 80°C for 1 hour. After
25 cooling to room temperature, the precipitated crystals were collected by filtration, washed with water, and dried at 60°C to thereby obtain 305.15 g (yield: 83%) of 3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]propionic acid as a light brown powder.
30 Melting point: 111.3-113.5°C

Reference Example 6 Production of methyl 3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]propionate

A solution (2.3 l) of 3-[2-(3,4-
35 diethoxyphenyl)thiazole-4-yl]propionic acid (254.5 g) in methanol

was ice-cooled, and 58 ml of thionyl chloride was added dropwise. After completion of the addition, the resulting mixture was heated under reflux for 2 hours and cooled to room temperature. The solvent was distilled off under reduced pressure, and the
5 residue was subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogencarbonate solution, and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography
10 (eluent: ethyl acetate/n-hexane=1/3). The solvent was distilled off under reduced pressure, and the residue was recrystallized from an ethyl acetate/n-hexane mixed solvent, to thereby obtain 219.35 g (yield: 68%) of methyl 3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]propionate as a white powder.
15 Melting point; 58.1-58.3°C

Reference Example 7 Production of 3-[2-(3,4-diethoxyphenyl)]-thiazole-4-yl]-N-methoxy-N-methylpropionamide
1-hydroxybenzotriazole (22.91 g, 149.6 mmol), 1-(3-
20 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSC) (28.68 g, 149.6 mmol), N,O-dimethylhydroxylamine hydrochloride (13.93 g, 136 mmol) and triethylamine (41.7 ml, 299.2 mmol) were added to a solution (1.0 l) of 3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]propionic acid (43.71 g, 136 mmol) in dichloromethane,
25 followed by stirring at room temperature for 4 hours. Water was added to separate the reaction mixture into layers, and the aqueous layer was further subjected to extraction with dichloromethane. The organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced
30 pressure, and the residue was purified by silica gel column chromatography (eluent: ethyl acetate/n-hexane=1/3). The solvent was distilled off under reduced pressure, and the residue was recrystallized from an ethyl acetate/n-hexane mixed solvent, to thereby obtain 42.4 g (yield: 68%) of 3-[2-(3,4-
35 diethoxyphenyl)thiazole-4-yl]-N-methoxy-N-methylpropionamide as

colorless prisms.

Melting point: 72.0-73.0°C

5 Example 1 Production of (E)-3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]-1-(2-methoxyphenyl)propenone

2-methoxyacetophenone (0.16 ml, 1.2 mmol) was added to a solution (5 ml) of 2-(3,4-diethoxyphenyl)thiazole-4-carboxaldehyde (310.5 mg, 1.12 mmol) in ethanol at room temperature. A 1M aqueous potassium hydroxide solution (2.24 ml, 10 2.24 mmol) was then added dropwise at the same temperature. After stirring at room temperature for 1 hour, water was added to the reaction mixture, followed by extraction with dichloromethane. The extract was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was 15 recrystallized from ethyl acetate/n-hexane, to thereby obtain 400 mg (yield: 94%) of (E)-3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]-1-(2-methoxyphenyl)propenone as a yellow powder.

Melting point: 130-131°C

20 Example 2 Production of (E)-3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]-1-(2-methoxyphenyl)propenone

Sodium hydride (353.3 mg, 8.83 mmol) was added to a solution (80 ml) of diethyl [2-(2-methoxyphenyl)-2-oxoethyl]phosphonate (2.30 g, 8.03 mmol) in THF at room 25 temperature. After stirring at the same temperature for 30 minutes, 2-(3,4-diethoxyphenyl)thiazole-4-carboxaldehyde (2.15 g, 7.75 mmol) was added, and the resulting mixture was stirred at room temperature for 22 hours. The solvent was distilled off under reduced pressure, and the residue was purified by silica 30 gel column chromatography (eluent: n-hexane/ethyl acetate=3/1 to 2/1). The solvent was distilled off under reduced pressure, and the residue was recrystallized from ethyl acetate/n-hexane, to thereby obtain 1.62 g (yield: 51%) of (E)-3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]-1-(2-methoxyphenyl)propenone as 35 yellow prisms.

Melting point: 130-131°C

Example 3 Production of (E)-3-[2-(3,4-dimethoxyphenyl)thiazole-4-yl]-1-(3,4-diacetoxyphenyl)propenone

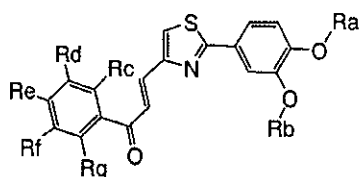
5 2-(3,4-dimethoxyphenyl)thiazole-4-carboxaldehyde (450 mg, 1.81 mmol) and 3,4-diacetoxybenzoyl methylene-triphenylphosphorane (900 mg, 1.81 mmol) were suspended in THF (25 ml), and the suspension was heated under reflux for 20 hours. After cooling, the solvent was distilled off under reduced
10 pressure, and the residue was purified by silica gel column chromatography (eluent: dichloromethane). The solvent was distilled off under reduced pressure, and the residue was recrystallized from ethyl acetate/n-hexane, to thereby obtain 380 mg (yield: 44.9%) of (E)-3-[2-(3,4-dimethoxyphenyl)thiazole-4-
15 yl]-1-(3,4-diacetoxyphenyl)propenone as a yellow powder.

Melting point: 163-164°C

Examples 4 to 34

 According to the production process of Example 1, the
20 following compounds of Examples 4 to 34 were produced (Table 1). Table 1 also shows the melting points of these compounds.

[Table 1]



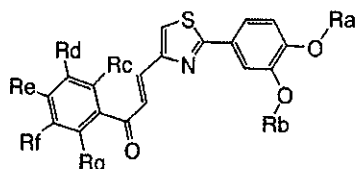
Examples	Ra	Rb	Rc	Rd	Re	Rf	Rg	Melting point (°C)	Salt
4	-C ₂ H ₅	-C ₂ H ₅	-OCH ₂ OCH ₃	-H	-OCH ₂ OCH ₃	-H	-OH	140.3 - 143	—
5	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-OCH ₂ OCH ₃	-OCH ₂ OCH ₃	-H	89.8 - 91.5	—
6	-CH ₃	-CH ₃	-H	-OH	-H	-OH	-H	164 - 168 (degrade)	hydrochloride
7	-CH ₃	-CH ₃	-H	-OH	-OH	-H	-H	162 - 165	hydrochloride
8	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-OCOCH ₃	-OCOCH ₃	-H	139 - 140	—
9	-C ₂ H ₅	-C ₂ H ₅	-OH	-H	-OH	-H	-OH	188 - 189	—
10	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-OH	-H	-H	133 - 134	—
11	-C ₂ H ₅	-C ₂ H ₅	-H	-OCH ₃	-OCH ₃	-OCH ₃	-H	155 - 156	—
12	-C ₂ H ₅	-C ₂ H ₅	-H	-Cl	-NH ₂	-Cl	-H	165 - 168	hydrochloride
13	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-OCH ₃	-OCH ₃	-H	152 - 153	—
14	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-H	-H	129 - 130	—
15	-C ₂ H ₅	-C ₂ H ₅	-OH	-H	-H	-H	-H	126 - 127	hydrobromide
16	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-OH	-H	144.5 - 146	—
17	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-CO ₂ CH ₃	-H	-H	150 - 151	—
18	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-CN	-H	-H	164 - 167	—
19	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-OH	-CO ₂ H	-H	195 - 196	—
20	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-OH	-CO ₂ CH ₃	-H	161.3 - 162.8	—
21	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-Cl	-H	-H	131 - 133	—
22	-CH ₃	-CH ₃	-H	-C(CH ₃) ₃	-OH	-C(CH ₃) ₃	-H	228 - 230	—
23	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-COCH ₃	-H	-H	128 - 129	—
24	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-NO ₂	-H	125 - 126	—
25	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-F	-H	-H	116 - 121	—
26	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-CH ₃	-H	-H	124 - 125.5	—
27	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-H	-NO ₂	142 - 143	—
28	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-NHCOCH ₃	-H	-H	199.5 - 201.5	—
29	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-Cl	-Cl	-H	138 - 139	—
30	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-NH ₂	-H	-H	148 - 150	—
31	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-OC ₂ H ₅	-H	-H	130 - 135	—
32	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-NO ₂	-H	-H	125 - 127	—
33	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-H	-CO ₂ CH ₃	132 - 133	—
34	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-CON(CH ₃) ₂	-H	-H	110 - 112	—

Examples 35 to 36

According to the production process of Example 1, the following compounds of Examples 35 and 36 were produced (Table 2). Table 2 also shows physicochemical characteristics of these

5 compounds.

[Table 2]

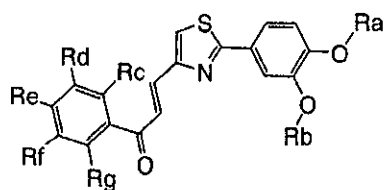


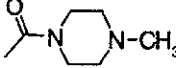
Examples	Ra	Rb	Rc	Rd	Re	Rf	Rg	NMR δ ppm(CDCl ₃)
35	-C ₂ H ₅	-C ₂ H ₅	-OCH ₂ OCH ₃	-H	-OCH ₂ OCH ₃	-H	-OCH ₂ OCH ₃	7.58(1H, d, 2.0 Hz), 7.47(1H, dd, J=2.0, 8.4 Hz), 7.35-7.33(3H, m), 6.92(1H, J=8.4Hz), 6.57(2H, s), 5.19(2H, s), 5.13(4H, s), 4.21(2H, q, J=7.0Hz), 4.13(2H, q, J=7.0Hz), 3.51(3H, s), 3.41(6H, s), 1.51(3H, t, J=7.0Hz), 1.49(3H, J=7.0Hz).
36	-CH ₃	-CH ₃	-H	-H	-OH	-CO ₂ CH ₃	-H	11.28(1H, s), 8.67(1H, d, J=2.2 Hz), 8.28(1H, dd, J=2.4, 8.8 Hz), 8.00(1H, d, J=15.0 Hz), 7.79(1H, d, J=15.0 Hz), 7.61(1H, d, J=2.4 Hz), 7.59(1H, dd, J=2.2, 8.2 Hz), 7.49(1H, s), 7.13(1H, d, J=8.8 Hz), 6.97(1H, d, J=8.2 Hz), 4.03(3H, s), 4.02(3H, s), 3.97(3H, s)

Examples 37 to 42

10 According to the production process of Example 1, the following compounds of Examples 37 to 42 were produced (Table 3). Table 3 also shows physicochemical characteristics of these compounds.

[Table 3]

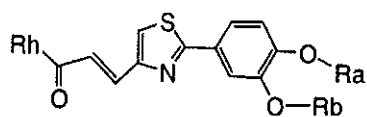


Examples	Ra	Rb	Rc	Rd	Re	Rf	Rg	Melting point (°C)	Salt
37	-CH ₃	-CH ₃	-H	-H	-OH	-H	-H	174 - 177	—
38	-CH ₃	-CH ₃	-H	-H	-O(CH ₂) ₂ N(C ₂ H ₅) ₂	-H	-H	178 - 183	trihydrochloride
39	-CH ₃	-CH ₃	-H	-H	-OH	-CO ₂ H	-H	227.4 - 228	—
40	-C ₂ H ₅	-C ₂ H ₅	-OCH ₃	-H	-H	-OCH ₃	-H	79 - 82	—
41	-CH ₃	-CH ₃	-H	-H		-H	-H	165 - 166	—
42	-C ₂ H ₅	-C ₂ H ₅	-H	-H		-H	-H	135 (degraded)	dihydrochloride

Examples 43 to 57

5 According to the production process of Example 1, the following compounds of Examples 43 to 57 were produced (Table 4). Table 4 also shows physicochemical characteristics of these compounds.

