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Description

This invention relates to pyrido[2,3-a]pyrimidine derivatives and physiologically acceptable salts thereof, a process for preparing such compounds, and pharmaceutical compositions containing such a compound as an active ingredient. The pyrido[2,3-a]pyrimidine derivatives and physiologically acceptable salts thereof in accordance with the present invention have a marked antagonistic effect on the "slow-reacting substance of anaphylaxis" (hereinafter abbreviated as SRS-A) and, therefore, can be used in the treatment of Type I allergic diseases induced by SRS-A.

SRS-A is strongly effective in causing contraction of smooth muscle and constitutes a substance responsible for Type I allergic diseases, particularly bronchial asthma and allergic rhinitis [Quarterly Journal of Experimental Physiology, Vol. 30, p. 121, 1940]. Leukotriene D₅ has been found to be a representative active component of this substance and the presence of an inhibitory effect on the in vivo activity of leukotriene D₅ is now considered to be a criterion of the usefulness of a drug for the treatment of Type I allergic diseases induced by SRS-A [Nature, Vol. 288, p. 494, 1980].

Drugs useful for the treatment of Type I allergic diseases induced by SRS-A are roughly divided into two types: drugs of the SRS-A release suppression type which act to prevent the release of SRS-A from mast cells or basophils and thereby inhibit its activity indirectly, and drugs of the SRS-A antagonistic type which act to antagonize the released SRS-A in the living body and thereby inhibit its activity directly. However, drugs of the SRS-A release suppression type are inherently used for the purpose of preventing the induction of allergic attacks by SRS-A and generally tend to lack effectiveness immediately after the onset of an attack. That is, they often fail to exhibit the so-called "rapid-acting property". In recent years, therefore, it has been eagerly desired from the viewpoint of an immediate effect on allergic attacks to develop a satisfactorily effective drug of the SRS-A antagonistic type.

9-Methyl-3-(3H-tetrazol-5-yl)-4H-pyrindo[2,3-a]pyrimidin-4-one potassium salt (hereinafter abbreviated as Compound TBX) is a conventionally known pyridopyrimidine compound and it has been reported that this compound is useful for the prevention of Type I allergic reactions [US-A 4 122 274].

However, a subsequent study has revealed that Compound TBX belongs to the SRS-A release suppression type (Japanese Journal of Allergology, Vol. 33, No. 9, p. 728, 1984). Moreover, a confirmatory experiment conducted by the present inventors has demonstrated that Compound TBX has no antagonistic effect on SRS-A as represented by leukotriene D₅. Accordingly, the present inventors have made an exhaustive study in the search for compounds antagonizing the in vivo activity of SRS-A and, in particular, leukotriene D₅. As a result, a novel compound having a marked antagonistic effect on leukotriene D₅ has surprisingly been discovered among compounds containing a pyrido[2,3-a]pyrimidine ring analogously to Compound TBX. The present invention has been completed on the basis of this discovery.

According to one feature of the present invention, there is provided a pyrido[2,3-a]pyrimidine derivative of general formula [I]:

\[
\begin{align*}
&\text{O} \\
&\text{CH₃} \\
&\text{HO} \\
&\text{OCH₂} \\
&\text{CH₂CH₂CH₃} \\
&\text{\text{CH₂CH₂CH₃}} \\
&\text{R} \\
&\text{N} \\
&\text{N} \\
&\text{N} \\
&\text{N} \\
&\text{N} \\
&\text{CH₂} \text{n} \\
&\text{H} \
\end{align*}
\]

where R is a hydrogen atom, a halogen atom or a methyl group, and n is 0, 1 or 2, or a physiologically acceptable salt thereof.

According to another feature of the present invention, there is provided a process for preparing pyrido[2,3-a]pyrimidine derivatives of the above general formula [I] and physiologically acceptable salts thereof.

According to yet another feature of the present invention, there is provided a pharmaceutical composition useful for the treatment of allergic diseases containing, as an active ingredient, a pyrido[2,3-a]pyrimidine derivative of the above general formula [I] or a physiologically acceptable salt thereof.

The pyrido[2,3-a]pyrimidine derivatives represented by the above general formula [I] (hereinafter referred to briefly as the present compounds [I]) can be prepared by reacting a nitrile compound of general formula [II]:

\[
\begin{align*}
&\text{O} \\
&\text{CH₃} \\
&\text{HO} \\
&\text{OCH₂} \\
&\text{CH₂CH₂CH₃} \\
&\text{\text{CH₂CH₂CH₃}} \\
&\text{R} \\
&\text{N} \\
&\text{N} \\
&\text{N} \\
&\text{N} \\
&\text{N} \\
&\text{CH₂} \text{n} \\
&\text{H} \
\end{align*}
\]
where R and n are as previously defined, with hydrazoic acid or a salt thereof.

Useful salts of hydrazoic acid include alkali metal salts such as sodium azide, potassium azide, etc.; alkaline-earth metal salts such as calcium azide, magnesium azide, etc.; salts formed by reaction with other metals, such as aluminum azide, tin azide, titanium azide, etc., and salts formed by reaction with organic bases, such as ammonium azide, aniline azide, etc. Although such salts of hydrazoic acid may be used alone, alkali metal salts of hydrazoic acid should preferably be converted to aluminum azide, tin azide, ammonium azide, aniline azide or the like in the reaction system by using them in combination with a Lewis acid (such as aluminum chloride, tin chloride or the like) or a suitable salt (such as ammonium chloride, aniline hydrochloride or the like). The most preferable combination comprises sodium azide and aluminum chloride or ammonium chloride.

Suitable reaction solvents include ethers such as tetrahydrofuran, dioxane, etc.; and polar solvents such as dimethylformamide, dimethyl sulfoxide, dimethylacetamide, hexamethylphosphorotriamide, etc. The reaction may be carried out by heating the reaction mixture at a temperature of 50 to 150°C for a period of time ranging from 1 minute to 72 hours.

The present compound [I] prepared as above may be purified by recrystallization, by silica gel column chromatography, by converting the present compound [I] to a suitable salt and then neutralizing this salt to effect crystallization (hereinafter referred to as the crystallization procedure), or by a combination of these procedures.

Recrystallization solvents suitable for use in purification by recrystallization include water, methanol, ethanol, n-propyl alcohol, isopropyl alcohol, dimethylformamide, dimethyl sulfoxide, hexamethylphosphorotriamide, acetic acid, acetonitrile, trifluoroacetic acid and tetrahydrofuran, as well as mixtures of two or more such solvents. Developing solvents suitable for use in purification by silica gel chromatography include various mixtures of a halogenated hydrocarbon (such as chloroform, dichloromethane or the like) and an alcohol (such as methanol, ethanol or the like). Salts suitable for use in the crystallization procedure include sodium salts, potassium salts, calcium salts, magnesium salts and ammonium salts, and suitable neutralizing agents include mineral acids such as hydrochloric acid, sulfuric acid, nitric acid, etc., and organic acids such as acetic acid, formic acid, etc. Reaction solvents suitable for use in this crystallization procedure include water and an alcohol such as methanol, ethanol, isopropyl alcohol, n-butyl alcohol or the like.

Physiologically acceptable salts of the present compounds [I] can be prepared by reacting the corresponding compound [I] with an alkali metal or alkaline-earth metal hydroxide (such as sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide or the like), an alkaline metal or alkaline-earth metal carbonate (such as sodium carbonate, potassium carbonate, calcium carbonate, magnesium carbonate or the like), an alcoholate of an alkali metal or an alkaline-earth metal (such as sodium, potassium, magnesium or the like), an organic amine (such as ethanolamine, methylephedrine or the like) or ammonia in water, an alcohol or a mixture thereof. Alcohols suitable for this purpose include methanol, ethanol, isopropyl alcohol, n-butyl alcohol and the like. The hydroxide, carbonate, alcoholate, organic amine or ammonia should be used in an amount of 0.5 to 6 moles, preferably 0.5 to 2 moles, per mole of the present compound [I].

The salt prepared as above may be purified by recrystallization, if necessary. Recrystallization solvents suitable for this purpose include water, methanol, ethanol, n-propyl alcohol, isopropyl alcohol, dimethylformamide, dimethyl sulfoxide, hexamethylphosphorotriamide, acetonitrile and tetrahydrofuran, as well as mixtures of two or more such solvents.

The present compound [I] or physiologically acceptable salts thereof prepared in the above-described manner may be dried according to any of the conventional methods including warming, through-flow drying, freeze-drying and the like.

The nitride derivatives represented by the above general formula [II] can be prepared by condensing 1 mole of a compound of general formula [III]:

\[
\text{CH}_3\text{N}\text{O} \quad \text{CH}_2\text{CH}_2\text{CH}_3 \\
\text{HO} \quad \text{OCH}_2 \\
\text{N}\text{CH}_2\text{CH}_2\text{CH}_3 \\
\text{O} \quad \text{R} \quad \text{(CH}_2)_n \quad \text{CN}
\]
where R and n are as previously defined and X is a chlorine or bromine atom, with 1 to 6 moles of 2,4-dihydroxy-3-n-propylacetophenone in the presence of an acid acceptor.

