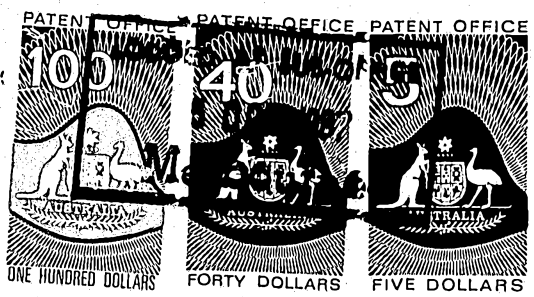
(CONVENTION. By one or more persons and/

COMMONWEAL

Patents



APPLICATION ACCEPTED AND AMENDMENTS ALLOWED 23-1-90

CONVENTION APPLICATION FOR A PATENT

FEE STAMP TO VALUE OF $.....145..... ATTACHED
MAIL OFFICER.....

(1) Here insert (in full) Name or Names of Applicant or Applicants, followed by Address (es).

We (1) HOECHST JAPAN LIMITED

of 10-16, 8-chome, Akasaka, Minato-ku, Tokyo, Japan

hereby apply for the grant of a Patent for an invention entitled: (2)

(2) Here insert Title of Invention.

THERAPEUTIC AGENT FOR THE TREATMENT OF PEPTIC ULCER DISEASE

which is described in the accompanying complete specification. This application is a Convention application and is based on the application numbered (3)

(3) Here insert number(s) of basic application(s)

236078/86

for a patent or similar protection made in (4) Japan

(4) Here insert Name of basic Country or Countries, and basic date or dates

on 6th October 1986

My/Our address for service is Messrs. Edwd. Waters & Sons, Patent Attorneys, 50 Queen Street, Melbourne, Victoria, Australia.

DATED this 2nd day of October 19 87

(5) Signature (s) of Applicant (s) or Seal of Company and Signatures of its Officers as prescribed by its Articles of Association.

(5) HOECHST JAPAN LIMITED

BY James Murray

James Murray

Registered Patent Attorney

LODGED AT SUB-OFFICE
5 OCT 1987
Melbourne

To:

Form 8

COMMONWEALTH OF AUSTRALIA

Patents Act 1952

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION UNDER PART XVI. FOR A PATENT.

In support of the Convention application made under Part XVI. of the Patents Act 1952 by HOECHST JAPAN LIMITED of 10-16, 8 chome, Asaka, Minato-ku, Tokyo, Japan for a patent for an invention entitled: Therapeutic agent for the treatment of peptic ulcer disease

Horst Waesche of

I, Apt. 2W 1-3-8 Jingumae, Shibuya-ku, Tokyo Japan

do solemnly and sincerely declare as follows:

1. I am authorized by HOECHST JAPAN LIMITED, the applicant for the patent to make this declaration on its behalf.

2. The basic application as defined by Section 141 of the Act was made in Japan
under No. 236078/86 on October 6, 1986
by HOECHST JAPAN LIMITED

3. a) Masao Sakurai, 2168-38 Takahagi, Hidaka-cho, Iruma-gun, Saitama-ken
b) Masayoshi Goto, 10-22-403, 3-chome, Takashimadaira, Itabashi-ku, Tokyo
c) Toshizo Tanaka, 9-1 Asahi-cho 2-chome, Kawagoe-shi, Saitama-ken
a) - c) Japan

is/are the actual inventor(s) of the invention and the facts upon which
HOECHST JAPAN LIMITED
is entitled to make the application are as follows:
The said
HOECHST JAPAN LIMITED
is the assignee of the said
Masao Sakurai, Masayoshi Goto, Toshizo Tanaka

4. The basic application referred to in paragraph 2 of this Declaration was the first application made in a Convention country in respect of the invention the subject of the application.