[Table 4]



Examples	Ra	Rb	Rh	Metting pont (°C)	Salt
43	-CH ₃	-CH ₃	-4-PYRIDYL	167 - 168	—
44	-CH ₃	-CH ₃	-3-PYRIDYL	168 - 169	—
45	-CH ₃	-CH ₃	-2-PYRIDYL	137 - 139	—
46	-CH ₃	-CH ₃	-2-FURYL	154 - 156	—
47	-CH ₃	-CH ₃	-2-THIENYL	157 - 158	—
48	-CH ₃	-CH ₃	-3-THIENYL	178 - 179	—
49	-C ₂ H ₅	-C ₂ H ₅	-2-PYRIDYL	92.2 - 93.8	—
50	-CH ₃	-CH ₃		175 - 177	—
51	-CH ₃	-CH ₃		152 - 153	—
52	-CH ₃	-CH ₃		176 - 177	—
53	-CH ₃	-CH ₃		197 - 199	—
54	-CH ₃	-CH ₃		146 - 147	—
55	-C ₂ H ₅	-C ₂ H ₅		116 - 117	—
56	-CH ₃	-CH ₃		147 - 149	dihydrochloride
57	-CH ₃	-CH ₃		222 - 224 (degraded)	—

Example 58 Production of methyl 2-[2-(3,4-diethoxyphenyl)thiazole-4-ylmethyl]-3-(3-ethoxypyridine-2-yl)-3-oxopropionate

Sodium hydride (239 mg, 6.0 mmol) and a drop of methanol were added to a solution (10 ml) of methyl 3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]propionate (1.0 g, 3.0 mmol) and methyl 3-ethoxypyridine-2-carboxylate (702 mg, 3.9 mmol) in dimethoxyethane, followed by heating under reflux for 2 hours. After cooling to room temperature, a saturated aqueous ammonium chloride solution was added to the reaction mixture, and the resulting mixture was subjected to extraction with ethyl acetate. The organic layer was washed with a saturated salt solution, and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: ethyl acetate/n-hexane=2/3). The solvent was distilled off under reduced pressure, to thereby obtain 740 mg (yield: 51%) of methyl 2-[2-(3,4-diethoxyphenyl)thiazole-4-ylmethyl]-3-(3-ethoxypyridine-2-yl)-3-oxopropionate as a yellow oil.

¹H NMR δ ppm (CDCl₃); 8.22 (1H, dd, J=1.3Hz, 4.3Hz), 7.44 (1H, d, J=2.1Hz), 7.4-7.2 (3H, m), 6.92 (1H, s), 6.85 (1H, d, J=8.4Hz), 5.29 (1H, t, J=7.4Hz), 4.2-4.0 (6H, m), 3.65 (3H, s), 3.6-3.4 (2H, m), 1.5-1.4 (9H, m)

Example 59 Production of ethyl 2-[2-(3,4-diethoxyphenyl)thiazole-4-ylmethyl]-3-oxo-3-phenylpropionate

3,4-diethoxythiobenzamide (0.63 g, 2.8 mmol) was added to a solution (20 ml) of ethyl 2-benzoyl-5-bromo-4-oxopentanoate (0.90 g, 2.8 mmol) in ethanol, followed by heating under reflux for 1.5 hours. After cooling to room temperature, the solvent was distilled off under reduced pressure, and the residue was subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogencarbonate solution and a saturated salt solution, and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, to

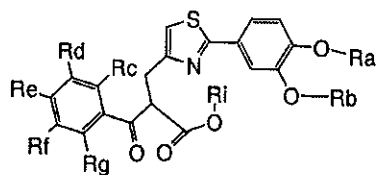
thereby obtain 1.43 g (yield: 65%) of ethyl 2-[2-(3,4-diethoxyphenyl)thiazole-4-ylmethyl]-3-oxo-3-phenylpropionate as a yellow oil.

5 NMR δ ppm(CDCl₃); 8.06-8.05(2H, m), 7.58-7.55(1H, m), 7.47-7.44(2H, m), 7.40(1H, d, J=2.0Hz), 7.36(1H, dd, J=2.0Hz, 8.4Hz), 6.90(1H, s), 6.86(1H, d, J=8.4Hz), 5.06-5.03(1H, m), 4.17-4.07(6H, m), 3.50-3.49(2H, m), 1.47(6H, t, J=7.0Hz), 1.15(3H, t, J=7.2Hz)

Examples 60 to 66

10 According to the production process of Example 58, the following compounds of Examples 60 to 66 were produced (Table 5). Table 5 also shows physicochemical characteristics of these compounds.

[Table 5]

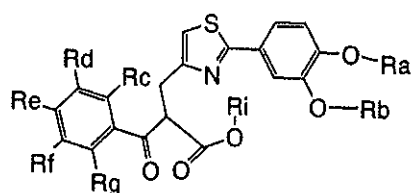


Examples	Ra	Rb	Rc	Rd	Re	Rf	Rg	Ri	NMR δ ppm(CDCl ₃)
60	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-Cl	-H	-OCH ₃	-CH ₃	7.71(1H, d, J=8.3Hz), 7.41(1H, d, J=2.0Hz), 7.35(1H, dd, J=2.0Hz, 8.3Hz), 6.98(1H, dd, J=1.8Hz, 8.4Hz), 6.92(1H, d, J=1.8Hz), 6.9-6.8(2H, m), 4.95(1H, dd, J=6.5Hz, 7.8Hz), 4.2-4.0(4H, m), 3.85(3H, s), 3.69(3H, s), 3.6-3.3(2H, m), 1.5-1.4(6H, m)
61	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-Cl	-OCH ₃	-CH ₃	7.5-7.3(4H, m), 7.04(1H, t, J=7.9Hz), 6.89(1H, s), 6.85(1H, d, J=8.4Hz), 5.09(1H, dd, J=6.6Hz, 8.0Hz), 4.2-4.0(4H, m), 3.84(3H, s), 3.70(3H, s), 3.5-3.4(2H, m), 1.5-1.4(6H, m)
62	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-H	-OC ₂ H ₅	-C ₂ H ₅	7.68(1H, dd, J=1.8Hz, 7.7Hz), 7.5-7.3(3H, m), 7.0-6.8(4H, m), 5.14(1H, t, J=7.3Hz), 4.2-4.0(8H, m), 3.6-3.3(2H, m), 1.5-1.3(9H, m), 1.13(3H, t, J=7.1Hz)
63	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-H	-N(CH ₃) ₂	-C(CH ₃) ₃	7.49(1H, d, J=1.9Hz), 7.43-7.2(3H, m), 7.0-6.8(4H, m), 5.28(1H, t, J=7.1Hz), 4.2-4.1(4H, m), 3.36(2H, dd, J=2.2Hz, 7.1Hz), 2.69(6H, s), 1.5-1.4(6H, m), 1.27(9H, s)
64	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-H	-OCH ₂ OCH ₃	-CH ₃	7.69(1H, dd, J=7.8Hz), 7.5-7.3(3H, m), 7.19(1H, d, J=8.4Hz), 7.1-7.0(1H, m), 6.88(1H, s), 6.85(1H, d, J=8.4Hz), 5.22(2H, s), 5.1-5.0(1H, m), 4.2-4.0(4H, m), 3.68(3H, s), 3.6-3.3(5H, m), 1.5-1.4(6H, m)
65	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-H	-OC ₆ H ₅	-CH ₃	7.80(1H, dd, J=1.8Hz, 7.8Hz), 7.4-7.2(5H, m), 7.2-6.9(4H, m), 6.9-6.8(3H, m), 5.13(1H, dd, J=6.2Hz, 8.3Hz), 4.2-4.0(4H, m), 3.7-3.3(5H, m), 1.5-1.4(6H, m)
66	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-H	-OCH ₃	-CH ₃	7.74(1H, dd, J=1.8Hz, 7.7Hz), 7.5-7.4(2H, m), 7.36(1H, dd, J=2.1Hz, 8.3Hz), 7.1-6.8(4H, m), 4.97(1H, t, J=7.2Hz), 4.2-4.0(4H, m), 3.85(3H, s), 3.69(3H, s), 3.6-3.3(2H, m), 1.5-1.4(6H, m)

Examples 67 to 71

5 According to the production process of Example 58, the following compounds of Examples 67 to 71 were produced (Table 6). Table 6 also shows physicochemical characteristics of these compounds.

[Table 6]

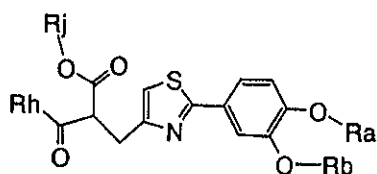


Examples	Ra	Rb	Rc	Rd	Re	Rf	Rg	Ri	MS(M+1)
67	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-H	-CN	-CH ₃	465
68	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-H	-OC ₂ H ₅	-CH ₃	484
69	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-H	-Cl	-CH ₃	474
70	-C ₂ H ₅	-C ₂ H ₅	-H	-Cl	-H	-H	-OCH ₃	-CH ₃	504
71	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-H	-CH ₃	-CH ₃	454

Examples 72 to 75

5 According to the production process of Example 58, the following compounds of Examples 72 to 75 were produced (Table 7). Table 7 also shows physicochemical characteristics of these compounds.

[Table 7]



Examples	Ra	Rb	Rh	Rj	MS(M+1)
72	-C ₂ H ₅	-C ₂ H ₅	-2-PYRIDYL	-CH ₃	441
73	-C ₂ H ₅	-C ₂ H ₅	-3-PYRIDYL	-CH ₃	441
74	-C ₂ H ₅	-C ₂ H ₅		-CH ₃	443
75	-C ₂ H ₅	-C ₂ H ₅		-CH ₃	455

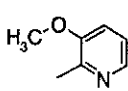
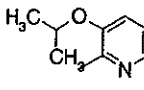
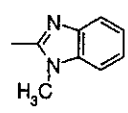
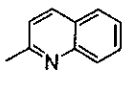
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Examples 76 to 82

According to the production process of Example 58, the

following compounds of Examples 76 to 82 were produced (Table 8). Table 8 also shows physicochemical characteristics of these compound.