Acid acceptors useful for this purpose include alkali metal carbonates such as sodium carbonate, potassium carbonate, etc., and alkali metal hydroxides such as sodium hydroxide, potassium hydroxide, etc. In the reaction system, potassium iodide may also be present as a reaction accelerator.

Suitable reaction solvents include methanol, ethanol, isopropyl alcohol, n-butyl alcohol, aceton, methyl ethyl ketone, diethyl ketone, cyclohexanone, dimethylformamide, dimethyl sulfoxide, mixtures of two or more such solvents, and mixtures of water and such solvents. The reaction is carried out by heating the reaction mixture at a temperature of 50 to 110°C for a period of time ranging from 1 minute to 72 hours.

The compounds represented by the above general formula [III] can be prepared (1) by halogenating a compound of the general formula [IV]:

where R and n are as previously defined, with the aid of a halogenating agent such as thionyl chloride, phosphorus trichloride, phosphoryl chloride, phosphorus tribromide, phosphoryl bromide or the like, or (2) by halogenating and dehydrating a compound of the general formula [V]:

where R and n are as previously defined, with the aid of a halogenating agent such as phosphoryl bromide, phosphoryl chloride, thionyl chloride or the like. Compounds of the above general formula [III] in which n is equal to 0 can also be prepared by halogenating a compound of the general formula [VI]:

where R is as previously defined, with the aid of N-chlorosuccinimide or N-bromosuccinimide.

The antagonistic effect on SRS-A of the present compounds [I] and physiologically acceptable salts thereof was tested according to the following experimental procedures using leukotriene D₅ which is a representative active component of SRS-A. The test compounds used for this purpose were the compounds enumerated below and considered to be typical examples of the present compounds [I] and physiologically acceptable salts thereof. The designation given in parentheses after the chemical name of each compound means its tentative name as used herein and corresponds to the respective one of the examples which will be described later.
9-[(4-Acetyl-3-hydroxy-2-n-propyloxy)phenyl]-3-[(H-4H-tetrazol]-5-yl]-4H-pyrido[2,2-a]pyrimidin-4-one (Example 1).
7-[(4-Acetyl-3-hydroxy-2-n-propyloxy)phenyl]-3-[(H-4H-tetrazol]-5-yl]-4H-pyrido[2,2-a]pyrimidin-4-one (Example 2).
8-[(4-Acetyl-3-hydroxy-2-n-propyloxy)phenyl]-3-[(H-4H-tetrazol]-5-yl]-4H-pyrido[2,2-a]pyrimidin-4-one (Example 3).
9-[(4-Acetyl-3-hydroxy-2-n-propyloxy)phenyl]-7-bromo-3-[(H-4H-tetrazol]-5-yl]-4H-pyrido[2,2-a]pyrimidin-4-one (Example 4).
9-[(4-Acetyl-3-hydroxy-2-n-propyloxy)phenyl]-7-methyl-3-[(H-4H-tetrazol]-5-yl]-4H-pyrido[2,2-a]pyrimidin-4-one (Example 5).
9-[(4-Acetyl-3-hydroxy-2-n-propyloxy)phenyl]-3-[(H-4H-tetrazol]-5-yl]-4H-pyrido[2,2-a]pyrimidin-4-one (Example 6).
7-[(4-Acetyl-3-hydroxy-2-n-propyloxy)phenyl]-3-[(H-4H-tetrazol]-5-yl]-4H-pyrido[2,2-a]pyrimidin-4-one (Example 7).
9-[(4-Acetyl-3-hydroxy-2-n-propyloxy)phenyl]-7-methyl-3-[(H-4H-tetrazol]-5-yl]-4H-pyrido[2,2-a]pyrimidin-4-one (Example 8).
9-[(4-Acetyl-3-hydroxy-2-n-propyloxy)phenyl]-3-[(2-[(H-4H-tetrazol]-5-yl)ethyl]-4H-pyrido[2,2-a]pyrimidin-4-one (Example 9).
8-[(4-Acetyl-3-hydroxy-2-n-propyloxy)phenyl]-3-[(2-[(H-4H-tetrazol]-5-yl)ethyl]-4H-pyrido[2,2-a]pyrimidin-4-one (Example 10).
9-[(4-Acetyl-3-hydroxy-2-n-propyloxy)phenyl]-7-bromo-3-[(2-[(H-4H-tetrazol]-5-yl)ethyl]-4H-pyrido[2,2-a]pyrimidin-4-one (Example 11).
9-[(4-Acetyl-3-hydroxy-2-n-propyloxy)phenyl]-3-[(H-4H-tetrazol]-5-yl]-4H-pyrido[2,2-a]pyrimidin-4-one potassium salt (Example 12).
9-[(4-Acetyl-3-hydroxy-2-n-propyloxy)phenyl]-3-[(2-[(H-4H-tetrazol]-5-yl)ethyl]-4H-pyrido[2,2-a]pyrimidin-4-one potassium salt (Example 13).

(i) in vitro tests

The antagonistic effect on leukotriene D3 of the present compounds [I] and physiologically acceptable salts thereof was tested by using the terminal ileum excised from a male guinea pig of the Hartley strain. Specifically, the terminal ileum was suspended, under aerated conditions, in 10 ml of Tyrode’s solution containing 5 × 10−6 M atropine and 1 × 10−6 M mepyramine. Then, a test compound and leukotriene D3 (manufactured by Wako Junyaku Co., Ltd.) were successively added thereto with an interval of 30 seconds. After the lapse of 4 to 6 minutes, the degree of contraction of the ileum was measured with a Model TO-IIS Isotonic Transducer (manufactured by Nippon Koden Co., Ltd.). The test compound and leukotriene D3 were used in such amounts as to give concentrations of 10−9 to 10−5 g/mc and 0.3 ng/mc, respectively.

The antagonistic effect on leukotriene D3 of each test compound was evaluated in terms of the concentration of the test compound at which the ileum contraction reaction induced by leukotriene D3 was inhibited by 50% (hereinafter referred to as IC50). Specifically, at varying concentrations of each test compound, the percent inhibition of contraction was calculated from the measured degree of contraction of the ileum according to the following equation:

\[
\text{Percent inhibition of contraction} = \frac{(\text{Degree of contraction without addition of test compound})}{(\text{Degree of contraction without addition of test compound})} \times 100
\]

On the basis of the data thus obtained, a dose-response curve was prepared and used to determine the IC50 value of the test compound. The results thus obtained are shown in Table I. For purposes of comparison, the antagonistic effect on leukotriene D3 of Compound TBX was tested in the same manner as described above and the result is also shown in Table I. Among the test compounds indicated, the compounds of Examples 1, 6 and 9 were prepared according to procedure a described in the respective examples.

65
Table 1

<table>
<thead>
<tr>
<th>Test compound</th>
<th>Antagonistic effect on leukotriene D₅ ( IC_{50} ) (( \mu g/ml ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound TBX</td>
<td>200</td>
</tr>
<tr>
<td>Example 1</td>
<td>0.03</td>
</tr>
<tr>
<td>Example 2</td>
<td>0.10</td>
</tr>
<tr>
<td>Example 3</td>
<td>0.20</td>
</tr>
<tr>
<td>Example 4</td>
<td>1.00</td>
</tr>
<tr>
<td>Example 5</td>
<td>0.80</td>
</tr>
<tr>
<td>Example 6</td>
<td>0.01</td>
</tr>
<tr>
<td>Example 7</td>
<td>0.10</td>
</tr>
<tr>
<td>Example 8</td>
<td>0.70</td>
</tr>
<tr>
<td>Example 9</td>
<td>0.005</td>
</tr>
<tr>
<td>Example 10</td>
<td>0.60</td>
</tr>
<tr>
<td>Example 11</td>
<td>0.90</td>
</tr>
<tr>
<td>Example 12</td>
<td>0.03</td>
</tr>
<tr>
<td>Example 13</td>
<td>0.005</td>
</tr>
</tbody>
</table>

As is evident from Table 1, it may be recognized that the present compounds [1] and physiologically acceptable salts thereof exhibit a marked antagonistic effect on leukotriene D₅ which cannot be predicted from Compound TBX.

(i) In vivo tests

Using male guinea pigs of the Hartley strain, weighing about 400 g, in groups of six, the inhibitory effect of the present compounds [1] and physiologically acceptable salts thereof on a Type I allergic reaction induced by leukotriene D₅ was tested in two dosage forms (i.e., by intravenous injection and by oral administration) according to the Konzert-Röessler procedure [Naunyn-Schmiedeberg's Archiv für Experimenterelle Pathologie und Pharmakologie, Vol. 195, p. 71, 1940]. Specifically, each guinea pig was anesthetized by intraperitoneal administration of 1.5 g/kg of urethane and an incision was made in the neck to expose the trachea. To the exposed trachea was connected a respirator (with a ventilation volume of 5-7 ml, a respiration rate of 70 per minute, and a pulmonary load pressure of 10 cmH₂O; manufactured by Ugo Basile Biological Research Apparatus Co.,) by way of a cannula. The volume of air overflowing through the branch of the cannula was measured by means of a Model 7020 Bronchosperm Transducer (manufactured by Ugo Basile Biological Research Apparatus Co.) and recorded with a Model RM-6000 Polygraph (manufactured by Nippon Koden Co., Ltd.).

