The present invention relates to the novel decursin derivatives, the preparation thereof and the composition comprising the same. The novel decursin derivatives of the present invention showed inhibiting activity of the release of MCP-1, IL-6 and IL-8 induced by dermite in THP-1 or EoL-1 cell, therefore the compounds can be useful in treating or preventing atopic dermatitis.

Title: COMPOSITION COMPRISING DECURSIN DERIVATIVE FOR TREATING AND PREVENTING ATOPIC DERMATITIS

Abstract: The present invention relates to the novel decursin derivatives, the preparation thereof and the composition comprising the same. The novel decursin derivatives of the present invention showed inhibiting activity of the release of MCP-1, IL-6 and IL-8 induced by dermite in THP-1 or EoL-1 cell, therefore the compounds can be useful in treating or preventing atopic dermatitis.

The present invention relates to the novel decursin derivatives, the preparation thereof and the composition comprising the same. The novel decursin derivatives of the present invention showed inhibiting activity of the release of MCP-1, IL-6 and IL-8 induced by dermite in THP-1 or EoL-1 cell, therefore the compounds can be useful in treating or preventing atopic dermatitis.
Description

COMPOSITION COMPRISING DECURSIN DERIVATIVE FOR TREATING AND PREVENTING ATOPIC DERMATITIS

Technical Field

[1] The present invention relates to a composition comprising decursin derivative for treating and preventing atopic dermatitis.

[2] Background Art

[3] Atopic dermatitis is a chronic inflammatory disease having chronic recurrent tendency, which is characterized by itching, psoriasis, eczema, and keratin etc (Hanifin J.M. et al., Guidelines of care for atopic dermatitis. J. Am. Acad. Dermatol., 50 pp39 1-404, 2004) and has been reported that it is caused by the hypersensitive immunologic response against environmental allergen such as the feces of mites, resulting in skin chronic inflammation (Oh J. W. et al., Nationwide study for epidemiological change of atopic dermatitis in school aged children between 1995-2000 and kindergarten aged children in 2003 in Korea; Pediatr. Allergy Respir. Dis., 13, pp227-237, 2003). Recently, the occurrence of atopic dermatitis has been sharply increased in the world. However the fundamental treatment of the disease could not be found yet and only the symptomatic treatment for the disease has been performed till now. (Williams H. C . Clinical practice, Atopic dermatitis. New England J. Med., 352, pp23 14-24, 2005).

[4] Various kinds of cytokines, such as EL-4, IL-3 etc and TGF- involved in fibrosis, are released during chronic inflammation progress and the released cytokines increase fibroblast activating IL-6, which causes to the differentiation and proliferation of fibroblast to reproduce too abundant extra cellular matrix resulting in the modification and fibrosis of cells and tissues. It has been reported that MCP-1 (Monocyte Chemoattractant Protein-1) is bound to chemokine receptor (CCR2) and the MCP-1-deficient mice lose its chemotaxic activity resulting in the debilitation of resistance against specific bacterial infection <I u B et al., Abnormalities in monocyte recruitment and cytokine expression in monocyte chemoattractant protein 1-deficient mice; J. Exp. Med., Ml, pp601-608, 1998>, similarly in the experiment performed by CCR2-deficient mice. MCP-1 has been reported to converse Th0 cells into Th2
cytokines-releasing cells (Karpus W. J. et al., MIP-I alpha and MCP-I differentially regulate acute and reapsing autoimmune encephalomyelitis as well as TH1/Th2 lymphocyte differentiation; J. Leukoc. Biol., 62, pp681-687, 1997). Intravenous injection of MCP-I reduces the reproduction of IL-12 and increases the reproduction of IL-4, which indicates that it may become worsen IgE-dependent allergic inflammations indirectly.

IL-8, an important inflammatory chemokine released from bronchial epithelial cells, plays important roles in initial stage of inflammatory response (Harada A et al., Essential involvement of interleukin-8 in acute inflammation; J. Leukoc. Biol., pp559-564, 1994), which causes to bronchial hyperresponsiveness resulting in allergic rhinitis or bronchial asthma (Fujimura M et al., Role of leukotriene B4 in bronchial hygiene hyperresponsiveness induced by interleukin 8; Eur. Respir. J., 6, pp306-311, 1998; kurashima K et al; Increase of chemokine levels in sputum precedes exacerbation of acute asthma attacks. J. Leukoc. Biol. 52, pp 313-316, 1996).

Angelica gigas belonged to Umbelliferae has been reported to comprise (+)-decursin, a dihydropyranocoumarin, and (+)-decursinols (7-hydroxy-8,8-dimethyl-7,8-dihydro-6 γ-pyrano(3,2-g)chromen-2-one) as main components (Bae E. A. et al., Anti-helicobacter pylori activity of herbal medicines; Biol. Pharm. Bull. 21, pp990, 1998).

However, there has been not reported or disclosed about therapeutic effect of various decursin derivatives synthesized from decursin on atopic dermatitis in any of above cited literatures, the disclosures of which are incorporated herein by reference.

Therefore, the present inventors have endeavored to synthesize the effective decursin derivatives for treating and preventing atopic dermatitis and to study the pharmacological effect of the compounds and finally, the present inventors have found that the compounds based on decursin are effective in treating and preventing atopic dermatitis as a medicine or health care food.

Disclosure of Invention
Technical Problem

According to one aspect, the present invention provides new decursin derivatives or the pharmaceutical acceptable salt thereof showing potent treating and preventing activity of atopic dermatitis.

The present invention also provides a pharmaceutical composition comprising new
decursin derivatives as an active ingredient in an amount effective to prevent and treat atopic dermatitis, together with a pharmaceutically acceptable carrier by inhibiting the release of MCP-I, IL-6 and IL-8 induced by mites.

[12] The present invention also provides a method for treating atopic dermatitis by inhibiting the release of MCP-I, IL-6 and IL-8 induced by mites in a mammal comprising administering to said mammal an effective amount of above-mentioned compounds, together with a pharmaceutically acceptable carrier thereof.

[13] The present invention also provides a use of above described compounds for the preparation of for manufacture of medicament employed for preventing or treating atopic dermatitis in human or mammal.

[14] The present invention also provides a health functional food comprising above compounds for the prevention or improvement of treating atopic dermatitis by inhibiting the release of MCP-I, IL-6 and IL-8 induced by mites as an active ingredient in an amount effective to preventing and improving atopic dermatitis.


[16] Accordingly, the present invention provides a novel compound represented by the following general formula (I), or the pharmaceutically acceptable salt thereof:

[17] Chemistry Figure 1

![Chemistry Figure 1](image)

[18] (I)

[19] wherein

[20] A is hydrogen atom, C-C lower alkyl group, dialkyl acryloyl group or cinnamoyl group of which phenyl group is unsubstituted or substituted with R'; wherein R' is optionally substituted at o-, m- and p-position with at least one selected from the group consisting of a hydrogen atom, hydroxyl group, acetate group, halogen atom, C lower alkyl group, lower alkoxy group, lower alkyl ester, and lower alkyl carboxy group.

[21] As preferable compounds of general formulae (I), the compounds of the present invention wherein A is hydrogen atom, methyl group, dimethyl acryloyl group or cinnamoyl group of which phenyl group is unsubstituted or substituted with R'; wherein R' is optionally substituted with at least one selected from the group consisting
of a hydrogen atom, methyl group, methoxy group and acetate group.

The most preferred compounds of general formula (I) are selected from the group consisting of:

- 8,8-dimethyl-6 H-pyrano[3,2-g]croton-2,7-dione 7-one,
- 8,8-dimethyl-6 H-pyrano[3,2-g]croton-2,7-dione 7-[O-(3,3-dimethyl acryloyl)-o]me,
- 8,8-dimethyl-6 H-pyrano[3,2-g]croton-2,7-dione 7-[O-(4-methoxycinnamoyl)-o]me,
- 8,8-dimethyl-6 H-pyrano[3,2-g]croton-2,7-dione 7-[O-(3,4-dimethoxyacryloyl)-o]me,
- 8,8-dimethyl-6 H-pyrano[3,2-g]croton-2,7-dione 7-[O-(3,4-diacetoxyacryloyl)-o]me,
- 8,8-dimethyl-6 H-pyrano[3,2-g]croton-2,7-dione 7-[O-(3,4-dimethoxyacryloyl)-o]me,
- 8,8-dimethyl-6 H-pyrano[3,2-g]croton-2,7-dione 7-[O-(3,4-diacetoxyacryloyl)-o]me.

Also, the present invention provides a novel compound represented by the following general formula (II), and the pharmaceutically acceptable salt thereof:

ChemistryFigure 2

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{S} \\
\text{B} \\
\end{array}
\]

(II)

Wherein,

- \( B \) is selected from the group consisting of hydrogen atom, hydroxyl group, \( C_{1-4} \) lower alkyl group, \( C_{1-6} \) lower alkoxy group, halogen atom, and 5- or 6- membered heterocyclic ring unsubstituted or substituted with \( C_{1-3} \) lower alkyl group or \( C_{1-3} \) lower alkoxy group.

As preferable compounds of general formulae (II), the compounds of the present invention wherein \( B \) is selected from the group consisting of methyl group, halogen atom, \( C_{1-3} \) lower alkyl group, \( C_{1-3} \) lower alkoxy group and phenyl group.

The most preferred compound of general formula (II) is selected from the group consisting of:

- Methane sulfonic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2 \( H.8H \)-pyrano[3,2-g] chromen-3-yl-ester,
- Benzene sulfonic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2 \( H.8H \)-pyrano[3,2-g] chromen-3-yl-ester.

The inventive compounds represented by general formula (I) and (II) can be transformed into their pharmaceutically acceptable salt and solvates by the con-
ventional method well known in the art. for the salts, aid-addition salt thereof formed by a pharmaceutically acceptable free acid thereof is useful and can be prepared by the conventional method. For example, after dissolving the compound in the excess amount of aid solution, the salts are precipitated by the water-miscible organic solvent such as methanol, ethanol, acetone or acetonitrile to prepare aid addition salt thereof and further the mixture of equivalent amount of compound and diluted acid with water or alcohol such as glycol monomethylether, can be heated and subsequently dried by evaporation or filtrated under reduced pressure to obtain dried salt form thereof.

As a free acid of above-described method, organic acid or inorganic acid can be used. For example, organic acid such as methansulfonic add, 2-toluensulfonic acid, acetic acid, trifluoroacetic acid, citric acid, maleic aid, suxinic acid, oxalic acid, benzoic acid, lactic acid, glycolt acid, gluconic acid, galacturonic acid, glutamic acid, glutaric acid, glucuronic acid, aspartic acid, ascorbic acid, carboxylic, acid, vanillic acid, hydroiodic acid and the like, and inorganic acid such as hydrochloric add, phosphoric acid, sulfuric acid, nitric acid, tartaric acid and the like can be used herein.

Further, the pharmaceutically acceptable metal salt form of inventive compounds may be prepared by using base. The alkali metal or alkali-earth metal salt thereof can be prepared by the conventional method, for example, after dissolving the compound in the excess amount of alkali metal hydroxide or alkali-earth metal hydroxide solution, the insoluble salts are filtered and remaining filtrate is subjected to evaporation and drying to obtain the metal salt thereof. As a metal salt of the present invention, sodium, potassium or calcium salt are pharmaceutically suitable and the corresponding silver salt can be prepared by reacting alkali metal salt or alkali-earth metal salt with suitable silver salt such as silver nitrate.

The pharmaceutically acceptable salt of the compound represented by general formula (I) and (H) comprise all the acidic or basic salt which may be present at the compounds, if it does not indicated specifically herein. For example, the pharmaceutically acceptable salt of the present invention comprise the salt of hydroxyl group such as the sodium, calcium and potassium salt thereof; the salt of amino group such as the hydrogen bromide salt, sulfuric acid salt, hydrogen sulfurous acid salt, phosphate salt, hydrogen phosphate salt, dihydrogen phosphate salt, acetate salt, siringe salt, citrate salt, tartarate salt, lactate salt, mandelate salt, methanesulfonate(mesylate) salt and p-toluenedisulfonate (tosylate) salt etc, which can be prepared by the conventional method well known in the art.
The compounds of the invention may be chemically synthesized by the methods which will be explained by following reaction schemes hereinafter, which are merely exemplary and in no way limit the invention. The reaction schemes show the steps for preparing the representative compounds of the present invention, and the other compounds also may be produced by following the steps with appropriate modifications of reagents and starting materials, which are envisaged by those skilled in the art.

GENERAL SYNTHETIC PROCEDURES

[Scheme 1]

At the 1st step in reaction, (+)-decursinol dissolved in anhydrous dichloromethane is react with pyridium chloromate and molecular sieve. The solvent which does not cause to adverse effect such as dichloromethane, chloroform, diethylether, tetrahydrofuram etc may be used in the reaction. It is preferable that the reaction temperature in the reaction can be performed at cool temperature to room temperature, preferably, at room temperature however it is not limited thereto. It is preferable that the reaction time in the reaction can be performed in the range from 30 min to 1 hr, more preferably, 1 hr with stirring to synthesize 8,8-dimethyl-6H-pyrano[3,2-g]chromen-2,7-dione (17). At the 2nd step in reaction, the reaction mixture of 8,8-dimethyl-6 H-pyrano[3,2-g]chromen-2,7-dione (17) dissolved in anhydrous ethanol is react with hydroxyl ammoniumchloride and pyridine. The solvent which does not cause to adverse effect such as dichloromethane, chloroform, diethylether, tetrahydrofuram etc may be used in the reaction. It is preferable that the reaction temperature in the reaction can be performed at the temperature ranging from room temperature to 100°C, preferably, 80°C, however it is not limited thereto. It is preferable that the reaction time in the reaction can be performed in the range from 30 min to 1 hr, more preferably, 1 hr with stirring to synthesize 8,8-dimethyl-6 H-pyrano[3,2-g]chromen-2,7-dione 7o-mel (18).
At the 1st step in reaction, 3,3-dimethyl acrylate (2a) is dissolved in anhydrous dichloromethane and oxalyl chloride is added thereto dropwisely. The solvent which does not cause to adverse effect such as dichloromethane, chloroform, diethylether, tetrahydrofuran etc may be used in the reaction. It is preferable that the reaction temperature in the reaction can be performed at the temperature ranging from cool temperature to room temperature, preferably, at room temperature, however it is not limited thereto. It is preferable that the reaction time in the reaction can be performed in the range from 3 hrs to 18 hrs, more preferably, 5 hrs with stirring to synthesize 3,3-dimethyl acryloyl chloride (19a). At the 2nd step in the reaction, (+)-decursinol is dissolved in anhydrous dichloromethane and 3,3-dimethyl acryloyl chloride (19a) and pyridine are added thereto at the temperature ranging from cool temperature to room temperature, preferably, at room temperature, however it is not limited thereto. It is preferable that the reaction time in the reaction can be performed in the range of 1 hr to 18 hrs, more preferably, 2 hrs ranging from room temperature. The concentrated residue is performed to Silicagel column chromatography to synthesize 8,8-dimethyl-6\(/J\)/-pyrano[3,2-\(g\)]chromen-2,7-dione 7-[0<3,3-dimethylacryloyl]-oxime (20a).