[Table 8]

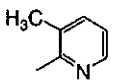
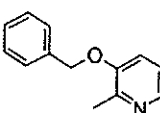
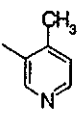
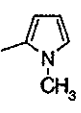
Examples	Ra	Rb	Rh	Rj	NMR δ ppm(CDCl ₃)
76	-C ₂ H ₅	-C ₂ H ₅	-2-FURYL	-CH ₃	7.60(1H, d, J=1.6Hz), 7.43(1H, d, J=2.0Hz), 7.4-7.3(2H, m), 6.89(1H, s), 6.86(1H, d, J=8.4Hz), 6.52(1H, dd, J=1.7Hz, 3.6Hz), 4.81(1H, t, J=7.4Hz), 4.2-4.0(4H, m), 3.71(3H, s), 3.48(2H, d, J=7.4Hz), 1.5-1.4(6H, m)
77	-C ₂ H ₅	-C ₂ H ₅	-4-PYRIDYL	-CH ₃	8.8-8.7(2H, m), 7.9-7.8(2H, m), 7.32(1H, d, J=1.9Hz), 7.3-7.2(1H, m), 6.90(1H, s), 6.83(1H, d, J=8.3Hz), 5.05(1H, dd, J=6.6Hz, 8.0Hz), 4.2-4.0(4H, m), 3.70(3H, s), 3.6-3.4(2H, m), 1.5-1.4(6H, m)
78	-C ₂ H ₅	-C ₂ H ₅		-CH ₃	8.23(1H, dd, J=1.2Hz, 4.4Hz), 7.5-7.3(4H, m), 6.92(1H, s), 6.85(1H, d, J=8.4Hz), 5.30(1H, dd, J=6.9Hz, 7.8Hz), 4.2-4.0(4H, m), 3.89(3H, s), 3.65(3H, s), 3.6-3.4(2H, m), 1.5-1.4(6H, m)
79	-C ₂ H ₅	-C ₂ H ₅		-CH ₃	8.21(1H, dd, J=1.7Hz, 4.0Hz), 7.45(1H, d, J=1.9Hz), 7.4-7.2(3H, m), 6.92(1H, s), 6.85(1H, d, J=8.4Hz), 5.28(1H, t, J=7.3Hz), 4.6-4.5(1H, m), 4.2-4.0(4H, m), 3.65(3H, s), 3.6-3.4(2H, m), 1.5-1.4(6H, m), 1.37(3H, s), 1.35(3H, s)
80	-C ₂ H ₅	-C ₂ H ₅		-CH ₃	7.89(1H, d, J=8.1Hz), 7.5-7.3(4H, m), 7.19(1H, dd, J=2.1Hz, 8.4Hz), 6.95(1H, s), 6.74(1H, d, J=8.4Hz), 5.59(1H, dd, J=6.0Hz, 8.9Hz), 4.2-3.9(7H, m), 3.71(3H, s), 3.7-3.4(2H, m), 1.5-1.3(6H, m)
81	-C ₂ H ₅	-C ₂ H ₅		-CH ₃	9.27(1H, d, J=1.5Hz), 8.73(1H, d, J=2.5Hz), 8.62(1H, dd, J=1.5Hz, 2.4Hz), 7.31(1H, d, J=2.1Hz), 7.3-7.2(1H, m), 6.91(1H, s), 6.81(1H, d, J=8.4Hz), 5.38(1H, dd, J=5.8Hz, 8.9Hz), 4.2-4.0(4H, m), 3.67(3H, s), 3.6-3.4(2H, m), 1.5-1.4(6H, m)
82	-C ₂ H ₅	-C ₂ H ₅		-CH ₃	8.27(1H, d, J=8.5Hz), 8.2-8.1(2H, m), 7.9-7.6(3H, m), 7.37(1H, d, J=2.0Hz), 7.29(1H, dd, J=2.1Hz, 8.4Hz), 6.93(1H, s), 6.80(1H, d, J=8.3Hz), 5.60(1H, dd, J=6.3Hz, 8.3Hz), 4.2-4.0(4H, m), 3.7-3.5(5H, m), 1.5-1.3(6H, m)

Examples 83 to 86

According to the production process of Example 58, the

following compounds of Examples 83 to 86 were produced (Table 9). Table 9 also shows physicochemical characteristics of these compounds.

[Table 9]

Examples	Ra	Rb	Rh	Rj	NMR δ ppm(CDCl ₃)
83	-C ₂ H ₅	-C ₂ H ₅		-CH ₃	8.5-8.4(1H, m), 7.56(1H, d, J=7.8Hz), 7.41(1H, d, J=2.0Hz), 7.4-7.2(2H, m), 6.91(1H, s), 6.84(1H, d, J=8.4Hz), 5.35(1H, dd, J=6.6Hz, 8.1Hz), 4.2-4.0(4H, m), 3.66(3H, s), 3.6-3.3(2H, m), 2.56(3H, s), 1.5-1.4(6H, m)
84	-C ₂ H ₅	-C ₂ H ₅		-CH ₃	8.3-8.2(1H, m), 7.5-7.3(9H, m), 6.91(1H, s), 6.82(1H, d, J=8.4Hz), 5.32(1H, t, J=7.4Hz), 5.17(2H, s), 4.2-4.0(4H, m), 3.65(3H, s), 3.6-3.4(2H, m), 1.5-1.4(6H, m)
85	-C ₂ H ₅	-C ₂ H ₅		-CH ₃	9.02(1H, s), 8.51(1H, d, J=5.0Hz), 7.4-7.3(2H, m), 7.15(1H, d, J=5.0Hz), 6.91(1H, s), 6.85(1H, d, J=8.3Hz), 5.1-5.0(1H, m), 4.2-4.0(4H, m), 3.70(3H, s), 3.6-3.4(2H, m), 2.43(3H, s), 1.5-1.4(6H, m)
86	-C ₂ H ₅	-C ₂ H ₅		-C(CH ₃) ₃	7.48(1H, d, J=2.1Hz), 7.40(1H, dd, J=2.1Hz, 8.3Hz), 7.14(1H, dd, J=1.7Hz, 4.2Hz), 6.9-6.8(3H, m), 6.11(1H, dd, J=2.5Hz, 4.2Hz), 4.64(1H, t, J=7.3Hz), 4.2-4.1(4H, m), 3.92(3H, s), 3.41(2H, d, J=7.4Hz), 1.5-1.4(6H, m), 1.37(9H, s)

5

Example 87 Production of 3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]-1-(3-ethoxypyridine-2-yl)-1-propanone

Methyl 2-[2-(3,4-diethoxyphenyl)thiazole-4-ylmethyl]-3-(3-ethoxypyridine-2-yl)-3-oxopropionate (730 mg, 1.5 mmol) was added to a mixture of acetic acid (4.5 ml) and hydrochloric acid (1.5 ml), followed by heating with stirring at 100 to 110°C for 6 hours. After cooling to room temperature, the reaction mixture was added to an aqueous solution of sodium carbonate (5.3 g, 0.05 mol), and the resulting mixture was subjected to extraction with ethyl acetate. The organic layer was washed with a saturated salt solution, and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: ethyl

10

15

acetate/n-hexane=3/4). The solvent was distilled off under reduced pressure, and the residue was recrystallized from ethanol, to thereby obtain 475 g (yield: 74%) of 3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]-1-(3-ethoxypyridine-2-yl)-1-propanone as colorless needles.

Melting point: 66.7-68.2°C

Example 88 Production of 3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]-1-(3-methoxypyridine-2-yl)-1-propanone

10 Triethylamine (0.19 ml, 1.36 mmol) and sulfur trioxide pyridine complex (0.11 g, 0.68 mmol) were added to a solution (5 ml) of 3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]-1-(3-methoxypyridine-2-yl)-1-propanone-1-ol (0.14 g, 0.34 mmol) in DMSO, and the resulting mixture was stirred at room temperature for 1
15 hour. Water was added to the reaction mixture, and extraction with diethyl ether was carried out three times. The organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by preparative thin-layer silica gel column
20 chromatography (eluent: dichloromethane/methanol=10/1). The solvent was distilled off under reduced pressure, to give 120 mg (yield: 86%) of 3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]-1-(3-methoxypyridine-2-yl)-1-propanone as a colorless oil. The oil was recrystallized from hydrous ethanol, to thereby obtain 3-[2-(3,4-
25 diethoxyphenyl)thiazole-4-yl]-1-(3-methoxypyridine-2-yl)-1-propanone as yellow needles.

Melting point: 79.2-79.7°C

Example 89 Production of 3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]-1-(2-methoxyphenyl)-1-propanone

30 (E)-3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]-1-(2-methoxyphenyl)propanone (1.62 g, 4.0 mmol) was dissolved in a mixed solvent of ethyl acetate (40 ml), methanol (10 ml) and DMF (10 ml), and 400 mg of 10% palladium/carbon was added to perform
35 catalytic reduction in a hydrogen atmosphere at room temperature

and atmospheric pressure for 4 hours. The reaction mixture was filtered, the solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: ethyl acetate/n-hexane=3/2 to 1/1). The solvent was
5 distilled off under reduced pressure, and the residue was recrystallized from diethyl ether, to thereby obtain 750 mg (yield: 46%) of 3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]-1-(2-methoxyphenyl)-1-propanone as colorless prisms.

Melting point: 68.9-69.3°C

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Example 90 Production of 3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]-1-thiazole-2-yl-1-propanone

A solution (2 ml) of thiazole (129 mg, 1.5 mmol) in THF was cooled to -70°C, and n-butyllithium (a 2.44M hexane solution)
15 (0.62 ml, 1.5 mmol) was added, and the resulting mixture was stirred at -70°C for 30 minutes. A solution (4 ml) of 3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]-N-methoxy-N-methylpropionamide (500 mg, 1.4 mmol) in THF was added to the reaction mixture, followed by stirring at -70°C for 3 hours. After heating to room
20 temperature, a saturated aqueous ammonium chloride solution was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated salt solution, and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was
25 purified by silica gel column chromatography (eluent: ethyl acetate/n-hexane=1/5). The solvent was distilled off under reduced pressure, and the residue was recrystallized from ethanol, to thereby obtain 350 mg (yield: 66%) of 3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]-1-thiazole-2-yl-1-propanone as
30 colorless needles.

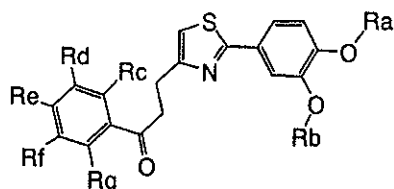
Melting point: 93.1-94.4°C

Examples 91 to 108

According to the production process of Example 87, the
35 following compounds of Examples 91 to 108 were produced (Table

10). Table 10 also shows physicochemical characteristics of these compounds.