Intravenous injection tests were carried out as follows: Each guinea pig was treated by intravenous injection of 1 mg/kg of gallamine triethiodide. Then, 20.0 to 6000.0 \( \mu g/kg \) of a test compound and 0.5 \( \mu g/kg \) of leukotriene D₅ were successively administered thereto through the cervical vein with an interval of 2 minutes. The volume of air overflowing as a result of the induced airway constriction reaction was measured. The test compound was used in the form of a solution in physiological saline containing sodium hydrogen carbonate or potassium carbonate.

Oral administration tests were carried out as follows:

1 to 30 mg/kg of a test compound was orally administered to each guinea pig 90 minutes before anesthesia with urethane. Then, the anesthetized guinea pig was treated by intravenous injection of 1 mg/kg of gallamine triethiodide and administration of 0.5 \( \mu g/kg \) of leukotriene D₅ through the cervical vein. The volume of air overflowing as a result of the induced airway constriction reaction was measured.

Both in the intravenous injection tests and the oral administration tests, leukotriene D₅ was used in the form of a solution in physiological saline.

Both in the intravenous injection tests and in the oral administration tests, the pharmacological effect on the Type I allergic reaction was evaluated in terms of the dose of the test compound at which the airway constriction reaction induced by leukotriene D₅ was inhibited by 50% (hereinafter referred to as ID₅₀), provided that ID₅₀ was expressed in \( \mu g/kg \) for the intravenous injection tests and in mg/kg for the oral administration tests. Specifically, at 4 to 6 different doses of each test compound ranging from 20.0 to 6000.0 \( \mu g/kg \) for the intravenous injection tests and from 1 to 30 mg/kg for the oral administration tests, the percent inhibition of the airway constriction reaction was calculated according to the following equation:
Percent inhibition = \( \frac{X - Y}{X} \times 100 \)

where \( X \) is the ratio of the incremental volume of overflowing air measured in the leukotriene D₅-treated group to the incremental volume of overflowing air measured when the airway of the guinea pig is perfectly constricted, and \( Y \) is the ratio of the incremental volume of overflowing air measured in the test compound- and leukotriene D₅-treated group to the incremental volume of overflowing air measured when the airway of the guinea pig is perfectly constricted. On the basis of the data thus obtained, a dose-response curve was prepared and used to determine the ID₅₀ value of the test compound.

The results thus obtained are shown in Table 2. For purposes of comparison, the ID₅₀ value of Compound TBX was determined in the same manner as described above in connection with the intravenous injection tests, except that its doses ranged from 5 to 10 mg/kg, and the result is also shown in Table 2. Among the test compounds indicated, the compounds of Examples 1, 6 and 9 used in the intravenous injection tests were prepared according to procedure a described in the respective examples, and those used in the oral administration tests were prepared according to procedure b.

<table>
<thead>
<tr>
<th>Test compound</th>
<th>Inhibitory effect on type I allergic reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ID₅₀ (intravenous; ( \mu )g/kg)</td>
</tr>
<tr>
<td>Compound TBX</td>
<td>10000 or greater</td>
</tr>
<tr>
<td>Example 1</td>
<td>97</td>
</tr>
<tr>
<td>Example 2</td>
<td>160</td>
</tr>
<tr>
<td>Example 3</td>
<td>170</td>
</tr>
<tr>
<td>Example 4</td>
<td>4900</td>
</tr>
<tr>
<td>Example 6</td>
<td>110</td>
</tr>
<tr>
<td>Example 8</td>
<td>1900</td>
</tr>
<tr>
<td>Example 9</td>
<td>38</td>
</tr>
<tr>
<td>Example 11</td>
<td>2900</td>
</tr>
<tr>
<td>Example 12</td>
<td>97</td>
</tr>
</tbody>
</table>

As is evident from Table 2, it may be recognized that the present compounds [[I]] and physiologically acceptable salts thereof can antagonistically and markedly inhibit leukotriene D₅-induced Type I allergic reactions as represented by the airway constriction reaction.

(iii) Toxicity test

The acute toxicity (LD₅₀) of several typical examples of the present compounds [I] and physiologically acceptable salts thereof was tested on 5-weeks-old male ddY strain mice and male SD strain rats. For this purpose, the compounds of Examples 1, 6 and 9 were selected as typical examples. For mice, the LD₅₀ values of these three compounds were not less than 4.0 \( \mu \)g/kg when administered orally, and not less than 100 mg/kg when administered intravenously. For rats, their LD₅₀ values were not less than 4.0 g/kg when administered orally, and not less than 200 mg/kg when administered intravenously.

As can be seen from the results of the above-described in vitro tests, in vivo tests and toxicity tests, the present compounds [I] and physiologically acceptable salts thereof are useful for the treatment of SRS-A induced Type I allergic diseases including, in particular, bronchial asthma and allergic rhinitis. They can also be used as anti-ulcer agents, anti-inflammatory agents or drugs for the treatment of ischemic heart diseases.

The present compounds [I] and physiologically acceptable salts thereof may be admixed with physiologically inert solid or liquid pharmaceutical carriers to form pharmaceutical compositions. These compositions may have a variety of dosage forms including injectable solutions, tablets, capsules, powders, fine granules, granules, liquids, suspensions and emulsions. The pharmaceutical carriers can be any of various pharmaceutical carriers usually used in such dosage forms, and examples thereof include excipients, binders and disintegrants, such as corn starch, dextrin, α-, β-, or γ-cyclodextrin, glucose, lactose, sucrose, methylcellulose, calcium carboxymethylcellulose, crystalline cellulose, magnesium stearate, sodium alginate, Witepsol W35, Witepsol E85, polyvinyl alcohol, light silicic acid anhydride, etc.; lubricants such as talc, stearic acid, waxes, hydroxypropylcellulose, boric acid, etc.; coating agents such as shellac, cellulose acetate phthalate, polyvinyl acetate diethylaminoacetate, etc.; solubilizing agents such as glycerol, propylene glycol, mannitol, etc.; emulsifying or suspending agents such as polyoxyethylene stearate, polyoxyethylene cetyl alcohol ether, gum arabic, polyvinylpyrrolidone, etc.; stabilizers such as sorbitol, Tween 80, Span 60, fats and oils, etc.; and various solvents.
In the above-described pharmaceutical compositions, the present compound [I] or a pharmaceutically acceptable salt thereof should be contained in such an amount that the daily dose of the active ingredient is in the range of 0.002 to 60 mg/kg, preferably 0.02 to 10 mg/kg, for purposes of oral administration or in the range of 1 to 1000 µg/kg, preferably 10 to 200 µg/kg, for purposes of intravenous injection.

The present invention is further illustrated by the following Reference Examples, non-limiting Examples and Pharmaceutical Compositions.

Reference Examples

1. 3.0 g (4.92 mmole) of 9-bromomethyl-3-cyano-4H-pyrido[2,3-d]pyrimidin-4-one, 0.97 g (5.00 mmole) of 2,4-dihydroxy-3-n-propylacetophenone and 0.60 g of anhydrous potassium carbonate were added to 100 ml of methyl ethyl ketone, and this mixture was heated under reflux for 45 minutes. After cooling, the crystals which separated out of the reaction solution were collected by filtration and washed with water to obtain 1.10 g (59% yield) of 9-[(4-acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-3-cyano-4H-pyrido[2,3-d]pyrimidin-4-one. These crystals had a melting point of 233-234°C.

The following 18 nitrile derivatives [II] were prepared in substantially the same manner as described above, except that the 9-bromomethyl-3-cyano-4H-pyrido[2,3-d]pyrimidin-4-one was replaced by each of the corresponding compounds [III] and the reaction conditions (such as the molar ratio of reactants, reaction solvent, reaction temperature, reaction time, etc.) were suitably modified. Thus, these nitrile derivatives [II] were obtained in a yield ranging from 50% to 85%:

7-[(4-Acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-3-cyano-4H-pyrido[2,3-d]pyrimidin-4-one.
8-[(4-Acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-3-cyano-4H-pyrido[2,3-d]pyrimidin-4-one.
9-[(4-Acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-7-bromo-3-cyano-4H-pyrido[2,3-d]pyrimidin-4-one.
10-[(4-Acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-3-cyano-7-methyl-4H-pyrido[2,3-d]pyrimidin-4-one.
11-[(4-Acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-3-cyanomethyl-4H-pyrido[2,3-d]pyrimidin-4-one.
12-[(4-Acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-3-cyanomethyl-7-methyl-4H-pyrido[2,3-d]pyrimidin-4-one.
13-[(4-Acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-3-(2-cyanoethyl)-4H-pyrido[2,3-d]pyrimidin-4-one.
14-[(4-Acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-3-(2-cyanoethyl)-7-methyl-4H-pyrido[2,3-d]pyrimidin-4-one.
15-[(4-Acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-7-bromo-3-(2-cyanoethyl)-4H-pyrido[2,3-d]pyrimidin-4-one.
16-[(4-Acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-3-(2-cyanoethyl)-7-methyl-4H-pyrido[2,3-d]pyrimidin-4-one.

