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<p>(21) International Application Number: PCT/JP96/02319 (22) International Filing Date: 20 August 1996 (20.08.96) (30) Priority Data: 7/228889 6 September 1995 (06.09.95) JP (71) Applicant (for all designated States except US): OTSUKA PHARMACEUTICAL CO., LTD. [JP/JP]; 9, Kanda-Tsukasacho 2-chome, Chiyoda-ku, Tokyo 101 (JP). (72) Inventors; and (75) Inventors/Applicants (for US only): TAKAHASHI, Toshio [JP/JP]; 6-5, Shugakuin Hinokitogecho, Sakyo-ku, Kyoto-shi, Kyoto 606 (JP). YAMANE, Tetsuro [JP/JP]; 5-21, Nishigamo Kamishodacho, Kita-ku, Kyoto-shi, Kyoto 603 (JP). (74) Agents: ASAMURA, Kiyoshi et al.; Room 331, New Ohtemachi Building, 2-1, Ohtemachi 2-chome, Chiyoda-ku, Tokyo 100 (JP).</p>		<p>(81) Designated States: AU, CA, CN, KR, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: USE OF A CARBOSTYRIL DERIVATIVE FOR INHIBITING CARCINOGENESIS</p>		
<div style="text-align: center;"> <p style="text-align: right;">(I)</p> </div>		
<p>(57) Abstract</p>		
<p>The present invention provides an agent for inhibiting carcinogenesis which comprises, as the active ingredient, a carbostyril derivative represented by general formula (I), (wherein R is a halogen atom) or a salt thereof.</p>		

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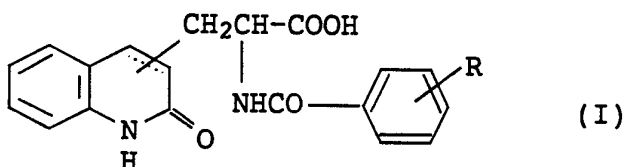
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DESCRIPTION

USE OF A CARBOSTYRIL DERIVATIVE FOR INHIBITING CARCINOGENESIS

FIELD OF THE INVENTION

The present invention relates to an agent for inhibiting carcinogenesis, specifically, it relates to an agent for inhibiting carcinogenesis of the digestive tract cancer. More particularly, the invention relates to an agent for inhibiting carcinogenesis comprising, as the active ingredient, a carbostyryl derivative represented by the following general formula (I),



[wherein R is a halogen atom (a fluorine atom, a chlorine atom, a bromine atom or an iodine atom); the substituted position of the substituent in the carbostyryl skeleton is 3- or 4-position in the carbostyryl skeleton; and the carbon-carbon bond between 3- and 4-positions in the carbostyryl skeleton is a single bond or a double bond]; or a salt thereof, preferably 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid or salt thereof.

BACKGROUND ART

The carbostyryl derivatives represented by the general formula (I) and processes for producing the same

are described in Japanese Patent Publication No. 63-35623, the usefulness of the carbostyryl derivatives as anti-gastric ulcer agents are described in Japanese Patent Application Kokai (Laid-open) No. 3-74329, and
5 processes for producing those carbostyryl derivatives having optical activities are described in Japanese Patent Application Kokai (Laid-open) No. 3-145468.

Further, inhibitory effect of carbostyryl derivatives of the present invention on reactive oxygen
10 metabolites is described in Japan. J. Pharmacol., Vol. 49, pp. 441-448 (1969), and the protectability of gastric mucous membrane by carbostyryl derivatives of the present invention is described in Folia Pharmacol. Japon., Vol. 97, pp. 371-380 (1991).

15 Furthermore, the usefulness of carbostyryl derivatives as agents for curing diabetes mellitus is described in International Publication No. WO 92/21342, the usefulness of carbostyryl derivatives as agents for protecting intestinal mucosa from disorders is described
20 in International Publication No. WO 94/12182, and the usefulness of carbostyryl derivatives as agents for inhibiting reduction in somatostatin secretion is described in International Publication No. WO 93/24043.

Hitherto, various terpenes, flavonoids and
25 steroids have been found as to the substances having the activity for inhibiting carcinogenesis. However, from a safety viewpoint, these substances have not been practically applied yet as to agents for inhibiting

carcinogenesis. Under the circumstances, it is expected the development of safety and effective substances for inhibiting carcinogenesis.

DISCLOSURE OF THE INVENTION

5 The present inventors have made an extensive study to find effective agents for inhibiting carcinogenesis. As a result, the inventors have found the fact that carbostyryl derivatives represented by the general formula (I) or salts thereof, particularly among of
10 these, 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid or a salt thereof possess excellent pharmacological activity for inhibiting carcinogenesis. Thus, the present invention has completed by said pharmacological finding.

15 In the present specification, the term "cancers" means cancers originated from the epitheliums existed in various parts of the body, for example, cancers originated from epitheliums of the skin, the tongue, the pharynx, the trachea, as well as cancers of
20 the digestive tracts, such as the esophagus, the stomach, the duodenum, the small intestine and the large intestine.

 The agents for inhibiting carcinogenesis of the present invention can be prepared into various forms
25 of common pharmaceutical preparations by formulating the carbostyryl derivative represented by the general formula (I) or a salt thereof.