[Table 10]



Examples	Ra	Rb	Rc	Rd	Re	Rf	Rg	Melting point (°C)	Salt
91	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-H	-H	113.3 - 113.6	—
92	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-OH	-OH	-H	153.2 - 153.8	hydrochloride
93	-CH ₃	-CH ₃	-H	-H	-OC ₂ H ₅	-OC ₂ H ₅	-H	141.3 - 142.4	—
94	-CH ₃	-CH ₃	-H	-H	-OCOCH ₃	-OCOCH ₃	-H	128 - 128.5	—
95	-C ₂ H ₅	-C ₂ H ₅	-OCH ₃	-H	-H	-OCH ₃	-H	97.8 - 98.5	—
96	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-H	-OCH ₃	68.9 - 69.3	—
97	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-H	-OC ₆ H ₅	118.2 - 119	—
98	-C ₂ H ₅	-C ₂ H ₅	-OH	-H	-H	-H	-H	113.7 - 114.9	—
99	-C ₂ H ₅	-C ₂ H ₅	-CF ₃	-H	-H	-H	-H	91.7 - 93	—
100	-C ₂ H ₅	-C ₂ H ₅	-OC ₂ H ₅	-H	-H	-H	-H	84.3 - 86.1	—
101	-C ₂ H ₅	-C ₂ H ₅	-F	-H	-H	-H	-H	82.5 - 83.5	—
102	-C ₂ H ₅	-C ₂ H ₅	-CN	-H	-H	-H	-H	113.7 - 114.8	—
103	-C ₂ H ₅	-C ₂ H ₅	-Br	-H	-H	-H	-H	66.1 - 67.9	—
104	-C ₂ H ₅	-C ₂ H ₅	-Cl	-H	-H	-H	-H	64.4 - 65.1	—
105	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-H	-CO ₂ CH ₃	91.7 - 92.9	—
106	-C ₂ H ₅	-C ₂ H ₅	-OCH ₃	-H	-Cl	-H	-H	102.8 - 104.2	—
107	-C ₂ H ₅	-C ₂ H ₅	-CH ₃	-H	-H	-H	-H	107.1 - 107.4	—
108	-C ₂ H ₅	-C ₂ H ₅	-OCH ₃	-H	-H	-Cl	-H	90.2 - 92	—

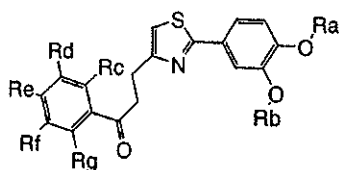
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Examples 109 to 114

According to the production process of Example 87, the following compounds of Examples 109 to 114 were produced (Table 11). Table 11 also shows physicochemical characteristics of these compounds.

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[Table 11]

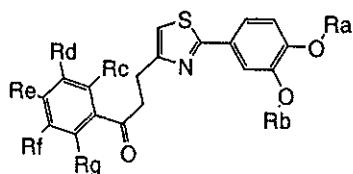


Examples	Ra	Rb	Rc	Rd	Re	Rf	Rg	NMR δ ppm(CDCl ₃)
109	-C ₂ H ₅	-C ₂ H ₅	-OCH ₃	-Cl	-H	-H	-H	7.6-7.3(4H, m), 7.10(1H, t, J=7.8Hz), 6.9-6.8(2H, m), 4.2-4.0(4H, m), 3.87(3H, s), 3.46(2H, t, J=7.1Hz), 3.21(2H, t, J=7.1Hz), 1.5-1.4(6H, m)
110	-C ₂ H ₅	-C ₂ H ₅	-N(CH ₃) ₂	-H	-H	-H	-H	7.49(1H, d, J=2.0Hz), 7.43-7.3(3H, m), 7.0-6.8(4H, m), 4.2-4.1(4H, m), 3.48(2H, t, J=7.3Hz), 3.18(2H, t, J=7.3Hz), 2.73(6H, s), 1.5-1.4(6H, m)
111	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-H	-CON(CH ₃) ₂	7.88(1H, d, J=7.4Hz), 7.6-7.3(4H, m), 7.3-7.2(1H, m), 6.9-6.8(2H, m), 4.2-4.1(4H, m), 3.45(2H, t, J=7.3Hz), 3.20(2H, t, J=7.2Hz), 3.14(3H, s), 2.76(3H, s), 1.5-1.4(6H, m)
112	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-H	-CO ₂ H	10.08(1H, br), 7.87(1H, d, J=7.1Hz), 7.7-7.3(5H, m), 6.92(1H, s), 6.89(1H, d, J=8.3Hz), 4.2-4.0(4H, m), 3.6-3.4(1H, m), 3.1-3.0(1H, m), 2.6-2.2(2H, m), 1.5-1.4(6H, m)
113	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-H	-C ₆ H ₅	7.5-7.3(11H, m), 6.87(1H, d, J=8.4Hz), 6.63(1H, s), 4.2-4.0(4H, m), 3.0-2.9(2H, m), 2.8-2.7(2H, m), 1.5-1.4(6H, m)
114	-C ₂ H ₅	-C ₂ H ₅	-OCH ₂ OCH ₃	-H	-H	-H	-H	7.69(1H, dd, J=7.8Hz), 7.5-7.3(3H, m), 7.19(1H, d, J=8.4Hz), 7.1-7.0(1H, m), 6.88(1H, s), 6.85(1H, d, J=8.4Hz), 5.22(2H, s), 5.1-5.0(1H, m), 4.2-4.0(4H, m), 3.68(3H, s), 3.6-3.3(5H, m), 1.5-1.4(6H, m)

Examples 115 to 147

5 According to the production process of Example 87, the following compounds of Examples 115 to 147 were produced (Table 12). Table 12 also shows physicochemical characteristics of these compounds.

[Table 12]



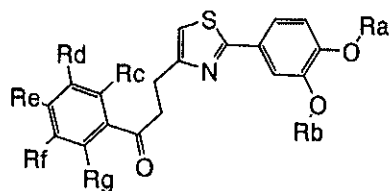
Examples	Ra	Rb	Rc	Rd	Re	Rf	Rg	MS(M+1)
115	-C ₂ H ₅	-C ₂ H ₅	-Cl	-H	-Cl	-SO ₂ NH ₂	-H	529
116	-C ₂ H ₅	-C ₂ H ₅	-OCH ₃	-H	-H	-SO ₂ NH ₂	-H	491
117	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-CN	-H	-H	407
118	-C ₂ H ₅	-C ₂ H ₅	-H	-OCH ₃	-H	-OCH ₃	-H	442
119	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-CH ₃	-H	396
120	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-CH ₃	-H	-H	396
121	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-N(CH ₃) ₂	-H	-H	425
122	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-N(CH ₃) ₂	-H	425
123	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-Br	-H	460
124	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-F	-H	-H	400
125	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-OCH ₃	-CN	-H	437
126	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-CH ₃	-OCH ₃	-H	426
127	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-H	-OCF ₃	466
128	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-Cl	-H	416
129	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-Cl	-H	-H	416
130	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-OCH ₃	-OCH ₃	-H	442
131	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-OCH ₃	-H	-H	412
132	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-CF ₃	-H	450
133	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-Cl	-Cl	450
134	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-H	-SCH ₃	428
135	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-OC ₄ H ₉	-H	-H	454
136	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-F	-H	400
137	-C ₂ H ₅	-C ₂ H ₅	-H	-Cl	-H	-H	-Cl	450
138	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-OCH ₃	-H	412
139	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-C ₆ H ₅	-H	-H	458
140	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-OC ₂ H ₅	-H	426
141	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-OC ₂ H ₅	-H	-H	426
142	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-OCH ₂ C ₆ H ₅	-H	-H	488
143	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-OCF ₃	-H	466
144	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-CF ₃	-H	-H	450
145	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-C ₄ H ₉	-H	-H	438
146	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-H	-OCH ₂ C ₆ H ₅	488
147	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-OH	-H	-H	398

Examples 148 to 152

According to the production process of Example 87, the
 5 following compounds of Examples 148 to 152 were produced (Table

13). Table 13 also shows physicochemical characteristics of these compounds.

[Table 13]



Examples	Ra	Rb	Rc	Rd	Re	Rf	Rg	MS(M+1)
148	-C ₂ H ₅	-C ₂ H ₅	-H	-H		-H	-H	448
149	-C ₂ H ₅	-C ₂ H ₅	-H	-H		-H	-H	449
150	-C ₂ H ₅	-C ₂ H ₅	-H	-H		-H	-H	448
151	-C ₂ H ₅	-C ₂ H ₅	-H	-H		-H	-H	449
152	-C ₂ H ₅	-C ₂ H ₅	-H	-H		-H	-H	467

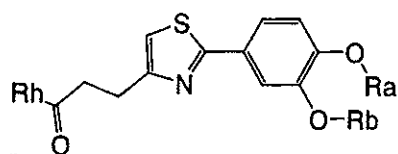
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Examples 153 to 157

According to the production process of Example 87, the following compounds of Examples 153 to 157 were produced (Table 14). Table 14 also shows physicochemical characteristics of these compounds.

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[Table 14]

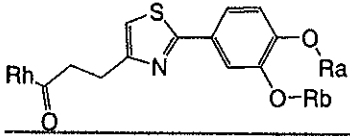
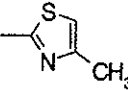
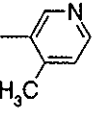
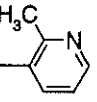
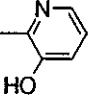
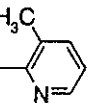
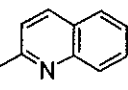
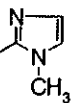
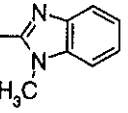
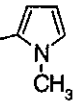


Examples	Ra	Rb	Rh	Melting point(°C)
153	-C ₂ H ₅	-C ₂ H ₅	-2-PYRIDYL	92.9 - 93
154	-C ₂ H ₅	-C ₂ H ₅	-2-FURYL	110.8 - 112.5
155	-C ₂ H ₅	-C ₂ H ₅	-2-THIENYL	106.5 - 107.4
156	-C ₂ H ₅	-C ₂ H ₅	-4-PYRIDYL	90.6 - 91.1
157	-C ₂ H ₅	-C ₂ H ₅	-3-PYRIDYL	107.5 - 108.0

Examples 158 to 167

- 5 According to the production process of Example 87, the following compounds of Examples 158 to 167 were produced (Table 15). Table 15 also shows physicochemical characteristics of these compounds.

[Table 15]

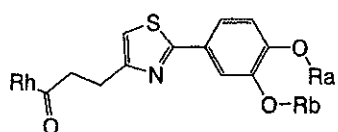
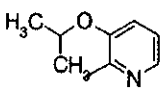
				
Examples	Ra	Rb	Rh	Melting point (°C)
158	-C ₂ H ₅	-C ₂ H ₅		59.5 - 60.5
159	-C ₂ H ₅	-C ₂ H ₅		118.7 - 119.6
160	-C ₂ H ₅	-C ₂ H ₅		109.1 - 110.5
161	-C ₂ H ₅	-C ₂ H ₅		81.7 - 83.1
162	-C ₂ H ₅	-C ₂ H ₅		87.0 - 87.6
163	-C ₂ H ₅	-C ₂ H ₅		92.1 - 93.1
164	-C ₂ H ₅	-C ₂ H ₅		117.9 - 119.2
165	-C ₂ H ₅	-C ₂ H ₅		80.3 - 81.9
166	-C ₂ H ₅	-C ₂ H ₅		107.7 - 108.5
167	-C ₂ H ₅	-C ₂ H ₅		92.8 - 94.2

Example 168

5

According to the production process of Example 87, the following compound of Example 168 was produced (Table 16). Table

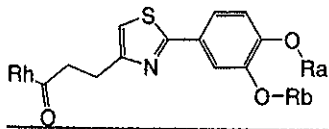
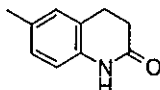
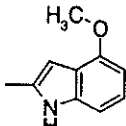
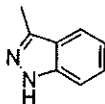
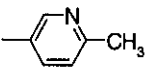
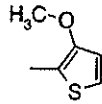
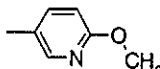
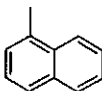
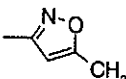
16 also shows physicochemical characteristics of the compound.
[Table 16]

				
Example	Ra	Rb	Rh	NMR δ ppm(DMSO-d6)
168	-C ₂ H ₅	-C ₂ H ₅		8.31-8.29(1H, m), 8.00(1H, d, J=8.7Hz), 7.8-7.7(1H, m), 7.53(1H, d, J=2.1Hz), 7.44(1H, dd, J=2.1Hz, 8.4Hz), 7.36(1H, s), 7.03(1H, d, J=8.5Hz), 4.9-4.7(1H, m), 4.1-4.0(4H, m), 3.50(2H, t, J=7.2Hz), 3.11(2H, t, J=7.2Hz), 1.4-1.2(12H, m)
				hydrochloride

5 Examples 169 to 178

According to the production process of Example 87, the following compounds of Examples 169 to 178 were produced (Table 17). Table 17 also shows physicochemical characteristics of these compounds.