Example 1

(Procedure a)

A mixture of 1.00 g (2.65 mmole) of 9-[(4-acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-3-cyano-4H-pyrido[2,3-d]pyrimidin-4-one, 0.97 g (7.27 mmole) of aluminum chloride, 1.43 g (21.99 mmole) of sodium oxide and 20 ml of tetrahydrofuran was heated under reflux for 2 hours. After cooling, the resulting reaction solution was diluted with ice water and then acidified with dilute hydrochloric acid. The precipitate so formed was collected by filtration and recrystallized from dimethylformamide to obtain 0.72 g (65% yield) of 9-[(4-acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-3-(1H-tetrazol-5-yl)-4H-pyrido[2,3-d]pyrimidin-4-one in the form of white crystals. These crystals had a melting point of 269-271°C (dec.).
Infrared absorption spectrum (KBr, cm⁻¹) 3240, 1680, 1625, 1270.
Analysis:
Calcd. for C₂₁H₂₀N₆O₄ (%) C, 59.99; H, 4.80; N, 19.99
Found (%) C, 60.12; H, 4.71; N, 19.73

(Procedure b)

A mixture of 1.00 g (2.65 mmoles) of 9-[(4-acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-3-cyano-4H-pyrido[2,3-a]pyrimidin-4-one, 0.97 g (7.27 mmoles) of aluminum chloride, 1.43 g (2.19 mmoles) of sodium azide and 20 mC of tetraphenylfuran was heated under reflux for 2 hours. After cooling, the resulting reaction solution was diluted with ice water and then acidified with dilute hydrochloric acid. The precipitate so formed was collected by filtration and dried. 1.09 g (2.59 mmoles) of this precipitate was suspended in 55 mC of methanol and then dissolved therein by adding 3.00 mC (2.55 mmoles) of a 5.6% ethanolic solution of potassium hydroxide. The resulting solution was filtered to remove any insoluble matter, and the filtrate was cooled. The precipitate which separated out was collected by filtration to obtain 0.88 g (74% yield) of 9-[(4-acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-3-[(4H-tetrazol-5-yl)-4H-pyrido][2,3-a]pyrimidin-4-one potassium salt. Subsequently, 0.88 g (1.92 mmoles) of this potassium salt was dissolved in 180 mC of water by warming and the resulting solution was neutralized with 1.23 mC (3.68 mmoles) of 3N hydrochloric acid. The precipitate so formed was collected by filtration to obtain 0.78 g (97% yield) of 9-[(4-acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-3-[(4H-tetrazol-5-yl)-4H-pyrido][2,3-a]pyrimidin-4-one in the form of a white powder. This powder had a melting point of 268-271°C (dec.) and its infrared absorption spectrum and elemental analysis were as follows:

Infrared absorption spectrum (KBr, cm⁻¹) 3240, 1680, 1625, 1270.
Analysis:
Calcd. for C₂₁H₂₀N₆O₄ (%) C, 59.99; H, 4.80; N, 19.99
Found (%) C, 59.95; H, 4.73; N, 20.06

The compounds of the following Examples 2-5 were prepared by repeating the above-described procedure a of Example 1 except that the 9-[(4-acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-3-cyano-4H-pyrido[2,3-a]pyrimidin-4-one (2.65 mmoles) was replaced by each of the corresponding nitrile derivatives [II] (2.65 mmoles).

Example 2

There was obtained 0.19 g (17% yield) of 7-[(4-acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-3-[(4H-tetrazol-5-yl)-4H-pyrido][2,3-a]pyrimidin-4-one in the form of white crystals. These crystals, which were recrystallized from acetonitrile, had a melting point of 256-260°C (dec.).

Infrared absorption spectrum (KBr, cm⁻¹) 3240, 1675, 1640, 1275.
Analysis:
Calcd. for C₂₁H₂₀N₆O₄ (%) C, 59.99; H, 4.80; N, 19.99
Found (%) C, 59.72; H, 4.94; N, 19.83

Example 3

There was obtained 0.26 g (23% yield) of 8-[(4-acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-3-[(4H-tetrazol-5-yl)-4H-pyrido][2,3-a]pyrimidin-4-one in the form of white crystals. These crystals, which were recrystallized from dimethylformamide, had a melting point of 263-272°C (dec.).

Infrared absorption spectrum (KBr, cm⁻¹) 3230, 1670, 1635, 1280.
Analysis:
Calcd. for C₂₁H₂₀N₆O₄ (%) C, 59.99; H, 4.80; N, 19.99
Found (%) C, 59.83; H, 4.79; N, 19.86
Example 4

There was obtained 0.12 g (9% yield) of 9-[(4-acetyl-3-hydroxy-2-n-propyloxy)methyl]-7-bromo-3-[(H-tetrazol-5-yl)-4H-pyrido][2,3-d]pyrimidin-4-one in the form of pale-yellow crystals. These crystals, which were recrystallized from a mixture of tetrahydrofuran and methanol, had a melting point of 240°C (dec.).

<table>
<thead>
<tr>
<th>Infrared absorption spectrum (KBr, cm⁻¹)</th>
<th>3225, 1700, 1620, 1275.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis:</td>
<td></td>
</tr>
<tr>
<td>Calcd. for C₂₁H₁₉BrN₂O₄ (% )</td>
<td>C, 50.51; H, 3.84; N, 16.83</td>
</tr>
<tr>
<td>Found (%)</td>
<td>C, 50.56; H, 3.90; N, 16.74</td>
</tr>
</tbody>
</table>

Example 5

There was obtained 0.59 g (5% yield) of 9-[(4-acetyl-3-hydroxy-2-n-propyloxy)methyl]-7-methyl-3-[(H-tetrazol-5-yl)-4H-pyrido][2,3-d]pyrimidin-4-one in the form of white crystals. These crystals, which were recrystallized from dimethylformamide, had a melting point of 279-280°C (dec.).

<table>
<thead>
<tr>
<th>Infrared absorption spectrum (KBr, cm⁻¹)</th>
<th>3230, 1670, 1530, 1275.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis:</td>
<td></td>
</tr>
<tr>
<td>Calcd. for C₂₂H₂₃N₂O₄ (% )</td>
<td>C, 60.82; H, 5.10; N, 19.35</td>
</tr>
<tr>
<td>Found (%)</td>
<td>C, 60.95; H, 5.03; N, 19.20</td>
</tr>
</tbody>
</table>

Example 6

(Procedure a)

A mixture of 1.04 g (2.65 mmole) of 9-[(4-acetyl-3-hydroxy-2-n-propyloxy)methyl]-3-cyanomethyl-4H-pyrido][2,3-d]pyrimidin-4-one, 1.00 g (8.69 mmole) of ammonium chloride, 1.21 g (8.61 mmole) of sodium azide and 30 mo of dimethylformamide was heated at 100-110°C for 8 hours with stirring. After cooling, the resulting reaction solution was poured into ice water and then acidified with dilute hydrochloric acid. The precipitate so formed was collected by filtration and recrystallized from dimethylformamide to obtain 0.55 g (48% yield) of 9-[(4-acetyl-3-hydroxy-2-n-propyloxy)methyl]-3-[(H-tetrazol-5-yl)methyl]-4H-pyrido][2,3-d]pyrimidin-4-one in the form of pale-yellow crystals. These crystals had a melting point of 250-253°C (dec.).

<table>
<thead>
<tr>
<th>Infrared absorption spectrum (KBr, cm⁻¹)</th>
<th>1680, 1630, 1265.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis:</td>
<td></td>
</tr>
<tr>
<td>Calcd. for C₂₃H₂₄N₂O₄ (% )</td>
<td>C, 60.82; H, 5.10; N, 19.35</td>
</tr>
<tr>
<td>Found (%)</td>
<td>C, 61.05; H, 5.08; N, 19.42</td>
</tr>
</tbody>
</table>

Procedure b

A mixture of 1.04 g (2.65 mmole) of 9-[(4-acetyl-3-hydroxy-2-n-propyloxy)methyl]-3-cyanomethyl-4H-pyrido][2,3-d]pyrimidin-4-one, 1.00 g (8.69 mmole) of ammonium chloride, 1.21 g (8.61 mmole) of sodium azide and 30 mo of dimethylformamide was heated at 100-110°C for 8 hours with stirring. After cooling, the resulting reaction solution was poured into ice water and then acidified with dilute hydrochloric acid. The precipitate so formed was collected by filtration and then dried. 1.0 g (2.53 mmole) of this precipitate was suspended in 70 mo of methanol and dissolved therein by adding 2.30 mo (2.30 mmole) of a 4.5% aqueous solution of sodium hydroxide. The resulting solution was filtered to remove any insoluble matter. The filtrate was evaporated to dryness under reduced pressure to obtain 1.05 g (9% yield) of 9-[(4-acetyl-3-hydroxy-2-n-propyloxy)methyl]-3-[(H-tetrazol-5-yl)methyl]-4H-pyrido][2,3-d]pyrimidin-4-one sodium salt. Subsequently, 1.05 g (2.30 mmole) of this sodium salt was dissolved in 260 mo of water and the resulting solution was neutralized with 1.50 mo (4.50 mmole) of 3N hydrochloric acid. The precipitate so formed was collected by filtration and then dried to obtain 0.97 g (97% yield) of 9-[(4-acetyl-3-hydroxy-2-n-propyloxy)methyl]-3-[(H-tetrazol-5-yl)methyl]-4H-pyrido][2,3-d]pyrimidin-4-one sodium salt.
a)pyrimidin-4-one in the form of a pale-yellow powder. This powder had a melting point of 248-253°C (dec.) and its infrared absorption spectrum and elemental analysis were as follows:

| Infrared absorption spectrum (KBr, cm⁻¹) | 1680, 1630, 1265. |
| Analysis: C, 60.82; H, 5.10; N, 19.35 |
| Found (%) C, 60.58; H, 5.32; N, 19.20 |

The compounds of the following Examples 7 and 8 were prepared by repeating the above-described procedure of Example 6 except that the 9-[(4-acetyl-3-hydroxy-2-n-propyloxy)methyl]-3-cyanoethyl-4H-pyrido[2,3-b]pyrimidin-4-one (2.65 mmoles) was replaced by each of the corresponding nitro derivatives [11] (2.65 mmoles).

