A NOVEL SALICYLIC ACID-MALTOL CONJUGATES

The present invention relates to a novel salicylic acid-maltol conjugates of formula (I), wherein R represents H, alkyl groups containing C1-5 carbon atoms or alkanoyl groups containing C1-5 carbon atoms. R1 represents H or alkyl groups containing C1-5 carbon atoms. A novel maltol esters of salicylic acid derivatives exhibit antioxidant and antithrombotic activities to a greater extent than salicylic acid derivatives.
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SPECIFICATION

1. Title of the Invention

A novel salicylic acid – maltol conjugates

2. Brief Description of the Drawings

5

Fig. 1 illustrates the NMR spectrum of maltol-acetylsalicylate ester;

Fig. 2 illustrates the NMR spectrum of maltol-salicylate ester; and

Fig. 3 illustrates the antipyretic effect of the compound described in Example 1.

3. Detailed Description of the Invention

10

The present invention relates to a novel salicylic acid-maltol conjugates

of the formula I and methods for preparing I.

\[
\text{OR}
\begin{array}{c}
\text{C} \\
\text{O} \\
\end{array}
\]

\[
\text{I}
\begin{array}{c}
\text{O} \\
\text{R}_1 \\
\end{array}
\]

wherein \( R \) represents \( H, \) alkyl groups containing \( C_1-5 \) carbon atoms or

alkanoyl groups containing \( C_1-5 \) carbon atoms. \( R_1 \) represents \( H \) or alkyl groups.
containing C1-5 carbon atoms.

Acetylsalicylic acid (aspirin) shows antipyretic, antianalgesic, antioxidant and antithrombotic activities. However, it induces gastric ulceration.

Maltol derivatives II are components of *Panax ginseng* and their structures are as follows:

\[
\begin{align*}
\text{OH} \quad \text{(II)} \\
\hline
\text{R}_1
\end{align*}
\]

wherein \( \text{R}_1 \) is as previously defined.

Maltol derivatives have been shown to exhibit antioxidant activities. Salicylic acid has been used as a keratolytic agent and a food preservative.

The present invention follows the observations that the novel maltol esters of salicylic acid derivatives show no salicylate-induced gastric ulceration activity, whereas exhibit antioxidant and antithrombotic activities to a greater extent than salicylic acid derivatives.

Therefore, the purpose of the presented invention is to provide the novel of the formula I which exhibit aforementioned pharmacological activities and little side effects.

The present invention also provides the synthetic methods of compounds
1. Compounds of the formula I are prepared with esterification of maltol derivatives II and salicylic acid derivatives III as follows:

\[
\text{(III)} \quad + \quad \text{(II)} \quad \rightarrow \quad \text{(I)}
\]

wherein \( R \) and \( R_1 \) are as described above and \( M \) is \(-H\) or an alkali metal.

The esterification of II with III can be done in the presence of either alkyl halides such as chloroform, methylenechloride and ethylenechloride, or amides such as formamide and acetamide, or ethers such as tetrahydrofuran and dioxane, or other organic solvents.

It is desirable to activate the carboxyl group of III. The activation can be achieved by treating III with halogenation agents to make acid halides or by other well-known methods used in organic synthesis.

The reaction of II with III which contains a carboxyl group can be
carried out in the presence of diamines such as N,N-dicyclohexylcarbodiimide or other esterification agents used in organic synthesis.

In case free acids are produced in the activation of the carboxyl group, the esterification should be conducted in the presence of tertiary amines or alkalis to remove the free acids.

The reaction is proceeded at the temperature ranging from 0°C to the b.p. of the solvent employed. The reaction usually goes to completion in 30 min to 48 hrs.

The present invention will now be described with the following examples and tests.

EXAMPLE 1

Acetylsalicylic acid (18.0 g, 0.10 mole), maltol (12.6 g, 0.10 mole), N,N-dicyclohexylcarbodiimide (22.7 g, 0.11 mole) were dissolved in 100 ml of methylenechloride and the solution was stirred for 6hrs at room temperature.

