Abstract:

Title: NOVEL 2,4,5-TRISUBSTITUTED-1'-THIAZOLE DERIVATIVES AND PHARMACEUTICALLY ACCEPTABLE SALT THEREOF; METHOD FOR PREPARATION, THERAPEUTIC AGENT FOR INFLAMMATORY DISEASE INDUCED BY SPC ACTIVITY CONTAINING 2,4,5-TRISUBSTITUTED-1,3-THIAZOLE DERIVATIVES AS AN EFFECTIVE INGREDIENT

Provided are a 2,4,5-trisubstituted-1,3-thiazole derivative represented by the following Chemical Formula 1, a pharmaceutically acceptable salt thereof, a method for preparation thereof, and a use thereof as an effective ingredient in a therapeutic agent for inflammatory disease induced by sphingosylphosphorylcholine (SPC). The 2,4,5-trisubstituted-1,3-thiazole derivative of the present invention has been confirmed to have superior inhibition activity against SPC receptor in an animal experiment using human-derived endothelial cells and mice. Thus, a pharmaceutical composition for treating inflammatory disease containing the 2,4,5-trisubstituted-1,3-thiazole derivative or a pharmaceutically acceptable salt thereof as an effective ingredient may be useful for treating inflammation, itching or skin infection associated with atopic dermatitis or other disease induced by SPC receptor.
[DESCRIPTION]

[Invention Title]

NOVEL 2,4,5-TRISUBSTITUTED-1,3-THIAZOLE DERIVATIVES AND PHARMACEUTICALLY
ACCEPTABLE SALT THEREOF, METHOD FOR PREPARATION THERAPEUTIC AGENT FOR
ANTIINFLAMMATORY DISEASE INDUCED BY SPC ACTIVITY CONTAINING 2,4,5-
TRISUBSTITUTED-1,3-THIAZOLE DERIVATIVES AS AN EFFECTIVE INGREDIENT

[Technical Field]

Example embodiments of the present invention relate to a 2,4,5-
trisubstituted-thiazole derivative, a pharmaceutically acceptable salt
thereof, a method for preparation thereof, and a therapeutic agent for
inflammatory disease induced by activity of sphingosylphosphoryl choline (SPC)
receptor containing the same as an effective ingredient, more particularly,
to a 2,4,5-trisubstituted-thiazole derivative as a novel compound exhibiting
inhibition activity against SPC receptor, a pharmaceutically acceptable salt
thereof, and pharmaceutical composition for treating inflammatory disease
containing the derivative or the pharmaceutically acceptable salt thereof as
an effective ingredient.

[Background Art]

Sphingosylphosphorylcholine (SPC) is the member of the Lysophospholipid
family along with structurally similar sphingosine-1-phosphate (SIP) and
lysophosphatidic acid (LPA). These materials act as important signaling
mediators in immune actions, including cell proliferation, migration,
inflammation, and the like.

SPC is produced from sphingomyelin, a component of the cell membrane,
by the action of the enzyme sphingomyelin deacylase [Higuchi K, Biocheni. J.,
2000, 350, 747-56]. SPC is known to be deeply associated with growth and
proliferation of various types of cells [Desai, Biochem. Biophys. Res.
Acta., 2005, 1734(1); 25-33], and the like.

A typical example of SPC-related diseases is atopic dermatitis. Atopic
dermatitis results in reduced antibacterial activity due to decreased lipid content in the stratum corneum and reduced resistance to external stimulants because of reduced barrier capability. As a result, it causes inflammatory reactions and itching. Since the itching may lead to secondary infections, the hyperimmune response may result in a vicious cycle.

While SPC exists hardly or at very low concentrations in healthy people, its concentration in the skin of atopic dermatitis patients increases thousands of times [Higuchi K, Biochem. J., 2000, 350, 747-756; Reiko Okamoto, Journal of Lipid Research, 2003, 44, 93-102]. It is the main cause of deficiency of intracellular lipids (ceramides) in the stratum corneum of atopic dermatitis patients [Junko Hara, J. Invest. Dermatol., 2000, 115, 406-413]. Further, SPC plays an important role in the abnormal cornification associated with the atopic disease [Higuchi, J. Lipid Res., 2001, 42, 1562-1570]. These researches suggest that SPC may be not only the direct cause of skin barrier function disorder characteristic of the atopic dermatitis, but also the cause of secondary inflammatory responses. Thus, the control of the production of SPC may lead to the development of a new therapeutic agent for skin inflammatory disease.

With regard to itching, which is a symptom of the atopic dermatitis afflicting the patient with pain and decreased quality of life, it was reported that LPA, which is structurally similar to SPC, induces itching [Hashimoto, Pharmacology, 2004, 72, 51-56]. Accordingly, it can be inferred that SPC may cause itching, too. Recently, it was shown that an intradermal injection of SPC may directly cause itching [WO 06/049451].

The inventors of the present invention have researched to develop novel compounds that can be used as pharmaceutical composition for treating inflammatory disease. They designed and synthesized a 2,4,5-trisubstituted-1,3-thiazole derivative, which has not yet been reported to exhibit inhibition activity against SPC receptor. Through experiments using human-derived endothelial cells and mice, they confirmed that the 2,4,5-trisubstituted-1,3-thiazole derivative has superior antiinflammatory effect and
completed the present invention.