DECLARED at Tokyo

this 28th day of July, 1987

HOECHST JAPAN LIMITED

H. Waesche - President

To the Commissioner of Patents

PAT 510

(12) PATENT ABRIDGMENT (11) Document No. AU-B-79358/87
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 595379

(54) Title
THERAPEUTIC AGENT FOR THE TREATMENT OF PEPTIC ULCER DISEASE

International Patent Classification(s)
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61-236078 06.10.86 JP JAPAN

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HOECHST JAPAN LIMITED

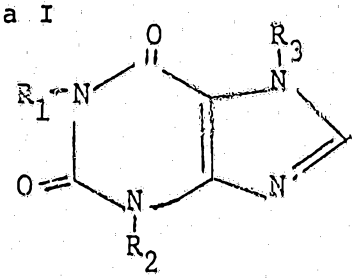
(72) Inventor(s)
MASAO SAKURAI; MASAYOSHI GOTO; TOSHIZO TANAKA

(74) Attorney or Agent
WATERMARK MELBOURNE

(56) Prior Art Documents
US 4289776
US 4511557
CA 1075690

(57) Claim

1. A method of treating a person suffering from peptic ulcer disease which comprises administering to such persons an effective amount of at least one compound of the general formula I



(I)

R_1 = 4-oxopentyl or 5-oxohexyl
R_2 = methyl or ethyl, and
R_3 = C_2-C_4-alkyl

in conjunction with a pharmaceutically acceptable carrier or excipient in the form of a pharmaceutical composition.

Form 10

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952-69

COMPLETE SPECIFICATION

(ORIGINAL)

Class Int. Class

Application Number:
Lodged:

595379

Complete Specification Lodged:
Accepted:
Published:

Priority :

Related Art :

This document contains the amendments made under Section 49 and is correct for printing.

Name of Applicant : HOECHST JAPAN LIMITED

Address of Applicant : 10-16, 8-chome, Akasaka, Minato-ku, Tokyo, Japan

Actual Inventor: MASAO SAKURAI, MASAYOSHI GOTO and TOSHIZO TANAKA

Address for Service : EDWD. WATERS & SONS,
50 QUEEN STREET, MELBOURNE, AUSTRALIA, 3000.

Complete Specification for the invention entitled:

THERAPEUTIC AGENT FOR THE TREATMENT OF PEPTIC ULCER DISEASE

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

HOECHST JAPAN LIMITED HOE 86/S 028 Dr.ME

THERAPEUTIC AGENT FOR THE TREATMENT OF PEPTIC ULCER DISEASE

This invention relates to pharmaceuticals suitable for use in the treatment of peptic ulcer disease. Peptic ulcer is an ulceration of the mucous membrane of the stomach and/or duodenum; the mucous membrane is damaged by the action of hydrochloric acid and pepsin due to its decreased resistance to the aggressive factors induced by various causes including physical and physiological stress.

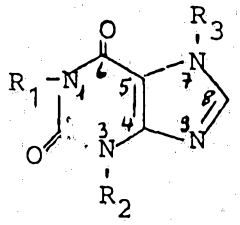
Until recently, sodium bicarbonate and aluminum compounds had been used to neutralize gastric acid as aggressive factor. The drugs commonly used now to treat peptic ulcer disease include anticholinergics, gastroprotective agents, drugs improving mucosal blood flow, and H_2-receptor antagonists.

Drugs for peptic ulcers are administered for a long period of time and are required to have the fewest adverse effects as well as high efficacy. However, the available drugs are not necessarily satisfactory in safety and efficacy. In addition there is another problem associated with the use of the drugs, namely the relapse of ulcer after drug treatment is stopped. For example, the H_2-receptor antagonists are very effective in improving gastric and duodenal ulcers by inhibiting gastric acid secretion but ulcers recur at high incidence after discontinued treatment with the drugs.

As a result of our extensive studies for superior therapeutics for peptic ulcer disease, we have found that 1,2,3,6-tetrahydro-3-methyl-1-(5-oxchexyl)-7-propyl-purine-2,6-dione (recommended International Nonproprietary Name:

propentofylline) and related compounds have high efficacy and safety enough to be new drugs suitable for use in the treatment of the disease.

The present invention provides a therapeutic agent for the treatment of peptic ulcer disease containing, as active ingredient, at least one compound of the general formula I



(I)

wherein R_1 is 4-oxopentyl or 5-oxohexyl, R_2 is methyl or ethyl, and R_3 is C_2-C_4-alkyl.