**Example 7**

There was obtained 0.44 g (38% yield) of 7-[(4-acetyl-3-hydroxy-2-n-propyloxy-methyl]-3-[(3H-tetrazol-5-yl)-methyl]-4H-pyrido[2,3-b]pyrimidin-4-one in the form of pale-yellow crystals. These crystals, which were recrystallized from acetic acid, had a melting point of 228-232°C (dec.).

| Infrared absorption spectrum (KBr, cm⁻¹) | 1675, 1635, 1275. |
| Analysis: C, 60.82; H, 5.10; N, 19.35 |
| Found (%) C, 60.80; H, 5.18; N, 19.30 |

**Example 8**

There was obtained 0.62 g (52% yield) of 9-[(4-acetyl-3-hydroxy-2-n-propyloxy)methyl]-7-methyl-3-[(3H-tetrazol-5-yl)-methyl]-4H-pyrido[2,3-b]pyrimidin-4-one in the form of white crystals. These crystals, which were recrystallized from dimethylformamide, had a melting point of 234-238°C (dec.).

| Infrared absorption spectrum (KBr, cm⁻¹) | 1670, 1625, 1265. |
| Analysis: C, 61.59; H, 5.38; N, 16.74 |
| Found (%) C, 61.76; H, 5.31; N, 18.86 |

**Example 9**

(Procedure a)

A mixture of 1.07 g (2.65 mmoles) of 9-[(4-acetyl-3-hydroxy-2-n-propyloxy)methyl]-3-(2-cyanethy1)-4H-pyrido[2,3-b]pyrimidin-4-one, 1.76 g (3.20 mmoles) of aluminum chloride, 2.57 g (39.53 mmoles) of sodium azide and 45 ml of tetrahydrofuran was heated under reflux for 23 hours. After cooling, the resulting reaction solution was poured into ice water and then acidified with dilute hydrochloric acid. The precipitate so formed was separated by filtration and recrystallized from acetonitrile to obtain 0.70 g (59% yield) of 9-[(4-acetyl-3-hydroxy-2-n-propyloxy)methyl]-3-[(3H-tetrazol-5-yl)-ethyl]-4H-pyrido[2,3-b]pyrimidin-4-one in the form of white crystals. These crystals had a melting point of 238-239°C (dec.).

| Infrared absorption spectrum (KBr, cm⁻¹) | 1670, 1620, 1270. |
| Analysis: C, 61.59; H, 5.39; N, 18.74 |
| Found (%) C, 61.64; H, 5.30; N, 18.76 |

(Procedure b)
A mixture of 1.07 g (2.65 mmole) of 9-[(4-acetyl-3-hydroxy-2-n-propoxyphenoxo)methyl]-3-(2-cyanoe- 
thyl)-4H-pyrido[2,3-a]pyrimidin-4-one, 1.76 g (15.20 mmole) of aluminum chloride, 2.57 g (39.53 mmole) 
of sodium azide and 45 mo of tetrydrofuran was heated under reflux for 23 hours. After cooling, the 
resulting reaction solution was poured into ice water and then acidified with dilute hydrochloric acid. The 
precipitate so formed was separated by filtration and then dried. 1.14 g (2.54 mmole) of this precipitate 
was suspended in 250 ml of water and dissolved therein by adding 2.69 ml (2.29 mmole) of a 5.6% aqueous 
solution of potassium hydroxide. After the resulting solution was filtered to remove any insoluble 
matter, the filtrate was freeze-dried to obtain 1.11 g (90% yield) of 9-[(4-acetyl-3-hydroxy-2-n-propoxy 
phenoxo)methyl]-3-[2-(IH-tetrazol-5-yl)-ethyl]-4H-pyrido[2,3-a]pyrimidin-4-one potassium salt. Subsequent-
ly, 1.11 g (2.28 mmole) of this potassium salt was dissolved in 250 ml of water and the resulting solution 
was neutralized with 1.50 ml (4.50 mmole) of 3N hydrochloric acid. The precipitate so formed was 
collected by filtration and then dried to obtain 1.00 g (98% yield) of 9-[(4-acetyl-3-hydroxy-2-n-propoxy 
phenoxo)methyl]-3-[2-(IH-tetrazol-5-yl)-ethyl]-4H-pyrido[2,3-a]pyrimidin-4-one in the form of a white pow-
der. This powder had a melting point of 236-239°C (dec.) and its infrared absorption spectrum and ele-
mental analysis were as follows:

<table>
<thead>
<tr>
<th>Infrared absorption spectrum (KBr, cm⁻¹)</th>
<th>1670, 1620, 1270.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis:</td>
<td></td>
</tr>
<tr>
<td>Calcd. for C₂₉H₂₆N₆O₄ (%)</td>
<td>C, 61.59; H, 5.39; N, 18.74</td>
</tr>
<tr>
<td>Found (%)</td>
<td>C, 61.32; H, 5.51; N, 18.63</td>
</tr>
</tbody>
</table>

The compounds of the following Examples 10 and 11 were prepared by repeating the above-described 
procedure a of Example 9 except that the 9-[(4-acetyl-3-hydroxy-2-n-propoxyphenoxo)methyl]-3-(2-cya-
noeethyl)-4H-pyrido[2,3-a]pyrimidin-4-one (2.65 mmole) was replaced by each of the corresponding ni-

**Example 10**

There was obtained 0.43 g (36% yield) of 8-[(4-acetyl-3-hydroxy-2-n-propoxyphenoxo)methyl]-3-[2-
(H-tetrazol-5-yl)-ethyl]-4H-pyrido[2,3-a]pyrimidin-4-one in the form of white crystals. These crystals, 
which were recrystallized from dimethylformamide, had a melting point of 226-230°C (dec.).

<table>
<thead>
<tr>
<th>Infrared absorption spectrum (KBr, cm⁻¹)</th>
<th>1675, 1620, 1265.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis:</td>
<td></td>
</tr>
<tr>
<td>Calcd. for C₂₉H₂₆N₆O₄ (%)</td>
<td>C, 61.58; H, 5.39; N, 18.74</td>
</tr>
<tr>
<td>Found (%)</td>
<td>C, 61.32; H, 5.48; N, 18.63</td>
</tr>
</tbody>
</table>

**Example 11**

There was obtained 0.25 g (88% yield) of 9-[(4-acetyl-3-hydroxy-2-n-propoxyphenoxo)methyl]-7-bromo-
3-[2-(IH-tetrazol-5-yl)-ethyl]-4H-pyrido[2,3-a]pyrimidin-4-one in the form of pale-yellow crystals. These 
crystals, which were recrystallized from acetonitrile, had a melting point of 220-223°C (dec.).

<table>
<thead>
<tr>
<th>Infrared absorption spectrum (KBr, cm⁻¹)</th>
<th>1680, 1630, 1275.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis:</td>
<td></td>
</tr>
<tr>
<td>Calcd. for C₂₉H₂₆BrN₆O₄ (%)</td>
<td>C, 52.38; H, 4.40; N, 15.94</td>
</tr>
<tr>
<td>Found (%)</td>
<td>C, 52.43; H, 4.38; N, 16.04</td>
</tr>
</tbody>
</table>

**Example 12**

1.00 g (2.38 mmole) of 9-[(4-acetyl-3-hydroxy-2-n-propoxyphenoxo)methyl]-3-[IH-tetrazol-5-yl]-4H-
pyrido[2,3-a]pyrimidin-4-one was suspended in 50 ml of methanol and dissolved therein by adding 2.75 
ml (2.34 mmole) of a 5.6% ethanolic solution of potassium hydroxide. The resulting solution was filtered 
to remove any insoluble matter, and the filtrate was cooled. The precipitate which separated out was 
collected by filtration to obtain 0.88 g (74% yield) of 9-[(4-acetyl-3-hydroxy-2-n-propoxyphenoxo)methyl]-3-
([IH-tetrazol-5-yl]-4H-pyrido[2,3-a]pyrimidin-4-one potassium salt in the form of a pale-yellow powder.
EP 0 217 673 B1

Infrared absorption spectrum (KBr, cm⁻¹) 1675, 1625, 1275.
Analysis:
Calcd. for C₂₃H₁₉KN₂O₄ (%)  C, 55.00; H, 4.18; N, 18.33
Found (%) C, 54.89; H, 4.23; N, 18.17

Example 13

1.00 g (2.23 mmoles) of 9-[(4-acetyl-3-hydroxy-2-n-propylphenoxy) methyl]-3-[2-[(H-tetrazol-5-yl)ethyl]-4H-pyrido][2,3-b]pyrimidin-4-one was suspended in 200 ml of water and dissolved therein by adding 2.62 ml (2.23 mmoles) of a 5.6% aqueous solution of potassium hydroxide. The resulting solution was filtered to remove any insoluble matter, and the filtrate was freeze-dried to obtain 1.06 g (96% yield) of 9-[(4-acetyl-3-hydroxy-2-n-propylphenoxy) methyl]-3-[2-[(H-tetrazol-5-yl)ethyl]-4H-pyrido][2,3-b]pyrimidin-4-one potassium salt in the form of a pale-yellow powder.