[Disclosure]
[Technical Problem]

In an aspect, the present invention provides a 2,4,5-trisubstituted-1,3-thiazole derivative prepared through an organic synthesis technique and a pharmaceutically acceptable salt thereof.

In another aspect, the present invention provides a use of the 2,4,5-trisubstituted-1,3-thiazole derivative or the pharmaceutically acceptable salt thereof as an effective ingredient of a pharmaceutical composition for treating inflammatory disease induced by activity of sphingosylphosphorylcholine (SPC) receptor.

[Technical Solution]

The present invention provides a 2,4,5-trisubstituted-1,3-thiazole derivative represented by the following Chemical Formula 1 and a pharmaceutically acceptable salt thereof:

[Chemical Formula 1]

\[
\begin{align*}
R^1 & \equiv \text{heteroaryl, phenyl or substituted phenyl, the substituted phenyl being substituted by 1-4 substituents selected from the group consisting of halogen, nitro, } \text{C}_1-\text{C}_5\text{ alkyl and } \text{C}_1-\text{C}_5\text{ alkoxy; } R^2 \equiv \text{amide having } \text{C}_1-\text{C}_{10}\text{ linear, branched or cyclic alkyl, } \text{C}_2-\text{C}_{10}\text{ alkenyl, } \text{C}_2-\text{C}_{10}\text{ alkynyl, heteroaryl, arylalkyl, C}_5-\text{C}_{10}\text{ heteroarylalkyl, phenyl or substituted phenyl, the substituted phenyl being substituted by 1-4 substituents selected from the group consisting of halogen, nitro, } \text{C}_1-\text{C}_5\text{ alkyl and } \text{C}_1-\text{C}_5\text{ alkoxy; and } R^3 \equiv \text{amine substituted by one or more } \text{C}_1-\text{C}_{10}\text{ linear, branched or cyclic alkyl, } \text{C}_1-\text{C}_{10}\text{.}
\end{align*}
\]
aryl, C$_1$-C$_{10}$ heteroaryl, C$_1$-C$_{10}$ arylalkyl or CrC$_{10}$ heteroarylalkyl, or piperazine \( \text{R}^4-N(\text{C} - \text{N} -) \) substituted by phenyl, C$_1$-C$_{10}$ linear, branched or cyclic alkyl, or heteroarylamide, the phenyl being substituted by 1-4 substituents selected from the group consisting of halogen, nitro, C$_1$-C$_{10}$ alkyl, C$_1$-C$_{10}$ alkoxy and C$_1$-C$_{10}$ haloalkyl.

The present invention further provides a method for preparation of the 2,4,5-trisubstituted-1,3-thiazole derivative represented by Chemical Formula 1 using an organic synthesis technique.

The present invention further provides a pharmaceutical composition for treating inflammatory disease induced by activity of sphingosylphosphoryl choline (SPC) receptor containing the 2,4,5-trisubstituted-1,3-thiazole derivative represented by Chemical Formula 1 or a pharmaceutically acceptable salt thereof as an effective ingredient.

The present invention further provides a pharmaceutical composition containing the 2,4,5-trisubstituted-1,3-thiazole derivative represented by Chemical Formula 1 or a pharmaceutically acceptable salt thereof as an effective ingredient for preventing scarring after injury and promoting wound healing.

The present invention further provides a modulator of chemotaxis-mediated symptoms containing the 2,4,5-trisubstituted-1,3-thiazole derivative represented by Chemical Formula 1 or a pharmaceutically acceptable salt thereof as an effective ingredient.
[Advantageous Effects]

The present invention provides a 2,4,5-trisubstituted-1,3-thiazole derivative prepared using an organic synthesis technique and a pharmaceutically acceptable salt thereof, which exhibits superior inhibition activity against sphingosylphosphoryl choline (SPC) receptor in an animal model experiment using human-derived endothelial cells and mice. The present invention further provides a pharmaceutical composition for treating inflammatory disease induced by activity of SPC receptor.

[Mode for Invention]

Hereinafter, the present invention will be described in more detail.

The present invention provides a 2,4,5-trisubstituted-1,3-thiazole derivative represented by the following Chemical Formula 1 and a pharmaceutically acceptable salt thereof:

\[ \text{Chemical Formula 1} \]

\[
\begin{array}{c}
\text{R}^1 \\
\text{N} \\
\text{R}^2 \\
\text{R}^3 \\
\text{S} \\
\text{O} \\
\end{array}
\]

In Chemical Formula 1, R is the same as defined above, and may be a substituent selected from the followings:

- \( \text{R} = \text{F}, \text{Cl}, \text{Br}, \text{O} \text{Me}, \text{NO}_2 \)
- \( \text{R} = \text{O}, \text{S} \)

\( \text{R}^2 \) is the same as defined above, and may be a substituent selected from the followings:
$R^3$ is the same as defined above, and may be a substituent selected from the followings:

\[ n = 0-5 \quad R = F, Cl, Br, OMe, NO_2 \quad X = O, S \]
In the 2,4,5-trisubstituted-1,3-thiazole derivative represented by Chemical Formula 1, \( R^1 \) may be selected from the group consisting of heteroaryl, phenyl and substituted phenyl; \( R^2 \) may be amide having \( C_1-C_5 \) linear, branched or cyclic alkyl, \( C_2-C_5 \) alkenyl, \( C_2-C_5 \) alkynyl, heteroaryl, arylalkyl, \( C_5-C_{10} \) heteroarylalkyl, phenyl or substituted phenyl; and \( R^3 \) may be amine substituted by one or more \( C_1-C_5 \) linear, branched or cyclic alkyl, \( C_1-C_5 \) aryl, \( C_1-C_5 \) heteroaryl, \( C_1-C_5 \) arylalkyl or \( C_1-C_5 \) heteroarylalkyl, or piperazine (\( ^n \text{N} \)) substituted by phenyl, \( C_1-C_5 \) linear, branched or cyclic alkyl, or heteroarylamide, the phenyl being substituted by 1-4 substituents selected from the group consisting of halogen, nitro, \( C_1-C_5 \) alkyl, \( C_1-C_{10} \) alkoxy and \( C_1-C_{10} \) haloalkyl.