Propentofylline of the above general formula wherein R_1 is 5-oxohexyl, R_2 is methyl, and R_3 is propyl is a xanthine derivative which has been shown to dilate cerebral blood vessels, improve cerebral energy metabolism, red blood cell deformability, and cerebral edema, and decrease blood viscosity (c.f. for example, U.S. Patent No. 4,289,776). We have found that in addition to the above pharmacological effects propentofylline and related compounds have improving effects on gastric ulcer. Pentoxifylline, substituted by methyl at the 7-position in propentofylline, has already been reported by Vorobyev and Samsonov to have antiulcer effects (Ter. Ark. 57, 52-55, 1985). However, the efficacy is not high enough to be a promising drug for peptic ulcer disease. The compounds of this invention have been shown, as described below, to be much more effective than pentoxifylline and to have low toxicity, indicating that they are effective antiulcer drugs producing a low incidence of side effects.

Possible administration routes of the compounds of this invention are oral, intravenous, subcutaneous, preferably intramuscular, and rectal. The clinical dose is about 300 - 900 mg/60 kg body weight, more preferably about 150 - 600 mg/60 kg body weight. Usable dosage forms are tablets, sugar-coated tablets, pills, capsules, powders, granules, suppositories, and injections. The tablets, sugar-coated tablets, capsules, and granules are desirable for oral, the injections for parenteral, and the suppositories for rectal administration.

The compounds of this invention can be used each as a monopharmacon or as a combination or in combination with other agents for the treatment of peptic ulcer disease including antacids.

For injection, the powder for injection is usable. In this case, the compounds of this invention are dissolved in water containing one or more adequate water-soluble excipients such as mannitol, sucrose, lactose, maltose, glucose, and fructose. Then the solution is put into the vial or ampule, which is sealed after lyophilization of the contents.

For oral administration, an enteric-coated preparation is possible in addition to the dosage forms listed above. In this case, the tablets, granules, or fine granules are prepared using the following as additives as required: excipients such as mannitol, sucrose, lactose, maltose, starch, silica, and calcium phosphate; lubricants such as talc and magnesium stearate; binders such as sodium carboxymethylcellulose, methylcellulose, gelatin, and gum arabic; and disintegrating aids such as calcium carboxymethylcellulose. Then, the tablets, granules, or fine granules are coated with one or more enteric bases with, if

required, a coloring agent such as titanium dioxide. The bases for enteric coating include cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetylsuccinate, polyvinyl alcohol phthalate, styrene-maleic anhydride copolymers, styrene-maleic acid copolymers, methyl methacrylate-methacrylic acid copolymers, and methyl acrylate-methacrylic acid copolymers. The enteric-coated granules or fine granules are preferably filled into capsules.

Enteric-coated capsules can be obtained by coating capsules manufatured by a conventional method with one or more of the enteric bases listed above or by manufacturing capsules with an enteric base alone or in admixture with gelatin.

Suppositories can be prepared as follows. The compounds of this invention are mixed homogenously with (a) a lipophilic base such as cacao butter or adeps solidus in various proportions or (b) a hydrophilic base such as polyethylene glycol or glycerol. The mixture containing the compounds of this invention is put into molds.

The weight ratio of the active ingredient(s) of the formula I and the respective carrier or excipient can vary within a very wide range; preferably it is within the range of about 1:100 to about 100:1.

The antiulcer effects and the toxicological profile of the compounds of this invention were as follows. The compounds tested are shown in Table 1. Pentoxifylline = 1,2,3,6-tetrahydro-3,7-dimethyl-1-(5-oxohexyl)-purine-2,6-dione was used as a reference drug for the pharmacological studies.

Table 1 Compounds of this invention

Compound No.	R_1	R_2	R_3
1	$CH_3-\overset{\overset{O}{\|}}{C}-(CH_2)_4-$	$-CH_3$	$-C_2H_5$
2*	$CH_3-\overset{\overset{O}{\|}}{C}-(CH_2)_4-$	$-CH_3$	$-(CH_2)_2-CH_3$
3	$CH_3-\overset{\overset{O}{\|}}{C}-(CH_2)_3-$	$-CH_3$	$-(CH_2)_2-CH_3$
Pentoxifylline (Reference)	$CH_3-\overset{\overset{O}{\|}}{C}-(CH_2)_4-$	$-CH_3$	$-CH_3$

