CONVENTION APPLICATION FOR A PATENT

(This form may be signed by the applicant or by the Australian Patent Attorney)

Insert full name(s) and address(es) of applicant(s)

SANDOZ LTD., of Lichtstrasse 35, CH-4002 BASEL, Switzerland,

hereby apply for the grant of a Patent for an invention entitled

"IMPROVEMENTS IN OR RELATING TO ORGANIC COMPOUNDS"

which is described in the accompanying complete specification. The application is a Convention application and is based on the application(s) for patent or similar protection made in SWITZERLAND

on 12th March, 1975 under No. 3129/75
24th July, 1975 under No. 9678/75

APPLICATION ACCEPTED AND AMENDED

ALLOEED

Our address for service is care of DAVIES & COLLISON, Patent Attorneys, of Cromwell Building, 374 Bourke Street, Melbourne, in the State of Victoria Commonwealth of Australia.

Dated this 11th day of March, 1976.

(a) Signature(s) of applicant(s).
If a Company, form to be executed in a manner binding on the Company according to its Articles of Association or the laws of the country.
(b) Seal of Company (if any).

(a) H. H. Grimston
(a member of the firm of DAVIES & COLLISON) for and on behalf of
SANDOZ LTD.

(b)

To:
THE COMMISSIONER OF PATENTS
COMMONWEALTH OF AUSTRALIA
PATENTS ACT 1952-1969

DECLARATION IN SUPPORT OF CONVENTION OR NON-CONVENTION APPLICATION FOR A PATENT OR PATENT OF ADDITION

(The declaration shall be made by the applicant, or, if the applicant is a body corporate, by a person authorized by the body corporate to make the declaration on its behalf).

In support of the Application made for a patent for an invention, entitled

"IMPROVEMENTS IN OR RELATING TO ORGANIC COMPOUNDS"

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Jean Kramer and Peter Rass, both of
We SANDOZ LTD., of
Lichtstrasse 35,
CH-4002 BASEL,
Switzerland,

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1. We are the applicant for the patent of addition.

2. (a) We are the actual inventor of the invention.

3. The basic application as defined by Section 141 of the Act was made in SWITZERLAND on the 12th March, 1975 by ANNEMARIE CLOSSE, WALTER HAEFLIGER, DANIEL HAUSER in SWITZERLAND on the 24th July, 1975 by ANNEMARIE CLOSSE, WALTER HAEFLIGER, DANIEL HAUSER

4. The basic application referred to in paragraph 3 of this Declaration was the first application made in a Convention country in respect of the invention the subject of the application.

Declared at BASEL on the 19th day of February, 1976.

SANDOZ Ltd.
Claim 1. A process for the production of benzofuranone compounds of formula I

\[
\begin{align*}
\text{R}_1 & \quad \text{R}_2 \\
\text{R}_3 & \quad \text{O} \\
\text{R}_1 & \quad \text{O}
\end{align*}
\]

wherein \( \text{R}_1 \) is alkyl of 1 to 10 carbon atoms, cyclo-alkyl of 3 to 8 carbon atoms or phenyl, \( \text{R}_2 \) is hydrogen or alkyl of 1 to 4 carbon atoms, and \( \text{R}_3 \) is halogen, nitro; methylthio; hydroxy; or alkyl, alkoxy, alkanoyloxy or alkanoylamino, each of 1 to 4 carbon atoms,

with the proviso that:

(i) when \( \text{R}_3 \) is in the 5-position and \( \text{R}_1 \) and \( \text{R}_3 \) are identical and signify a straight alkyl chain \( \text{R}_2 \) is alkyl; and that

(ii) when \( \text{R}_1 \) is methyl and \( \text{R}_2 \) is hydrogen, \( \text{R}_3 \) is other than 4-methyl, 5-hydroxy or 5-methoxy,
which process comprises lactonising a compound of formula II,

\[
\text{II}
\]

wherein \( R_1, R_2, \) and \( R_3 \) are as defined above.
Commonwealth of Australia
Patents Act 1952-1992

Complete Specification
(Original)

For Office Use:

Class

Int. Class

Application Number:

Lodged:

Complete Specification Lodged:

Accepted:

Published:

Priority:

Related Art:

Name of Applicant: Sandoz Ltd.,

Address of Applicant: Lichtstrasse 35, CH-4002 Basle, Switzerland,

Actual Inventor(s): Annemarie Closse, Walter Hapfliger and Daniel Hauser

Address for Service: Davies & Collison, Patent Attorneys,
Gromwell Building, 374 Bourke Street, Melbourne, 3000