The present invention further provides a method for the preparation of the 2,4,5-trisubstituted-1,3-thiazole derivative represented by Chemical Formula 1.

The 2,4,5-trisubstituted-1,3-thiazole derivative represented by Chemical Formula 1 of the present invention may be prepared by an organic synthesis technique, according to the following Scheme 1:

[Scheme 1]
wherein $R_1$, $R_2$ and $R_3$ are the same as defined above.

In detail, the method for the preparation of the 2,4,5-trisubstituted-1,3-thiazole derivative represented by Chemical Formula 1 according to the present invention comprises:

reacting methylcyanocarbonimidodithionate represented by Chemical Formula 2 with a 2-haloacetophenone derivative to synthesize a 4-amino-1,3-thiazole represented by Chemical Formula 3 in which the substituent $R_1$ is introduced;

reacting the 4-amino group of the compound represented by Chemical Formula 3 with chlorocarboxylic acid to synthesize a 4-N-acyl-1,3-thiazole represented by Chemical Formula 4 in which the substituent $R_2$ is introduced;

oxidizing the sulfanyl group of the compound represented by Chemical Formula 4 with m-chloroperbenzoic acid (m-CPBA) to synthesize a 2-sulfonyl-4-N-acyl-1,3-thiazole represented by Chemical Formula 5; and

reacting the compound represented by Chemical Formula 5 with a primary or secondary amine to synthesize the 2,4,5-trisubstituted-1,3-thiazole derivative represented by Chemical Formula 1.

The reaction process, composition of the solvent system and reaction
condition in accordance with the present invention will be described in detail.

In the first step, dimethyl formamide (DMF), acetone, methanol or ethanol is used as solvent. Preferably, DMF may be used. In this step, the substituent R₁ and a base may be used in an amount of about 2 equivalents, respectively. Preferably, they may be used in an amount of about 1.5 equivalents, respectively, considering economy. The base may be N,N-diisopropylethylamine, triethylamine (Et₃N), sodium methoxide (NaOMe), sodium ethoxide (NaOEt), or the like. The substituent R is the same as defined above, and may be an alkyl halide.

In the second step, acetonitrile (MeCN) or dichloromethane (CH₂Cl₂) is used as solvent. In this step, a base and the substituent R₂ may be used in an amount of about 2 equivalents, respectively. Preferably, they may be used in an amount of about 1.5 equivalents, respectively, considering economy. The base may be pyridine, triethylamine, or the like. The substituent R₂ substituent is the same as defined above, and may be a chlorocarboxylic acid.

In the third step, dichloromethane is used as solvent. In this step, tn-CPBA or hydrogen peroxide may be used in an amount of about 4 equivalents, respectively. Preferably, they may be used in an amount of about 2.5 equivalents, respectively, considering economy.

In the fourth step, dioxane or dichloromethane is used, and the substituent R₃ and a base are used for the addition reaction to obtain the wanted 2,4,5-trisubstituted-1,3-thiazole derivative represented by Chemical Formula 1. In this step, the base and the substituent R₃ may be used in an amount of about 2 equivalents, respectively. Preferably, they may be used in an amount of about 1.5 equivalents, respectively, considering economy. The base may be pyridine, triethylamine, or the like. The substituent R₃ substituent is the same as defined above, and may be a primary or secondary amine.
In the preparation of the 2,4,5-trisubstituted-1,3-thiazole derivative represented by Chemical Formula 1 according to the present invention, the progress of reaction of each step may be confirmed by TLC. Structural analysis of the reaction intermediates represented by Chemical Formulas 3, 4 and 5 may be carried out by NMR or mass spectroscopy after separation and purification.

The present invention further provides a pharmaceutical composition for treating inflammatory disease induced by activity of sphingosylphosphoryl choline (SPC) receptor containing the 2,4,5-trisubstituted-1,3-thiazole derivative represented by Chemical Formula 1 or a pharmaceutically acceptable salt thereof as an effective ingredient.

The pharmaceutical composition for treating inflammatory disease may comprise N-(5-benzoyl-2-[4-(2-methoxyphenyl)piperazin-1-yl]thiazoyl-4-yl)pivalamide (Compound No. 1-76, see Table 1 below) or N-(5-benzoyl-2-[2-(piperidin-1-yl)ethylamido]thiazoyl-4-yl)-4-fluorobenzamide (Compound No. 1-94, see Table 1) of the 2,4,5-trisubstituted-1,3-thiazole derivative represented by Chemical Formula 1, as an effective ingredient.