[Table 17]

				
Examples	Ra	Rb	Rh	MS(M+1)
169	-C ₂ H ₅	-C ₂ H ₅		451
170	-C ₂ H ₅	-C ₂ H ₅		451
171	-C ₂ H ₅	-C ₂ H ₅		422
172	-C ₂ H ₅	-C ₂ H ₅		386
173	-C ₂ H ₅	-C ₂ H ₅		397
174	-C ₂ H ₅	-C ₂ H ₅		418
175	-C ₂ H ₅	-C ₂ H ₅		386
176	-C ₂ H ₅	-C ₂ H ₅		413
177	-C ₂ H ₅	-C ₂ H ₅		432
178	-C ₂ H ₅	-C ₂ H ₅		387

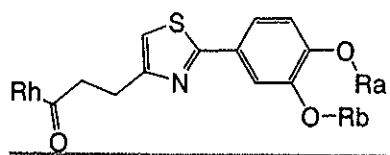
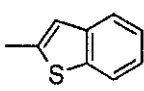
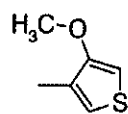
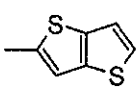
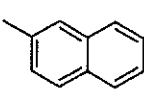
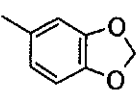
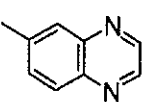
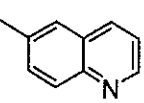
Examples 179 to 185

5

According to the production process of Example 87, the following compounds Examples 179 to 185 were produced (Table 18). Table 18 also shows physicochemical characteristics of these

compounds.

[Table 18]

				
Examples	Ra	Rb	Rh	MS(M+1)
179	-C ₂ H ₅	-C ₂ H ₅		438
180	-C ₂ H ₅	-C ₂ H ₅		418
181	-C ₂ H ₅	-C ₂ H ₅		444
182	-C ₂ H ₅	-C ₂ H ₅		432
183	-C ₂ H ₅	-C ₂ H ₅		426
184	-C ₂ H ₅	-C ₂ H ₅		434
185	-C ₂ H ₅	-C ₂ H ₅		433

5 Example 186 Production of 3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]-1-(2-methoxyphenyl)-1-propanol

Sodium borohydride (20 mg, 0.53 mmol) was added to a mixed solution of 3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]-1-(2-methoxyphenyl)-1-propanone (458 mg, 1.11 mmol) in THF (10 ml) and methanol (10 ml) at room temperature, and the resulting mixture was stirred at the same temperature for 1 hour. A saturated aqueous ammonium chloride solution was added to the reaction

mixture, followed by extraction with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: ethyl acetate/n-hexane=2/1). The solvent was distilled off under reduced pressure, and the residue was recrystallized from a diethyl ether/n-hexane mixed solvent, to thereby obtain 336 mg (yield: 73%) of 3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]-1-(2-methoxyphenyl)-1-propanol as a white powder.

10 Melting point: 78.2-79°C

Example 187 Production of 3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]-1-(3-methoxypyridine-2-yl)-1-propanol dihydrochloride

According to the production process of Example 186, 3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]-1-(3-methoxypyridine-2-yl)-1-propanol dihydrochloride was produced.

Melting point: 161.0-161.5°C

Example 188 Production of 3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]-1-(3-methoxypyridine-2-yl)-1-propanol

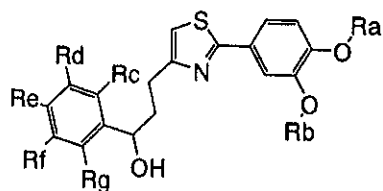
A solution of 2-bromo-3-methoxypyridine (1.65 g, 8.78 mmol) in THF was cooled to -78°C, and 5.23 ml (8.16 mmol) of a 1.57 N solution of n-butyllithium in n-hexane was added dropwise. The resulting mixture was stirred at the same temperature for 45 minutes, and a solution (15 ml) of 3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]propionaldehyde (1.34 g, 4.39 mmol) in THF was added dropwise. After stirring at the same temperature for 30 minutes, the temperature of the mixture was raised to -30°C over a period of 30 minutes. A saturated aqueous ammonium chloride solution was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated salt solution, and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: ethyl acetate/n-hexane=1/1). The solvent was distilled

off under reduced pressure, and the residue was purified by preparative thin-layer silica gel column chromatography (eluent: ethyl acetate/n-hexane=1/2). The solvent was distilled off under reduced pressure, to thereby obtain 470 mg (yield: 26%) of 3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]-1-(3-methoxypyridine-2-yl)-1-propanol as a yellow oil.

Examples 189 to 208

According to the production process of Example 186, the following compounds of Examples 189 to 208 were produced (Table 19). Table 19 also shows physicochemical characteristics of these compounds.

[Table 19]

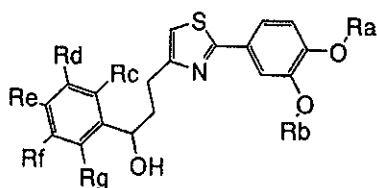


Examples	Ra	Rb	Rc	Rd	Re	Rf	Rg	MS(M+1)
189	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-H	-H	384
190	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-CN	-H	-H	409
191	-C ₂ H ₅	-C ₂ H ₅	-H	-OCH ₃	-H	-OCH ₃	-H	444
192	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-CH ₃	-H	398
193	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-CH ₃	-H	-H	398
194	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-N(CH ₃) ₂	-H	-H	426(M+)
195	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-N(CH ₃) ₂	-H	427
196	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-H	-Br	462
197	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-H	-OC ₂ H ₅	428
198	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-Br	-H	462
199	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-F	-H	-H	402
200	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-OCH ₃	-CN	-H	439
201	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-CH ₃	-OCH ₃	-H	428
202	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-H	-OCF ₃	468
203	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-H	-OCH ₃	414
204	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-Cl	-H	-H	418
205	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-H	-Cl	418
206	-C ₂ H ₅	-C ₂ H ₅	-H	-Cl	-H	-H	-OCH ₃	448
207	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-CF ₃	-H	452
208	-C ₂ H ₅	-C ₂ H ₅	-H	-OCH ₃	-H	-H	-OCH ₃	444

Examples 209 to 225

5 According to the production process of Example 186, the following compounds of Examples 209 to 225 were produced (Table 20). Table 20 also shows physicochemical characteristics of these compounds.

[Table 20]

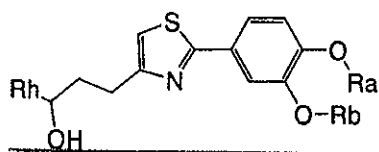
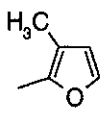
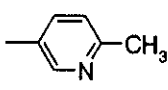
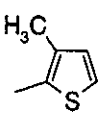
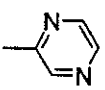
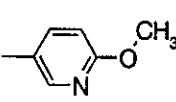
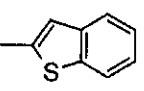
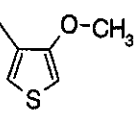
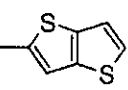


Examples	Ra	Rb	Rc	Rd	Re	Rf	Rg	MS(M+1)
209	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-Cl	-Cl	452
210	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-H	-SCH ₃	430
211	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-F	-H	402
212	-C ₂ H ₅	-C ₂ H ₅	-H	-Cl	-H	-H	-Cl	452
213	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-OCH ₃	-H	414
214	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-C ₆ H ₅	-H	-H	460
215	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-OC ₂ H ₅	-H	428
216	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-H	-F	402
217	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-OCF ₃	-H	468
218	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-CF ₃	-H	-H	452
219	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-H	-CF ₃	452
220	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-C ₄ H ₉	-H	-H	440
221	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-H	-H	-CN	409
222	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-OCH ₃	-OCH ₃	-H	444
223	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-OCH ₃	-H	-H	414
224	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-OC ₄ H ₉	-H	-H	456
225	-C ₂ H ₅	-C ₂ H ₅	-H	-H	-OC ₂ H ₅	-H	-H	428

Examples 226 to 237

5 According to the production process of Example 186, the following compounds of Examples 226 to 237 were produced (Table 21). Table 21 also shows physicochemical characteristics of these compounds.

[Table 21]

				
Examples	Ra	Rb	Rh	MS(M+1)
226	-C ₂ H ₅	-C ₂ H ₅	-2-FURYL	374
227	-C ₂ H ₅	-C ₂ H ₅	-3-PYRIDYL	385
228	-C ₂ H ₅	-C ₂ H ₅	-4-PYRIDYL	385
229	-C ₂ H ₅	-C ₂ H ₅	-2-THIENYL	390
230	-C ₂ H ₅	-C ₂ H ₅		388
231	-C ₂ H ₅	-C ₂ H ₅		399
232	-C ₂ H ₅	-C ₂ H ₅		404
233	-C ₂ H ₅	-C ₂ H ₅		386
234	-C ₂ H ₅	-C ₂ H ₅		415
235	-C ₂ H ₅	-C ₂ H ₅		440
236	-C ₂ H ₅	-C ₂ H ₅		420
237	-C ₂ H ₅	-C ₂ H ₅		446

Example 238

- 5 Production of 2-{3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]propyl}-3-methoxypyridine dihydrochloride

Hydrazine hydrate (0.18 ml, 3.6 mmol) and potassium hydroxide (136 mg, 2.4 mmol) were added to a solution (5 ml) of 3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]-1-(3-methoxypyridine-2-yl)-1-propanone (500 mg, 1.2 mmol) in diethylene glycol, and the
5 resulting mixture was heated to 150°C and stirred for 1 hour. After cooling to room temperature, water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated salt solution, and dried over anhydrous magnesium sulfate. The solvent was distilled
10 off under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: ethyl acetate/n-hexane=3/4). The solvent was distilled off under reduced pressure, and the residue was dissolved in 4 ml of ethanol. A 1N hydrogen chloride ethanol solution (1.6 ml) was added, the solvent was
15 distilled off under reduced pressure, and the residue was recrystallized from an ethanol/ethyl acetate mixed solvent, to thereby obtain 320 mg (yield: 73%) of 2-{3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]propyl}-3-methoxypyridine dihydrochloride as a white powder.
20 Melting point: 169.4-171.2°C

Example 239 Production of 2-{3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]propionyl}benzonitrile

Zinc (II) cyanide (purity of 60 %) (140 mg, 0.7 mmol)
25 and tetrakis(triphenylphosphine)palladium (19 mg, 0.016 mmol) were added to a solution (1 ml) of 1-(2-bromophenyl)-3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]propane-1-one (150 mg, 0.33 mmol) in DMF, and the mixture was stirred with heating in an argon
30 atmosphere at 100°C for 2 hours. After cooling to room temperature, water and ethyl acetate was added to the reaction mixture, the resulting mixture was filtered through Celite, and the filtrate was separated into layers. The organic layer was washed with a saturated salt solution and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced
35 pressure, and the residue was purified by silica gel column

chromatography (eluent: ethyl acetate/n-hexane=3/4). The solvent was distilled off under reduced pressure, and the residue was recrystallized from ethanol, to thereby obtain 70 mg (yield: 53%) of 2-{3-[2-(3,4-diethoxyphenyl)thiazole-4-

5 yl]propionyl}benzonitrile as colorless needles.