Infrared absorption spectrum (KBr, cm⁻¹) 1670, 1620, 1275.
Analysis:
Calcd. for C₂₉H₂₂KN₂O₄ (%)  C, 58.77; H, 4.76; N, 17.28
Found (%) C, 58.61; H, 4.63; N, 17.16

In addition, the nine compounds enumerated below were prepared in substantially the same manner as described above in Examples 1, 6, 9 and 13.
9-[(4-Acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-8-chloro-3-[(H-tetrazol-5-yl)-4H-pyrido][2,3-b]pyrimidin-4-one.
9-[(4-Acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-6-fluoro-3-[(H-tetrazol-5-yl)-4H-pyrido][2,3-b]pyrimidin-4-one.
7-[(4-Acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-8-chloro-3-[(H-tetrazol-5-yl)-4H-pyrido][2,3-b]pyrimidin-4-one.
9-[(4-Acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-8-methyl-3-[(H-tetrazol-5-yl)-4H-pyrido][2,3-b]pyrimidin-4-one.
7-[(4-Acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-8-bromo-3-[(H-tetrazol-5-yl)methyl]-4H-pyrido[2,3-b]pyrimidin-4-one.
8-[(4-Acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-9-chloro-3-[(H-tetrazol-5-yl)methyl]-4H-pyrido[2,3-b]pyrimidin-4-one.
9-[(4-Acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-6-fluoro-3-[(2-[(H-tetrazol-5-yl)ethyl]-4H-pyrido][2,3-b]pyrimidin-4-one.
7-[(4-Acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-8-methyl-3-[(2-[(H-tetrazol-5-yl)ethyl]-4H-pyrido][2,3-b]pyrimidin-4-one.
9-[(4-Acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-3-[(H-tetrazol-5-yl)methyl]-4H-pyrido[2,3-b]pyrimidin-4-one sodium salt.

Pharmaceutical composition 1 (tablets)

<table>
<thead>
<tr>
<th>Component</th>
<th>% by weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Compound of example 1 (procedure b)</td>
<td>10.0</td>
</tr>
<tr>
<td>(2) Lactose</td>
<td>56.0</td>
</tr>
<tr>
<td>(3) Corn starch</td>
<td>15.0</td>
</tr>
<tr>
<td>(4) Crystalline cellulose</td>
<td>15.0</td>
</tr>
<tr>
<td>(5) Hydroxypropylcellulose</td>
<td>3.0</td>
</tr>
<tr>
<td>(6) Magnesium stearate</td>
<td>1.0</td>
</tr>
</tbody>
</table>

100.0

The above ingredients (1)-(5) were blended together. After the addition of water, the resulting mixture was granulated and then dried. The granules so formed were adjusted to a predetermined size range, and the ingredient (6) was added thereto. The resulting mixture was compressed to form tablets each containing 10 mg of the active ingredient. Other tablets were also prepared in the same manner as described above, except that the compound of Example 1 used as the active ingredient was replaced by each of the compounds of Examples 6 and 9 (both prepared according to procedure b).
According to conventional procedure, the above ingredients were blended together and then granulated. The granules so formed were filled into capsules, each of which contained 10 mg of the active ingredient. Other capsules were also prepared in the same manner as described above, except that the compound of Example 9 used as the active ingredient was replaced by each of the compounds of Examples 1 and 6 (both prepared according to procedure b).

Claims for the contracting states: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

I. A pyrido[2,4-d]pyrimidine derivative of the general formula

\[
\begin{align*}
\text{O} & \\
\text{C} & \\
\text{CH}_3 & \\
\text{N} & \\
\text{O} & \\
\text{R} & \\
\text{N} & \\
\text{O} & \\
\text{C} & \\
\text{CH}_2\text{CH}_2 & \\
\text{CH}_3 & \\
\text{N} & \\
\text{O} & \\
\text{R} & \\
\text{N} & \\
\text{O} & \\
\text{C} & \\
\text{CH}_3 & \\
\end{align*}
\]

where R is a hydrogen atom, a halogen atom or a methyl group, and n is 0, 1 or 2, or a physiologically acceptable salt thereof.

2. A compound as claimed in claim 1 which is any one of the following compounds, 9-[[4-acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-3-([H-tetrazol-5-yi)-4H-pyrido[2,4-d]pyrimidin-4-one, 7-[[4-acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-3-([H-tetrazol-5-yi)-4H-pyrido[2,4-d]pyrimidin-4-one, 8-[[4-acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-3-([H-tetrazol-5-yi)-4H-pyrido[2,4-d]pyrimidin-4-one, 9-[[4-acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-3-7-bromo-3-([H-tetrazol-5-yi)-4H-pyrido[2,4-

3. A compound as claimed in claim 1 wherein the physiologically acceptable salt is a potassium or sodium salt.

4. A compound as claimed in claim 3 which is 9-[[4-acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-3-([H-tetrazol-5-yi)-4H-pyrido[2,4-d]pyrimidin-4-one potassium salt or 9-[[4-acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-3-2-([H-tetrazol-5-yi)-4H-pyrido[2,4-d]pyrimidin-4-one potassium salt.

5. A process for preparing pyrido[2,4-d]pyrimidine derivatives of general formula
where R is a hydrogen atom, a halogen atom or a methyl group, and n is 0, 1 or 2, and physiologically acceptable salts thereof, which comprises reacting a nitrile derivative of general formula

where R and n are as previously defined, with hydrazoic acid or a salt thereof, and then optionally forming a salt thereof.

6. A process as claimed in claim 5 wherein the salt of hydrazoic acid is aluminum azide or ammonium azide formed in the reaction system by using sodium azide in combination with aluminum chloride or ammonium chloride, respectively.

7. A process as claimed in either of claims 5 and 6 wherein the treatment for the formation of a salt is carried out by using potassium hydride or sodium hydride.

8. A pharmaceutical composition comprising a pyrido[1,2-a]pyrimidine derivative of general formula

where R is a hydrogen atom, a halogen atom or a methyl group, and n is 0, 1 or 2, or a physiologically acceptable salt thereof.

9. A pharmaceutical composition as claimed in claim 8 wherein the compound of formula I is selected from the group consisting of 9-[(4-acetyl-3-hydroxy-2-n-propylenoxy)methyl]-3-[(H-tetrazol-5-y)4H-pyrido[2,1-a]pyrimidin-4-one, 9-[(4-acetyl-3-hydroxy-2-n-propylenoxy)methyl]-3-[[H-tetrazol-5-y]methyl]-4H-pyrido[1,2-a]pyrimidin-4-one and 9-[(4-acetyl-3-hydroxy-2-n-propylenoxy)methyl]-3-[[H-tetrazol-5-y]methyl]-4H-pyrido[1,2-a]pyrimidin-4-one, as well as the potassium salts thereof.

10. The use of a compound as claimed in any one of claims 1 to 4 for the manufacture of a medicament for the treatment of allergic diseases.

II. The use as claimed in claim 10 wherein the allergic disease is bronchial asthma and/or allergic rhinitis.
Claims for the contracting states: AT, ES, GR

1. A process for preparing a pyrido[1,2-a]pyrimidine derivative of general formula [I]:

\[
\begin{align*}
    & \text{CH}_3\text{C} & \text{HO} & \text{OCH}_2 & \text{R} \\
    & \text{CH}_2\text{CH}_2\text{CH}_3 & & & \text{N} & \text{N} \\
\end{align*}
\]

where R is a hydrogen atom, a halogen atom or a methyl group, and n is 0, 1 or 2 or a physiologically acceptable salt thereof, which comprises reacting a nitrile derivative of general formula [II]:

\[
\begin{align*}
    & \text{CH}_3\text{C} & \text{HO} & \text{OCH}_2 & \text{R} \\
    & \text{CH}_2\text{CH}_2\text{CH}_3 & & & \text{CN} \\
\end{align*}
\]

where R and n are as previously defined, with hydrazoic acid or a salt thereof; and then optionally forming a salt thereof.