At the 1st step in reaction, annamic acid is dissolved in anhydrous benzene and the mixture of thionyl chloride and \(N,N\)-dimethylformamide is added thereto to react together. The solvent which does not cause to adverse effect such as dichloromethane,
chloroform, diethylether, tetrahydrofuran etc may be used in the reaction. It is preferable that the reaction temperature in the reaction can be performed at the temperature ranging from room temperature to 100°C, preferably, at 80°C, however it is not limited thereto. It is preferable that the reaction time in the reaction can be performed in the range from 3 hrs to 18 hrs, more preferably, 5 hrs with stirring to synthesize cinnamoyl chloride (7a). At the 2.\textsuperscript{nd} step in reaction, the reaction mixture of 8,8-dimethyl-6-\(H\)-pyrano[3,2-\(g\)]chromen-2,7-dione 7-\((0\text{-cinnamoyl-o»me})\) (18) is dissolved in anhydrous dichloromethane to react with cinnamoyl chloride (7a). The concentrated residue is performed to Silkagel column chromatography to synthesize 8,8-dimethyl-6-\(H\)-pyrano[3,2-\(g\)]chromen-2,7-dione 7-\((0\text{-cinnamoyl-o»me})\) (21a).

At the 1\textsuperscript{st} step in reaction, decursinol and triethylamine are dissolved in anhydrous dichloromethane to react with sulfonyle chloride. The reaction solvent which does not cause to adverse effect such as dichloromethane, chloroform, diethylether, tetrahydrofuran etc may be used in the reaction. It is preferable that the reaction temperature in the reaction can be performed at cool temperature to room temperature, preferably, at room temperature, however it is not limited thereto. It is preferable that the reaction time in the reaction can be performed in the range from 5 hrs to 20 hrs, more preferably, 15 hrs with stirring to synthesize methan sulfonic aixi 2,2-dimethyl-8ox\(\text{>3,4-dihydro-}\) \(2H\text{-pyrano[3,2-}\text{g}]chromen-3-y1-ester\) (16a).

The inventive composition comprising novel decursin derivatives represented by the general formula (I) to (II) or the pharmaceutically acceptable salt thereof is proved to have potent treating and preventing effect on atopic dermatitis being confirmed by the various in vitro and in vivo experiments such as the inhibition test on the release of MCP-1, IL-6, and IL-8 induced by mites. Accordingly, the composition can be useful as a pharmaceutical composition and health functional food for the prevention and...
The present invention provides to a pharmaceutical composition comprising decursin derivative represented by general formula (I) and (II) as an active ingredient in an amount effective to prevent and treat atopic dermatitis, together with a pharmaceutically acceptable carrier by inhibiting the release of MCP-I, IL-6 and IL-8 induced by mites.

The present invention also provides a method for treating atopic dermatitis by inhibiting the release of MCP-I, IL-6 and IL-8 induced by mites in a mammal comprising administering to said mammal an effective amount of decursin derivative represented by general formula (I) and (II), together with a pharmaceutically acceptable carrier thereof.

The present invention also provides a use of decursin derivative represented by general formula (I) and (II) for the preparation of for manufacture of medicament employed for preventing or treating atopic dermatitis in human or mammal.

The present invention also provides a health functional food comprising decursin derivative represented by general formula (I) and (II) for the prevention or improvement of treating atopic dermatitis by inhibiting the release of MCP-I, IL-6 and IL-8 induced by mites as an active ingredient in an amount effective to preventing and improving atopic dermatitis.

Also, the present invention provides to a pharmaceutical composition comprising decursin derivative represented by the following general formula (III) as an active ingredient in an amount effective to prevent and treat atopic dermatitis, together with a pharmaceutically acceptable carrier by inhibiting the release of MCP-I, IL-6 and IL-8 induced by mites:

Chemistry Figure 3

Wherein

\[ R_1 \text{ is } C_{-C} \text{ alkyl group, } C_{-C} \text{ alkenyl group, } C_{-C} \text{ alkynyl group unsubstituted or substituted with at least one } R' \text{ or } A \text{ group; of which } R^1 \text{ is halogen atom, nitro group, amine group or } C_{-C} \text{ lower alkyl group; and} \]
A group is

wherein

A is at least one optionally at o-, m- or p- position, selected from the group consisting of a hydrogen atom, hydroxyl group, acetate group, halogen atom, lower alkyl group, lower alkoxy group and lower alky ester group;

n is an integer of 0 to 4.

As preferable compounds of general formula (III), the compounds of the present invention wherein R is halogen atom or alkyl group, alkynyl group, unsubstituted or substituted with alkyl lower alkyl group or A group, of which A is at least one optionally at o-, m- or p- position, selected from group consisting of a hydrogen atom, hydroxyl group, methyl group, ethyl group, methoxy group, ethoxy group and acetyl group; n is an integer of 0 to 1.

The most preferred compound of general formula (III) is one selected from the group consisting of:

- 3-Methyl-but-2-enolic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester, Cw-2-Methyl-but-2-enolic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester, 7γ-3-Methyl-but-2-enolic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester, Pent-2-enolic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester, But-3-enolic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester, Chloro-acetic acid 2,2-dimethyl-8ox>3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester, Trichloro-acetic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester, Pentanoic acid 2,2-dimethyl-8-th β-thiol-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester, Decanoic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester, 3-phenyl acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester;
pyrano[3,2-g]chromen-3-yl-ester, 3-(4-methoxy-phenyl)-acrylic acid
dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester,
3-(4-hydroxy-phenyl)-acrylic acid. 2,2-dimethyl-8-oxo-3,4-dihydro-
2H,8H-pyrano[3,2-g]chromen-3-yl-ester, 3-(3,4-dimethoxy-phenyl)-acrylic acid
2,2-dimethyl-8-oxo-3,4-dihydro-
2H,8H-pyrano[3,2-g]chromen-3-yl-ester,
3-(3,4,5-trimethoxy-phenyl)-acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro-
2H,8H-pyrano[3,2-g]chromen-3-yl-ester, 3-(3,4,5-trihydroxy-phenyl)-acrylic acid
2,2-dimethyl-8-oxo-3,4-dihydro-
2H,8H-pyrano[3,2-g]chromen-3-yl-ester,
3-(2-methoxy-phenyl)-acrylic acid
2,2-dimethyl-8-oxo-3,4-dihydro-
2H,8H-pyrano[3,2-g]chromen-3-yl-ester,
3-(2-hydroxy-phenyl)-acrylic acid
2,2-dimethyl-8-oxo-3,4-dihydro-
2H,8H-pyrano[3,2-g]chromen-3-yl-ester,
3-(3-methoxy-phenyl)-acrylic acid
2,2-dimethyl-8-oxo-3,4-dihydro-
2H,8H-pyrano[3,2-g]chromen-3-yl-ester,
3-(2,3-dimethoxy-phenyl)-acrylic acid
2,2-dimethyl-8-oxo-3,4-dihydro-
2H,8H-pyrano[3,2-g]chromen-3-yl-ester,
3-(2,4-dimethoxy-phenyl)-acrylic acid
2,2-dimethyl-8-oxo-3,4-dihydro-
2H,8H-pyrano[3,2-g]chromen-3-yl-ester,
3-(2,5-dimethoxy-phenyl)-acrylic acid
2,2-dimethyl-8-oxo-3,4-dihydro-
2H,8H-pyrano[3,2-g]chromen-3-yl-ester,
3-(2,4,5-trimethoxy-phenyl)-acrylic acid
2,2-dimethyl-8-oxo-3,4-dihydro-
2H,8H-pyrano[3,2-g]chromen-3-yl-ester,
3-(4-nitro-phenyl)-acrylic acid
2,2-dimethyl-8-oxo-3,4-dihydro-
2H,8H-pyrano[3,2-g]chromen-3-yl-ester,
3-(3-hydroxy-phenyl)-acrylic acid
2,2-dimethyl-8-oxo-3,4-dihydro-
2H,8H-pyrano[3,2-g]chromen-3-yl-ester,
3-(3-xethoxy-phenyl)-acrylic acid
2,2-dimethyl-8-oxo-3,4-dihydro-
2H,8H-pyrano[3,2-g]chromen-3-yl-ester,
3-(3,4-dihydroxy-phenyl)-acrylic acid
2,2-dimethyl-8-oxo-3,4-dihydro-
2H,8H-pyrano[3,2-g]chromen-3-yl-ester,
3-(3,4-diacetoxy-phenyl)-acrylic acid
2,2-dimethyl-8-oxo-3,4-dihydro-
2H,8H-pyrano[3,2-g]chromen-3-yl-ester,
3-(4-hydroxy-3-methoxy-phenyl)-acrylic acid
2,2-dimethyl-8-oxo-3,4-dihydro-
2H,8H-pyrano[3,2-g]chromen-3-yl-ester,
3-(4-acetoxy-3-methoxy-phenyl)-acrylic acid
2,2-dimethyl-8-oxo-3,4-dihydro-
2H,8H-pyrano[3,2-g]chromen-3-yl-ester,
3-(4-acetoxy-3,4-dimethoxy-phenyl)-acrylic acid
2,2-dimethyl-8-oxo-3,4-dihydro-
2H,8H-pyrano[3,2-g]chromen-3-yl-ester, Benzoic acid
2,2-dimethyl-8-oxo-3,4-dihydro-
2H,8H-pyrano[3,2-g]chromen-3-yl-ester, 3,4,5-trihydroxy-benzobenzoic acid
2,2-dimethyl-8-oxo-3,4-dihydro-
2H,8H-pyrano[3,2-g]chromen-3-yl-ester and 3,4,5-triacetoxy-benzoic acid
2,2-dimethyl-8-oxo-3,4-dihydro-
2H,8H-pyrano[3,2-g]chromen-3-yl-ester.
Also, the present invention provides to a pharmaceutical composition comprising decursin derivative represented by the following general formula (IV) as an active ingredient in an amount effective to prevent and treat atopic dermatitis, together with a pharmaceutically acceptable carrier by inhibiting the release of MCP-I, IL-6 and IL-8 induced by mites:

ChemistryFigure 4

[IV]

Wherein,

C is a hydrogen atom, C-1 lower alkyl group or ketone group.

As preferable compounds of general formulae (IV), the compounds of the present invention wherein C is at least one selected from the group consisting of a hydrogen atom or ketone group.

The most preferred compound of general formula (IV) is one selected from the group consisting of:

8,8-dimethyl-6H-pyrano[3,2-g]chromen-2,7-dione, 8,8-dimethyl-6H-pyrano[3,2-g]chromen-2-one.

Accordingly, it is another object of the present invention to provide the pharmaceutical composition comprising an efficient amount of the compound represented by general formula (III) to (IV) or the pharmaceutically acceptable salt thereof as an active ingredient in amount effective to treat or prevent atopic dermatitis disease, together with pharmaceutically acceptable carriers or diluents.

It is another object of the present invention to provide the pharmaceutical composition comprising an efficient amount of the compound represented by general formula (III) to (IV) or the pharmaceutically acceptable salt thereof as an active ingredient in amount effective to treat or prevent atopic dermatitis disease, together with pharmaceutically acceptable carriers or diluents.

The present invention also provides a method for treating atopic dermatitis by inhibiting the release of MCP-I, IL-6 and IL-8 induced by mites in a mammal comprising administering to said mammal an effective amount of decursin derivative represented by general formula (III) and (IV), together with a pharmaceutically...
acceptable carrier thereof.

[81] In accordance with the other aspect of the present invention, there is also provided a use of the compound represented by general formula (III) to (FV) or the pharmaceutically acceptable salt thereof for manufacture of medicines employed for treating or preventing atopic dermatitis disease in mammals including human as an active ingredient in an amount effective to treat or prevent atopic dermatitis disease.

[82] In accordance with the other aspect of the present invention, there is also provided a use of the compound represented by general formula (III) to (IV) or the pharmaceutically acceptable salt thereof for manufacture of medicines employed for treating or preventing atopic dermatitis disease in mammals including human as an active ingredient in an amount effective to treat or prevent atopic dermatitis.

[83] The compound according to the present invention can be provided as a pharmaceutically composition containing pharmaceutically acceptable carriers, adjuvants or diluents, for example, the compound of the present invention can be dissolved in oils, propylene glycol or other solvents which are commonly used to produce an injection. Suitable examples of the carriers include physiological saline, polyethylene glycol, ethanol, vegetable oils, isopropyl myristate, etc. but are not limited to them. Rtopical administration, the compound of the present invention can be formulated in the form of ointments and creams.

[84] Hereinafter, the following formulation methods and excipients are merely exemplary and in no way limit the invention.

[85] The compound of the present invention in pharmaceutical dosage forms may be used in the form of their pharmaceutically acceptable salts, and also may be used alone or in appropriate association, as well as in combination with other pharmaceutically active compounds.

[86] The compound of the present invention may be formulated into preparations for injections by dissolving, suspending, or emulsifying them in aqueous solvents such as normal saline, 5% Dextrose, or non-aqueous solvent such as vegetable oil, synthetic aliphatic acid glycerides, esters of higher aliphatic acids or propylene glycol. The formulation may include conventional additives such as solubilizers, isotonic agents, suspending agents, emulsifying agents, stabilizers and preservatives.

[87] The desirable dose of the inventive compound varies depending on the condition and the weight of the subject, severity, drug form, route and period of administration, and may be chosen by those skilled in the art. However, in order to obtain desirable effects, it is generally recommended to administer at the amount ranging 0.0001 - 100
mg/kg, preferably 0.001-10 mg/kg by weight/day of the inventive compound of the present invention. The dose may be administered in single or divided into several times per day. In terms of composition, the compound should be present between 0.0001 to 10% by weight, preferably 0.0001 to Y\text{kk} by weight based on the total weight of the composition.

The pharmaceutic composition of present invention can be administered to a subject animal such as mammals (rat, mouse, domestic animals or human) via various routes. All modes of administration are contemplated, for example, administration can be made by inhaled, orally, rectally or by intravenous, intramuscular, subcutaneous, intrathecal, epidural or intracerebroventricular injection.

The novel (+)-decursin derivatives represented by general formula (I) to (IV) of the present invention also can be used as a main component or additive and aiding agent in the preparation of various functional health food and health care food.

Accordingly, it is the other object of the present invention to provides a health functional food comprising decursin derivative represented by general formula (I), (II), (III) or (IV) for the prevention or improvement of treating atopic dermatitis by inhibiting the release of MCP-1, EL-6 and IL-8 indited by mites as an active ingredient in an amount effective to preventing and improving atopic dermatitis.

The term "a functional health food" defined herein the functional food having enhanced functionality sirh as physical functionality or physiological functionality by adding the compound of the present invention to conventional food to prevent or improve cancer disease in human or mammal.

It is the other object of the present invention to provide a health care food comprising decursin derivatives represented by the following general formula (I)-(FV), or the pharmacologically acceptable salt thereof, together with a sitologkally acceptable additive for the prevention and alleviation of cancer disease.

The term "a health care food" defined herein the food containing the compound of the present invention showing no specific intended effect but general intended effect in a small amount of quantity as a form of additive or in a whole amount of quantity as a form of capsule, pill, tablet etc.

The term "a sitologically acceptable additive" defined herein any substance the intended use which results or may reasonably be expected to result-directly or indirectly-in its becoming a component or otherwise affecting the characteristics of any food for example, thickening agent, maturing agent, bleaching agent, sequesterants, humectant, antkaking agent, clarifying agents, curing agent, emulsifier,
stabilizer, thickener, bases and acid, foaming agents, nutrients, coloring agent, flavoring agent, sweetener, preservative agent, antioxidant, etc, which shall be explained in detail as follows.

If a substance is added to a food for a specific purpose in that food, it is referred to as a direct additive and indirect food additives are those that become part of the food in trace amounts due to its packaging, storage or other handling.

Above described health foods can be contained in food, health beverage, dietary therapy etc, and may be used as a form of powder, granule, tablet, chewing tablet, capsule, beverage etc for preventing or improving cancer disease.