* Propentofylline

1. Antiulcer effects

1.1 Protective effect on gastric ulcer induced by restraint plus water-immersion stress in rats

Male Sprague-Dawley rats weighing 250 - 300 g were used in groups of 5 - 24. The animals were given the compounds by the oral route after fasting overnight. Immediately, under light ether anesthesia they were placed in a restraint box and immersed in water at 20°C for 6 or 7 hours. Then the animals were sacrificed, and their stomachs were isolated, inflated with 4 ml of 1 % formalin for 10 minutes, opened along the greater curvature, and examined for the presence of gastric erosions. The longest axis of each erosion induced on the glandular section of the stomach was measured, and the sum of the lengths was defined as an ulcer index. The results are shown in Tables 2 and 3.

Table 2 Protective effect on stress-induced gastric ulcer in rats (Dose dependency)

Compound	Dose (mg/kg, po)	No. of animals	Ulcer index (mm)	Inhibition (%)
Control (Distilled water)	0	12	37.3±5.1	-
Compound 2 (=propento-fylline)	5	6	22.6±9.8	39.4
	10	6	13.3±5.4*	64.3
	25	6	9.1±3.1*	75.6
Control (Distilled water)	0	10	32.9±5.9	-
Pentoxi-fylline	10	10	24.4±4.0	25.8
	25	10	15.8±4.1*	52.0
	50	8	5.3±1.2**	83.9

** $P < 0.01$, * $P < 0.05$ (P = significance)

Each value represents the mean±S.E. (Standard Error)

Table 3 Protective effect on stress-induced gastric ulcer in rats (Efficacy comparison)

Compound	Dose (mg/kg, po)	No. of animals	Ulcer index (mm)	Inhibition (%)
Control (Distilled water)	0	24	19.7±2.9	-
Compound 1	10	5	4.5±0.9**	77.2
2	10	5	8.6±2.3*	56.3
3	10	5	6.5±1.6**	67.0
Pentoxi-fylline	10	5	17.2±5.6	12.7

** $P < 0.01$, * $P < 0.05$

Each value represents the mean±S.E.

1.2 Protective effect on ethanol-induced gastric ulcer in rats

Male Sprague-Dawley rats weighing 250 - 300 g were used in groups of 5 - 21. After fasting overnight, the animals were given orally the compounds. Thirty minutes later they received absolute ethanol (1 ml/body) orally and were sacrificed after 60 minutes. The stomach was removed and examined for erosions. The ulcer index was obtained in the same way as under 1.1. The results are shown in Tables 4 and 5.

Table 4 Protective effect on ethanol-induced gastric ulcer in rats (Dose dependency)

Compound	Dose (mg/kg, po)	No. of animals	Ulcer index (mm)	Inhibition (%)
Control (Distilled water)	0	14	132.5±12.3	-
Compound 2	10	10	51.0±13.2**	61.5
	25	10	32.6± 9.1**	75.4
	50	8	13.6± 9.3**	89.7
Pentoxifylline	10	10	65.8±12.1**	50.3
	25	10	47.8±15.3	63.9
	50	10	18.7± 6.2**	85.9

** $P < 0.01$

Each value represents the mean±S.E.

Table 5 Protective effect on ethanol-induced gastric ulcer in rats (Efficacy comparison)

Compound	Dose (mg/kg, po)	No. of animals	Ulcer index (mm)	Inhibition (%)
Control (Distilled water)	0	21	164.7±19.4	-
Compound 1	10	5	25.3±10.9**	84.6
2	10	5	21.6± 4.6**	86.9
Pentoxifylline	10	5	34.9±10.9**	78.8

** $P < 0.01$

Each value represents the mean±S.E.

1.3 Inhibitory effect on gastric hemorrhage in rats

The method of Maeda-Hagiwara and Watanabe (Eur. J. Pharmacol. 89, 243-250, 1983) was used. Male Sprague-Dawley rats weighing 250 - 350 g were employed in groups of 10 - 14. After 24 hours fasting, the pylorus was ligated under light ether anesthesia. Then, 200 mg/kg of 2-deoxy-D-glucose was administered intravenously in combination with 40 mg/kg of indomethacin suspended in 0.5 % carboxymethyl-cellulose by the subcutaneous route. After 1 hour the test compounds were injected intraperitoneally. Two hours later, the animals were exsanguinated under ether anesthesia and their stomachs were isolated. Gastric juice was collected and filtered. The amount of discharged blood was expressed as that of hemoglobin in mg per rat. The results are given in Table 6.