2. A process as claimed in claim 1 wherein the salt of hydrazoic acid is an alkali metal salt selected from the group consisting of sodium azide and potassium azide, an alkaline-earth metal salt selected from the group consisting of calcium azide and magnesium azide, a salt formed by reaction with other metal selected from the group consisting of aluminum azide, tin azide and titanium azide or a salt formed by reaction with an organic base selected from the group consisting of ammonium azide and aniline azide.

3. A process as claimed in claim 2 wherein the alkali metal salt is used in combination with a Lewis acid such as aluminum chloride or tin chloride, or a suitable salt such as ammonium chloride or aniline chloride to be converted into aluminum azide, tin azide, ammonium azide or aniline azide in the reaction system.

4. A process as claimed in any one of claims 1, 2 and 3 wherein the reaction is carried out in a reaction solvent selected from the group consisting of tetrahydrofuran, dioxane, dimethylformamide, dimethyl sulfoxide, dimethylacetamide, hexamethylphosphorotriamide for 1 minute to 72 hours at a temperature of 50 to 150°C.

5. A process as claimed in any one of claims 1 to 4 where a resulting compound of formula [I] as defined in claim 1 is purified by converting it to a suitable salt thereof and then neutralizing this salt to effect crystallization.

6. A process as claimed in claim 5 wherein the suitable salt is sodium salt, potassium salt, calcium salt, magnesium salt or ammonium salt, and the neutralizing agent is hydrochloric acid, sulfuric acid, nitric acid, acetic acid or formic acid.

7. A process as claimed in any one of claims 1 to 4 wherein the treatment for the formation of a salt is carried out by using sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydroxide or potassium hydroxide.

8. A process as claimed in claim 1 where the nitrile derivative of formula [II] as defined in claim 1 is prepared by condensing 1 mole of a compound of general formula [III]:

\[
\begin{align*}
    & \text{R} & \text{XCH}_2 & \text{N} & \text{O} & \text{CN} \\
\end{align*}
\]
where R and n are as defined in claim 1, and X is a chlorine or bromine atom, with 1 to 6 moles of 2,4-dihydroxy-3-n-propylacetophenone in the presence of an acid acceptor.

9. A process for preparing a pharmaceutical composition useful for the treatment of allergic diseases which comprises admixing a compound of formula [1] as defined in claim 1 or a physiologically acceptable salt thereof with one or more physiologically inert solid or liquid pharmaceutical carriers.

10. A process as claimed in claim 9 wherein the allergic diseases include bronchial asthma and allergic rhinitis.

Patentansprüche für die Vertragsstaaten: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Pyrido[1,2-a]pyrimidinderivate der allgemeinen Formel

\[
\begin{align*}
\text{CH}_3 & \quad \text{N} \\
\text{CH}_2 & \quad \text{N} \\
R & \quad \text{N} \\
\text{OCH}_2 & \\
\text{CH}_2 & \quad \text{CH}_2 \\
\end{align*}
\]

wobei R ein Wasserstoffatom, eine Halogenatom oder eine Methylgruppe und n 0, 1 oder 2 oder ein physiologisch akzeptables Salz davon ist.

2. Verbindung nach Anspruch 1, die eine der folgenden Verbindungen darstellt:

- 9'-[(4-Acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-3-(1H-tetrazol-5-yl)-4H-pyrido[1,2-a]pyrimidin-4-on,
- 7'-[(4-Acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-3-(1H-tetrazol-5-yl)-4H-pyrido[1,2-a]pyrimidin-4-on,
- 8'-[(4-Acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-3-(1H-tetrazol-5-yl)-4H-pyrido[1,2-a]pyrimidin-4-on,
- 9'-[(4-Acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-7-brom-3-(1H-tetrazol-5-yl)-4H-pyrido[1,2-a]pyrimidin-4-on,
- 9'-[(4-Acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-7-brom-3-(1H-tetrazol-5-yl)-4H-pyrido[1,2-a]pyrimidin-4-on,
- 7'-[(4-Acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-3-(1H-tetrazol-5-yl)-4H-pyrido[1,2-a]pyrimidin-4-on,
- 9'-[(4-Acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-7-brom-3-(1H-tetrazol-5-yl)-4H-pyrido[1,2-a]pyrimidin-4-on,
- 8'-[(4-Acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-7-brom-3-(1H-tetrazol-5-yl)-4H-pyrido[1,2-a]pyrimidin-4-on.

3. Verbindung nach Anspruch 1, dadurch gekennzeichnet, daß das physiologisch akzeptable Salz ein Kalium- oder Natriumsalz ist.

4. Verbindung nach Anspruch 3, welche ein Kaliumsalz mit der chemischen Formel 9'-(4-Acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-3-(1H-tetrazol-5-yl)-4H-pyrido[1,2-a]pyrimidin-4-on oder 9'-[(4-Acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-7-brom-3-[2-(1H-tetrazol-5-yl)]äthyl]-4H-pyrido[1,2-a]pyrimidin-4-on ist.

5. Verfahren zur Herstellung von Pyrido[1,2-a]pyrimidinderivaten der allgemeinen Formel
wo R ein Wasserstoffatom, ein Halogenatom oder eine Methylgruppe repräsentiert und n 0, 1 oder 2 und physiologisch akzeptable Salze davon darstellt, beinhaltend die Reaktion eines Nitrilerivats der allgemeinen Formel

wo R und n wie oben definiert sind, mit Stickstoffwasserstoffsäure oder einem Salz dieser Säure und anschließend gegebenenfalls Bildung eines Salzes davon.


7. Verfahren nach einem der Ansprüche 5 oder 6, dadurch gekennzeichnet, daß die Behandlung zur Bildung eines Salzes unter Verwendung von Kaliumhydroxid oder Natriumhydroxid durchgeführt wird.

8. Pharmazeutische Zusammensetzung beinhaltend ein Pyrido[1,2-a]pyrimidinderivat der allgemeinen Formel

wobei R ein Wasserstoffatom, ein Halogenatom oder eine Methylgruppe und n 0, 1 oder 2 oder ein physiologisch akzeptables Salz davon ist.

9. Pharmazeutische Zusammensetzung nach Anspruch 8, dadurch gekennzeichnet, daß die Verbindung von Formel I aus der aus 9-[(4-Acetyl-3-hydroxy-2-n-propyloxy)phenoxymethyl]-3-(1H-tetrazol-5-yI)-4H-pyrido[1,2-a]pyrimidin-4-on, 9-[(4-Acetyl-3-hydroxy-2-n-propyloxy)phenoxymethyl]-3-(1H-tetrazol-5-yI)methyl-4H-pyrido[1,2-a]pyrimidin-4-on und 9-[(4-Acetyl-3-hydroxy-2-n-propyloxy)phenoxymethyl]-3-[2-(1H-tetrazol-5-yI)äthyl]-4H-pyrido[1,2-a]pyrimidin-4-on bestehenden Gruppe sowie den Kaliumsalzen derselben gewählt wird.

10. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 4 zur Herstellung eines Medikament zur Behandlung allergischer Krankheiten.

11. Verwendung nach Anspruch 10, dadurch gekennzeichnet, daß die allergische Krankheit Bronchialasthma und/oder Heuschnupfen ist.
Patentansprüche für die Vertragsstaaten: AT, ES, GR

1. Verfahren zur Herstellung eines Pyrido[1,2-a]pyrimidinderivats der allgemeinen Formel [I]:

wobei R ein Wasserstoffrest, eine Halogenatome oder eine Methylgruppe und n 0, 1 oder 2 oder ein physiologisch akzeptables Salz davon ist, beinhaltend die Reaktion eines Nitriderivats der allgemeinen Formel [II]:

wobei R und n wie oben definiert sind, mit Stickstoffwasserstoffsäure oder einem Salz dieser Säure und anschließend gegebenenfalls Bildung eines Salzes daraus.


4. Verfahren nach einem der Ansprüche 1, 2 und 3, dadurch gekennzeichnet, daß die Reaktion bei einer Temperatur von 50 bis 150°C 1 Minute bis 72 Stunden lang in einem Reaktionslösungsmittel durchgeführt wird, das aus der Tetrahydrofuran, Dioxan, Dimethylformamid, Dimethylsulfoxid, Dimethylacetamid und Hexamethylphosphortriämid umfassenden Gruppe gewählt wird.

5. Verfahren nach einem der Ansprüche 1 bis 4, bei dem eine sich ergebende Verbindung der Formel [I], gemäß der Definition von Anspruch 1, gereinigt wird, indem man sie in ein geeignetes Salz daraus umwandelt und dieses Salz dann zum Zweck der Kristallisation neutralisiert.


7. Verfahren nach einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, daß die Behandlung zur Bildung eines Salzes unter Verwendung von Natriumhydroxid, Kaliumhydroxid, Natriumkarbonat, Kaliumpotassium oder Kaliumalkoholat durchgeführt wird.