Also, above described compounds can be added to food or beverage for prevention and improvement of atopic dermatitis. The amount of above described compound in food or beverage as a functional health food or health care food may generally range from about 0.01 to 100 w/w % of total weight of food for functional health food composition. In particular, although the preferable amount of the compound of the present invention in the functional health food, health care food or special nutrient food may be varied in accordance to the intended purpose of each food, it is preferably used in general to use as a additive in the amount of the compound of the present invention ranging from about 0.01 to 5% in food such as noodles and the like, from 40 to 100% in health care food on the ratio of 100% of the food composition.

Providing that the health beverage composition of present invention contains above described compound as an essential component in the indicated ratio, there is no particular limitation on the other liquid component, wherein the other component can be various deodorant or natural carbohydrate etc such as conventional beverage. Examples of aforementioned natural carbohydrate are monosaccharide such as glucose, fructose etc; disaccharide such as maltose, sirrose etc; conventional sugar siEh as dextrin, cyclodextrin; and sugar alcohol such as xylitol, and erythritol etc As the other deodorant than aforementioned ones, natural deodorant such as taumatin, stevia extract such as levaudioside A, glycyrrhizin et al., and synthetic deodorant such as saxharin, aspartam et al., may be useful favorably. The amount of above described natural carbohydrate is generally ranges from about 1 to 20 g, preferably 5 to 12 g in the ratio of 100 ml of present beverage composition.

The other components than aforementioned composition are various nutrients, a vitamin, a mineral or an electrolyte, synthetic flavoring agent, a coloring agent and improving agent in case of cheese; chocolate et al., pectic acid and the salt thereof, alginic acid and the salt thereof, organic add, protective colloidal adhesive, pH
controlling agent, stabilizer, a preservative, glycerin, alcohol, carbonizing agent used in carbonate beverage et al. The other component than aforementioned ones may be fruit juice for preparing natural fruit juice, fruit juice beverage and vegetable beverage, wherein the component can be used independently or in combination. The ratio of the components is not so important but is generally range from about 0 to 20 w/w % per 100 w/w % present composition. Examples of addable food comprising aforementioned extract therein are various food, beverage, gum, vitamin complex, health improving food and the like.

The present invention is more specifically explained by the following examples. However, it should be understood that the present invention is not limited to these examples in any manner.

Advantageous Effects

As described in the present invention, the novel decursin derivatives of the present invention showed potent inhibiting activity of the release of MCP-I, BL-6 and IL-8 induced by dermite in THP-I or EoL-I cell, therefore the compounds can be useful in treating or preventing atopic dermatitis.

Best Mode for Carrying Out the Invention

It will be apparent to those skilled in the art that various modifications and variations can be made in the compositions, use and preparations of the present invention without departing from the spirit or scope of the invention.

The present invention is more specifically explained by the following examples. However, it should be understood that the present invention is not limited to these examples in any manner.

The following Reference Example, Examples and Experimental Examples are intended to further illustrate the present invention without limiting its scope.

Mode for the Invention

Reference Example 1. Reagent and Instrument

$^1$H-NMR (400MHZ) spectrometer (JNM-AL 400, JEa Ltd. Japan), Melting pointer (Yamako, MD-S3, Japan) and MS spectrum (PE SCK API 2000 MS/MS, Canada) were used in the experiment. All the reagents used in the experiment were procured from Aldrich Chemical Co. and the 1st grade solvent was used as the other solvent. Rf purification, silica gel column chromatography (Silica gel, Merck,
230-400 mesh) was used.

[109]

Reference Example 2. THP-I Culture

THP-I cell (2.0 x 10⁵/ml; human acute monocyte leukemia cell; American Type Culture Collection (Manassas, VA, USA), a human monocyte, was cultured in RPMI 1640 medium containing 10⁴ U/ml of penicillin, 10 µg/ml of streptomycin, 25 µg/ml of amphotericin B and 10% FBS at 37°C in CO₂ incubator for 3 days.

[112]

Reference Example 3. EoL-I Culture

EoL-I cell (2.0 x 10⁵/ml; eosinophil leukemia cell; the RIKEN Bio Resource center (Tsukuba, Japan), a human eosinophil, was cultured in RPMI 1640 medium containing 10⁴ U/ml of penicillin, 10 mg/ml of streptomycin, 25 µg/ml of amphotericin B and 10% FBS at 37°C in CO₂ incubator for 3 days.

[115]

Example 1. 3-Methyl-but-2-enoi acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (3a)

As shown in the above-described reaction formulae, the mixture of 3-methyl-but-2-enoi acid (410mg, 4.06 mmol), 1,3-cyclohexylcarbodiimide (DCC, 1.68g, 1.12mmol) and 4-dimethylaminopyridine (DMAP, 198mg, 1.62 mmol) were dissolved in anhydrous dichloromethane. (+)-decursinol was added thereto to react together with stirring for 24 hours. The reaction solution was washed with dichloromethane, filtrated and concentrated in vacuo. The concentrates were performed to Silica gel column chromatography to obtain semi-solid form of 3-Methyl-but-2-enoi aid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (3a).

yield: 64.0% ;

[120] R = 0.35(n-hexane:ethyl acetate=2: 1);
Example 2. Cis-2-methyl-but-2-enoic acid 2,2 dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (3b)

Excepting that 3-methyl-but-2-enoic acid (2a) was substituted with cis-2-methyl-but-2-enoic acid (2b), all the procedure was performed in a similar method to Example 1 to obtain oil type of Cis-2-methyl-but-2-enoic acid 2,2 dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (3b).

yield: 56.3% ;
R=0.35(n-hexane:ethyl acetate=2:1);

Example 3. Trans-2-methyl-but-2-enoic acid 2,2 dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (3c)

Excepting that 3-methyl-but-2-enoic acid (2a) was substituted with trans-2-methyl-but-2-enoic acid (2c), all the procedure was performed in a similar method to Example 1 to obtain oil form of Trans-2-methyl-but-2-enoic acid 2,2 dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (3c).

yield: 43.9% ;
R = 0.48(n-hexane:ethyl acetate=2:1);

Example 4. 2-Methyl-acryl acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (3d)
Excepting that 3-methyl-but-2-enoic acid (2a) was substituted with 2-methyl-acryl acid (2d), all the procedure was performed in a similar method to Example 1 to obtain semi-solid form of 2-methyl-acryl acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (3d).

yield: 93.3% ;

R =0.52(n-hexane:ethyl acetate=1:1) ;

$^1$H NMR(CDC$_3$, 400MHz): ppm 7.56(d, /=9.6Hz, IH), 7.14(s, IH), 6.79(s, IH), 6.22(d, /=9.6Hz, IH), 5.08(s, IH), 5.07(t, /=5.2Hz, IH), 3.20(dd, /=4.8, 16.8Hz, IH), 2.88(dd, /=5.6, 17.2Hz, IH), 1.90(t, /=5.6, 17.2Hz, IH), 1.38(s, 3H), 1.37(s, 3H);

MS(m/z) : 315 (M+H) +

Example 5. Pent-2-enoic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (3e)

Excepting that 3-methyl-but-2-enoic acid (2a) was substituted with Pent-2-enoic acid (2e), all the procedure was performed in a similar method to Example 1 to obtain oil form of Pent-2-enoic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (3e).

yield: 92.1% ;

R =0.40(n-hexane:ethyl acetate=2:1) ;

$^1$H NMR(CDC$_3$, 400MHz): ppm 7.58(d, /=9.6Hz, IH), 7.15(s, IH), 6.79(s, IH), 6.23(d, /=9.6Hz, IH), 5.08(d, /=15.6Hz, IH), 5.11(t, /=4.8Hz, IH), 3.20(dd, /=4.8, 17.2Hz, IH), 2.88(dd, /=4.8, 17.2Hz, IH), 2.197(m, 2H), 1.39(s, 3H), 1.37(s, 3H), 1.04(t, /=7.6Hz, 3H);

MS(m/z) : 329 (M+H) +

Example 6. But-2-enoic acid 2,2-dimethyl-8-oxo-3,4-dihydro-v2H,8H-pyrano[3,2-g]chromen-3-yl-ester (3f)

Excepting that 3-methyl-but-2-enoic acid (2a) was substituted with but-3-enoic acid (2f), all the procedure was performed in a similar method to Example 1 to obtain oil form of but-2-enoic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (3f).

yield: 90.2% ;

R =0.65(n-hexane:ethyl acetate=1:1);

$^1$H NMR(CDC$_3$, 400MHz): ppm 7.58(d, /=9.6Hz, IH), 7.15(s, IH), 6.79(s, IH), 6.23(d, /=9.6Hz, IH), 5.08(d, /=15.6Hz, IH), 5.11(t, /=4.8Hz, IH), 3.20(dd, /=4.8, 17.2Hz, IH), 2.88(dd, /=4.8, 17.2Hz, IH), 2.197(m, 2H), 1.39(s, 3H), 1.37(s, 3H), 1.04(t, /=7.6Hz, 3H);
7=9.6Hz, IH), 5.866(m, IH), 5.176(m, 2H), 5.063(t, 7=4.8Hz, IH), 3.190(dd, 7=4.8, 17.2Hz, IH), 3.096(m, 2H), 2.856(dd, 7=5.2, 17.2Hz, IH), 1.373(s, 3H), 1.355(s, 3H);

[157] MS(w/z) : 315 (M+H)^+
[158]

[159] **Example 7. Pent-4-enolic acid** 2,2-dimethyl-8-oxo-3,4-dihydro-2\(^\text{H}\)-pyrano[3,2-\(g\)]chromen-3-yl-ester (3g)

Excepting that 3-methyl-but-2-enolic acid (2a) was substituted with Pent-4-enolic acid (2g), all the procedure was performed in a similar method to Example 1 to obtain oil form of pent-4-enolic acid 2,2-dimethyl-8-oxo>3,4-dihydro-2\(^\text{H,8H}\)-pyrano[3,2- g] chromen-3-yl-ester (3g).

[160] yield: 81.0% ;
[161] \(R=0.51\)(n-hexane:ethyl acetate=2:1);
[162] \(^1\text{H} \text{NMR(CDCl}_3\) : ppm 7.580(d, 7=9.6Hz, IH), 7.146(s, IH), 6.792(s, IH), 6.231(d, 7=9.6Hz, IH), 5.790(m, IH), 5.056-4.957(m, 3H), 3.178(dd, 7=4.8, 17.2Hz, IH), 2.837(dd, 7=5.2, 17.2Hz, IH), 2.433(m, 2H), 2.356(t, 7=6.4Hz, 2H), 1.374(s, 3H), 1.352(s, 3H);
[163] MS(m/z) : 329 (M+H)^+
[164]

[165] **Example 8. Acetic acid** 2,2-dimethyl-8-oxo-3,4-dihydro-2\(^\text{H}\)-pyrano[3,2- \(g\)]chromen-3-yl-ester (3h)

Excepting that 3-methyl-but-2-enolic acid (2a) was substituted with acetic add (2h), all the procedure was performed in a similar method to Example 1 to obtain solid form of acetic acid 2,2-dimethyl-8-oxo>3,4-dihydro-2\(^{\text{H,8H}}\)-pyrano[3,2- g] chromen-3-yl-ester (3h).

[166] yield: 89.8% ;
[167] m.p 125-126 °C;
[168] \(R=0.38\)(n-hexane:ethyl acetate=1:1);
[169] \(^1\text{H} \text{NMR(CDCl}_3\) : ppm 7.579(d, 7=9.6Hz, IH), 7.153(s, IH), 6.791(s, IH), 6.229(d, 7=9.6Hz, IH), 5.050(t, 7=4.8Hz, IH), 3.184(dd, 7=4.0, 17.2Hz, IH), 3.004(dd, 7=4.8, 17.4Hz, IH), 2.041(s, 3H), 1.422(s, 3H), 1.378(s, 3H);
[170] MS(m/z) : 289 (M+H)^+
[171]

[172] **Example 9. Chloro-acetic acid** 2,2-diaethyl-8-oxo-3,4-dihydro-2\(^{\text{If,8f}}\)-pyrano[3,2- g]chiOmen-3-yl-ester (3i)

Excepting that 3-methyl-but-2-enolic acid (2a) was substituted with chloro acetic
aid (2i), all the procedure was performed in a similar method to Example 1 to obtain solid form of chloro-acet acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,5H-pyran[3,2-g]-chromen-3-yl-ester (3i)

yield: 96.2%;
m.p 147-148 °C;
R =0.46 («-hexane:ethyl acetate=1:1);

[176] 1H NMR(CDCl₃): ppm 7.579(d, J=9.6Hz, IH), 7.160(s, IH), 6.794(s, IH), 6.235(d, J=9.6Hz, IH), 5.128(t, J=4.8Hz, IH), 4.088(d, J=14.8Hz, IH), 1.400(s, 3H), 1.375(s, 3H);

[179] MS(m/z): 323 (M+H)

Example 10. Trichloro-acetic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyran[3,2-g]-chromen-3-yl-ester (5a)

As shown in the above-described reaction formulae, (+)-decurcinol (20mg, 0.081 mmol) in 100 ml round flask was dissolved in 20ml of anhydrous di±lorome thane. Pyridine (13.1 μℓ, 0.162mmol) and trichloro acetyl chloride (4a) were added thereto and stirred 2 hrs at room temperature. The reaction solution was filtrated and concentrated in vacuo. The concentrates were performed to Silica gel column chromatography to obtain semi-solid form of trichloro-acetic acid (5a).

yield: 87.5%;
R = 0.60(n-hexane:ethyl acetate=1: 1);

[183] 1H NMR(CDCl₃): ppm 7.578(d, J=9.6 Hz, IH), 7.178(s, IH), 6.185(s, IH), 6.245(d, J=9.6Hz, IH), 5.138(t, J=5.2Hz, IH), 3.292(dd, J=4.8, 16.8Hz, IH), 2.997(dd, J=4.8, 17.2Hz, IH), 2.907(dd, J=5.2, 17.2Hz, IH), 1.450(s, 3H), 1.435(s, 3H);

[185] MS(« v/z): 392(M+H)⁺

Example 11. Pentanoic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyran[3,2-g]-chromen-3-yl-ester (5b)
Excepting that trichloroacetyl chloride (4a) was substituted with pentanoyl chloride (4b), all the procedure was performed in a similar method to Example 10 to obtain oil form of pentanoic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyran[3,2-g] chromen-3-yl-ester (5b).

yield: 90.7% ;

R = 0.39(n-hexane:ethyl acetate=2:1);

H NMR(CDC13): ppm 7.576(d, /=9.6Hz, IH), 7.145(s, IH), 6.788(s, IH), 6.224(d, /=9.6Hz, IH), 5.044(t, /=5.2Hz, IH), 3.180(dd, /=4.8, 16.8Hz, IH), 2.837(dd, 7=4.8, 16.8Hz, IH) 2.313(1, /=7.6Hz, 2H), 1.580(m, 2H), 1.372(s, 3H), 1.355(s, 3H), 1.377-1.256(m, 2H), 0.876(t, /=7.2Hz, 3H);

MS(m/z) : 329 (M+H) +

Example 12. Decanoic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyran[3,2-g] chromen-3-yl-ester (5c)

Excepting that trichloroacetyl chloride (4a) was substituted with decanoyl chloride (4c), all the procedure was performed in a similar method to Example 10 to obtain oil form of decanoic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyran[3,2-g] chromen-3-yl-ester (5c).

yield: 93.0% ;

R = 0.49(n-hexane: ethyl acetate=2:1);

H NMR(CDC13): ppm 7.574(d, /=9.2Hz, IH), 7.143(s, IH), 6.788(s, IH), 6.227(d, /=9.2Hz, IH), 5.043(t, /=4.8Hz, IH), 3.178(dd, 7=4.8, 16.8Hz, IH), 2.839(dd, 7=4.8, 17.2Hz, IH), 2.323(t, /=8.0Hz, 2H), 1.615(m, 2H), 1.406(s, 3H), 1.373(s, 3H), 1.336-1.256(m, 12H), 0.888(t, /=7.2Hz, 3H);

MS(m/2) : 331 (M+H) +

Table 1

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<th>No.</th>
<th>Compound</th>
<th>M.W.</th>
<th>Structure</th>
</tr>
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<td>1</td>
<td>3a</td>
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| 2  | 3b | cis-2-Methyl-but-2-enoic acid  
2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester |
<table>
<thead>
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<tr>
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</table>
| 3  | 3c | trans-2-Methyl-but-2-enoic acid  
2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester |
|    |    | ![Chemical Structure](image2)                                             |
| 4  | 3d | 2-Methyl-acrylic acid  
2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester |
|    |    | ![Chemical Structure](image3)                                             |
| 5  | 3e | Pent-2-enoic acid  
2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester |
|    |    | ![Chemical Structure](image4)                                             |

Table 2
Table 3

<table>
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<th>M.W.</th>
<th>structure</th>
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<td>But-3-enoic acid 2,2-dimethyl-8-oxo-3,4-dihyd ro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester</td>
<td>314.33</td>
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<td>7</td>
<td>3g</td>
<td>Pent-4-enoic acid 2,2-dimethyl-8-oxo-3,4-dihyd ro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester</td>
<td>323.36</td>
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<td>Acetic acid 2,2-dimethyl-8-oxo-3,4-dihyd ro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester</td>
<td>288.30</td>
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<td>9</td>
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<td>391.68</td>
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</table>

Example 13. 3-Phenyl-acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (8a)
As shown in the above-described reaction formula, cinnam acid (6a, 1.81g, 12.2mmol) in 100 ml round flask was dissolved in 20 ml of anhydrous benzene. Two drop of N,N-dimethyl formamide and thionyl chloride (4.44 ml, 60.9mmol) were added thereto to reflux for 5 hours at 70-80 °C. The reaction solution was cooled to room temperature and concentrated in vacuo to obtain cinnamoyl chloride (7a). The reaction solution was dissolved in anhydrous dichloromethane.