After removing N,N-dicyclohexylurea by filtration, the filtrate was washed sequentially with water, 5% acetic acid and water. The solution was then dried with Na₂SO₄. Following filtration and concentration, the needle crystal of maltol-acetylsalicylate ester (compound A) was obtained in n-hexane/ethanol (1:3). NMR spectrum is shown in Fig.1.
mp: approximately 105°C.

MS [m/z]: 288(M⁺), 246(C₁₃H₁₃O₆), 121(C₇H₅O₂).

¹H NMR (CDCl₃) [δ ppm]: 8.21(1H, dd, J=1.9, 7.7), 8.07(1H, d, J=5.7),
7.74(1H, dt, J=1.9, 7.7), 7.43(1H, dt, J=1.3, 7.7), 7.24(1H, dd, J=1.3,
7.7) 6.48(1H, d, J=5.6), 2.32(3H, s), 2.25(3H, s).

EXAMPLE 2

Maltol-salicylate ester was obtained following the method of EXAMPLE 1.

NMR spectrum is shown in Fig. 2.

mp: approximately 99°C

EXAMPLE 3

ENZYMATIC METHOD OF MALTOL-SALICYLATE ESTER PREPARATION

An aceton powder (1.8 g) of rat livers was suspended in 50ml of 0.1 M
phosphate buffer (pH 7.4) and stirred for 12 hrs at 4°C. The resulting
suspension was centrifuged at 8,000 rpm for 5 min. To 10ml of supernatant thus
obtained was added 30 ml of 10% Tween-30 solution containing maltol-
acetylsalicylate ester. The mixture was incubated at 37°C for 1 hr, and
extracted twice with 30 ml of CHCl₃. The extracts were then added and
concentrated to dryness. The dried residue was dissolved in 5 ml of methanol
and allowed to stand at 4°C. Following filtration, 200 mg of maltol-salicylate ester was obtained as the needle crystal. NMR spectrum was equivalent to that obtained in EXAMPLE 2.

TEST 1

5 DETERMINATION OF ANTIOXIDANT ACTIVITY

Animal: male ICR mouse weighing 20-25g

Sample: Compound A.

References: 1. Maltol (10% DMF saline)

2. Aspirin (10% DMF saline).

10 TBA reagents: Thiobarbituric acid (0.3%) and SDS (0.4%) were dissolved in 7.5% acetate buffer (pH 4.0)

Experimental procedures:

Antioxidant activities were determined following the method of Okawa et al. (Biochemistry (Japan) (1977), 49(8), 829). Mouse livers were homogenized with ten volumes of saline. To 10 ml of homogenize was added 10 ml of the sample solution, and the mixture was incubated at 37°C for 3 hrs. Then 3.6 ml of TBA reagents were added to the mixture and the resulting mixture was heated at 98°C for 1 hr. After the temperature was reduced to 24°C, the reaction mixture was extracted with 2 ml of butanol and the butanol phase was separated by centrifugation.
The absorbance at 532 nm of the butanol phase was measured. The results are shown in Table 1. Compound A exhibited antioxidant activity at concentrations higher than $2.5 \times 10^{-5}$ M.

**TABLE I**

Antioxidant Activities of Maltol, Aspirin and Maltol–Acetylsalicylate ester (Compound A). % Inhibition of Malondialdehyde (MDA) Generation in Mouse Liver Homogenate (in vitro)