Melting point: 113.7-114.8°C

Example 240 Production of methyl 2-{3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]propionyl}benzoate

10 Sodium hydrogencarbonate (79 mg, 0.94 mmol) and methyl iodide (0.04 ml, 0.56 mmol) were added to a solution (4 ml) of 2-{3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]propionyl}benzoic acid (200 mg, 0.47 mmol) in DMF, followed by stirring at room temperature overnight. Water was added to the reaction mixture, and extraction with ethyl acetate was performed. The organic layer was washed with a saturated salt solution, and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: ethyl acetate/n-hexane=1/3). The solvent was distilled off under reduced pressure, and the residue was recrystallized from ethanol, to thereby obtain 190 mg (yield: 92%) of methyl 2-{3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]propionyl}benzoate as colorless needles.

Melting point: 91.7-92.9°C

25

Example 241 Production of 2-{3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]propionyl}-N,N-dimethylbenzamide

1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (WSC) (54 mg, 0.29 mmol), 1-hydroxybenzotriazol (HOBT) (43 mg, 0.29 mmol), and a 50% aqueous dimethylamine solution (0.025 ml, 0.29 mmol) were added at room temperature to a solution (2 ml) of 2-{3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]propionyl}benzoic acid (100 mg, 0.24 mmol) in DMF, followed by stirring at the same temperature for 2 hours. Water was added to the reaction mixture, and extraction with ethyl acetate was performed. The organic layer

35

was washed with a saturated aqueous sodium hydrogencarbonate solution, water and a saturated salt solution in this order, and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by

5 silica gel column chromatography (eluent: ethyl acetate/n-hexane=1/3). The solvent was distilled off under reduced pressure, to thereby obtain 65 mg (yield: 61%) of 2-{3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]propionyl}-N,N-dimethylbenzamide as a colorless oil.

10 NMR δ ppm(CDCl₃); 7.88(1H, d, J=7.4Hz), 7.6-7.3(4H, m), 7.3-7.2(1H, m), 6.9-6.8(2H, m), 4.2-4.1(4H, m), 3.45(2H, t, J=7.3Hz), 3.20(2H, t, J=7.2Hz), 3.14(3H, s), 2.76(3H, s), 1.5-1.4(6H, m)

Example 242 Production of 3-[2-(3,4-dimethoxyphenyl)thiazole-4-yl]-1-(3,4-diacetoxyphenyl)propanone

Acetic anhydride (2 ml, 20 mmol) was added dropwise at room temperature to a solution (4 ml) of 3-[2-(3,4-dimethoxyphenyl)thiazole-4-yl]-1-(3,4-dihydroxyphenyl)propanone (320 mg, 0.78 mmol) in pyridine at room temperature, followed by

20 stirring at the same temperature for 1 hour. Methanol (10 ml) was added to the reaction mixture, stirring was carried out at room temperature for 1 hour, and the solvent was distilled off under reduced pressure. Subsequently, water was added, and extraction with ethyl acetate was performed. The residue was purified by

25 silica gel column chromatography (eluent: ethyl acetate). The solvent was distilled off under reduced pressure, and the residue was recrystallized from an ethyl acetate/n-hexane mixed solvent, to thereby obtain 195 mg (yield: 54%) of 3-[2-(3,4-dimethoxyphenyl)thiazole-4-yl]-1-(3,4-diacetoxyphenyl)propanone

30 as colorless needles.

Melting point: 128-128.5°C

Example 243 Production of 3-[2-(3,4-dimethoxyphenyl)thiazole-4-yl]-1-(3,4-diethoxyphenyl)propanone

35 Ethyl iodide (0.48 ml, 6.0 mmol) and potassium

carbonate (0.62 g, 4.5 mmol) were added at room temperature to a solution (7 ml) of 3-[2-(3,4-dimethoxyphenyl)thiazole-4-yl]-1-(3,4-dihydroxyphenyl)propanone (0.58 g, 1.5 mmol) in DMF, followed by stirring at 60°C for 1 hour. After cooling to room temperature, ethyl acetate was added to the reaction mixture, the resulting mixture was filtered, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate/n-hexane=1/2). The solvent was distilled off under reduced pressure, and the residue was recrystallized from an ethyl acetate/n-hexane mixed solvent, to thereby obtain 290 mg (yield: 44%) of 3-[2-(3,4-dimethoxyphenyl)thiazole-4-yl]-1-(3,4-diethoxyphenyl)propanone as a white powder.

Melting point: 141.3-142.4°C

Examples 244 to 247

According to the production process of Example 186, the following compounds of Examples 244 to 247 were produced (Table 22).

[Table 22]

Ex.	Compound	MS (M+1)
244	3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]-1-naphthalene-1-yl-1-propanol	434
245	3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]-1-naphthalene-2-yl-1-propanol	434
246	3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]-1-quinoxaline-6-yl-1-propanol	436
247	1-benzo[1,3]dioxol-5-yl-3-[2-(3,4-diethoxyphenyl)thiazol-4-yl]-1-propanol	428

Example 248

According to the production process of Example 58, the following compound was produced.

Methyl 2-[2-(3,4-diethoxyphenyl)thiazole-4-ylmethyl]-2-(3-ethoxypyridine-2-yl)-3-oxobutyrates

$^1\text{H NMR}$ (CDCl₃); 8.22 (1H, dd, J=1.4 Hz, 4.3 Hz), 7.5-7.3 (4H, m), 6.9-6.8 (2H, m), 4.8-4.6 (1H, m), 4.2-4.0 (4H, m), 3.90 (3H, s), 3.65 (3H, s), 3.0-2.8 (2H, m), 2.6-2.3 (2H, m), 1.5-1.4 (6H, m)

Example 249

According to the production process of Example 87, the following compound was produced.

3-[2-(3,4-diethoxyphenyl)thiazole-4-yl]-1-(3-ethoxypyridine-2-yl)-1-butanone

$^1\text{H NMR}$ (CDCl₃); 8.30-8.20 (1H, m), 7.51 (1H, d, J=1.8 Hz), 7.5-7.3 (3H, m), 6.9-6.8 (2H, m), 4.3-4.1 (4H, m), 3.89 (3H, s), 3.20 (2H, t, J=7.3 Hz), 2.91 (2H, t, J=7.5 Hz), 2.2-2.1 (2H, m), 1.5-1.4 (6H, m)

Example 250

According to the production process of Example 90, the following compound was produced.

2-[2-(3,4-diethoxyphenyl)thiazole-4-yl]-1-(2-methoxyphenyl)-ethanone

$^1\text{H NMR}$ (CDCl₃); 7.79 (1H, dd, J=1.8, 7.7 Hz), 7.49 (1H, d, J=2.1 Hz), 7.49-7.46 (1H, m), 7.42 (1H, dd, J=2.1, 8.4 Hz), 7.06 (1H, s), 7.03-7.00 (1H, m), 6.98 (1H, d, J=8.4 Hz), 6.88 (1H, d, J=8.4 Hz), 4.55 (2H,

s), 4.18(2H, q, J=7.0Hz), 4.14(2H, q, J=7.0Hz), 3.92(3H, s),
1.48(3H, t, J=7.0Hz), 1.47(3H, t, J=7.0Hz)

Test Example 1 Confirmatory test for phosphodiesterase (PDE) 4
5 inhibitory activity

Using the compounds of Examples 1, 78, 87, 88, 99, 100,
106, 107, 158, 162, 165, 167, 174, 175, 187, 227, 238 and 239 as
test substances, the following test was conducted to evaluate
their phosphodiesterase (PDE) 4 inhibitory activity.

10 (1) Mass preparation of plasmids

Plasmids containing genes coding for human PDE4D
(HPDE4D) (stored in Otsuka America Pharmaceutical, Inc., Maryland
Research Laboratories) were transformed into *Escherichia coli*,
and mass cultured. The plasmids were then purified using
15 EndoFree™ Plasmid Mxi Kit (Qiagen).

(2) Mass expression and purification of PDE4D

African green monkey kidney-derived COS-7 cells (RCB
0539) were subcultured in a DMEM medium containing 100 units/ml
penicillin, 100 µm/ml streptomycin and 10% FBS. The plasmids
20 prepared in (1) were transfected into the cells, using
LipofectAMINE™ 2000 Reagent (hereinafter referred to as "LF2000",
a product of Invitroge), according to the attached protocol. For
comparison, pcDNA3.1 was transfected as a control vector. The
COS-7 cells were inoculated into 10 cm diameter petri dishes on
25 the day before transfection, so that the cells reached 90%
confluence on the day of transfection. Twelve micrograms of the
plasmids diluted with 0.9 ml of OPTI-MEM I (Invitrogen) (a
plasmid solution; Solution A) and 30 µl of LF2000 diluted with
0.9 ml of OPTI-MEM I (a LF2000 solution; Solution B) were
30 prepared per petri dish, and allowed to stand at room temperature
for 5 minutes. Solutions A and B were then mixed together and
allowed to stand at room temperature for 20 minutes. The mixture
was added to the cultured cells, and incubation was performed
overnight at 37°C in an atmosphere of 5% CO₂. The culture medium
35 was changed on the following day, incubation was continued

overnight, and the cells were collected by the following procedure. First, the cells were washed once with PBS (Sigma), and 2 ml of Trypsin-EDTA solution (Sigma) was added per petri dish, spread over the dish and removed. The cells were then
5 allowed to stand at 37°C for 2 to 3 minutes, separated from the petri dish and suspended in a medium. The suspension was placed in a centrifuge tube, and centrifuged at 200 x g and 4°C for 5 minutes. The supernatant was then removed. The cells were further washed with PBS and stored at -80°C. A KHEM buffer (50 mM
10 Hepes, 50 mM KCl, 10 mM EGTA, 1.92 mM MgCl₂, pH 7.2) containing 1 mM DTT, 40 µg/ml PMST, 156 µg/ml benzamidine, 1 µg/ml apotinin, 1 µg/ml leupeptin, 1 µg/ml pepstatin A, and 1 µg/ml antipain was added to the cells that had been stored, and the resulting mixture was placed in a glass homogenizer and homogenized on ice.
15 The cell suspension was centrifuged at 100 x g and 4°C for 5 minutes, and the supernatant was further centrifuged at 100,000 x g for 1 hour. Thereafter, the supernatant was dispensed into new tubes as a PDE4D enzyme solution, and stored in an ultra-low-temperature freezer. The protein concentration of the PDE4D
20 enzyme solution was then measured.