Step 2

(+)-decursinol (2g, 8.12mmol) was dissolved in anhydrous dichloromethane in 100ml of round flask. Cinnamoyl chloride (7a) dissolved in mixture solvent of pyridine (1.97 ml, 24.4 mM) and anhydrous dichloromethane (30 ml) was added thereto and stirred for 2 hours at room temperature. The reaction solution was concentrated in vacuo and the concentrates were performed to Silica gel column chromatography to obtain solid form of 3-phenyl-acrylic add 2,2-dimethyl-1,8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (8a).

Example 14. 3-(4-Methoxy-phenyl) acrylic acid
2,2-dimethyl-8-oxo-3,4-dihydro-2H-pyrano[3,2-b]chromen-3-yl-ester (8b)

Excepting that ãnnamic arid (6a) used in the 1st step of Example 13 was substituted with 4-methoxy ãnnamic: acid (6b), all the procedure was performed in a similar method to Example 13 to obtain solid form of 3-(4-methoxy-phenyl)-acrylic acid 2,2-dimethyl-8-o>3,4-dihydro- 2H,8H-pyrano[3,2-g]chromen-3-yl-ester (8b).

yield: 91.2% ;

m.p 68 °C;

R = 0.20(n-hexane: ethyl acetate=2: 1);

Example 15. 3-(4-Hydroxy-phenyl)-acrylic acid

2,2-dimethyl-8-oxo-3,4-dihydro- 2H,8H-pyrano[3,2-g]chromen-3-yl-ester (8c)

3-(4-methoxy-phenyl)-acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro- 2H,8H-pyrano[3,2-g]chromen-3-yl-ester (100mg, 0.246 mmol) in 100 ml of round flask was dissolved in anhydrous dSbhoromethane (20 ml). IM borone tri bromide (2.46ml, 2.46mmol) was added thereto dropwisely and stirred for 2 hrs at room temperature. The reaction solution was ooled with an ice water (200 ml) and stirred for 10 min. The solution was extracted with ethyl acetate, dehydrated with anhydrous KMnO 4 and concentrated in vacuo. The concentrates were performed to Silica gel column chromatography to obtain solid form of 3-(4-hydroxy-phenyl)-acrylic add 2,2-dimethyl-8-oxo-3,4-dihydro- 2H,8H-pyrano[3,2-g]chromen-3-yl-ester (8c).

yield: 82.3% ;

m.p 104 °C;

R = 0.32(n-hexane:ethyl acetate=1:1);

Example 16. 3-(3,4-Dimethoxy-phenyl)acrylic acid

2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-b]chromen-3-yl-ester (8d)
Excepting that cinnamic acid (6a) used in the 1st step of Example 13 was substituted with 3,4-dimethoxy cinnamic acid (6d), all the procedure was performed in a similar method to Example 13 to obtain solid form of 3-(3,4-dimethoxy-phenyl)-acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (8d).

Example 17. 3-(3,4,5-Trimethoxy-phenyl)-acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (8e)

Excepting that cinnamic acid (6a) used in the 1st step of Example 13 was substituted with 3,4,5-trimethoxy cinnamic acid (6e), all the procedure was performed in a similar method to Example 13 to obtain solid form of 3-(3,4,5-trimethoxy-phenyl)-acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (8e).

Example 18. 3-(3,4,5-Trihydroxy-phenyl)-acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (8f)

Excepting that 3-(4-methoxy-phenyl)-acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (8b) of Example 15 was substituted with 3-(3,4,5-trimethoxy-phenyl)-acrylic acid
2,2-dimethyl-8-o>o-3,4-dehydro- 2H,8H'-pyrano[3,2-^]chromen-3-yl-ester (8e), all the procedure was performed in a similar method to Example 15 to obtain white solid form of 3-(3,4,5-trihydroxy-phenyl)- acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro- 2H,8H'-pyrano[3,2-^]chromen-3-yl-ester (8f).

yield: 18.2%;
m.p 144 °C;
R = 0.44 (chloroform:methanol=5:1);
1H NMR (acetone-d 6): ppm 7.849(d, J=9.6Hz, IH), 7.453(m, 2H), 6.737(s, IH), 6.720(s, 2H), 6.204(m, 2H), 5.195(t, J=4.8Hz, IH), 3.310(dd, J=16.8, 4.8Hz, IH), 2.937(dd, J=16.8, 4.8Hz, IH), 1.417(s, 6H);

MS(m/z): 425 (M+H)+

Example 19. 3-(2-Methoxy-phenyl)acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro- 2H,8H'-pyrano[3,2-^]chromen-3-yl-ester (8g)

Excepting that tinnamic acid (6a) used in the 1" step of Example 13 was substituted with 2-methoxy cinnamic acid (6g), all the procedure was performed in a similar method to Example 13 to obtain white solid form of 3-(2-methoxy-phenyl)- acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro- 2H,8H'-pyrano[3,2-^]chromen-3-yl-ester (8g).

yield: 81.8%;
m.p 72 °C;
R = 0.48 (n-hexane:ethyl acetate=1:1);
1H NMR(CDCl3): ppm 7.996(d, J=16.4Hz, IH), 7.589(d, J=9.6Hz, IH), 7.472(d, J=6.4Hz, IH), 7.352(t, J=7.8Hz, IH), 7.173(s, IH), 6.960–6.895(m, 2H), 6.804(s, IH), 6.508(d, J=16.0Hz, IH), 6.235(d, J=9.6Hz, IH), 5.194(t, J=5.0Hz, IH), 3.871(s, 3H), 3.242(dd, J=5.0, 17.2Hz, IH), 2.942(dd, J=5.0, 17.2Hz, IH), 1.437(s, 3H), 1.396(s, 3H).

Example 20. 3-(2-Hydroxy-phenyl)acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro- 2H,8H'-pyrano[3,2-^]chromen-3-yl-ester (8h)

Excepting that 3-(4-methoxy-phenyl)-acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro- 2H,8H'-pyrano[3,2-^]chromen-3-yl-ester (8b) of Example 15 was substituted with 3-(2-methoxy-phenyl)-acrylic acid 2,2-dimethyl-8-oxo-3,4-dehydro- 2H,8H'-pyrano[3,2-^]chromen-3-yl-ester (8g), all the procedure was performed in a similar method to Example 15 to obtain white solid form of 3-(2-hydroxy-phenyl)-acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro- 2H,8H'-pyrano[3,2-^]chromen-3-yl-ester (8h).
pyrano[3,2-g]chromen-3-yl-ester (8h).

yield: 58.5% ;

m.p 106 °C;

R = 0.39 (rc-hexane:ethyl acetate=l:l);

$^1$H NMR(3,2- $^g$ chromen-3-yl-ester (8h).

Example 21. 3-(3-Methoxy-phenyl)acrylic acid

2,2-dimethyl-8-oxo-3,4-dihydro-2 $^f$ff-pyrano[3,2-$^g$]chromen-3-yl-ester (8i)

Excepting that cinnamic arid (6a) used in the 1 " step of Example 13 was substituted with 3-methoxy cinnamic arid (6i), all the procedure was performed in a similar method to Example 13 to obtain white solid form of 3-(3-methoxy-phenyl)-acrylic arid 2,2-dimethyl-8-o7D-3,4-dihydro- 2$^H,8H$-pyrano[3,2- $^g$]chromen-3-yl-ester (8i).

yield: 90.9% ;

m.p 72 °C;

R = 0.51 (n-hexane: ethyl acetate=l:l);

$^1$H NMR(CDCl$_3$) : ppm 7.644(d, 7=16.0Hz, IH), 7.584(d, 7=9.6Hz, IH), 7.282(t, 7=8.4Hz, IH), 7.175(s, IH), 7.088(d, 7=8.0Hz, IH), 6.932(dd, 7=4.0, 8.4Hz, IH), 6.135(s, IH), 6.403(d, 7=15.6Hz, IH), 6.236(d, 7=9.6Hz, IH), 5.199(t, 7=4.8Hz, IH), 3.813(s, 3H), 3.248(dd, 7=4.8, 17.2Hz, IH), 2.943(dd, 7=4.8, 17.2Hz, IH), 1.440(s, 3H), 1.394(s, 3H);

MS(m/z) 407 (M+H)$^+$. 

Example 22. 3-(2,3-Dimethoxy-phenyl)acrylic acid

2,2-dimethyl-8-oxo-3,4-dihydro-2 $^f$ff-pyrano[3,2-$^g$]chromen-3-yl-ester (8j)

Excepting that cinnamic arid (6a) used in the 1 " step of Example 13 was substituted with 2,3-dimethoxy cinnamic arid (6j), all the procedure was performed in a similar method to Example 13 to obtain white solid form of 3-(2,3-dimethoxy-phenyl)-acrylic arid 2,2-dimethyl-8-o7D-3,4-dihydro- 2$H,8H$-pyrano[3,2- $^g$]chromen-3-yl-ester (8j).
yield: 25.0% ;
m.p 149 °C;
R = O.43(n-hexane:ethyl acetate=1:1);

$^1$H NMR(CDC$_3$): ppm 8.021(d, /=16.0Hz, IH), 7.585(d, /=9.6Hz, IH), 7.174(s, IH), 7.121(d, /=6.8Hz, IH), 7.032(t, /=8.0Hz, IH), 6.939(d, /=8.8Hz, IH), 6.829(s, IH), 6.449(d, /=16.8Hz, IH), 6.232(d, /=9.6Hz, IH), 5.192(t, /=4.8Hz, IH), 3.868(s, IH), 3.832(s, 3H), 3.249(dd, /=4.8, 17.2Hz, IH), 2.945(dd, /=4.8, 17.2Hz, IH), 1.435(s, 3H), 1.400(s, 3H);

MS(m/z) 437 (M+H)$^+$. 

Example 23. 3-(2,4-Dimethoxy-phenyl>acrylic acid
2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (8k)

Excepting that cinnamon arid (6a) used in the 1$^\text{st}$ step of Example 13 was substituted with 2,4-dimethoxy cinnamon arid (6k), all the procedure was performed in a similar method to Example 13 to obtain white solid form of 3-(2,4-dimethoxy-phenyl)-acrylic arid 2,2-dimethyl-8-oxo3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (8k).

yield: 25.0% ;
m.p 149 °C ;
R = O.43(n-hexane:ethyl acetate=1:1);

$^1$H NMR(CDC$_3$): ppm 8.021(d, /=16.0Hz, IH), 7.585(d, /=9.6Hz, IH), 7.174(s, IH), 7.121(d, /=6.8Hz, IH), 7.032(t, /=8.0Hz, IH), 6.939(d, /=8.8Hz, IH), 6.829(s, IH), 6.449(d, /=16.8Hz, IH), 6.232(d, /=9.6Hz, IH), 5.192(t, /=4.8Hz, IH), 3.868(s, IH), 3.832(s, 3H), 3.249(dd, /=4.8, 17.2Hz, IH), 2.945(dd, /=4.8, 17.2Hz, IH), 1.435(s, 3H), 1.400(s, 3H);

MS(m/z) 437 (M+H)$^+$. 

Example 24. 3-(2,5-Dimethoxy-phenyl>acrylic acid
2,2-dimethyl-S-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (81)

Excepting that rinnamic arid (6a) used in the 1$^\text{st}$ step of Example 13 was substituted with 2,4-dimethoxy rinnamic arid (6l), all the procedure was performed in a similar method to Example 13 to obtain pale yellow solid form of 3-(2,5-dimethoxy-phenyl)-acrylic arid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (81).

yield: 38.7% ;

yield: 25.0% ;
m.p 149 °C;
R = O.43(n-hexane:ethyl acetate=1:1);

$^1$H NMR(CDC$_3$): ppm 8.021(d, /=16.0Hz, IH), 7.585(d, /=9.6Hz, IH), 7.174(s, IH), 7.121(d, /=6.8Hz, IH), 7.032(t, /=8.0Hz, IH), 6.939(d, /=8.8Hz, IH), 6.829(s, IH), 6.449(d, /=16.8Hz, IH), 6.232(d, /=9.6Hz, IH), 5.192(t, /=4.8Hz, IH), 3.868(s, IH), 3.832(s, 3H), 3.249(dd, /=4.8, 17.2Hz, IH), 2.945(dd, /=4.8, 17.2Hz, IH), 1.435(s, 3H), 1.400(s, 3H);

MS(m/z) 437 (M+H)$^+$. 