Complete Specification for the invention entitled:

Benzotriazolone Derivatives

"Improvements in or Relating to Organic Compounds"

The following statement is a full description of this invention, including the best method of performing it known to us:—

1.
The present invention relates to benzofuranone compounds.

In accordance with the invention there are provided new compounds of formula I,

\[ \text{I} \]

wherein \( R_1 \) is alkyl of 1 to 10 carbon atoms, cycloalkyl, of 3 to 8 carbon atoms or phenyl,

\( R_2 \) is hydrogen or alkyl of 1 to 4 carbon atoms,

and \( R_3 \) is halogen; nitro; methylthio; hydroxy; or alkyl, alkoxy, alkanoyloxy or alkanoylamino each of 1 to 4 carbon atoms,

with the proviso that:

i) when \( R_3 \) is in the 5-position and \( R_1 \) and \( R_3 \) are identical and signify a straight alkyl chain \( R_2 \) is alkyl; and that

ii) when \( R_1 \) is methyl and \( R_2 \) is hydrogen, \( R_3 \) is other than 4-methyl, 5-hydroxy or 5-methoxy.

Further, in accordance with the invention, a compound of formula I may be obtained by a process comprising lactonizing a compound of formula II,
wherein \( R_1, R_2 \) and \( R_3 \) are as defined above.

A group of compounds suitably prepared by this process are compounds of formula I as defined above with the further proviso that when \( R_1 \) is alkyl of 1 to 5 carbon atoms and \( R_2 \) is halogen, alkyl or alkoxy, \( R_2 \) is alkyl.

When \( R_1 \) is cycloalkyl, this radical preferably signifies cyclopentyl or cycloheptyl, especially, however, cyclohexyl. When \( R_1 \) is alkyl, this preferably contains 3 to 6, especially 3 or 4 carbon atoms and is preferably branched and specially signifies isobutyl or isopropyl.

When \( R_2 \) is alkyl, this preferably signifies methyl.

The substituent \( R_3 \) preferably signifies halogen, i.e. chlorine, bromine or fluorine, and preferably signifies chlorine. When \( R_3 \) is alkyl or alkoxy, this preferably contains 1 or 2 carbon atoms. When \( R_3 \) is an alkanoyloxy or alkynoylamino radical, this preferably contains 2 carbon atoms. \( R_3 \) is preferably in the 5-position.

The lactonization of compounds of formula II in accordance with the process of the invention is effected in accordance with conventional methods, as described in Example 1.
The compounds of formula II, used as starting materials, may be obtained in accordance with known methods. These compounds may be obtained in the usual manner from the corresponding compounds of formula II wherein R₂ and R₃ are hydrogen, and wherein the hydroxy group in the nine structure may optionally be protected temporarily by an alkoxy group, and the free carboxyl group may be protected temporarily by an ester group.

In the following non-limitative Examples all temperatures are indicated in degrees Centigrade and are uncorrected.
**EXAMPLE 1:** 5-chloro-6-cyclohexyl-2,3-dihydrobenzofuran-2-one

5 g of 3'-chloro-4'-cyclohexyl-6'-hydroxyphenylacetic acid are dissolved in toluene with heating, 50 mg of p-toluenesulphonic acid are added, and the mixture is boiled in a water separator for 3 hours. The oil obtained after evaporation is purified on a 100-fold quantity of silica gel Merck. The desired product is eluted with chloroform and recrystallized from methylene chloride/petroleum ether. The crystals have an M.P. of 100-102°.

The following compounds of formula I are produced in analogous manner, whereby R₁, R₂ and R₃ have the following significances:

<table>
<thead>
<tr>
<th>Example</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>Melting point</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td></td>
<td>H</td>
<td>5-Br</td>
<td>124 - 126 °</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>H</td>
<td>7-Br</td>
<td>108 - 109 °</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>H</td>
<td>5-NO₂</td>
<td>132 - 133 °</td>
</tr>
<tr>
<td>5</td>
<td>CH₃</td>
<td>5-Cl</td>
<td></td>
<td>92 - 93 °</td>
</tr>
<tr>
<td>6</td>
<td>Cl₃</td>
<td>5-NO₂</td>
<td></td>
<td>94 - 95 °</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>H</td>
<td>5-Cl</td>
<td>111 - 112 °</td>
</tr>
<tr>
<td>Example</td>
<td>R₁</td>
<td>R₂</td>
<td>R₃</td>
<td>Melting point</td>
</tr>
<tr>
<td>---------</td>
<td>----</td>
<td>----</td>
<td>---------</td>
<td>---------------</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>H</td>
<td>5-CH₃</td>
<td>157 - 158 °</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>CH₃</td>
<td>5-Cl</td>
<td>88 - 89 °</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>H</td>
<td>5-CH₃</td>
<td>77 - 78 °</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>CH₃</td>
<td>5-OCH₃</td>
<td>amorphous</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>H</td>
<td>5-CH₃CO₂H</td>
<td>195 - 196 °</td>
</tr>
<tr>
<td>13</td>
<td></td>
<td>H</td>
<td>5-CH₃S</td>
<td>104 - 105 °</td>
</tr>
<tr>
<td>14</td>
<td>CH₃</td>
<td>CH₂</td>
<td>H</td>
<td>5-Cl</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td>H</td>
<td>5-OH</td>
<td>amorphous</td>
</tr>
<tr>
<td>16</td>
<td></td>
<td>H</td>
<td>5-CH₃CO₂</td>
<td>amorphous</td>
</tr>
</tbody>
</table>
The compounds of formula I exhibit pharmacological activity. In particular they exhibit oedema and inflammation inhibitory activity as indicated in standard tests, for example in the carrageen oedema test, in the Adjuvans arthritis test and the granuloma cyst test in the rat and in the UV erythema test in the guinea-pig.

In standard tests the compounds of formula I exhibit further effects, such as an anti-pyretic effect, an analgesic effect, or an inhibition of PG synthetase or of Collagen-induced blood platelet aggregation.

The compounds are therefore indicated for use as inhibitors of oedema and inflammations. An indicated daily dose is from 60 to 300 mg, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from about 15 to about 150 mg of the compound, or in sustained release form.

The Example 1 and 7 compounds exhibit especially interesting activity.

The present invention also provides a pharmaceutical composition comprising a compound of formula I, in association with a pharmaceutical carrier or diluent. Such compositions may be in the form of, for example, a solution or a tablet.

Conveniently there are provided compounds of formula I, wherein \( R_1 \) is alkyl of 1 to 5 carbon atoms, \( R_2 \) is hydrogen, and \( R_3 \) is halogen, lower alkyl or lower alkoxy in the form of a pharmaceutical composition.
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A process for the production of benzofuranone compounds of formula I,

\[ \text{I} \]

wherein \( R_1 \) is alkyl of 1 to 10 carbon atoms, cycloalkyl of 3 to 8 carbon atoms or phenyl,

\( R_2 \) is hydrogen or alkyl of 1 to 4 carbon atoms, and

\( R_3 \) is halogen; nitro; methylthio; hydroxy; or alkyl, alkoxy, alkanoyloxy or alkancylamino, each of 1 to 4 carbon atoms,

with the proviso that:

i) when \( R_3 \) is in the 5-position and \( R_1 \) and \( R_3 \) are identical and signify a straight alkyl chain \( R_2 \) is alkyl; and

ii) when \( R_1 \) is methyl and \( R_2 \) is hydrogen, \( R_3 \) is other than 4-methyl, 5-hydroxy or 5-methoxy,

which process comprises lactonising a compound of formula II,

\[ \text{II} \]
wherein $R_1$, $R_2$ and $R_3$ are as defined above.

2. A process for the production of a compound of formula I, as defined in Claim 1, substantially as hereinbefore defined with reference to any one of the Examples.

3. A compound of formula I, whenever produced by a process of Claim 1 or 2.

4. A compound of formula I, as defined in Claim 1.

5. A compound of Claim 4 with the further proviso that when $R_1$ is alkyl of 1 to 5 carbon atoms and $R_3$ is halogen, alkyl or alkoxy, $R_2$ is alkyl.

6. A compound of Claim 1, wherein $R_1$ is cyclohexyl or branched alkyl of 3 to 6 carbon atoms and $R_3$ is halogen or alkyl in the 5-position.

7. A compound of Claim 6, wherein $R_1$ is cyclohexyl or branched alkyl of 3 or 4 carbon atoms and $R_3$ is chlorine, bromine, fluorine or methyl.

8. A compound of Claim 6 or 7, wherein $R_2$ is hydrogen.

9. A compound of Claim 6, wherein $R_1$ is cyclohexyl, $R_2$ is hydrogen and $R_3$ is chlorine.

10. A pharmaceutical composition comprising a compound of any one of Claims 3 to 9 in association with a pharmaceutical carrier or diluent thereof.

DATED this 12 day of February 1980.

DAVIES & COLLISON
Patent Attorneys for SANDOZ LTD.