The 2,4,5-trisubstituted-1,3-thiazole derivative of the present invention was confirmed to have an antagonistic effect in selective cell proliferation induced by SPC (see Table 2). Therefore, it may be effective for atopic dermatitis or other skin disease caused by excessive cell division and proliferation induced by SPC. Further, because excessive cell division and proliferation during wound healing may result in scars through inflammatory response, the 2,4,5-trisubstituted-1,3-thiazole derivative of the present invention, which inhibits the excessive cell division and proliferation, may be used to prevent unwanted scarring. In addition, it may be used to facilitate wound healing after injury.

Further, in tetradecanoylphorbol acetate (TPA)-induced inflammatory response test, the 2,4,5-trisubstituted-1,3-thiazole derivative of the present invention reduced ear edema and inhibited MPO activity, comparable to hydrocortisone which is commonly used to treat inflammation (see Table 4).
Accordingly, the 2,4,5-trisubstituted-1,3-thiazole derivative of the present invention may be effective in treating inflammation, itching, skin infections, etc. associated with atopic dermatitis or other disease, and may be useful as a pharmaceutical composition for preventing scarring after injury and promoting wound healing.

Further, the present invention provides a modulator of chemotaxis-mediated symptoms containing the 2,4,5-trisubstituted-1,3-thiazole derivative represented by Chemical Formula 1 or a pharmaceutically acceptable salt thereof as an effective ingredient.

Chemotaxis is the phenomenon in which endothelial cells or immune cells are attracted by specific materials such as cytokines or chemokines. By this, immune cells move to inflamed area or endothelial cells migrate to result in angiogenesis.

The 2,4,5-trisubstituted-1,3-thiazole derivative represented by Chemical Formula 1 according to the present invention was confirmed to be able to strongly inhibit the migration of endothelial cells or immune cells induced by SPC (see Table 3).

Accordingly, a modulator of chemotaxis-mediated symptoms comprising the 2,4,5-trisubstituted-1,3-thiazole derivative represented by Chemical Formula 1 according to the present invention or a pharmaceutically acceptable salt thereof as an effective ingredient may inhibit angiogenesis caused by the migration of endothelial cells and may control the amplification of immune response to antigens from outside.

The modulator of chemotaxis-mediated symptoms may comprise N-{5-benzoyl-2-[4-(2-methoxyphenyl)piperazin-1-yl]thiazoyl-4-yl}pivalamide (Compound No. 1-76) of the 2,4,5-trisubstituted-1,3-thiazole derivative represented by Chemical Formula 1 as an effective ingredient.

Specific examples of the chemotaxis-mediated symptoms that can be controlled by the modulator of chemotaxis-mediated symptoms according to the present invention may include inflammation, itching and skin infection associated with atopic dermatitis or other disease.
The pharmaceutically acceptable salt according to the present invention may be one that can be prepared by a method commonly used in the related art. For example, a pharmaceutically acceptable acid salt may be prepared using an inorganic acid such as hydrochloric acid, hydrogen bromide, sulfuric acid, sodium bisulfate, phosphoric acid, carbonic acid, etc. or an organic acid such as formic acid, acetic acid, oxalic acid, benzoic acid, citric acid, tartaric acid, gluconic acid, gentisic acid, fumaric acid, lactobionic acid, salicylic acid, acetylsalicylic acid (aspirin), etc. or an organic acid such as formic acid, acetic acid, oxalic acid, benzoic acid, citric acid, tartaric acid, gluconic acid, gentisic acid, fumaric acid, lactobionic acid, salicylic acid, acetylsalicylic acid (aspirin), etc., a metal salt may be prepared using an alkali metal ion such as sodium, potassium, etc., or other pharmaceutically acceptable salt may be prepared using an ammonium ion.

Further, a commonly used non-toxic pharmaceutically acceptable carrier, modifier or excipient may be added to the 2,4,5-trisubstituted-1,3-thiazole derivative of the present invention or a pharmaceutically acceptable salt thereof to prepare a pharmaceutical composition in oral or parenteral preparation forms common in the pharmaceutical field, e.g. tablet, capsule, troche, liquid, suspension, etc.

The administration dose of the compound of the present invention may vary depending on the age, body weight and sex of the patient, administration route, physical conditions and severity of disease. For an adult patient weighing 70 kg, a usual dosage may be 0.01-1,000 mg/day. Depending on the physician's or pharmacist's decision, it may be administered once or several times a day at predetermined intervals.

Hereinafter, the present invention will be described in detail through examples.

However, the following examples are only for illustrating the present invention, and the scope of the present invention is not limited by them.

Example 1: Synthesis of 2,4,5-trisubstituted-1,3-thiazole (Chemical Formula 1-1)

Step 1: Conversion of potassium (E)-methylcyanocarbonimidodithionate
Potassium (E)-methylcyanocarbonimidodithionate (1.53 g, 8.98 mmol) represented by Chemical Formula 2 was dissolved in DMF (20 mL). After adding 2-bromoacetophenone (PhCOCH₂Br; 2.00 g, 10.0 mmol) and triethylamine (Et₃N; 1.80 mL, 12.9 mmol), reaction was carried out at 80°C for 3 hours while stirring. Then, after cooling to room temperature, the reaction mixture was dissolved in 100 mL of EtOAc and washed with 100 mL of brine. After drying the organic layer using Na₂SO₄, the reaction mixture was filtered and concentrated. The concentrated reaction mixture was purified by recrystallization (hexane:EtOAc = 3:1) to obtain [4-amino-2-(methylthio)thiazole-5-yl] (phenyl)methanone (1.95 g, 77%) represented by Chemical Formula 3-1.