Example 24. 3-(2,5-Dimethoxy-phenyl>acrylic acid
2,2-dimethyl-S-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (81)

Excepting that rinnamic arid (6a) used in the 1$^\text{st}$ step of Example 13 was substituted with 2,4-dimethoxy rinnamic arid (6l), all the procedure was performed in a similar method to Example 13 to obtain pale yellow solid form of 3-(2,5-dimethoxy-phenyl)-acrylic arid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (81).

yield: 38.7% ;
Example 25. 3-(2,4,5-Trimethoxy-phenyl)-acrylic acid
2,2-dimethyl-8-oxo-3,4-dihydro-2'H-pyrano[3,2-g]chromen-3-yl-ester (8m)

Excepting that cinnamic acid (6a) used in the 1st step of Example 13 was substituted with 2,4,5-trimethoxy cinnamic acid (6m), all the procedure was performed in a similar method to Example 13 to obtain yellow solid form of 3-(2,4,5-Trimethoxy-phenyl)-acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2'H.8H-pyrano[3,2-g]chromen-3-yl-ester (8m).

yield: 33.5% ;
m.p 93 °C;
R = 0.29 (n-hexane:ethyl acetate=1:1);
1H NMR(CDCl3): ppm 7.986(d, /=13.6Hz, IH), 7.586(d, /=9.6Hz, IH), 7.173(s, IH), 6.966(s, IH), 6.833(s, IH), 6.478(s, IH), 6.325(d, /=16.0Hz, IH), 6.232(d, /=9.2Hz, IH), 5.196(t, /=4.8Hz, IH), 3.922(s, 3H), 3.855(s, 3H), 3.840(s, 3H), 3.238(dd, /=4.8, 17.2Hz, IH), 2.940(dd, /=4.8, 17.2Hz, IH), 1.443(s, 3H), 1.393(s, 3H);
MS(m/z): 483 (M+H)+

Example 26. 3-(4-Nitro-phenyl)-acrylic acid
2,2-dimethyl-8-oxo-3,4-dihydro-2'H-pyrano[3,2-g]chromen-3-yl-ester (8n)

Excepting that cinnamic acid (6a) used in the 1st step of Example 13 was substituted with 4-nitro cinnamic acid (6n), all the procedure was performed in a similar method to Example 13 to obtain solid type of 3-(4-Nitro-phenyl)-acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2'H.8H-pyrano[3,2-g]chromen-3-yl-ester (8n).

yield: 65.7% ;
m.p 193 °C;
R = 0.42 (n-hexane:ethyl acetate=1:1);
[320] $^1$H NMR (CDCl$_3$): ppm 8.237 (d, $\delta$=8.8Hz, 2H), 7.727~7.623 (m, 3H), 7.598 (d, $\delta$=9.2Hz, 1H), 7.218 (s, 1H), 6.840 (s, 1H), 6.560 (d, $\delta$=11.2Hz, 1H), 6.248 (d, $\delta$=9.6Hz, 1H), 5.225 (t, $\delta$=4.8Hz, 1H), 3.272 (dd, $\delta$=4.8, 17.2Hz, 1H), 2.958 (dd, $\delta$=4.8, 17.2Hz, 1H), 1.449 (s, 3H), 1.403 (s, 3H);

[321] MS (m/z) 422 (MH-H)$^+$.  

[322]

Example 27. 3-(3-Hydroxy-phenyl)-acrylic acid  
2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (11a)

[324]

Step 1

As shown in the above-described reaction formula, acetic anhydride (11.5 ml, 25.6 mM) in 100ml of round flask was added to 3-hydroxy cinnamic acid (9a, 2g, 12.8 mmol) and excess pyridine (10ml). The reaction solution was stirred for 24 hrs at room temperature and concentrated with vacuo. The concentrates were performed to Silica gel column chromatography to obtain 3-acetoxy cinnamic acid (9b) to use in following steps.

[325] Step 2.3

Excepting that cinnamic acid (6a) used in the 1-th step of Example 13 was substituted with 3-acetoxy cinnamic acid (9b), all the procedure was performed in a similar method to Example 13 to obtain solid type of 3-(3-acetoxy-phenyl)-acrylic arid 2,2-dimethyl-8-TH-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (11b) to use in following steps.

[330] Step 4

1.8g of 3-(3-acetoxy-phenyl)-acrylic arid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (lib) was dissolved in 60 ml of acetone and 3N HCl (20ml) was added thereto. The reaction solution was performed to reflux for 12 hrs at
50 °C to 60 °C and cooled to room temperature to concentrate in vacuo. The concentrate was dissolved in ethyl acetate and distilled water to fractionate and the collected ethyl xetate layer was dehydrated with anhydrous KMnO₄. The solution was filtered and concentrated with vacuo. The concentrates were performed to SiIica gel column chromatography to obtain solid form of 3-(3-hydroxy-phenyl)-acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro 2H,8H-pyrano[3,2-g]chromen-3-yl-ester (11a).

yield: 88.1% ;

m.p 105 °C;

\[ R = 0.21 (n\text{-}hexane:ethyl acetate=1:1); \]

\[ \text{\textsuperscript{1}H NMR(acetone-d\textsubscript{6}) : ppm 7.863(d, \textit{J}=9.2Hz, IH), 7.622(d, \textit{J}=15.6Hz, IH), 7.442(s, IH), 7.252(t, \textit{J}=7.8Hz, IH), 7.168(d, \textit{J}=7.6Hz, IH), 7.111(s, IH), 6.915(d, \textit{J}=8.4Hz, IH), 6.751(s, IH), 6.489(d, \textit{J}=16.0Hz, IH), 6.213(d, \textit{J}=9.6Hz, IH), 5.229(t, \textit{J}=4.6Hz, IH), 3.337(dd, \textit{J}=4.2, 17.2Hz, IH), 2.987(dd, \textit{J}=4.4, 17.6Hz, IH), 1.432(s, 3H), 1.422(s, 3H); \]

\[ \text{M}$(m/z)$ : 393 (M+H) \]

Example 28. 3-(3-Acetoxy-phenyl)-acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (lib)

Steps 1.2.3

All the procedure was performed in a similar method to Example 27 to obtain solid form of 3-(3-acetoxy-phenyl)-acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (11b).

yield: 87.0% ;

m.p 181 °C;

\[ R = 0.31 (n\text{-}hexane:ethyl acetate=1:1); \]

\[ \text{\textsuperscript{1}H NMR(acetone-d\textsubscript{6}) : ppm 7.840(d, \textit{J}=9.6Hz, IH), 7.684(d, \textit{J}=16.0Hz, IH), 7.558(d, \textit{J}=7.6Hz, IH), 7.451(m, 3H), 7.180(dd, \textit{J}=2.4, 7.6Hz, IH), 6.737(s, IH), 6.574(d, \textit{J}=15.6Hz, IH), 6.198(d, \textit{J}=9.6Hz, IH), 5.232(t, \textit{J}=4.4Hz, IH), 3.336(dd, \textit{J}=4.2, 17.6Hz, IH), 2.984(dd, \textit{J}=4.8, 17.6Hz, IH), 2.258(s, 3H), 1.430(s, 3H), 1.422(s, 3H); \]

\[ \text{MS(m/z) : 435 (M+H) +} \]

Example 29. 3-(3,4-Dihydroxy-phenyl)-acrylic acid 2,2-dimethyl-8-oxo-3,4-d-hydro-2H,8H-pyrano[3,2^-g]chromen-3-yl-ester (lie)

Excepting that 3-hydroxy cinnamic acid (9a) used in the I° step of Example 27
was substituted with 3,4-dihydroxy rinnamb acid (9c, 7g, 38.9mmol), all the
procedure was performed in a similar method to Example 27 to obtain solid form of
3-(3,4-Dihydroxy-phenyl)-acrylic acid, 2,2-dimethyl-8-oxo-3,4-dihydro-
pyrano[3,2-\text{g}]chromen-3-yl-ester (11c).

Example 30. 3-(3,4-Diacetoxy-phenyl)-acrylic acid

2,2-dimethyl-8-oxo-3,4-dihydro-2\textsubscript{H,8H} pyrano[3,2-\text{g}]chromen-3-yl-ester (lid)

Excepting that 3-hydroxy cinnamic acid (9a) used in the 1\textsuperscript{st} step of Example 27 was substituted with 3,4-diacetoxy cinnamic acid (9c, 7g, 38.9mmol), all the procedure was performed in a similar method to Example 27 to obtain solid form of 3-(3,4-\textalpha acetoxy-phenyl)-acrylic acid, 2,2-dimethyl-8-oxo-3,4-dihydro-
2\textsubscript{H,8H} pyrano[3,2-\text{g}]chromen-3-yl-ester (lid).

Example 31. 3-(4-Hydroxy-3-methoxy-phenyl)-acrylic acid

2,2-dimethyl-8-oxo-3,4-dihydro-2\textsubscript{H,8H} pyrano[3,2-\text{g}]chromen-3-yl-ester (lie)

Excepting that 3-hydroxy cinnamic acid (9a) used in the 1\textsuperscript{st} step of Example 27 was substituted with 4-hydroxy cinnamic acid (9c, 5g, 25.7mmol), all the procedure was performed in a similar method to Example 27 to obtain solid form of 3-(4-hydroxy-3-methoxy phenyl)-acrylic acid, 2,2-dimethyl-8-oxo-3,4-dihydro-2\textsubscript{H,8H} -
yield: 91.8% ;

m.p 102 °C;

R = 0.32 (n-hexane: ethyl acetate=1:1);

$^1$H NMR(CC6D6): ppm 7.843(d, $\Delta_f = 9.6$, IH), 7.616(d, $\Delta_f = 16.0$, IH), 7.424(s, IH), 7.357(s, IH), 7.123(dd, $\Delta_f = 2.0$, 8.0, IH), 6.851(d, $\Delta_f = 8.4$, IH), 6.740(s, IH), 6.387(d, $\Delta_f = 15.6$, IH), 6.198(d, $\Delta_f = 9.6$, IH), 5.221(t, $\Delta_f = 4.6$, IH), 3.895(s, 3H), 3.321(dd, $\Delta_f = 4.6$, 17.2, IH), 2.963(dd, $\Delta_f = 4.4$, 17.6, IH), 5.221(t, $\Delta_f = 4.6$, IH), 3.895(s, 3H), 3.321(dd, $\Delta_f = 4.6$, 17.2, IH), 2.963(dd, $\Delta_f = 4.4$, 17.6, IH), 1.421(s, 3H), 1.413(s, 3H);

MS($m/z$): 423 (M+H)$^+$

Example 32. 3-(4-Acetoxy-3-methoxy-phenyl)-acrylic acid

2,2-dimethyl-8-oxo-3,4-dihydro-pyrano[3,2-g]chromen-3-yl-ester (Hf)

Steps 1, 2, 3

Excepting that 3-hydroxy cinnamic add (9a) used in the 1st step of Example 27 was substituted with 4-hydroxy-3-methoxy-cinnamic acid (9e, 5g, 25.7mmol), all the procedure was performed in a similar method to Example 27 to obtain solid form of 3-(4-acetoxy-3-methoxy-phenyl)-acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro-pyrano[3,2-g]chromen-3-yl-ester (Hf).

yield: 42.4% ;

m.p 98 °C;

R = 0.40(n-hexane:ethyl acetate=1:1);

$^1$H NMR(acetone-d6): ppm 7.843(d, $\Delta_f = 9.6$, IH), 7.679(d, $\Delta_f = 16.0$, IH), 7.424(s, IH), 7.357(s, IH), 7.123(dd, $\Delta_f = 2.0$, 8.0, IH), 6.851(d, $\Delta_f = 8.4$, IH), 6.740(s, IH), 6.387(d, $\Delta_f = 15.6$, IH), 6.198(d, $\Delta_f = 9.6$, IH), 5.221(t, $\Delta_f = 4.6$, IH), 3.895(s, 3H), 3.321(dd, $\Delta_f = 4.6$, 17.2, IH), 2.963(dd, $\Delta_f = 4.4$, 17.6, IH), 5.221(t, $\Delta_f = 4.6$, IH), 3.895(s, 3H), 3.321(dd, $\Delta_f = 4.6$, 17.2, IH), 2.963(dd, $\Delta_f = 4.4$, 17.6, IH), 1.421(s, 3H), 1.413(s, 3H);

MS($m/z$): 465 (M+H)$^+$

Example 33. 3-(4-Acetoxy-3,5-dimethoxy-phenyl)-acrylic acid

2,2-dimethyl-8-oxo-3,4-dihydro-pyrano[3,2-g]chromen-3-yl-ester (Ilg)

Steps 1, 2, 3

Excepting that 3-hydroxy cinnamic add (9a) used in the 1st step of Example 27 was substituted with 4-hydroxy-3,5-dimethoxy-cinnamic acid (9e, 500g, 2.23mmol), all the procedure was performed in a similar method to Example 27 to obtain solid form of
3-(4-acetoxy-3,5-dimethoxy-phenyl)- εcrylic arid 2,2-dimethyl-8 θ }o-3,4-dihyciro-
2H,8H -pyrano[3,2-g]chromen-3-y1-ester (11g).

yield: 10.8%;
m.p 121 °C;
R = 0.42 (α-hexane:ethyl acetate=1:1);
1H NMR(CDCl3): ppm 7.614(d, J=9.2Hz, IH), 7.582(d, J=2.4Hz, IH), 7.189(s, IH),
6.826(s, IH), 6.739(s, 2H), 6.362(d, J=16.0Hz, IH), 6.227(d, J=9.2Hz, IH), 5.21 l(t,
J=4.8Hz, IH), 3.801(s, 6H), 3.255(dd, J=4.8, 18.0Hz, IH), 2.935(dd, J=4.8, 18.0Hz,
IH), 2.331(8, 3H), 1.451(s, 3H), 1.397(s, 3H);
MS(w/z) : 495 (M+H) +
Table 4

<table>
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<tr>
<th>No.</th>
<th>No.</th>
<th>Compound</th>
<th>M.W.</th>
<th>Structure</th>
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<tbody>
<tr>
<td>13</td>
<td>8a</td>
<td>3-Phenyl-acrylic acid 2,2-dimethyl-8-oxy-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester</td>
<td>376.40</td>
<td><img src="image1" alt="Structure" /></td>
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<tr>
<td>14</td>
<td>8b</td>
<td>3-(4-Methoxy-phenyl) acrylic acid 2,2-dimethyl-8-oxy-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester</td>
<td>406.43</td>
<td><img src="image2" alt="Structure" /></td>
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<tr>
<td>15</td>
<td>8c</td>
<td>3-(4-Hydroxy-phenyl) acrylic acid 2,2-dimethyl-8-oxy-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester</td>
<td>392.40</td>
<td><img src="image3" alt="Structure" /></td>
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<tr>
<td>16</td>
<td>8d</td>
<td>3-(3,4-Dimethoxy-phenyl) acrylic acid 2,2-dimethyl-8-oxy-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester</td>
<td>436.45</td>
<td><img src="image4" alt="Structure" /></td>
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<tr>
<td>17</td>
<td>8e</td>
<td>3-(3,4,5-Trimehxyo-phenyl) acrylic acid 2,2-dimethyl-8-oxy-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester</td>
<td>466.48</td>
<td><img src="image5" alt="Structure" /></td>
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<td>Compound</td>
<td>M.W.</td>
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<tr>
<td>18</td>
<td>8f</td>
<td>3-((3,4,5-trihydroxy-phenyl)-acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester</td>
<td>424.40</td>
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<tr>
<td>19</td>
<td>8g</td>
<td>3-((2-Methoxy-phenyl)-acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester</td>
<td>406.43</td>
<td><img src="image" alt="Structure" /></td>
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<tr>
<td>20</td>
<td>8h</td>
<td>3-((2-Hydroxy-phenyl)-acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester</td>
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Table 6

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<tr>
<td>21</td>
<td>8i</td>
<td>3-((3-Methoxy-phenyl)-acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester</td>
<td>406.43</td>
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<tr>
<td>22</td>
<td>8j</td>
<td>3-((2,3-Dimethoxy-phenyl)-acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester</td>
<td>438.45</td>
<td><img src="image" alt="Structure" /></td>
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<td>23</td>
<td>8k</td>
<td>3-((2,4-Dimethoxy-phenyl)-acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester</td>
<td>438.45</td>
<td><img src="image" alt="Structure" /></td>
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<td>24</td>
<td>8l</td>
<td>3-((2,5-Dimethoxy-phenyl)-acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester</td>
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Table 7
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<td>25</td>
<td>8m</td>
<td>3-(2,4,5-Trinethoxy-phenyl)-acrylic acid</td>
<td>482.52</td>
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<td>26</td>
<td>8n</td>
<td>3-(4-Nitro-phenyl)-acrylic acid</td>
<td>424.40</td>
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<td>27</td>
<td>11a</td>
<td>3-(3-Hydroxy-phenyl)-acrylic acid</td>
<td>392.40</td>
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<tr>
<td>28</td>
<td>11b</td>
<td>3-(3-Acetoxy-phenyl)-acrylic acid</td>
<td>434.44</td>
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Table 8