Table 6 Inhibitory effect on gastric hemorrhage in rats

Compound	Dose (mg/kg, ip)	No. of animals	Amount of hemoglobin (mg/rat)
Control (Physiological saline)	0	14	26.0±3.8
Compound 2	12.5	10	27.0±3.0
	25	10	14.4±1.4*
	50	10	12.5±1.6**
Pentoxifylline	25	10	19.6±2.0
	50	10	17.3±2.3

** $P < 0.01$, * $P < 0.05$

Each value represents the mean±S.E.

2. Toxicological profile

LD_{50} values of compound 2 for mice and rats were 900 and 1,150 mg/kg for oral dosing and 168 and 180 mg/kg for intravenous injection, respectively. Comparable LD_{50} values for the compounds of this invention were found after intraperitoneal administration to mice with 250 - 500 mg/kg for compound 1, 296 mg/kg for compound 2, and 300 - 600 mg/kg for compound 3.

Compound 2 was administered orally to rats at 150 and 50 mg/kg/day for 3 months. This study included: observation of toxic signs during the treatment; macroscopic and microscopic examinations of main organs including the brain, heart, liver, kidney, bone marrow, adrenal, and lung; and biochemical tests of the blood and urine. There were no abnormalities at either level of treatment except that slight salivation occurred at 150 mg/kg/day.

Examples of the invention will be as follows.

Example 1

An injectable preparation was prepared as follows. Compound 2 (20 g) and sodium chloride (16 g) were added to distilled water for injection to make 2,000 ml. The solution was filtered through a 0.22 μm Millipore filter and divided at 5 ml into 5 ml ampules, which were sealed and sterilized in an autoclave.

Example 2

Tablets each containing 115 mg of Compound 2 were prepared by a conventional method from a mixture of 500 g of Compound 2 with 250 g of lactose, 150 g of corn starch, 150 g of calcium carboxymethylcellulose, 42 g of talc, 5 g of magnesium stearate, and 3 g of silica. The tablets were coated with a suspension containing 500 ml of water, 40 g of hydroxypropylmethylcellulose, 2 g of polyethyleneglycol with the average molecular weight of 6000, 3.5 g of titanium dioxide and 3 g of talc.

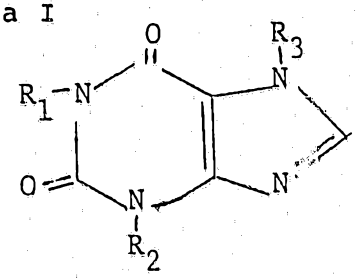
Effects of the invention:

As revealed by our studies described above, the compounds of this invention were shown to possess potent antiulcer effects and low toxicity. For example, Compound 2 was (a) approximately 2 to 3 times more effective than pentoxifylline in improving stress-induced gastric ulcers, and had (b) inhibitory effects on gastric hemorrhage while pentoxifylline did not have a statistically significant effect, and (c) low toxicity.

The results indicate that the compounds of this invention are potent therapeutics for peptic ulcer disease which possess an excellent tolerability and inhibit gastric hemorrhage in patients with peptic ulcers.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method of treating a person suffering from peptic ulcer disease which comprises administering to such persons an effective amount of at least one compound of the general formula I



(I)

R_1 = 4-oxopentyl or 5-oxohexyl
R_2 = methyl or ethyl, and
R_3 = C_2-C_4-alkyl

in conjunction with a pharmaceutically acceptable carrier or excipient in the form of a pharmaceutical composition.

2. A method as claimed in Claim 1 characterized in that in the general formula I

R_1 = 5-oxohexyl,
R_2 = methyl, and
R_3 = propyl.

3. A method as claimed in Claim 1 or 2 wherein said compound is administered in an amount of 300-900 mg/60 kg body weight of the person.

4. A method as claimed in Claim 1 or 2 wherein said

compound is administered in an amount of 150-600 mg/60 kg body weight of the person.

DATED this 2nd day of January, 1990

HOECHST JAPAN LTD

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