$^1$H NMR (500 MHz, CDCl₃) δ 2.72 (s, 3H), 6.83 (br s, 2H), 7.44-7.52 (m, 3H), 7.75-7.77 (m, 2H); m/z ([M+1]$^+$) 251.

Step 2: N-acetylation of 4-amino-1,3-thiazole (Chemical Formula 3-1)

4-Amino-1,3-thiazole (1.08 g, 4.31 mmol) represented by Chemical Formula 3-1 was dissolved in 10 mL of acetonitrile. After adding acetyl chloride (CH₃COCl; 0.53 mL, 7.50 mmol) and pyridine (0.60 mL, 7.42 mmol), reaction was carried out at room temperature for 6 hours while stirring. Then, the reaction mixture was dissolved in 50 mL of EtOAc and washed with 50
mL of brine. After drying the organic layer using Na₂SO₄, the reaction mixture was filtered and concentrated. The concentrated reaction mixture was purified by silica gel column chromatography (hexane:EtOAc = 3:1) to obtain N-[5-benzoyl-2-(methylthio)thiazole-4-yl]acetamide (1.06 g, 84%) represented by Chemical Formula 4-1.

\[
\text{\textsuperscript{1}H NMR (500 MHz, CDC13) } \delta 2.31 (s, 3H), 2.77 (s, 3H), 7.46-7.51 (m, 2H), 7.58 (m, 1H), 7.66-7.81 (m, 2H), 11.63 (s, 1H); m/z ([M+1]⁺) 293.
\]

Step 3: Oxidation of 4-N-acetyl-1,3-thiazole (Chemical Formula 4-1)

4-N-acetyl-1,3-thiazole (0.96 g, 3.28 mmol) represented by Chemical Formula 4-1 was dissolved in 10 mL of dichloromethane. After adding m-chloroperbenzoic acid (m-CPBA; 1.84 g, 8.21 mmol) at room temperature, reaction was carried out at room temperature for 12 hours while stirring. Then, the reaction mixture was dissolved in 50 mL of EtOAc and sequentially washed with 50 mL of saturated Na₂S₂O₃ solution, 50 mL of saturated NaHCO₃ solution and 50 mL of brine. After drying the organic layer using Na₂SO₄, the reaction mixture was filtered and concentrated. The concentrated reaction mixture was purified by silica gel column chromatography (hexane:EtOAc = 2:1) to obtain N-[5-benzoyl-2-(methylsulfonyl)thiazole-4-yl]acetamide (1.01 g, 95%) represented by Chemical Formula 5-1.

\[
\text{\textsuperscript{1}H NMR (500 MHz, CDC13) } \delta 2.33 (s, 3H), 3.43 (s, 3H), 7.53-7.67 (m, 3H), 7.84-7.86 (m, 2H), 10.89 (s, 1H); m/z ([M+1]⁺) 325.
\]

Step 4: Addition of amine to 2-sulfonyl-4-N-acetyl-1,3-thiazole (Chemical Formula 5-1)
2-Sulfonyl-4-N-acetyl-1,3-thiazole (50 mg, 0.15 mmol) represented by Chemical Formula 5-1 was dissolved in 5 mL of dioxane. After adding diethylamine (Et2NH; 0.031 mL, 0.30 mmol) and triethylamine (0.056 mL, 0.40 mmol), reaction was carried out at room temperature for 12 hours while stirring. Then, the reaction mixture was dissolved in 20 mL of EtOAc and washed with 20 mL of brine. After drying the organic layer using Na2SO4, the reaction mixture was filtered and concentrated. The concentrated reaction mixture was purified by silica gel column chromatography (hexane:EtOAc = 3:1) to obtain N-[5-benzoyl-2-(diethylamino)thiazole-4-yl]acetamide (41 mg, 87%) represented by Chemical Formula 1-1.

1H NMR (500 MHz, CDC13) δ 1.26-1.29 (m, 6H), 2.47 (s, 3H), 3.56 (m, 4H), 7.43-7.51 (m, 3H), 7.74-7.75 (m, 2H), 11.58 (s, 1H); m/z ([M+1]+) 318.

Examples 2-150: Synthesis of 2,4,5-trisubstituted-1,3-thiazole derivatives

2,4,5-Trisubstituted-1,3-thiazole derivatives represented by Chemical Formula 1 were synthesized in the same manner as in Example 1, with the substituents R₁, R₂ and R₃ being listed in Table 1. Analysis result for the synthesized 2,4,5-trisubstituted-1,3-thiazole derivatives is also given in the table.

[Chemical Formula 1]
Experimental Example 1: Control of cell division and proliferation

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Treatment of cells with SPC results in excessive cell division and proliferation, which may lead to pathological symptoms such as atopic dermatitis or other skin disease [Desai, Biochem. Biophys. Res. Commun., 1991, 181, 361-366]. The effects of the compounds prepared in Examples on the cell division and proliferation induced by SPC was tested as follows.