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<tr>
<td>29</td>
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<td>3-(3,4-Dihydroxy-phenyl)-acrylic acid</td>
<td>408.40</td>
<td><img src="image5" alt="Structure" /></td>
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<tr>
<td>30</td>
<td>11d</td>
<td>3-(3,4-Diacetoxy-phenyl)-acrylic acid</td>
<td>492.13</td>
<td><img src="image6" alt="Structure" /></td>
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<tr>
<td>31</td>
<td>11e</td>
<td>3-(4-Hydroxy-3-methoxy-phenyl)-acrylic acid</td>
<td>422.43</td>
<td><img src="image7" alt="Structure" /></td>
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</table>

Table 9
Example 34. Benzoic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (14a)

Step 2.3

Excepting that aminic acid (6a) used in the 1st step of Example 13 was substituted with benzoic acid (12a), all the procedure was performed in a similar method to Example 13 to obtain semi-solid form of benzoic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (14a).

yield: 93.2% ;

R=0.52 (n-hexane: ethyl acetate=1:1);

\[^1\text{H}\] NMR (CDCl\textsubscript{3}) : ppm 7.972(d, /=9.6Hz, 2H), 7.557(m, 2H), 7.417(t, 7=7.8Hz, 2H), 7.166(s, 1H), 6.845(s, 1H), 6.227(d, /=9.6Hz, 1H), 5.296(t, 7=4.8Hz, 1H), 3.300(dd, /=4.4, 17.6Hz, 1H), 3.004(dd, 7=4.8, 17.6Hz, 1H), 1.474(s, 3H), 1.428(s, 3H);

MS (m/z) : 351 (M+H) 

Example 35. 3,4,5-trihydroxy-benzoic acid

2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (14b)
As shown in the above-described reaction formula in Example 34, 3,4,5-trihydroxy benzoic acid (3g, 17.6mmol) is dissolved in acetic anhydride (11.5ml, 25.6mM) in 100ml of round flask and 2 to 3 drop of conosulfuric acid were added thereto. The reaction solution was refluxed at 80°C for 10 mins and cooled to room temperature. 30 fold volume of iced water was poured thereto with stirring and left alone at room temperature for 2 hours to filtrate the precipitate. The precipitate was washed with distilled water and dried at 40°C for 12 hours to obtain 3,4,5-trihydroxy benzoic acid (12c).

Excepting that cinnamic acid (6a) used in the 1st step of Example 13 was substituted with 3,4,5-triacetoxy benzoic acid (12c, 5g, 0.017 mM), all the procedure were performed by the similar method to the procedure disclosed in Example 13 to obtain 3,4,5-triacetoxy benzoic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (14c).

Excepting that 3-(3-acetoxy-phenyl)-acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (11b) used in the 4th step of Example 27 was substituted with 3,4,5-triacetoxy benzoic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (14c, 1.8g, 3.43 mM), all the procedure were performed by the similar method to the step 4 of Example 27 to obtain 1.5g of solid 3,4,5-triacetoxy benzoic acid 2,2-dimethyl-8-oJO-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (14b).

**Example 36. 3,4,5-Triacetoxy-benzoic acid**

2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (14c)

**Step 1**

**Step 2.3**

**Step 4**

**Example 36. 3,4,5-Triacetoxy-benzoic acid**

2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (14c)
All the procedure was performed in the similar method to the steps 1, 2, 3 of Example 35 to obtain solid form of 3,4,5-triacetoxy-benzoic acid 2,2-dimethyl-8-oxo-3,4-dihydro- \(2H,8H\)-pyrano[3,2-g]chromen-3-yl-ester (14c).

yield: 28.8%;
m.p 97 °C;
\( R = 0.44(n\text{-hexane:ethyl acetate}=1:2) \);

\( ^1H \text{ NMR(acetone-d}_6 \text{)} \) ppm 7.848(d, \( /=9.6\text{Hz}, \text{ IH})\), 7.740(s, 2H), 7.435(s, \text{ IH}), 6.765(s, \text{ IH}), 6.209(d, \( /=9.6\text{Hz}, \text{ IH})\), 5.359(t, \( /=4.4, 17.6\text{Hz}, \text{ IH})\), 3.403(dd, \( /=4.2, 17.6\text{Hz}, \text{ IH})\), 3.123(dd, \( /=4.4, 17.6\text{Hz}, \text{ IH})\), 2.317(s, 3H), 2.283(m, 6H), 1.479(s, 3H), 1.457(s, 3H);

MS(m/z) : 525 (M+H)

Table 10

<table>
<thead>
<tr>
<th>No.</th>
<th>Compound</th>
<th>M.W.</th>
<th>structure</th>
</tr>
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<td>14a</td>
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<tr>
<td>95</td>
<td>14b</td>
<td></td>
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<tr>
<td>96</td>
<td>14c</td>
<td></td>
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</tr>
</tbody>
</table>

Example 37. Methane sulfonic acid 2,2-dimethyl-8-oxo-3,4-dihydro-\(2H,8H\)-pyrano[3,2-g]chromen-3-yl-ester (16a)

As shown in the above-described reaction scheme, the mixture of decursinol (1, 20mg, 0.081mmol) and triethylamine (TEA, 34µl, 0.024mmol) was dissolved in 5ml
of anhydrous dichloromethane. Methane sulfonyl chloride (il µ Jt, 0.406mmol) was added thereto in cold water dropwisely. The reaction solution was stirred for 15 hrs at room temperature and half volume of the solution was concentrated at room temperature. The concentrates were performed to Silica gel column chromatography to obtain solid form of methane sulfonic acid 2,2-dimethyl-8-oxo-3,4-dehydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester (16a).

yield: 91.2% ;
m.p 174 °C;
R = 0.32(rt-hexane:ethyl acetate=1 :1);

1H NMR(CDCl3 ppm 7.591(d, J=9.6Hz, IH), 7.197(s, IH), 6.786(s, IH), 6.244(d, 7 =9.6Hz, IH), 4.884(t, J=4.8Hz, IH), 3.293(dd, /=4.8, 17.6Hz, IH), 3.179(dd, J=4.8, 17.6Hz, IH), 3.067(s, 3H), 1.456(s, 3H), 1.407(s, 3H);

MS(wi/z) : 325 (M+H)+

Example 38. Benzene sulfonic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2H^H-pyranof[3,2-g]chromtn-3-yl-ester (16b)

Excepting that methane sulfonyl chloride (15a) used in Example 37 was substituted with benzene sulfonyl chloride (15b), all the procedure was performed in the similar method to the procedure disclosed in Example 37 to obtain solid form of benzene sulfonic acid 2,2-dimethyl-8-oxo-3,4-dehydro-2H,S./.-pyrano[3,2- g]chromen-3-yl-ester (16b).

yield: 36.2% ;
m.p 64 °C;
R = 0.21(n-hexane:ethyl acetate=2:1);

1H NMR(CDCl3 ppm 7.907(d, /=7.6Hz, 2H), 7.682(m, IH), 7.567(m, 3H), 7.085(s, IH), 6.744(s, IH), 6.236(d, /=9.2Hz, IH), 4.706(t, /=5.2Hz, IH), 3.173(dd, /=5.2, 18.0Hz, IH), 3.036(dd, /=5.2, 18.0Hz, IH), 1.283(s, 3H), 1.245(s, 3H);

MS(W’z) : 387 (M+H)+
Example 39. 8,8-Dimethyl-7H-pyrano[3,2-g]chromen-2,7-dione (17)

As shown in the above-described reaction formulae, the mixture of pyridinium chlorochromate (PCC, 1.74g, 8.12mmol) and molecular sieve 4 Å (2g, wt/wt=2/1) in 100ml of round flask were dissolved in anhydrous dichloromethane (150 ml). The reaction solution was stirred for 5 mins in cold ice. Decursinol (1g, 4.06mmol) was added thereto and stirred for 1 hrs at 0 °C. Half volume of the reaction solution was filtrated and concentrated with vaccuo at room temperature. The concentrates were performed to Silica gel column chromatography to obtain yellow solid form of 8,8-dimethyl-7H-pyrano[3,2-g]chromen-2,7-dione (17).

Example 40. 8,8-Dimethyl-7H-pyrano[3,2-g]chromen-2,7-dione 7-oxime (18)
As shown in the above-described reaction formulae, 8,8-dimethyl-67/-pyrano[3,2- g]chromen-2,7-dione (17, 788mg, 3.23mmol) in 100ml of round flask was dissolved in anhydrous ethanol (20 ml). Hydroxy ammonium chloride (NHOHCl, 336mg, 4.85mmol) and pyridine (391 µL, 4.85mmol) were added thereto. The reaction solution was stirred for 1 hrs at 80°C with reflux and cooled to room temperature. The residue was concentrated, recrystallized with hexane and ethylacetate and filtrated with hexane with washing. The recrystallized substance was purified with Silica gel column chromatography to obtain pale yellow solid form of 8,8-dimethyl-67f-pyrano[3,2- g]chromen-2,7-dione 7-oxime (18).

yield: 83.0% ;
m.p : 217 °C ;
Rf = 0.30 (n-hexane:ethyl acetate=2:1) ;
1H NMR(CDCl3) ppm 7.614(d, /=9.6Hz, IH), 7.253(s, IH), 6.858(s, IH), 6.277(d, 7=9.6, IH), 3.851(s, 2H), 1.525(s, 6H) ;
MS(m/z) : 260 (M+H)+

Example 41. 8,8-Dimethyl-tff -pyrano[3,2- g]chromen-2,7-dione 7-[O -(3,3-dimethylacryloyl)-oxime] (20)

As shown in the above-described reaction formulae, 3,3-dimethylacrylic acid (2a, 100mg, 0.999mmole) was dissolved in 3ml of anhydrous dichloromethane and stirred in cold ice under nitrogen atmosphere, oxalyl chloride(356.8 µL, 3.996mmol) was added thereto dropwisely and stirred at 0° for 5 hours. The reaction solution was cooled to room temperature and concentrated to obtain 3,3-dimethylacryloyl chloride (19a) to dissolve in anhydrous dichloromethane.
Step 2
8,8-dimethyl-6'H-pyrano[3,2-g]chromen-2,7-dione 7-Imine (18, 103.5mg, 0.399 mmole) was dissolved in anhydrous dichloromethane (30ml). 3,3-dimethyl acryloyl chloride (19a) dissolved in pyridine (96.9µl, 1.197mmol) and 20ml of anhydrous dichloromethane was added thereto dropwisely and stirred at room temperature for 2 hours. The residue was concentrated and performed to silica gel column chromatography to obtain yellow solid form of 8,8-dimethyl-6'H-pyrano[3,2-g]chromen-2,7-dione 7-[O-(3,3-dimethylacryloyl)oxime] (20).

Yield: 66.8% ; m.p : 147°C ;

R = 0.26 (n-hexane:ethyl acetate=2:1) ;

1H NMR (CDCl3): ppm 7.612(d, /=9.4Hz, 1H), 7.243(s, IH), 6.885(s, IH), 6.288(d, /¼9.4Hz, IH), 5.830(s, IH), 3.914(s, 2H), 2.254(s, 3H), 1.991(s, 3H), 1.620(s, 6H),

MS (m/z) : 342 (M+H)+

Example 42. 8,8-Dimethyl-6'H-pyrano[3,2-g]chromen-2,7-dione 7-[O-cinnamoyl-oxime] (21a)

Step 1
As shown in the above-described reaction formulae, cinnamic acid (6a, 85.7mg, 0.579mmole) was dissolved in 6ml of anhydrous benzene. 2 drops of N,N-dimethylformamide and thionyl chloride (SOCl2, 211µl, 2.893mmol) were added thereto dropwisely and refluxed at 70-80° for 5 hours. The reaction solution was cooled to room temperature and concentrated to obtain cinnamoyl chloride (7a) to dissolve in anhydrous dichloromethane.

Step 2
8,8-Dimethyl-6'H-pyrano[3,2-g]chromen-2,7-dione 7-oxime (18, 100mg, 0.386 mmole) was dissolved in anhydrous dichloromethane (30ml). cinnamoyl chloride (7a)
dissolved in pyridine (93.6 µl, 1.158 mmol) and 20 ml of anhydrous dichloromethane was added thereto dropwise and stirred at room temperature for 2 hours. The residue was concentrated and performed to silica gel column chromatography to obtain white solid form of 8,8-dimethyl-\(H\)-pyranot[2,3-Z]-chromen-8,7-dione \(\rightarrow\) \(O\) -
namoyl-oxime (21a).

Yield: 60.7 %;

m.p: 175 °C;

\(R = 0.44\) (n-hexane:ethyl acetate=1:1);

\(^1\text{H NMR (CDCl}3\text{): ppm 7.867(d, }J=16.0\text{Hz, IH), 7.609(m, 3H), 7.436(m, 3H), 7.279(s, IH), 6.912(d, }J=8.8\text{Hz, IH), 6.614(d, }J=16.0\text{Hz, IH), 6.304(d, }J=9.4\text{Hz, IH), 3.999(s, 2H), 1.654(s, 6H)}\)

\(MS(m/z): 390\ (M+H)^+\)

Example 43. 8,8-Dimethyl-tfff-pyrano[3,2-g]chromen-2,7-dione \(\rightarrow\) \(O\) -
methoxycinnamoyl-oxime (21b)

Excepting that cinnamic acid (6a) used in the 1st step of Example 42 was substituted with 4-methoxy cinnamic acid (6b), all the procedure was performed in the similar method to the procedure disclosed in Example 42 to obtain white solid form of 8,8-dimethyl-\(H\)-pyranot[3,2-g]chromen-2,7-dione 7\[O\] \(-(4\)-methoxycinnamoyl)\)-oxime (21b).

Yield: 62.4 %;

m.p: 175 °C;

\(R = 0.39\) (n-hexane:ethyl acetate=1:1);

\(^1\text{H NMR (CDCl}3\text{): ppm 7.820(d, }J=16.0\text{Hz, IH), 7.625(d, }J=9.6\text{Hz, IH), 7.546(d, }J=8.8\text{Hz, }2\text{H), 7.278(s, IH), 6.942(d, }J=8.8\text{Hz, }2\text{H), 6.908(s, IH), 6.476(d, }J=16.0\text{Hz, IH), 6.302(d, }J=9.6\text{Hz, IH), 3.994(s, 2H), 3.865(s, 3H), 1.650(s, 6H)}\)

\(MS(m/z): 420\ (M+H)^+\)

Example 44. 8,8-Dimethyl-tfff-pyrano[3,2-g]chromen-2,7-dione \(\rightarrow\) \(O\) -
(3,4-dimethoxycinnamoyl)oxime (21d)

Excepting that cinnamic acid (6a) used in the 1st step of Example 42 was substituted with 3,4-dimethoxy cinnamic acid (6d), all the procedure was performed in the similar method to the procedure disclosed in Example 42 to obtain pale yellow solid form of 8,8-dimethyl-\(H\)-pyranot[3,2-g]chromen-2,7-dione 7\[O\] \(-(3,4\)-dimethoxycinnamoyl)\)-oxime (21d).
Yield: 56.0 % ;
m.p : 202 °C;
R = 0.26 (n-hexane:ethyl acetate=1:1) ;
\[ {\ H} \text{NMR (CDCl}_{3} \text{): ppm 7.80(d, } J=16.0\text{Hz, 1H), 7.615(d, } J=9.4\text{Hz, 1H), 7.275(s, 1H), 7.184(d, } J=8.4, 2.0\text{Hz, 1H), 7.100(d, } J=2.0\text{Hz, 1H), 6.904(m, 2H), 6.459(d, } J=16.0\text{Hz, 1H), 6.298(d, } J=9.4\text{Hz, 1H), 3.999(s, 2H), 3.948(s, 2H), 3.940(s, 3H), 1.651(s, 6H)} \right]

\[ MS(m/z) : 450 (M\text{+H}) ^+ \]

Example 45. 8,8-Dimethyl-6H-pyrano[3,2-g]chromen-2,7-dione l-[0 - (3,4,5-trimethoxycinnamoyl)oxide] (21e)

Excepting that d\text{imamic acid (6a) used in the 1\text{st} step of Example 42 was substituted with 3,4,5-trimethoxycinnamic acid (6e), all the procedure was performed in the similar method to the procedure disclosed in Example 42 to obtain yellow solid form of 8,8-dimethyl-6H-pyrano[3,2-g]chromen-2,7-dione 7-[0 - (3,4,5-trimethoxycinnamoyl)oxide] (21e).