8. Verfahren nach Anspruch 1, wobei das Nitriderivat der Formel [II], wie in Anspruch 1 definiert, durch Kondensation eines Mols einer Verbindung der allgemeinen Formel [III]:
Revidications pour les états contractants: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Dérivé de la pyrido[1,2-a]pyrimidine répondant à la formule générale:

2. Composé selon la revendication 1 qui est l'un des composés suivants:
   9-[(4-acétyl-3-hydroxy-2-n-propylphénoxy)méthyl]-3-(1H-tétrazoil-5-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
   7-[(4-acétyl-3-hydroxy-2-n-propylphénoxy)méthyl]-3-(1H-tétrazoil-5-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
   8-[(4-acétyl-3-hydroxy-2-n-propylphénoxy)méthyl]-3-(1H-tétrazoil-5-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
   9-[(4-acétyl-3-hydroxy-2-n-propylphénoxy)méthyl]-7-bromo-3-(1H-tétrazoil-5-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
   9-[(4-acétyl-3-hydroxy-2-n-propylphénoxy)méthyl]-7-méthyl-3-(1H-tétrazoil-5-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
   9-[(4-acétyl-3-hydroxy-2-n-propylphénoxy)méthyl]-3-(1H-tétrazoil-5-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
   7-[(4-acétyl-3-hydroxy-2-n-propylphénoxy)méthyl]-3-(1H-tétrazoil-5-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
   9-[(4-acétyl-3-hydroxy-2-n-propylphénoxy)méthyl]-7-méthyl-3-[1H-tétrazoil-5-yl]méthyl]-4H-pyrido[1,2-a]pyrimidin-4-one,
   9-[(4-acétyl-3-hydroxy-2-n-propylphénoxy)méthyl]-7-bromo-3-[1H-tétrazoil-5-yl]éthyl]-4H-pyrido[1,2-a]pyrimidin-4-one,
   8-[(4-acétyl-3-hydroxy-2-n-propylphénoxy)méthyl]-3-[2-(1H-tétrazoil-5-yl)éthyl]-4H-pyrido[1,2-a]pyrimidin-4-one ou
   9-[(4-acétyl-3-hydroxy-2-n-propylphénoxy)méthyl]-7-bromo-2-[2-(1H-tétrazoil-5-yl)éthyl]-4H-pyrido[1,2-a]pyrimidin-4-one.

3. Composé selon la revendication 1, dans lequel le sel physiologiquement acceptable est un sel de potassium ou de sodium.

4. Composé selon la revendication 3, qui est le sel de potassium de la 9-[(4-acétyl-3-hydroxy-2-n-propylphénoxy)méthyl]-3-[1H-tétrazoil-5-yl]-4H-pyrido[1,2-a]pyrimidin-4-one ou le sel de potassium de la 9-[(4-acétyl-3-hydroxy-2-n-propylphénoxy)méthyl]-3-[2-(1H-tétrazoil-5-yl)éthyl]-4H-pyrido[1,2-a]pyrimidin-4-one.
5. Procédé de préparation de dérivés de la pyrido[1,2-a]pyrimidine répondant à la formule générale:

[Chemical structure diagram]

dans laquelle R est un atome d'hydrogène, un atome d'halogène ou un groupe méthyle, et n est 0, 1 ou 2, et leurs sels physiologiquement acceptables, qui comprend le fait de faire réagir un dérivé nitrile répondant à la formule générale:

[Chemical structure diagram]

dans laquelle R et n sont tels que précédemment définis, avec l'acide hydrazolique ou un de ses sels, puis facultativement de former un sel de ceux-ci.

6. Procédé selon la revendication 5, dans lequel le sel de l'acide hydrazolique est l'azide d'aluminium ou l'azide d'ammonium formé dans le système réactionnel en utilisant l'azide de sodium en association avec le chlorure d'aluminium ou le chlorure d'ammonium, respectivement.

7. Procédé selon l'une ou l'autre des revendications 5 et 6, dans lequel le traitement pour la formation d'un sel est effectué en utilisant de l'hydroxyde de potassium ou de l'hydroxyde de sodium.

8. Composition pharmaceutique comprenant un dérivé de la pyrido[1,2-a]pyrimidine répondant à la formule générale:

[Chemical structure diagram]

dans laquelle R est un atome d'hydrogène, un atome d'halogène ou un groupe méthyle, et n est 0, 1 ou 2, ou un de ses sels physiologiquement acceptables.

9. Composition pharmaceutique selon la revendication 8, dans laquelle le composé répondant à la formule I est choisi dans le groupe constitué de la 9-{[4-acétyl-3-hydroxy-2-n-propylphénoxy]méthyl}-3-(1H-tétrazol-5-y1)-4H-pyrido[1,2-a]pyrimidin-4-one, de la 9-{[4-acétyl-3-hydroxy-2-n-propylphén oxy]méthyl}-3-{[1H-tétrazol-5-y1]méthyl}-4H-pyrido[1,2-a]pyrimidin-4-one et de la 9-{[4-acétyl-3-hydroxy-2-n-propylphén oxy]méthyl}-3-{[2-(1H-tétrazol-5-y1)éthyl]}-4H-pyrido[1,2-a]pyrimidin-4-one, ainsi que de leurs sels de potassium.

10. Utilisation d'un composé selon l'une quelconque des revendications 1 à 4, pour la fabrication d'un médicament pour le traitement des maladies allergiques.

11. Utilisation selon la revendication 10, dans laquelle la maladie allergique est l'asthme bronchique et/ou la rhinite allergique.
Revendications pour les états contractants: AT, ES, GR

1. Procédé de préparation d'un dérivé de la pyrido[1,2-a]pyrimidine répondant à la formule générale (I):

\[
\text{[I]}
\]

dans laquelle R est un atome d'hydrogène, un atome d'halogène ou un groupe méthyle et n est 0, 1 ou 2, ou un de ses sels physiologiquement acceptables, qui comprend le fait de réagir un dérivé nitrile répondant à la formule générale (II):

\[
\text{[II]}
\]

dans laquelle R et n sont tels que précédemment définis, avec l'acide hydroxolique ou un de ses sels, puis de former si on le désire un sel de celui-ci.

2. Procédé selon la revendication 1, dans lequel le sel de l'acide hydroxolique est un sel de métal alcalin choisi dans le groupe constitué de l'azide de sodium et de l'azide de potassium, un sel de métal alcalino-terreux choisi dans le groupe constitué de l'azide de calcium et de l'azide de magnésium, un sel formé par réaction avec un autre métal choisi dans le groupe constitué de l'azide d'aluminium, de l'azide d'étain, et de l'azide de titane ou un sel formé par réaction avec une base organique choisi dans le groupe constitué de l'azide d'ammonium et de l'azide d'aniline.

3. Procédé selon la revendication 2, dans lequel le sel de métal alcalin est utilisé en association avec un acide de Lewis tel que le chlorure d'aluminium ou le chlorure d'étain, ou un sel approprié tel que le chlorure d'ammonium ou le chlorure d'aniline pour être transformé en azide d'aluminium, en azide d'étain, en azide d'ammonium ou en azide d'aniline dans le système réactionnel.

4. Procédé selon l'une quelconque des revendications 1, 2 et 3, dans lequel la réaction est effectuée dans un solvant réactionnel choisi dans le groupe constitué du tétrahydrofurane, du dioxyane, du diméthylformamide, du sulfonyde de diméthyle, du diméthylacétamide, de l'hexaméthylphosphorotriamide pendant 1 minute à 72 heures à une température de 50 à 150°C.

5. Procédé selon l'une quelconque des revendications 1 à 4, dans lequel le composé répondant à la formule (I) tel que défini dans la revendication 1 obtenu est purifié en le transformant en un de ses sels appropriés, puis en neutralisant ce sel pour effectuer la cristallisation.

6. Procédé selon la revendication 5, dans lequel le sel approprié est le sel de sodium, le sel de potassium, le sel de calcium, le sel de magnésium ou le sel d'ammonium, et l'agent neutralisant est l'acide chlorhydrique, l'acide sulfurique, l'acide nitrique, l'acide acétique ou l'acide formique.

7. Procédé selon l'une quelconque des revendications 1 à 4, dans lequel le traitement pour la formation d'un sel est effectué en utilisant l'hydroxyde de sodium, l'hydroxyde de potassium, le carbonate de sodium, le carbonate de potassium, un alcoolate de sodium ou un alcoolate de potassium.

8. Procédé selon la revendication 1, dans lequel le dérivé nitrile répondant à la formule (II) tel que défini dans la revendication 1 est préparé en condensant 1 mole d'un composé répondant à la formule générale (II):
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dans laquelle R et n sont tels que définis dans la revendication 1, et X est un atome de chlore ou de bromo, avec 1 à 6 moles de 2,4-dihydroxy-3-n-propylacétophénone en présence d'un accepteur d'acide.

9. Procédé de préparation d'une composition pharmaceutique utilisable pour le traitement de maladies allergiques, qui comprend le fait de mélanger un composé répondant à la formule (I) tel que défini dans la revendication 1, ou un de ses physiologiquement acceptables avec un ou plusieurs supports pharmaceutiques solides ou liquides, physiologiquement inertes.

10. Procédé selon la revendication 9, dans lequel les maladies allergiques comprennent l'asthme bronchique et la rhinite allergique.