$10^5$ (normally $1x10^4$-$10^6$) NIH 3T3 cells (American Type Culture Collection, Manassas, VA, USA) were cultured on a culture plate. Then, they were cultured in an RPMI medium free of bovine serum for 24 hours until serum starvation. After treating with the compounds prepared in Examples or with FTY720 (fingolimod), an agonist of sphingosine-1-phosphate (S1P), as control compound at concentrations of 0.001 $\mu M$, 0.01 $\mu M$, 0.1 $\mu M$ and 1 $\mu M$, the cells were cultured for 30 minutes. Then, after adding SPC (Biomol, Plymouth Meeting, PA, USA) at a concentration of 7 $\mu M$, the cells were cultured for 24 hours at $37^\circ C$. Cell proliferation was measured by [3H]-thymidine incorporated into DNA strands during cell division [Beales IL, Life Sci., 2004, 75, 83-95]. Proliferation rate (%) was calculated by the following Equation 1, and the result is given in the following Table 2.

\[
\text{Proliferation rate (\%)} = \frac{\text{(Test compound treated group)} - \text{(SPC non-treated group)}}{\text{(SPC treated group)} - \text{(SPC non-treated group)}} \times 100
\]

### [Table 2]

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<tr>
<th>Examples</th>
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<th>SPC inhibition IC\text{50} (\mu M)</th>
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As seen from Table 2, the compounds of the present invention prepared
in Examples exhibited antagonistic effect against selective cell proliferation induced by SPC. Because inflammatory response due to excessive cell division and proliferation during wound healing after injury results in scars, the material which inhibits cell division and proliferation may be used to prevent unwanted scarring. And, the material which enhances cell division and proliferation may be used to promote wound healing after injury.

Especially, the compounds of Examples 1-1 and 1-76 inhibited the cell division and proliferation induced by SPC in a dose-dependent manner. It is to be noted that FTY720, an agonist of SlP, which has a chemical structure similar to that of SPC and shares some of membrane receptors, did not inhibit the cell division and proliferation induced by SPC. Accordingly, it is conjectured that the inhibition of cell division and proliferation is due to the inherent structural activity of the compound of the present invention, and the compound of the present invention may be used to prevent scarring caused by inflammatory response due to excessive cell division and proliferation during wound healing after injury.

Experimental Example 2: Inhibition of chemotactic cell migration induced by SPC

Recently, it was reported that SPC plays an important role in chemotactic cell migration similarly to vascular endothelial growth factor (VEGF) [Boguslawski et al., Biochem. Biophys. Res. Commun., 2000, 272, 603-609]. Chemotaxis, the phenomenon in which cells are attracted by specific materials such as cytokines or chemokines, is critical to the migration of immune cells or endothelial cells. The effect of the compound prepared in Examples on the chemotactic migration of cells induced by SPC was tested by the Boyden chamber technique.

A 25 x 80 mm polycarbonate membrane (Neuro Probe, Inc.) having 8 μm pores was immersed in 0.01% gelatin, 0.1% acetic acid solution. After coating overnight, the membrane was allowed to be dried at room temperature.

Human umbilical vein endothelial cells (HUVECs) cultured in a complete
EBM-2 medium containing 2% fetal bovine serum (FBS) were cultivated for 4 hours in a EBM-2 medium (Cambrex, Catalog No. CC-3121) without containing bovine serum until serum starvation, and harvested with trypsin/EDTA solution. The HUVECs were suspended in a EBM-2 medium containing 0.1% bovine serum albumin (BSA), transferred to a silicone-coated Eppendorf tube, and treated with the test compound of Example 1-78 at concentrations of 0, 0.1, 1 and 10 µg/mL, at 37°C for 30 minutes. 27 µL of EBM-2 medium with or without containing 10 µM SPC was added to each well of the lower compartment of a Boyden chamber. The gelatin-coated membrane was placed so that a glossy surface faced downward. A gasket was placed thereon and the upper compartment was assembled. The HUVEC cells treated with the compound were transferred to the upper compartment, 5x10^4 (56 µL) each, and cultured for 8 hours at 37°C in a CO2 incubator. The membrane was separated, stained with a Diff-Quik stain (Sysmex Corporation), washed with deionized water, and attached on a slide glass so that a glossy surface faced upward. The cells attached on the upper portion of the membrane were cautiously wiped out using KimWipes or a swab. Photographs were taken arbitrarily, 5 fields per each well (x 200), in order to count the cells. Inhibition rate (%) was calculated by the following Equation 2, and the result is given in the following Table 3.

[Equation 2]

\[
\text{Inhibition rate (\%)} = \frac{(\text{SPC treated group}) - (\text{Test compound treated group})}{(\text{SPC treated group}) - (\text{SPC non-treated group})} \times 100
\]

<table>
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<th>Example</th>
<th>Inhibition rate (%)</th>
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<tr>
<td>1-76</td>
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<tr>
<td>0.1 µg/mL</td>
<td>43</td>
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<tr>
<td>1 µg/mL</td>
<td>61</td>
</tr>
<tr>
<td>10 µg/mL</td>
<td>72</td>
</tr>
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</table>

As seen from Table 3, the compound of Example 1-76 strongly inhibited the chemotactic cell migration induced by SPC. This suggests that, by inhibiting the migration of endothelial cells or immune cells, the compound
may control the process of angiogenesis in tumors or amplification of immune response to antigens from outside.

Experimental Example 3: Control of inflammatory response in mouse TPA-induced ear inflammation model

In order to confirm the inhibition effect against inflammatory response, experiment was carried out as follows using a Tetradecanoyl phorbol acetate (TPA)-induced inflammation model, as follows.

The TPA-induced inflammation model is widely used to test the mechanism of inflammatory response and the efficiency of inhibiting substance [De Young LM et al., Agents and Actions, 1989, 26, 335-341]. TPA is a potent tumor promoter resulting in inflammatory response. When applied on the ear of a subject, it results in erythema and edema. This inflammatory response can be measured by the increased activity of myeloperoxidase (MPO), which is essential when white blood cells attack bacteria.