Yield: 72.8 % ;
m.p : 175°C ;
R = 0.24(n-hexane:ethyl acetate=1:1) ;
\[ {\ H} \text{NMR (CDCl}_{3} \text{): ppm 7.776(d, } J=16.0\text{Hz, 1H), 7.617(d, } J=9.4\text{Hz, 1H), 7.277(s, 1H), 6.912(s, 1H), 6.814(s, 2H), 6.487(d, } J=16.0\text{Hz, 1H), 6.303(d, } J=9.4\text{Hz, 1H), 4.005(s, 2H), 3.923(s, 9H), 1.653(s, 6H)} \right]

Example 46. 8,8-Dimethyl-1f#-pyrano[3,2-g]chromen-2,7-dione l-[0 - (3-acetoxy cinnamoyl)oxime] (22a)

All the procedure was performed with the similar method to the 1\text{st} step of Example 27 to obtain 3-acetoxy cinnamic acid (9b).
Step 2

Excepting that cinnamic acid (6a) used in the 1st step of Example 42 was substituted with 3-acetoxy cinnamic acid (9b), all the procedure was performed in the similar method to the procedure disclosed in Example 42 to obtain yellow solid form of 8,8-dimethyl-6 \( H \)-pyrano[3,2-g]chroinen-2,7-dione 7-[O-(3-acetoxy cinnamoyl)-o\[\text{oxime}]] (22a).

Yield: 91.5 %;
m.p : 160°C;
R = 0.47(n-hexane:ethyl acetate=1:1);
\( ^1 \)H NMR(CDCl\(_3\)) : d ppm 7.823(d, J=100Hz, IH), 7.625(d, J=9.4Hz, IH), 7.443(d, J=2.4Hz, 2H), 7.342(s, IH), 7.282(s, IH), 7.164(m, IH), 6.905(s, IH), 6.591(d, J=16Hz, IH), 6.301(d, J=9.4Hz, IH), 3.989(s, 2H), 2.325(s, 3H), 1.649(s, 6H);
MS(m/z) : 448 (M+H)\(^+\).

Example 47. 8,8-Dimethyl-6 \( H \)-pyrano[3,2-g]chroinen-2,7-dione 7-[O-(3,4-diacetoxy cinnamoyl)-oxime] (22b)

Step 1

Excepting that cinnamic acid (9a) used in the 1st step of Example 27 was substituted with 3,4-diaceotoxy cinnamic acid (9c, 7g, 38.9mmole), all the procedure was performed in the similar method to the procedure disclosed in the 1st step of Example 27 to obtain 3,4-diaceotoxy cinnamic acid(9d).

Yield: 77.1 %;
m.p : 192°C;
R = 0.23(n-hexane:ethyl acetate=1:1);
\( ^1 \)H NMR(CDCl\(_3\)) : d ppm 7.794(d, J=16.4 Hz, IH), 7.625(d, J=9.4Hz, IH), 7.462(m, 2H), 7.268(m, 2H), 6.907(s, IH), 6.544(d, J=16.4Hz, IH), 6.303(d, J=9.4Hz, IH), 3.947(s, 2H), 2.308(s, 3H), 2.298(s, 3H), 1.647(s, 6H);
Example 48. 8,8-Dimethyl-5H-pyrano[3,2-g]chromen-2-one (23)

1. (+He αursnol)

Decursinol (1, 100mg, 0.406 mmole) and triphenylphosphine (213mg, 0.821 mmole) in 100 ml of round flask were dissolved in anhydrous dichloromethane (4ml) and acetonitrile (4ml) and refluxed at 70-80°C for 2 hours. Half of the reaction solution was concentrated and the concentrate was performed to Silica gel column chromatography to obtain white solid form of 8,8-dimethyl-6H-pyrano[3,2-g]chromen-2-one (23).

Yield: 95.6 %

MP: 124°C

R_f = 0.69 (n-hexane:ethyl acetate=1:1)

^1H NMR (CDCl_3): d ppm 7.576 (d, 7=9.2Hz, 1H), 7.045 (s, 1H), 6.724 (s, 1H), 6.339 (d, 7=10.0Hz, 1H), 6.219 (d, 7=9.6Hz, 1H), 5.688 (d, 7=9.6Hz, 1H), 1.468 (s, 6H);

MS (m/z): 229 (M+H)^+

Table 12
<table>
<thead>
<tr>
<th>No.</th>
<th>No.</th>
<th>Compound</th>
<th>M.W.</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>39</td>
<td>17</td>
<td>8,8-Dimethyl 6H-pyran[3.2-g]chromen-2,7-dione</td>
<td>244.24</td>
<td><img src="image1" alt="Structure1" /></td>
</tr>
<tr>
<td>40</td>
<td>18</td>
<td>8,8-Dimethyl 6H-pyran[3.2-g]chromen-2,7-dione 7-oxime</td>
<td>259.26</td>
<td><img src="image2" alt="Structure2" /></td>
</tr>
<tr>
<td>41</td>
<td>20a</td>
<td>8,8-Dimethyl 6H-pyran[3.2-g]chromen-2,7-dione 7-[O-(3,3-dimethyl acryloyl)-oxime]</td>
<td>341.36</td>
<td><img src="image3" alt="Structure3" /></td>
</tr>
<tr>
<td>42</td>
<td>21a</td>
<td>8,8-Dimethyl 6H-pyran[3.2-g]chromen-2,7-dione 7-[O-(cinnamoyl)-oxime]</td>
<td>389.40</td>
<td><img src="image4" alt="Structure4" /></td>
</tr>
<tr>
<td>43</td>
<td>21b</td>
<td>8,8-Dimethyl 6H-pyran[3.2-g]chromen-2,7-dione 7-[O-(4-methoxycinnamoyl)-oxime]</td>
<td>419.43</td>
<td><img src="image5" alt="Structure5" /></td>
</tr>
</tbody>
</table>

Table 13
Experimental Example 1. The effect on the release of MCP-1/IL-6/IL-8 induced by mite in THP-1 cell

To determine the inhibitory effect of the decursin derivatives prepared in Examples on the release of MCP-1/IL-6/IL-8 induced by mite in THP-1, following experiment using by human acute monocyctic leukemia cell line (THP-I; American Type Culture Collection (Manassas, VA, USA)) was performed and the result was determined by ELISA method pursuant to the manufacture’s manual (BD bioscience).

The THP-I cell line prepared in Reference Example was distributed to 24 well plates containing RPMI medium including 0.5% FBS in a concentration of 2.0x10^6/ml and incubated in 5% CO incubator at 37 °C for 16 hours. After the incubation, 100μg/ml of the decursin derivatives prepared in Examples was added thereto and 1 microgram/ml of HDE was treated therewith for 24 hours. The level of MCP-1, IL-6 and IL-8 in the supernatant was determined by ELISA method and the result was shown in following Tables 14 and 15.
<table>
<thead>
<tr>
<th>compound</th>
<th>MCP-1 (pg/ml)</th>
<th>IL-6 (pg/ml)</th>
<th>IL-8 (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>347</td>
<td>147</td>
<td>2151</td>
</tr>
<tr>
<td>3a</td>
<td>51</td>
<td>29</td>
<td>1820</td>
</tr>
<tr>
<td>3b</td>
<td>75</td>
<td>62</td>
<td>2372</td>
</tr>
<tr>
<td>3c</td>
<td>ND*</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>3d</td>
<td>36</td>
<td>19</td>
<td>221</td>
</tr>
<tr>
<td>3e</td>
<td>138</td>
<td>106</td>
<td>2196</td>
</tr>
<tr>
<td>3f</td>
<td>524</td>
<td>177</td>
<td>2316</td>
</tr>
<tr>
<td>3g</td>
<td>361</td>
<td>135</td>
<td>2184</td>
</tr>
<tr>
<td>3h</td>
<td>354</td>
<td>122</td>
<td>2273</td>
</tr>
<tr>
<td>3i</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>5a</td>
<td>309</td>
<td>113</td>
<td>2190</td>
</tr>
<tr>
<td>5b</td>
<td>251</td>
<td>111</td>
<td>2307</td>
</tr>
<tr>
<td>5c</td>
<td>122</td>
<td>83</td>
<td>2158</td>
</tr>
<tr>
<td>8a</td>
<td>169</td>
<td>77</td>
<td>1784</td>
</tr>
<tr>
<td>8b</td>
<td>74</td>
<td>85</td>
<td>1903</td>
</tr>
<tr>
<td>8c</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>8d</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>8e</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>8f</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>8g</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>8h</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>8i</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>8j</td>
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<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>8k</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>8l</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>8m</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>8n</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

Table 14
At the result, the level of MCP-I, IL-6 and IL-8 in normal control group showed 31, 19 and 181 pg/ml respectively and those after the treatment of mite allergen were increased to 342, 148 and 2319 pg/ml respectively. However, those levels of MCP-I, IL-6 and IL-8 after the treatment of positive control (dexamethasone) were decreased to 29, 18 and 132 pg/ml respectively. The level of MCP-I after the treatment of test samples prepared in Examples, i.e., compounds 3d, 11a, 11c, 14c, 16a, and 23 was also decreased to the almost equivalent level to that in positive control group and the level of IL-6 after the treatment of test samples prepared in Examples, i.e., compounds 3d, 11a, 11c, 14c, 16a, and 23 was also decreased to the almost equivalent levels to that in positive control group. The level of IL-8 after the treatment of test samples prepared in Examples, especially, compounds 3d and 11c was also decreased to the almost equivalent level to that in positive control group. In summary, the test treatment group treated with compounds 3d, 11c, 14c, 16a, 18 and 23, decreased the levels of MCP-I, IL-6 and IL-8.

### Table: Concentration of MCP-I, IL-6, and IL-8

<table>
<thead>
<tr>
<th>Compound</th>
<th>MCP-I (pg/ml)</th>
<th>IL-6 (pg/ml)</th>
<th>IL-8 (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11a</td>
<td>37</td>
<td>35</td>
<td>1446</td>
</tr>
<tr>
<td>11b</td>
<td>102</td>
<td>118</td>
<td>1899</td>
</tr>
<tr>
<td>11c</td>
<td>28</td>
<td>19</td>
<td>122</td>
</tr>
<tr>
<td>11d</td>
<td>31</td>
<td>19</td>
<td>642</td>
</tr>
<tr>
<td>11e</td>
<td>37</td>
<td>59</td>
<td>1825</td>
</tr>
<tr>
<td>11f</td>
<td>38</td>
<td>40</td>
<td>1452</td>
</tr>
<tr>
<td>11g</td>
<td>44</td>
<td>39</td>
<td>1310</td>
</tr>
<tr>
<td>14a</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>14b</td>
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<td>2905</td>
</tr>
<tr>
<td>14c</td>
<td>33</td>
<td>30</td>
<td>2826</td>
</tr>
<tr>
<td>15a</td>
<td>41</td>
<td>27</td>
<td>1013</td>
</tr>
<tr>
<td>16b</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>17</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>18</td>
<td>53</td>
<td>38</td>
<td>1579</td>
</tr>
<tr>
<td>20a</td>
<td>188</td>
<td>111</td>
<td>2569</td>
</tr>
<tr>
<td>21a</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>21b</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>21c</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>21d</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>21e</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>22a</td>
<td>171</td>
<td>69</td>
<td>2714</td>
</tr>
<tr>
<td>22b</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>23</td>
<td>37</td>
<td>26</td>
<td>1721</td>
</tr>
<tr>
<td>Normal</td>
<td>31</td>
<td>19</td>
<td>181</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>342</td>
<td>148</td>
<td>2319</td>
</tr>
<tr>
<td>dexamethasone</td>
<td>29</td>
<td>18</td>
<td>132</td>
</tr>
</tbody>
</table>

### Experimental Example 2.

The effect on the release of MCP-...
1/IL-6/IL-8 induced by mite in EoL-I

To determine the inhibitory effect of the decursin derivatives prepared in Examples on the release of MCP-1/IL-6/IL-8 induced by mite in EoL-I cell, following experiment using by human eosinophil (eosinophilic leukemia cell; EoL-I; the RIKEN Bio Resource center (Tsukuba, Japan)) was performed and the result was determined by ELISA method pursuant to the manufacture's manual (BD bioscience).

The EoL-I cell line prepared in Reference Example was distributed to 24 well plates containing RPMI medium including 0.5% FBS in a concentration of 2.0x10^6/ml and incubated in 5% CO_2 incubator at 37 °C for 16 hours. After the incubation, 10 microgram/ml of the decursin derivatives prepared in Examples was treated therewith for 1 hour and 1 microgram/ml of HDE was treated therewith for 24 hours. The level of MCP-1, IL-6 and IL-8 in the supernatant was determined by ELISA method and the result was shown in following Tables 16 and 17.

Table 16

<table>
<thead>
<tr>
<th>compound</th>
<th>MCP-1 (pg/ml)</th>
<th>IL-6 (pg/ml)</th>
<th>IL-8 (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>198</td>
<td>312</td>
<td>449</td>
</tr>
<tr>
<td>3a</td>
<td>111</td>
<td>235</td>
<td>1846</td>
</tr>
<tr>
<td>3b</td>
<td>129</td>
<td>2177</td>
<td></td>
</tr>
<tr>
<td>3c</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>3d</td>
<td>72</td>
<td>39</td>
<td>534</td>
</tr>
<tr>
<td>3e</td>
<td>182</td>
<td>304</td>
<td>3911</td>
</tr>
<tr>
<td>3f</td>
<td>311</td>
<td>321</td>
<td>1410</td>
</tr>
<tr>
<td>3g</td>
<td>304</td>
<td>281</td>
<td>1404</td>
</tr>
<tr>
<td>3h</td>
<td>391</td>
<td>219</td>
<td>1073</td>
</tr>
<tr>
<td>3i</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>5a</td>
<td>302</td>
<td>277</td>
<td>1426</td>
</tr>
<tr>
<td>5b</td>
<td>466</td>
<td>320</td>
<td>1783</td>
</tr>
<tr>
<td>5c</td>
<td>238</td>
<td>208</td>
<td>1388</td>
</tr>
<tr>
<td>8a</td>
<td>208</td>
<td>566</td>
<td>1627</td>
</tr>
<tr>
<td>8b</td>
<td>138</td>
<td>401</td>
<td>1173</td>
</tr>
<tr>
<td>8c</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>8d</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>8e</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>8f</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>8g</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>8i</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>8k</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>8l</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>8m</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>8n</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

Table 17
At the result, the level of MCP-I, IL-6 and IL-8 in normal control group showed 91, 73 and 403 pg/ml respectively and those after the treatment of mite allergen were increased to 247, 281 and 812 pg/ml respectively. However, those levels of MCP-1, IL-6 and IL-8 after the treatment of positive control (dexamethasone) were decreased to 73, 69 and 361 pg/ml respectively. The level of MCP-I after the treatment of test samples prepared in Examples, i.e., compounds 3d, lla-e, 14b-c, 18 and 23 was also decreased to the almost equivalent level to that in positive control group and the level of IL-6 after the treatment of test samples prepared in Examples, i.e., compounds 3d and lie was also decreased to the almost equivalent levels to that in positive control group. The level of IL-8 after the treatment of test samples prepared in Examples, especially, compounds 3d, lie and 28 was also decreased to the almost equivalent level to that in positive control group. In summary, the test treatment group treated with compounds 3d, lie, and 23, decreased the levels of MCP-I, IL-6 and IL-8.