<table>
<thead>
<tr>
<th>Final Concentration (M)</th>
<th>Maltol</th>
<th>% Inhibition Aspirin</th>
<th>Compound A</th>
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<tbody>
<tr>
<td>$1.3 \times 10^{-5}$</td>
<td>5.2 ± 2.6</td>
<td>-</td>
<td>4.3 ± 2.1</td>
</tr>
<tr>
<td>$6.3 \times 10^{-5}$</td>
<td>13.4 ± 6.7</td>
<td>4.6 ± 2.3</td>
<td>2.3 ± 1.1</td>
</tr>
<tr>
<td>$2.5 \times 10^{-4}$</td>
<td>94.8 ± 2.6</td>
<td>0.8 ± 0.4</td>
<td>58.9 ± 7.0</td>
</tr>
<tr>
<td>$2.5 \times 10^{-3}$</td>
<td>99.4 ± 0.3</td>
<td>8.4 ± 4.2</td>
<td>91.9 ± 4.1</td>
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</table>

**TEST 2**

**DETERMINATION OF ANTIPYRETIC ACTIVITY**

Animal: Male ICR mouse weighing 17–21 g (5 mice as a group).

Sample: Compound A (160 mg/kg, 500 mg/kg in 1% CMC).

Reference: Aspirin (100 mg/kg in 1% CMC).

Pyrogen: Typhoid vaccine (0.1 ml/mouse, i.p.).

Experimental procedures:

Antipyretic activities were measured according to Winter et al. with
some modifications (Winter, C.A. et al. (1963), J. Pharmacol Exptl. Therap., 141, 369). Rectal temperature was measured using digitalized thermometer inserted 3 cm deep at one hr intervals. Typhoid vaccine was injected to mouse i.p. at zero time. After 2 hrs, aspirin and sample (compound in EXAMPLE 1) were orally given to mouse.

As shown in Fig. 3, the antipyretic potency of compound A was five times lower than that of aspirin.

TEST 3

A DETERMINATION OF ANTIINFLAMMATORY ACTIVITY BY CARRAGEEIN-INDUCED EDEMA TEST

Animal: Male Sprague Dawley rats weighing approx. 170g (5 rats as a group).

Sample: Compound A (300 mg/kg, 450 mg/kg in 1% CMC).

Reference: Phenylbutazone (100 mg/kg in 1% CMC)

Medication: Oral administration.

Experimental procedures:

The inhibitions of Carrageenin-induced edema by compound A and aspirin was measured according to Winster et al. (Winter, C.A., Risley, E.A. and Nuss, G.W. (1963), J. Pharmacol. Exptl. Therap., 141, 369). Samples were administered orally at 6 hrs and 30 min before Carrageenin injection. Edema was induced with subcutaneous injection of 0.05 ml of 1% Carrageenin in saline solution in a hind paw of rat. Then, the volume of edema was measured at time intervals.
results are shown in Table II. It was determined that compound A had no anti-
inflammatory effect when used at doses of 300 and 450 mg/kg.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose mg/kg</th>
<th>No. of P.O. Animals</th>
<th>% Increment of Edema (mean ± S.E)</th>
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<tbody>
<tr>
<td>Control</td>
<td>CMC</td>
<td>5</td>
<td>28.1±6.48 48.0±7.51 55.9±7.73 74.6±24.06 73.4±28.53</td>
</tr>
<tr>
<td>Phenylbutazone</td>
<td>100</td>
<td>4</td>
<td>11.8±6.26 20.9±6.88 21.9±9.22 36.2±14.45 42.5±6.35</td>
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<tr>
<td>Compound A</td>
<td>300</td>
<td>5</td>
<td>46.5±13.98 51.2±9.47 56.1±11.50 69.4±13.89 81.9±9.96</td>
</tr>
<tr>
<td>Compound A</td>
<td>400</td>
<td>4</td>
<td>20.3±6.85 33.8±3.19 50.2±6.43 58.4±6.09 66.2±8.52</td>
</tr>
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</table>

B. DETERMINATION OF PROTEIN STABILIZING ACTIVITY

Sample: Compound A (1 x 10⁻³ M in 5% DMF solution

Experimental procedures:

The protein stabilizing activity of the sample was analyzed as described by Mizushima (Mizushima, Y. (1965), Lancet, 1, 169). Briefly, 2 ml of 0.75% BSA in 0.1M phosphate-buffered saline (pH 5.3) was mixed with 1 ml of appropriately diluted test sample solution. After standing at room temperature for 15 min, the reaction mixture was incubated at 66.5°C and 0°C for 3 min and 15 min, respectively. The degree of heat denaturation of BSA was estimated by the
turbidity of colloidal precipitate, whose absorbance at 570 nm was measured.