Forty 6-week-old male ICR mice were prepared. TPA (Sigma Aldrich Korea) dissolved in acetone at 125 µg/mL was applied on the left ears of the mice, 20 µl per each. One hour later, acetone, 0.3% test compounds dissolved in acetone, or 0.3% hydrocortisone (Sigma Aldrich Korea) dissolved in acetone was applied on the TPA-applied area, 20 µl per each. 6 hours later, TPA was applied again on the same area, 20 µl per each. 24 hours later, the mice were euthanized by cervical dislocation, and the left ears were taken to measure weight and MPO activity. Inhibition rate (%) was calculated by the following Equation 3, and the result is given in the following Table 4.

\[
\text{Inhibition rate (\%)} = \frac{(\text{TPA treated group}) - (\text{Test compound treated group})}{(\text{TPA treated group}) - (\text{TPA non-treated group})} \times 100
\]

[Table 4]
As seen from Table 4, the compound of Example 1-76 was superior in inhibiting ear edema caused by TPA-induced inflammatory response and MPO activity, comparable to hydrocortisone, which is commonly used as antiinflammatory drug. This result signifies that the compound of Example 1-76 inhibited the infiltration of neutrophils at the inflammation area.

Preparation Example 1: Preparation of tablet (compression)

5.0 mg of the compound represented by Chemical Formula 1, as an effective ingredient, was sieved, mixed with 14.1 mg of lactose, 0.8 mg of crospovidone USNF and 0.1 mg of magnesium stearate, and compressed into a tablet.

Preparation Example 2: Preparation of tablet (wet granulation)

5.0 mg of the compound represented by Chemical Formula 1, as an effective ingredient, was sieved, and mixed with 16.0 mg of lactose and 4.0 mg of starch. 0.3 mg of Polysorbate 80 dissolved in pure water was added in an adequate amount and subjected to granulation. After drying and sieving, the granule was mixed with 2.7 mg of colloidal silicon dioxide and 2.0 mg of magnesium stearate. The granule was compressed into a tablet.

Preparation Example 3: Preparation of powder and capsule

5.0 mg of the compound represented by Chemical Formula 1, as an
effective ingredient, was sieved, and mixed with 14.8 mg of lactose, 10.0 mg of polyvinylpyrrolidone and 0.2 mg of magnesium stearate. The mixture was filled in a hard No. 5 gelatin capsule using an appropriate apparatus.

Preparation Example A: Preparation of injection

100 mg of the compound represented by Chemical Formula 1, as an effective ingredient, was mixed with 180 mg of mannitol, 26 mg of Na2HPO4·12H2O and 2,974 mg of distilled water to prepare an injection.

The invention has been described in detail with reference to example embodiments thereof. However, it will be appreciated by those skilled in the art that changes may be made in these embodiments without departing from the principles and spirit of the present invention, the scope of which is defined in the accompanying claims and their equivalents.

[Industrial Applicability]

As described above, the present invention

1) provides a 2,4,5-trisubstituted-1,3-thiazole derivative and a pharmaceutically acceptable salt thereof through a solid-phase chemical synthesis technique,

2) elucidates superior inhibition activity of the 2,4,5-trisubstituted-1,3-thiazole derivative against sphingosylphosphoryl choline (SPC) receptor through an animal experiment using human-derived endothelial cells and mice, and

3) provides an inhibitor of SPC receptor and a pharmaceutical composition for treating inflammatory disease induced by SPC containing the 2,4,5-trisubstituted-1,3-thiazole derivative as an effective ingredient, and a use thereof.
[CLAIMS]

[Claim 1]

A 2,4,5-trisubstituted-1,3-thiazole derivative represented by the following Chemical Formula 1 or a pharmaceutically acceptable salt thereof:

[Chemical Formula 1]

\[
\begin{array}{c}
\text{N} \\
\text{S} \\
\text{R}^1 \\
\text{R}^2 \\
\text{R}^3 \\
\end{array}
\]

wherein \( R^1 \) is heteroaryl, phenyl or substituted phenyl, the substituted phenyl being substituted by 1-4 substituents selected from the group consisting of halogen, nitro, \( C_1-C_5 \) alkyl and \( C_1-C_5 \) alkoxy; \( R^2 \) is amide having \( C_1-C_{10} \) linear, branched or cyclic alkyl, \( C_2-C_{10} \) alkenyl, \( C_2-C_{10} \) alkynyl, heteroaryl, arylalkyl, \( C_5-C_{10} \) heteroarylalkyl, phenyl or substituted phenyl, the substituted phenyl being substituted by 1-4 substituents selected from the group consisting of halogen, nitro, \( C_1-C_5 \) alkyl and \( C_1-C_5 \) alkoxy; and \( R^3 \) is amine substituted by one or more \( C_1-C_{10} \) linear, branched or cyclic alkyl, \( C_1-C_{10} \) aryl, \( C_1-C_{10} \) heteroaryl, \( C_1-C_{10} \) arylalkyl or \( C_1-C_{10} \) heteroarylalkyl, or piperazine (\( \overset{\text{N}}{\text{N}} \overset{\text{N}}{\text{N}} \)) substituted by phenyl, \( C_1-C_{10} \) linear, branched or cyclic alkyl, or heteroarylamide, the phenyl being substituted by 1-4 substituents selected from the group consisting of halogen, nitro, \( C_1-C_{10} \) alkyl, \( C_1-C_{10} \) alkoxy and \( C_1-C_{10} \) haloalkyl.