(3) Determination of dilution factor of PDE4D enzyme solution

The PDE4D enzyme solution prepared in (2) was diluted 10-, 25-, 50-, 100-, 200-, 400- and 800-fold with 20 mM Tris-HCl (pH 7.4), and the PDE4D activities of the diluted enzyme
25 solutions were measured by the method described in (4) to determine the optimum dilution factor to obtain a PDE4D enzyme solution in which degraded cAMP constituted 10 to 30% of the total cAMP.

(4) Measurement of PDE4D inhibitory activity

30 The necessary amount of each test substance was weighed out and dissolved in 100% DMSO to a concentration of 10 mM. The resulting solutions were stored in a freezer as test substance stock solutions. Before the inhibitory activity measurement, the stock solutions were melted, diluted 2-fold with 100% DMSO to a
35 concentration of 5 mM, and further diluted with 100% DMSO to

obtain test substance solutions with 10 graded concentrations. Each test substance solution was added to a 1.2 ml tube containing 23 μ l of 20 mM Tris-HCl (pH 7.4). Twenty five microliters of the PDE4D enzyme solution at the optimum dilution
5 factor determined in (3) was added under ice cooling, and 50 μ l of a substrate solution, which contained 2 μ M [3 H]cAMP obtained by dilution with 20 mM Tris-HCl (pH 7.4) containing 10 mM MgCl₂, was added. The final DMSO concentration in the reaction mixture was 2%. After stirring, the mixture was incubated at 30°C for 10
10 minutes. After completion of the incubation, the tubes were placed in a boiling water bath for 3 minutes to terminate the reaction. The tubes were cooled in ice, and 25 μ l of 0.2 μ g/ml snake venom solution was added. After stirring, incubation was carried out at 30°C for 10 minutes. After completion of
15 incubation, 0.4 ml of a Dowex 1 x 8 resin solution prepared using a EtOH:H₂O (1:1) mixture was added. After stirring, the mixture was allowed to stand at room temperature for at least 1 hour. Fifty microliters of each of the supernatants in the tubes was placed in a well of a Topcount plate, and the plate was dried
20 overnight. The radioactivity (cpm) of [3 H] was measured using a Topcount. Specifying the radioactivity of [3 H] as X cpm, the radioactivity of the total [3 H]cAMP added in the reaction system as T cpm, and the protein concentration of the reaction mixture as Y mg/ml, the PDE4D activity in the reaction mixture was found
25 from the following equation.

$$\text{PDE4D activity (pmol/min/mg)} = \frac{391.67}{50} \times \frac{X}{T} \times \frac{10^{-11}}{10} \times 10^{12} \times \frac{1}{0.1} \times \frac{1}{Y}$$

To find the PDE4D inhibitory activities of the test substances, cpm in the absence of the test substances, from which cpm in the absence of the enzyme had been subtracted, was set as
30 100%, and the rates of inhibition by the test substances were expressed as percentages of control. Thereafter, the IC₅₀ value (the concentration that inhibits the PDE4 activity by 50%) of each test substance was calculated.

Table 23 shows the results. The results demonstrate that the compounds represented by Formula (1) have excellent PDE4 inhibitory activity.

[Table 23]

Test substance	IC ₅₀ value (μM)
Compound of Example 1	0.0236
Compound of Example 78	0.0100
Compound of Example 87	0.0002
Compound of Example 88	0.0004
Compound of Example 99	0.0290
Compound of Example 100	0.0023
Compound of Example 106	0.0057
Compound of Example 107	0.0058
Compound of Example 158	0.0057
Compound of Example 162	0.0016
Compound of Example 165	0.0150
Compound of Example 167	0.0100
Compound of Example 174	0.0100
Compound of Example 175	0.0330
Compound of Example 187	0.0066
Compound of Example 227	0.0290
Compound of Example 238	0.0072
Compound of Example 239	0.0097

5

Test Example 2 Measurement of TNF-α production inhibitory activity

The following tests were performed to evaluate TNF-α production inhibitory activity.

(1) Separation of human peripheral blood mononuclear cells

10

A peripheral blood sample was obtained from a healthy adult donor who had signed a written informed consent. Thirty milliliters of the blood sample, which had been heparinized, was dispensed into a Leucosep tube (Greiner) containing 16 ml of a lymphocyte separation solution (Nakarai Chemical, Ltd.) under the

15

filter barrier, and centrifuged at 1000 x g for 15 minutes.

The intermediate layer corresponding to a mononuclear cell fraction was collected in a 50 ml centrifuge tube, and washed twice with a RPMI 1640 medium. After trypan blue staining, the viable count was determined and adjusted to 2×10^6 cells/ml with
5 RPMI 1640 medium.

(2) Induction of TNF- α production

E. coli (Serotype 055:B5)-derived LPS, which had been dissolved in a RPMI 1640 medium to a concentration of 5mg/ml, sterilized by filtration and stored in a freezer, was melted and
10 diluted with a RPMI 1640 medium to 10 μ g/ml. The test substances were dissolved in DMSO to obtain solutions with a concentration of 50 times the final use concentration. One microliter of each of the graded concentration test substance solutions, 149 μ l of RPMI 1640 medium, 50 μ l of LPS solution (final concentration: 1
15 μ g/ml), 50 μ l of fetal bovine serum, and 50 ml of the peripheral blood mononuclear cell suspension were dispensed to each well of a 48-well plate and incubated at 37°C for 24 hours.

(3) Measurement of TNF- α concentration

After completion of the incubation, the culture
20 supernatant was collected from each well, and the TNF- α concentration in the supernatant was measured by ELISA method (Human TNF- α Eli-pair, Diaclone). The TNF- α concentration caused by LPS stimulation in the absence of test substances was set as 100%, and the rates of inhibition by the test substances were
25 expressed as percentages of the control, and the IC₅₀ value (the concentration that inhibits TNF- α production by 50%) of each test substance was calculated.

Table 24 shows the results. The results demonstrate that the compounds represented by Formula (1) have IFN- α
30 production inhibitory activity.

[Table 24]

Test Substance	IC ₅₀ value (μM)
Compound of Ex. 1	0.008
Compound of Ex. 48	0.25
Compound of Ex. 51	0.8
Compound of Ex. 52	0.13
Compound of Ex. 56	0.16
Compound of Ex. 89	0.007
Compound of Ex. 91	0.543
Compound of Ex. 153	0.183

Test Example 3 Measurement of IL-4 production inhibitory activity

5 The following tests were performed to evaluate IL-4 production inhibitory activity.

(1) Separation of mouse spleen cells

The abdomens of six- to ten-week-old male BALB/c mice were incised under ether anesthesia, and the spleens were excised. The spleens were separated into pieces by forcing them through a
10 mesh using a glass pestle, and the spleen cells were suspended in RPMI 1640 medium. The suspension was filtered through a Cell Strainer and centrifuged at 100 x g for 10 minutes. The cell pellets were suspended in a red blood cell solution (0.75% ammonium chloride, 17 mM tris-hydrochloric acid buffer) and
15 centrifuged. Thereafter, a RPMI 1640 medium was added to the cell pellets to resuspend the cells. After centrifugation, the cells were washed twice, and the viable count was determined by trypan blue staining and adjusted to 2×10^6 cells/ml with RPMI 1640 medium.

20 (2) Induction of IL-4 production

ConA, which had been dissolved in a cell culture solution (a RPMI 1640 medium containing 10% fetal bovine serum) to a concentration of 5 mg/ml, sterilized by filtration and stored in a freezer, was melted and diluted with a cell culture
25 solution to 50 μg/ml. The test substances were dissolved in DMSO, diluted with a cell culture solution to a concentration of 10

times the final use concentration. Fifty microliters of each of the graded concentration test substance solutions, 150 μ l of cell culture solution, 50 μ l of ConA solution (final concentration: 5 μ l/ml) and 20 μ l of mouse spleen cell suspension were dispensed to each well of a 48-well plate and incubated at 37°C for 48 hours.

(3) Measurement of IL-4 concentration

After completion of the incubation, the culture supernatant was collected from each well, and the IL-4 concentration of the supernatant was measured by the ELISA method (mouse IL-4 EIA kit, BD Pharmingen). The IL-4 concentration caused by ConA stimulation in the absence of test substances was set as 100%, the rates of inhibition by the test substances were expressed as percentages of the control, and the IC₅₀ value of each test substance was calculated as the test substance concentration that inhibits IL-4 production by 50%.

Formulation Example 1 Ointment

One gram of the compound of the present invention was dispersed in 10 g of liquid paraffin to obtain a dispersion. A base was prepared by heating and mixing 3 g of paraffin, 5 g of white beeswax and 81 g of white petrolatum, and cooled, and when it had cooled to about 60°C, the above dispersion was added. After mixing, the mixture was cooled to obtain an ointment.

Formulation Example 2 Cream

One gram of the compound of the present invention was dispersed in an aqueous solution containing 10 g of purified water and 1 g of polyoxyethylene hydrogenated castor oil 60, to obtain a dispersion. An emulsion base, comprising 25 g of white petrolatum, 20 g of stearyl alcohol, 12 g of propylene glycol, 3 g of polyoxyethylene hydrogenated castor oil 60, 1 g of glyceryl monostearate, 0.1 g of methyl paraoxybenzoate, 0.1 g of propyl paraoxybenzoate and 26.8 g of purified water, was prepared with heating. The obtained emulsion base was cooled, and when it had cooled to 60°C, the above dispersion was added. After mixing, the

mixture was cooled to obtain a cream.

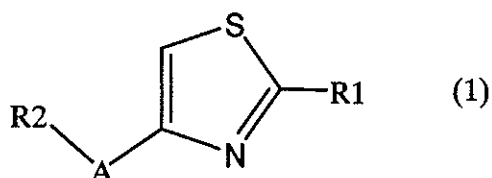
[Industrial Applicability]

5 The compound of the present invention exhibits specific inhibitory activity against PDE4, and thus is useful as an active ingredient of a PDE4 inhibitor.

Further, the compound of the present invention, based on its specific inhibitory activity against PDE4, is useful as a preventive or therapeutic agent for atopic dermatitis and various
10 other diseases.