The results indicated that compound A did not contain protein stabilizing activity (data not shown).

C. DETERMINATION OF ANTITHROMBOTIC ACTIVITY

Animal: Male Sprague Dawley rats weighing 180-250g.

Sample: Compound A (1 x 10^{-3} M) in 5% DMF solution.

Experimental procedures:

Rats were anaesthetized with ether and 9 volumes of blood were collected by heart puncture with 1 volume of 3.12% sodium citrate. Combined blood samples were centrifuged at 1,200 rpm for 20 min at 4°C to obtain platelet-rich plasma.

Following centrifugation at 3,000 rpm for 10 min at 4°C, the resulting precipitates (platelets) were resuspended in 0.01 M phosphate-buffered saline (pH 7.4). To 1 ml of this solution was added 0.1 ml of the sample solution. After 30 min incubation at 37 °C, 10 units of thrombin was added and the reaction mixture was incubated for 1 hr. The platelet aggregation was observed with naked eyes. Compound A (1 x 10^{-3} M) showed no antithrombotic activity.

TEST 4

GASTRIC ULCERATION EXPERIMENT

Animal: Male Sprague Dawley rats weighing 160-210 g (6 rats as a group).

Sample: Compound A (100 mg/kg, 200 mg/kg, 800 mg/kg in 1% CMC).
Reference: Aspirin (200 mg/kg in 1% CMC).

Medication: Oral administration.

Experimental procedures:

The experiments of gastric ulceration were carried out according to Murakami et al. (Murakami, M. et al. (1982), Jap. J. Pharmacol., 32, 299).

Rats were deprived of food but allowed free access to water for 24 hrs (water was removed 2 hrs before experiments). Samples suspended in 1% CMC solution were removed. The stomachs were then inflated by injecting 10 ml of 2% formalin through the esophageal orifice and immersed in 2% formalin for 10 min.

Subsequently, the stomachs were incised along the greater curvature and the length of each lesion in the glandular portion was measured. The sum of the lengths (mm) of all lesions for each rat was used as the ulcer index. The results are shown in Table III.

Table III

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose (mg/kg)</th>
<th>No. of Animals</th>
<th>Ulcer Index (mm) (mean ± S.E.)</th>
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<tbody>
<tr>
<td>Control</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>Aspirin</td>
<td>200</td>
<td>5</td>
<td>29.3 ± 6.15 (5/5)</td>
</tr>
<tr>
<td>Compound A</td>
<td>100</td>
<td>5</td>
<td>0</td>
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<tr>
<td>Compound A</td>
<td>200</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>compound A</td>
<td>800</td>
<td>6</td>
<td>0.7 ± 0.61 (1/6)</td>
</tr>
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</table>
The number in parenthesis indicates the number of rats that exhibited gastric ulcer.

The results indicated that compound A did not cause gastric ulcer at 5 times higher dose than aspirin.

5 TEST 5

DETERMINATION OF THE BLEEDING TIME

To the experimental groups, equivalent doses of compound A and aspirin were administered separately for 10 days.

As shown Table IV, compound A prolonged the bleeding time by 50%.