Hereinafter, the formulating methods and kinds of exquisients will be described, but
the present invention is not limited to them. The representative preparation examples were described as follows.

[579]

[580] The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the present invention, and all such modifications as would be obvious to one skilled in the art are intended to be included within the scope of the following claims.

[581]

[582] Hereinafter, the formulating methods and kinds of excipients will be described, but the present invention is not limited to them. The representative preparation examples were described as follows.

[583]

[584] Preparation of powder

[585] Compound (lie) 20mg

[586] Lactose 100mg

[587] Talc 10mg

[588] Powder preparation was prepared by mbdng above components and filling sealed package.

[589]

[590] Preparation of tablet

[591] Compound (lie) 10mg

[592] Com Starch 100mg

[593] Lactose 100mg

[594] Magnesium Stearate 2mg

[595] Tablet preparation was prepared by mbng above components and entablettig.

[596]

[597] Preparation of capsule

[598] Compound (lie) 10mg

[599] Corn starch 100mg

[600] Lactose 100mg

[601] Magnesium Stearate 2mg

[602] Tablet preparation was prepared by mbing above components and filling gelatin capsule by conventional gelatin preparation method.

[603]

[604] Preparation of injection
Compound (1c) 10mg
Distilled water for injection optimum amount
PH controller optimum amount
Injection preparation was prepared by dissolving active component, controlling pH to about 7.5 and then filling all the components in 2ampule and sterilizing by conventional injection preparation method.

Preparation of liquid
Compound (lie) 20mg
Sugar 5~10g
Citric acid 0.05-0.3%
Caramel 0.005-0.02%
Vitamin C 0.1-1%
Distilled water 79-94%
CO₂ gas 0.5-0.82%
Liquid preparation was prepared by dissolving active component, filling all the components and sterilizing by conventional liquid preparation method.

Preparation of health care food
Compound (11c) 1000mg
Vitamin mixture optimum amount
Vitamin A acetate 70mg
Vitamin E 1.0mg
Vitamin B₁ 0.13mg
Vitamin B₂ 0.15mg
Vitamin B₆ 0.5mg
Vitamin B₁₂ 0.2mg
Vitamin C 10mg
Biotin 10mg
Amide nicotinic acid 1.7mg
RBIK aid 50mg
Calcium pantothenic acid 0.5mg
Mineral mixture optimum amount
Ferrous sulfate 1.75mg
[637] Zinc oxide 0.82mg
[638] Magnesium carbonate 25.3mg
[639] Monopotassium phosphate 15mg
[640] Dicalcium phosphate 55mg
[641] Potassium citrate 90mg
[642] Calcium carbonate 100mg
[643] Magnesium chloride 24.8mg
[644] The above-mentioned vitamin and mineral mixture may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the present invention.

[645]

[646] Preparation of health beverage

[647] Compound (1c) 1000mg
[648] Citric acid 1000mg
[649] Oligosaccharide 100g
[650] Apricot concentration 2g
[651] Taurine 1g
[652] Distilled water 900mL

[653] Health beverage preparation was prepared by dissolving active component, mg, stirred at 85°C for 1 hour, filtered and then filling all the components in 1000mL ample and sterilizing by conventional health beverage preparation method.

[654]

[655] The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the present invention, and all such modifications as would be obvious to one skilled in the art are intended to be included within the scope of the following claims.

[656] Industrial Applicability

[657] As described in the present invention, the novel decursin derivatives of the present invention showed potent inhibiting activity of the release of MCP-1, IL-6 and IL-8 induced by dermite in THP-1 or EoL-1 cell, therefore the compounds can be useful in treating or preventing atopic dermatitis.
Claims

[1] A novel compound represented by the following general formula (I), or the pharmaceutically acceptable salt thereof:

![Chemical structure image]

wherein
- A is hydrogen atom, C₁⁻C₄ lower alkyl group, dialkyl acryloyl group or cinnamoyl group of which phenyl group is unsubstituted or substituted with R';
- R' is optionally substituted at o-, m- and p- position with at least one selected from the group consisting of a hydrogen atom, hydroxyl group, acetate group, halogen atom, C₁⁻C₄ lower alkyl group, lower alkoxy group, lower alkyl ester, and lower alkyl carboxy group.

[2] The compound according to claim 1, wherein A is hydrogen atom, methyl group, dimethyl acryloyl group or cinnamoyl group of which phenyl group is unsubstituted or substituted with R'; wherein R' is optionally substituted with at least one selected from the group consisting of a hydrogen atom, methyl group, methoxy group and acetate group.

[3] The compound according to claim 2, wherein said compound is selected from the group consisting of:
- 8,8-dimethyl-6 H-pyrano[3,2-g]chromen-2,7-dione 7-oxime, 8,8-dimethyl-6 H-pyrano[3,2-g]chromen-2,7-dione 7-[0-(3,3-dimethylacryloyl)oxime],
- 8,8-dimethyl-1-6 H-pyrano[3,2-g]chromen-2,7-dione 7-(0-cinnamoyl-oxime),
- 8,8-dimethyl-6 H-pyrano[3,2-g]chromen-2,7-dione 7-[O-(4-methoxycinnamoyl)-oxime], 8,8-dimethyl-6 H-pyrano[3,2-g]chromen-2,7-dione 7-[0-(3,4,5-trimethoxyrinnamoyl)-oxime],
- 8,8-dimethyl-6 H-pyrano[3,2-g]chromen-2,7-dione 7-[O-(3,4-acetoxycinnamoyl)-oxime], and
- 8,8-dimethyl-6 H-pyrano[3,2-g]chromen-2,7-dione 7-[O-(3,4-diacetoxycinnamoyl)-oxime].

[4] A pharmaceutical composition comprising decursin derivative represented by
general formula (I) as set forth in claim 1 as an active ingredient in an amount effective to prevent and treat atopic dermatitis, together with a pharmaceutically acceptable carrier by inhibiting the release of MCP-I, IL-6 and IL-8 induced by mites.

[5] A novel compound represented by the following general formula (II), and the pharmaceutically acceptable salt thereof:

![Chemical Structure](image)

Wherein,

B is selected from the group consisting of hydrogen atom, hydroxyl group, C₁⁻⁴ lower alkyl group, C₁⁻⁴ lower alkoxy group, halogen atom, and 5- or 6-membered heterocyclic ring unsubstituted or substituted with C₁⁻³ lower alkyl group or C₁⁻³ lower alkoxy group.

[6] The compound according to claim 5, wherein B is selected from the group consisting of methyl group, halogen atom, C₁⁻³ lower alkyl group, C₁⁻³ lower alkoxy group and phenyl group.

[7] The compound according to claim 6, wherein said compound is selected from the group consisting of: methane sulfonic acid 2,2-dimethyl-8-o?D-3,4-dihydro-2 H₈H-pyran[3,2-g] chromen-3-yl-ester, and benzene sulfonic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2 H₈H-pyran[3,2-g]chromen-3-yl-ester.

[8] A pharmaceutical composition comprising decursin derivative represented by the following general formula (III) as an active ingredient in an amount effective to prevent and treat atopic dermatitis, together with a pharmaceutically acceptable carrier by inhibiting the release of MCP-I, IL-6 and DL-8 induced by mites:
wherein
R_i is C_{1-20} alkyl group, C_{2-20} alkenyl group, C_{2-20} alkynyl group unsubstituted or substituted with at least one R'; or A group; of which R' is halogen atom, nitro group, amine group or C_{1-4} lower alkyl group; and

A group is

wherein
A is at least one optionally at o-, m- or p- position, selected from the group consisting of a hydrogen atom, hydroxyl group, acetate group, halogen atom, C_{1-4} lower alkyl group, C_{1-4} lower alkoxy group and C_{1-4} lower alkyl ester group;

n is an integer of 0 to 4.

[9] The composition according to claim 8, wherein R is halogen atom or C_{1-10} alkyl group, C_{1-10} alkenyl group, C_{1-10} alkynyl group unsubstituted or substituted with C_{1-4} lower alkyl group or A group; of which A is at least one optionally at o-, m- or p- position, selected from group consisting of a hydrogen atom, hydroxyl group, methyl group, ethyl group, methoxy group, ethoxy group and acetyl group; n is an integer of 0 to 1.

[10] The composition according to claim 9, wherein said compound is one selected from the group consisting of;

3-Methyl-but-2-enio acid, 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester, C_{6s}-2-Methyl-but-2-enio acid
2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester, Trans-2-Methyl-but-2-enio acid, 2,2-dimethyl-8-oxo-3,4-dihydro-2tf,S-pyrano[3,2-g]chromen-3-yl-ester, 2-methyl-acrylic acid, 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester, Pent-2-enio acid
2,2-dimethyl-8-o>o-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester, But-3-enio acid, 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester, Pent-4-enio acid, 2,2-dimethyl-8cx)-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester, Acetic acid, 2,2-dimethyl-8-oxo-3,4-dihydro-2H,8H-pyrano[3,2-g]chromen-3-yl-ester.
pyrano[3,2- g]chromen-3-yl-ester, Chloro-acetic acid
2,2-dimethyl-8-oxo-3,4-dihydro-
2H,8H-pyrano[3,2- g]chromen-3-yl-ester,
Trichloro-acetic acid add 2,2-dimethyl-8-oxo-3,4-dihydro-
2H,8H-pyrano[3,2- g]chromen-3-yl-ester,
Pentanoic acid 2,2-dimethyl-8-oxo-3,4-dihydro-
2H,8H-pyrano[3,2- g]chromen-3-yl-ester, Decanoic acid
2,2-dimethyl-8-oxo-3,4-dihydro-
2H,8H-pyrano[3,2- g]chromen-3-yl-ester,
3-phenyl-acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro-
2H,8H-pyrano[3,2- g]chromen-3-yl-ester,
3-(4-methoxy-phenyl)-acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro-
2H,8H-pyrano[3,2- g]chromen-3-yl-ester,
3-(4-hydroxy-phenyl)-acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro-
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2H,8H-pyrano[3,2- g]chromen-3-yl-ester,
3-(4-nitro-phenyl)-acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro-
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3-(3-hydroxy-phenyl)-acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro-
2H,8H-pyrano[3,2- g]chromen-3-yl-ester,
3-(3-acetoxy-phenyl)-acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro-
2H,8H-pyrano[3,2- g]chromen-3-yl-ester,
3-(3,4-dihydroxy-phenyl)-acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro-
2H,8H-pyrano[3,2- g]chromen-3-yl-ester,
3-(4-acetoxy-3-methoxy-phenyl)-acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro-
2\text{H} \cdot \text{S}\text{H}-\text{pyrano}\{3,2-\text{g}\}\text{chromen}-3\text{-yl-ester},

3-(4-acetoxy-3,4-dimethoxy-phenyl)-acrylic acid 2,2-dimethyl-8-oxo-3,4-dihydro-
2\text{H} \cdot \text{S}\text{H}-\text{pyrano}\{3,2-\text{g}\}\text{chromen}-3\text{-yl-ester},

Benzoic acid 2,2-dimethyl-8-oxo-3,4-dihydro-
2\text{H} \cdot \text{S}\text{H}-\text{pyrano}\{3,2-\text{g}\}\text{chromen}-3\text{-yl-ester},

3,4,5-trihydroxy-benzoic acid 2,2-dimethyl-8-oxo-3,4-dihydro-
2\text{H} \cdot \text{S}\text{H}-\text{pyrano}\{3,2-\text{g}\}\text{chromen}-3\text{-yl-ester} and
3,4,5-triacetoxy-benzoic acid 2,2-dimethyl-8-oxo-3,4-dihydro-
2\text{H} \cdot \text{S}\text{H}-\text{pyrano}\{3,2-\text{g}\}\text{chromen}-3\text{-yl-ester}.

[11]
A pharmaceutical composition comprising decursin derivative represented by the following general formula (IV) as an active ingredient in an amount effective to prevent and treat atopic dermatitis, together with a pharmaceutically acceptable carrier by inhibiting the release of MCP-I, IL-6 and IL-8 induced by mites:

![Chemical Structure](image)

Wherein,
C is a hydrogen atom, C-\text{1} \cdot \text{C} lower alkyl group or ketone group.

[12]
The composition according to claim 11, wherein C is at least one selected from the group consisting of a hydrogen atom or ketone group.

[13]
The composition according to claim 12, wherein said compound is one selected from the group consisting of;
8,8-dimethyl- \text{S}\text{H}-\text{pyrano}\{3,2-\text{g}\}\text{chromen}-2\text{-one},
8,8-dimethyl- \text{S}\text{H}-\text{pyrano}\{3,2-\text{g}\}\text{chromen}-2\text{-one}.

[14]
A health functional food comprising decursin derivative represented by general formula (T), (TT), (III) or (FV) for the prevention or improvement of atopic dermatitis by inhibiting the release of MCP-I, IL-6 and IL-8 induced by mites as an active ingredient in an amount effective to preventing and improving atopic dermatitis.

[15]
The health care food according to claim 14, the health care food is a form of powder, granule, tablet, capsule or beverage.

[16]
A use of decursin derivative represented by general formula (T), (II), (III) or (TV) for the preparation of for manufacture of medicament employed for preventing
or treating atopic dermatitis in human or mammal.

[17] A method for treating atopic dermatitis by inhibiting the release of MCP-I, IL-6 and CL-8 induced by mites in a mammal comprising administering to said mammal an effective amount of decursin derivative represented by general formula (I), (II), (III) or (IV), together with a pharmaceutically acceptable carrier thereof.
INTERNATIONAL SEARCH REPORT

PCT/KR2008/001017

A. CLASSIFICATION OF SUBJECT MATTER

C07D 493/04(2006.01)

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 as above

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)
eKIPASS, STN(REG, CA)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<td>KR 2006-0078344 A (CHOL, S O et al) 05 JULY 2006 See claims 1-14</td>
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<td>A</td>
<td>KR 2002-0073624 A (KOREA CHUNGANG EDUCATIONAL FOUNDATION) 28 SEPTEMBER 2002 See abstract and claims 1-2</td>
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<td>WO 00/023074 A1 (CHONG, S Y et al) 27 APRIL 2000 See abstract and claims 1-8</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
  "E" earlier application or patent but published on or after the international filing date
  "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
  "O" document referring to an oral disclosure, use, exhibition or other means
  "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search 28 MAY 2008 (28 May 2008)

Date of mailing of the international search report 28 MAY 2008 (28.05.2008)

Name and mailing address of the ISA/KR

Korean Intellectual Property Office
Government Complex-Daejeon, 139 Seonsa-ro, Seo-gu, Daejeon 302-701, Republic of Korea

Facsimile No 82-42-472-7140

Authorized officer

KOH, Tae Woog

Telephone No 82-42-481-5605

Form PCT/ISA/210 (second sheet) (April 2007)
**INTERNATIONAL SEARCH REPORT**

**International application No**

PCT/KR2008/001017

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<td>Claim 17 pertains to methods for treatment of the human or animal body by therapy as well as diagnostic methods, and thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39 l(iv) of the Regulations under the PCT, to search</td>
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**Remark on Protest**

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation
- No protest accompanied the payment of additional search fees

Form PCT/ISA/210 (continuation of first sheet (2)) (April 2007)
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