CLAIMS

1. A compound represented by Formula (1), an optical isomer thereof, or a salt thereof:



5

wherein R1 is a di-C₁₋₆ alkoxyphenyl group;

R2 is any one of the following groups (a) to (t):

- (a) a phenyl group in which the phenyl ring may be substituted with one or more members selected from the group consisting of (a-1) hydroxy groups, (a-2) halogen atoms, (a-3) unsubstituted or halogen-substituted C₁₋₆ alkyl groups, (a-4) unsubstituted or halogen-substituted C₁₋₆ alkoxy groups, (a-5) C₁₋₆ alkoxy-C₁₋₆ alkoxy groups, (a-6) amino-C₁₋₆ alkoxy groups which may be substituted with a C₁₋₆ alkyl group or groups, (a-7) methylenedioxy groups, (a-8) carboxyl groups, (a-9) phenoxy groups, (a-10) C₁₋₆ alkoxy-carbonyl groups, (a-11) C₁₋₆ alkanoyloxy groups, (a-12) C₁₋₆ alkanoyl groups, (a-13) cyano groups, (a-14) nitro groups, (a-15) C₁₋₆ alkylcarbamoyl groups, (a-16) aminosulfonyl groups, (a-17) amino groups which may be substituted with a C₁₋₆ alkyl group or groups, (a-18) C₁₋₆ alkanoylamino groups, (a-19) C₁₋₆ alkylthio groups, (a-20) phenyl groups, (a-21) pyrazolyl groups, (a-22) imidazolyl groups, (a-23) triazolyl groups, (a-24) morpholino groups, (a-25) pyrrolidinyl groups, (a-26) piperazinyl-carbonyl groups which may be substituted with a C₁₋₆ alkyl group or groups, and (a-27) phenyl-C₁₋₆ alkoxy groups;
- (b) a naphthyl group;
- (c) a pyridyl group in which the pyridine ring may be substituted with one or more members selected from the group consisting of (c-1) hydroxy groups, (c-2) C₁₋₆ alkyl groups, (c-3) C₁₋₆ alkoxy groups, (c-4) phenyl-C₁₋₆ alkoxy groups, and (c-5) C₁₋₆

alkoxycarbonyl groups;

(d) a furyl group in which the furan ring may be substituted with a C₁₋₆ alkyl group or groups;

(e) a thienyl group in which the thiophene ring may be

5 substituted with one or more members selected from the group consisting of (e-1) halogen atoms, (e-2) C₁₋₆ alkyl groups, and (e-3) C₁₋₆ alkoxy groups;

(f) an isoxazolyl group in which the isoxazolyl ring may be substituted with a C₁₋₆ alkyl group or groups;

10 (g) a thiazolyl group in which the thiazole ring may be substituted with one or more members selected from the group consisting of (g-1) C₁₋₆ alkyl groups, and (g-2) phenyl groups which may be substituted with a C₁₋₆ alkoxy group or groups;

(h) a pyrrolyl group in which the pyrrole ring may be substituted
15 with a C₁₋₆ alkyl group or groups;

(i) an imidazolyl group in which the imidazole ring may be substituted with a C₁₋₆ alkyl group or groups;

(j) a tetrazolyl group;

(k) a pyrazinyl group;

20 (l) a thienothienyl group;

(m) a benzothienyl group;

(n) an indolyl group in which the indole ring may be substituted with a C₁₋₆ alkoxy groups or groups;

(o) a benzimidazolyl group in which the benzimidazole ring may be
25 substituted with a C₁₋₆ alkyl group or groups;

(p) an indazolyl group;

(q) a quinolyl group;

(r) a 1,2,3,4-tetrahydroquinolyl group in which the 1,2,3,4-tetrahydroquinoline ring may be substituted with an oxo group or
30 groups;

(s) a quinoxaliny group; and

(t) a 1,3-benzodioxolyl group; and

A is any one of the following groups (i) to (vi):

(i) -CO-B- wherein B is a C₁₋₆ alkylene group;

35 (ii) -CO-Ba- wherein Ba is a C₂₋₆ alkenylene group;

- (iii) -CH(OH)-B- wherein B is as defined above;
- (iv) -COCH(COOR₃)-Bb- wherein R₃ is a C₁₋₆ alkyl group and Bb is a C₁₋₆ alkylene group; and
- (v) -Bc- wherein Bc is a C₂₋₆ alkylene group.

5

2. A compound according to Claim 1, wherein, in Formula (1), R₁ is a 3,4-di-C₁₋₆ alkoxyphenyl group; an optical isomer thereof; or a salt thereof

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3. A compound according to Claim 1, wherein, in Formula (1), R₂ is (a) a phenyl group in which the phenyl ring may be substituted with one or more members selected from the group consisting of (a-1) hydroxy groups, (a-2) halogen atoms, (a-3) unsubstituted or halogen-substituted C₁₋₆ alkyl groups, (a-4) unsubstituted or halogen-substituted C₁₋₆ alkoxy groups, (a-5) C₁₋₆ alkoxy-C₁₋₆ alkoxy groups, (a-6) amino-C₁₋₆ alkoxy groups which may be substituted with a C₁₋₆ alkyl group or groups, (a-7) methylenedioxy groups, (a-8) carboxyl groups, (a-9) phenoxy groups, (a-10) C₁₋₆ alkoxycarbonyl groups, (a-11) C₁₋₆ alkanoyloxy groups, (a-12) C₁₋₆ alkanoyl groups, (a-13) cyano groups, (a-14) nitro groups, (a-15) C₁₋₆ alkylcarbamoyl groups, (a-16) aminosulfonyl groups, (a-17) amino groups which may be substituted with a C₁₋₆ alkyl group or groups, (a-18) C₁₋₆ alkanoylamino groups, (a-19) C₁₋₆ alkylthio groups, (a-20) phenyl groups, (a-21) pyrazolyl groups, (a-22) imidazolyl groups, (a-23) triazolyl groups, (a-24) morpholino groups, (a-25) pyrrolidinyl groups, (a-26) piperazinylcarbonyl groups which may be substituted with a C₁₋₆ alkyl group or groups, and (a-27) phenyl-C₁₋₆ alkoxy groups;
- 30 (c) a pyridyl group in which the pyridine ring may be substituted with one or more members selected from the group consisting of (c-1) hydroxy groups, (c-2) C₁₋₆ alkyl groups, (c-3) C₁₋₆ alkoxy groups, (c-4) phenyl-C₁₋₆ alkoxy groups, and (c-5) C₁₋₆ alkoxycarbonyl groups;
- 35 (d) a furyl group in which the furan ring may be substituted with

a C₁₋₆ alkyl group or groups;

(e) a thienyl group in which the thiophene ring may be substituted with one or more members selected from the group consisting of (e-1) halogen atoms, (e-2) C₁₋₆ alkyl groups, and

5 (e-3) C₁₋₆ alkoxy groups;

(g) a thiazolyl group in which the thiazole ring may be substituted with one or more members selected from the group consisting of (g-1) C₁₋₆ alkyl groups, and (g-2) phenyl groups which may be substituted with a C₁₋₆ alkoxy group or groups;

10 (h) a pyrrolyl group in which the pyrrole ring may be substituted with a C₁₋₆ alkyl group or groups; or

(i) an imidazolyl group in which the imidazole ring may be substituted with a C₁₋₆ alkyl group or groups; an optical isomer thereof; or a salt thereof.

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4. A compound according to Claim 1, wherein, in Formula (1), A is (i) -CO-B- wherein B is an ethylene group, a methylene group or a trimethylene group; (ii) -CO-Ba- wherein Ba is a vinylidene group; (iii) -CH(OH)-B- wherein B is a methylene group or an ethylene group; (iv) -COCH(COOR₃)-Bb- wherein R₃ is a methyl group, an ethyl group or a tert-butyl group and Bb is a methylene group or an ethylene group; or (v) -Bc- wherein Bc is an ethylene group, a trimethylene group or a tetramethylene group; an optical isomer thereof; or a salt thereof.

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5. A compound according to Claim 1, wherein, in Formula (1), R₁ is a 3,4-di-C₁₋₆ alkoxyphenyl group;

R₂ is (a) a phenyl group in which the phenyl ring may be substituted with one or more members selected from the group consisting of (a-1) hydroxy groups, (a-2) halogen atoms, (a-3) unsubstituted or halogen-substituted C₁₋₆ alkyl groups, (a-4) unsubstituted or halogen-substituted C₁₋₆ alkoxy groups, (a-5) C₁₋₆ alkoxy-C₁₋₆ alkoxy groups, (a-6) amino-C₁₋₆ alkoxy groups which may be substituted with a C₁₋₆ alkyl group or groups, (a-7) methylenedioxy groups, (a-8) carboxyl groups, (a-9) phenoxy

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- groups, (a-10) C₁₋₆ alkoxy carbonyl groups, (a-11) C₁₋₆ alkanoyloxy groups, (a-12) C₁₋₆ alkanoyl groups, (a-13) cyano groups, (a-14) nitro groups, (a-15) C₁₋₆ alkyl carbamoyl groups, (a-16) aminosulfonyl groups, (a-17) amino groups which may be
- 5 substituted with a C₁₋₆ alkyl group or groups, (a-18) C₁₋₆ alkanoylamino groups, (a-19) C₁₋₆ alkylthio groups, (a-20) phenyl groups, (a-21) pyrazolyl groups, (a-22) imidazolyl groups, (a-23) triazolyl groups, (a-24) morpholino groups, (a-25) pyrrolidinyl groups, (a-26) piperazinyl carbonyl groups which may be
- 10 substituted with a C₁₋₆ alkyl group or groups, and (a-27) phenyl-C₁₋₆ alkoxy groups;
- (c) a pyridyl group in which the pyridine ring may be substituted with one or more members selected from the group consisting of
- (c-1) hydroxy groups, (c-2) C₁₋₆ alkyl groups, (c-3) C₁₋₆ alkoxy
- 15 groups, (c-4) phenyl-C₁₋₆ alkoxy groups, and (c-5) C₁₋₆ alkoxy carbonyl groups;
- (d) a furyl group in which the furan ring may be substituted with a C₁₋₆ alkyl group or groups;
- (e) a thienyl group in which the thiophene ring may be
- 20 substituted with one or more members selected from the group consisting of (e-1) halogen atoms, (e-2) C₁₋₆ alkyl groups, and (e-3) C₁₋₆ alkoxy groups;
- (g) a thiazolyl group in which the thiazole ring may be substituted with one or more members selected from the group
- 25 consisting of (g-1) C₁₋₆ alkyl groups, and (g-2) phenyl groups which may be substituted with a C₁₋₆ alkoxy group or groups;
- (h) a pyrrolyl group in which the pyrrole ring may be substituted with a C₁₋₆ alkyl group or groups;
- (i) an imidazolyl group in which the imidazole ring may be
- 30 substituted with a C₁₋₆ alkyl group or groups; and

A is (i) -CO-B- wherein B is as defined above;

(ii) -CO-Ba wherein Ba is as defined above; (iii) -CH(OH)-B- wherein B is as defined above; (iv) -COCH(COOR₃)-Bb- wherein R₃ and Bb are as defined above; or (v) -Bc- wherein Bc is as defined

35 above; an optical isomer thereof; or a salt thereof.

6. A pharmaceutical composition comprising a compound according to Claim 1, an optical isomer thereof, or a salt thereof.

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7. A phosphodiesterase 4 inhibitor comprising as an active ingredient a compound according to Claim 1, an optical isomer thereof, or a salt thereof.

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8. A preventive or therapeutic agent for atopic dermatitis, comprising as an active ingredient a compound according to Claim 1, an optical isomer thereof, or a salt thereof.

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9. A method for treating atopic dermatitis, comprising the step of administering to a human or non-human mammal an effective amount of a compound according to Claim 1, an optical isomer thereof, or a salt thereof.

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10. Use of a compound according to Claim 1, an optical isomer thereof, or a salt thereof, for producing a preventive or therapeutic agent for atopic dermatitis.

11. Use of a compound according to Claim 1, an optical isomer thereof, or a salt thereof, for producing a phosphodiesterase 4 inhibitor.

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