[Claim 2]

The 2,4,5-trisubstituted-1,3-thiazole derivative or the pharmaceutically acceptable salt thereof as set forth in claim 1, wherein, in Chemical Formula 1, \( R \) is selected from the group consisting of heteroaryl, phenyl and...
zubstituted phenyl; R<sup>2</sup> is amide having C<sub>1</sub>-C<sub>5</sub> linear, branched or cyclic alkyl, C<sub>2</sub>-C<sub>5</sub> alkenyl, C<sub>2</sub>-C<sub>5</sub> alkynyl, heteroaryl, arylalkyl, C<sub>5</sub>-C<sub>10</sub> heteroarylalkyl, phenyl or substituted phenyl; and R<sub>i</sub> is amine substituted by one or more C<sub>1</sub>-C<sub>5</sub> linear, branched or cyclic alkyl, C<sub>1</sub>-C<sub>5</sub> aryl, C<sub>1</sub>-C<sub>5</sub> heteroaryl, C<sub>1</sub>-C<sub>5</sub> arylalkyl or C<sub>1</sub>-C<sub>5</sub> heteroarylalkyl, or phenyl, C<sub>1</sub>-C<sub>2</sub> linear, branched or cyclic alkyl, or piperazine (N-N) substituted by phenyl or heteroarylamide, the phenyl being substituted by 1-4 substituents selected from the group consisting of halogen, nitro, C<sub>1</sub>-C<sub>5</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkoxy and C<sub>1</sub>-C<sub>10</sub> haloalkyl.

[Claim 3]

A method for the preparation of a 2,4,5-trisubstituted-1,3-thiazole derivative comprising:

- reacting methylcyanocarbonimidodithionate represented by the following Chemical Formula 2 with a 2-haloacetophenone derivative to synthesize a 4-amino-1,3-thiazole represented by the following Chemical Formula 3 in which the substituent R<sup>1</sup> is introduced;

- reacting the 4-amino group of the compound represented by Chemical Formula 3 with chlorocarboxylic acid to synthesize a 4-N-acyl-1,3-thiazole represented by the following Chemical Formula 4 in which the substituent R<sup>2</sup> is introduced;

- oxidizing the sulfanyl group of the compound represented by Chemical Formula 4 with m-chloroperbenzoic acid (m-CPBA) to synthesize a 2-sulfonyl-4-N-acyl-1,3-thiazole represented by the following Chemical Formula 5; and

- reacting the compound represented by Chemical Formula 5 with a primary or secondary amine to synthesize the 2,4,5-trisubstituted-1,3-thiazole derivative represented by the following Chemical Formula 1:

[Scheme 1]
wherein $R_1$, $R_2$ and $R_3$ are the same as defined in claim 1.

[Claim 4]

A pharmaceutical composition for treating inflammatory disease induced by sphingosylphosphoryl choline (SPC) containing the 2,4,5-trisubstituted-1,3-thiazole derivative represented by Chemical Formula 1 or the pharmaceutically acceptable salt thereof as set forth in claim 1 as an effective ingredient.

[Claim 5]

The pharmaceutical composition for treating inflammatory disease induced by SPC as set forth in claim 3, wherein the 2,4,5-trisubstituted-1,3-thiazole derivative represented by Chemical Formula 1 is $N[5$-benzoyl-$2$-[4-(2-methoxyphenyl)piperazin-1-yl]thiazoyl-4-yl]pivalamide or $N[5$-benzoyl-$2$-[2-(piperidin-1-yl)ethyl amido]thiazoyl-4-yl]$-4$-fluorobenzamide.

[Claim 6]

The pharmaceutical composition for treating inflammatory disease induced by SPC as set forth in claim 3, wherein the inflammatory disease is selected from the group consisting of inflammation, itching and skin infection associated with atopic dermatitis or other disease.

[Claim 7]

A pharmaceutical composition for preventing scarring after injury and
promoting wound healing containing the 2,4,5-trisubstituted-1,3-thiazole
derivative represented by Chemical Formula 1 or the pharmaceutically
acceptable salt thereof as set forth in claim 1 as an effective ingredient.
**A. CLASSIFICATION OF SUBJECT MATTER**

*C07D 277/44(2006.01)i, A61K 31/426(2006.01)i, A61P 29/00(2006.01)i*

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 8 C07D 277/44, A61K 31/42, A61P 29/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN (Registry, CAplus)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>LEE, ILL, YOUNG, et al 'Traceless solid-phase synthesis of 2,4,5-trisubstituted thiazoles ' Synlett 2005, No 16, pp 2483-2485, ISSN 0936-5214 See compounds If-Ih, table 2, scheme 1</td>
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☐ Further documents are listed in the continuation of Box C  ☑ See patent family annex

* Special categories of cited documents
  - "A" document defining the general state of the art which is not considered to be of particular relevance
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  - "O" document referring to an oral disclosure use, exhibition or other means
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Date of the actual completion of the international search

06 MARCH 2009 (06 03 2009)

Date of mailing of the international search report

06 MARCH 2009 (06.03.2009)

Name and mailing address of the ISA/KR

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Facsimile No 82-42-472-7140

Authorized officer

SUNG Sun Young

Telephone No 82-42-481-8405

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