Table IV

The Effects of Aspirin and Compound A on the Bleeding Time

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose (mg/kg)</th>
<th>No. of Animals</th>
<th>Bleeding Time Days</th>
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<tr>
<td></td>
<td>P.O. 2 4 6 8 10</td>
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<tr>
<td>Control</td>
<td>0</td>
<td>7-9</td>
<td>238.3±45.6 388.2±33.8 391.1±38.9 339.1±54.5 314.8±42.3</td>
</tr>
<tr>
<td>Aspirin</td>
<td>15</td>
<td>7-9</td>
<td>353.5±74.7 372.7±50.1 516.6±119.4 493.6±88.6 441.9±46.2</td>
</tr>
<tr>
<td>Compound A</td>
<td>15</td>
<td>6-9</td>
<td>339.6±53.9 396.9±56.0 429.4±50.6 518.3±102.8 472.1±57.4</td>
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<td>45</td>
<td>8</td>
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The number in parenthesis indicates percent increment.
* Significance, P < 0.05

20 TEST 6

ACUTE TOXICITY TEST
When administered orally, compound A showed little toxicity in mouse (LD$_{50}$=2.14 g/kg).

In conclusion, the compound described in the present invention exhibited an antioxidant activity at concentrations higher than $2.5 \times 10^{-4}$ M and an equivalent antipyretic activity at five times higher dose compared to aspirin.

On the other hand, compound A showed little side effects as it did not cause gastric ulceration, whereas aspirin at four times lower dose caused ulceration.

Therefore, the compound described in the present invention is a new acetylsalicylate derivative which sustains the antioxidant activity of the maltol derivatives and exhibits the antipyretic and antiinflammatory activities.
4. What is claimed is:

1. A compound of the following formula I

![Chemical Structure](image)

\[ \text{wherein } R \text{ represents } H, \text{ alkyl groups containing } C_1-6 \text{ carbon atoms or alkanoyl groups containing } C_1-6 \text{ carbon atoms, } R_1 \text{ represents } H \text{ or alkyl groups containing } C_1-6 \text{ carbon atoms.} \]

2. A method of preparing a compound of the formula I

![Chemical Structure](image)

\[ \text{wherein } R \text{ represents } H, \text{ an alkyl group containing } C_1-6 \text{ carbon atoms or an alkanoyl group containing } C_1-6 \text{ carbon atoms and } R_1 \text{ represents } H \text{ or an alkyl group containing } C_1-6 \text{ carbon atoms.} \]

by reacting a compound of the formula II
5 wherein \( R \) is defined above,

or their activated derivatives with a compound of the formula III

10 wherein \( R \) is defined above,

or their activated derivatives.

3. A method preparing a compound of the formula I

wherein \( R \) represents hydrogen atom and \( R_1 \) represents \( H \) or an alkyl group.
containing C<sub>1</sub>–<sub>5</sub> carbon atoms,

by enzymatic hydrolysis of a compound of the formula I

wherein R represents an alkyl group containing C<sub>1</sub>–<sub>5</sub> carbon atoms.
FIG. 3

Temp. (°C)

37.0
36.0
35.0

1 0 1 2 3 4 5 6
hrs

I  Control
II  Aspirin  100 mg/kg
III  Compound A  500 mg/kg
### INTERNATIONAL SEARCH REPORT

**International Application No.** PCT/KR 91/00015

### I. CLASSIFICATION OF SUBJECT MATTER

According to International Patent Classification (IPC) or to both National Classification and IPC

| Int. Cl. 5: | C 07 D 309/40 // A 61 K 31/35 |

### II. FIELDS SEARCHED

**Minimum Documentation Searched**

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**Documentation Searched other than Minimum Documentation**

to the extent that such documents are included in the fields searched.

### III. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>EP, A2, 0 339 454 (L. GIVAUDAN &amp; CIE Société Anonyme) 02 November 1989 (02.11.89), see claim 1; formula III.</td>
<td>(1-3)</td>
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**References:**

* **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 document 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 another 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
  - **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.
  - **A** document member of the same patent family

### IV. CERTIFICATION

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**International Searching Authority:**

AUSTRIAN PATENT OFFICE

**Signature of Authorized Officer:**

[Signature]

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