The pharmaceutical preparations are prepared by formulating with commonly employed diluents or excipients, such as fillers, extenders, binders, wetting agents, disintegrants, surfactants, lubricants and the like. The pharmaceutical preparations can be shaped into various forms depending upon the curing purposes, thus, typical examples of the forms are tablets, pills, powders, liquid medicines, suspensions, emulsions, granules, capsules, suppositories, injection preparations (liquid, suspension and the like), aerosol preparations, syrup preparations and preparations for external use and the like. Further, sustained release preparations can also be prepared by formulating with suitable resins.

For the purpose of shaping into the form of tablets, any known carriers which are used widely in this field can be applied, for example, excipients such as lactose, white sugar, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose, silicic acid and the like; binders such as water, ethanol, propanol, simple syrup, glucose solution, starch solution, gelatin solution, carboxymethyl cellulose, shellac, methyl cellulose, potassium phosphate, polyvinyl pyrrolidone and the like; disintegrators such as dry starch, sodium alginate, agar powder, laminarin powder, sodium hydrogen-carbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulfate, monoglycerides of stearic

acid, starch, lactose and the like; disintegration inhibitors such as white sugar, stearin, cacao butter, hydrogenated oils and the like; absorption accelerators such as quaternary ammonium base, sodium lauryl sulfate and the like; humectants such as glycerin, starch and the like; adsorbents such as starch, lactose, kaolin, bentonite, colloidal silicic acid and the like; lubricants such as refined talc, stearic acid salts, boric acid powder, polyethylene glycols and the like.

10 In case of necessity, the tablets can be prepared in the form of common coated tablets, for example, sugar-coated tablets, gelatin film-coated tablets, enteric film-coated tablets, film-coated tablets, or in the form of double-layers tablets, multiple-layers tablets and the

15 like.

For the purpose of shaping into the form of pills, any known carriers which are widely used in this field can be applied, for example, excipients such as glucose, lactose, starch, cacao butter, hydrogenated

20 vegetable oils, kaolin, talc and the like; binders such as arabic gum powder, tragacanth gum powder, gelatin, ethanol and the like; and disintegrators such as laminarin, agar-agar and the like can be exemplified.

For the purpose of shaping into the form of

25 suppositories, any known carriers which are widely used in this field can be applied, for example, polyethylene glycols, cacao butter, higher alcohols, esters of higher

alcohol, gelatin, semi-synthesized glycerides and the like can be exemplified.

For the purpose of shaping into the form of injection preparations, they can be prepared to
5 solutions, emulsions or suspensions. Generally they are sterilized and preferably made isotonic to the blood. In preparing the injection preparations as in the form of solutions, emulsions or suspensions, any known diluents which are widely used in this field can be
10 applied. For example, water, ethanol, propylene glycol, ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol, fatty acid esters of polyoxyethylene sorbitan and the like can be exemplified. In the case of make the injection preparations isotonic to the blood,
15 sufficient amount of sodium chloride, glucose or glycerin may be contained therein. Additionally, a dissolving adjuvant, a buffer solution, an analgesic agent and the like which are commonly used may be contained therein. In case of necessity, a coloring
20 agent, a preservatives, a perfume, a flavoring agent, a sweetening agent and other medicines may be contained therein.

External preparations are prepared in the form of common pharmaceutical preparations for external use.
25 As to common pharmaceutical preparations for external use are including, for example, a liquid medicine, a medicinal oil, a lotion, a liniment, an oleoginous ointment, an emulsion type ointment, such as O/W type

hydrophilic ointment and W/O type water-absorbing ointment, a water-soluble ointment, a pasta, a plaster, a patch, a cream, an emulsion and the like, and these forms of pharmaceutical preparations for external use are not restricted within the scope of these examples. Each one of these forms of pharmaceutical preparations for external use can be prepared by common methods.

In shaping of these external preparations, various base materials which are widely used in this field can be also applied. For example, at least one oleoginuous base can be used singly, or mixture of two or more of them can be used widely; or at least one water-soluble ointment base can be used singly, or mixture of two or more of them can be used widely. Concrete examples of these ointment base are fats and oils such as peanut oil, sesame oil, soybean oil, safflower oil, avogado oil, sunflower oil, corn oil, rapeseed oil, cotton seed oil, castor oil, camellia oil, coconut oil, olive oil, poppy seed oil, cacao butter, beef tallow, lard, wool fat and the like; modified bases obtained by subjecting these fats and oils to chemical changes such as hydrogenation; mineral oils such as petrolatum, paraffin, silicone oil, squalane and the like; higher fatty acid esters such as isopropyl myristate, n-butyl myristate, isopropyl linoleate, acetyl ricinoleate, stearyl ricinoleate, propyl ricinoleate, isopropyl ricinoleate, isobutyl ricinoleate, heptyl ricinoleate, diethyl sebacate and diisopropyl adipate; higher

aliphatic alcohols such as cetyl alcohol and stearyl alcohol; waxes such as bleached bees wax, spermaceti, Japan wax, lanolin, carnauba wax, shellac wax and the like; higher fatty acids such as stearic acid, oleic acid, palmitic acid and the like; mixtures of mono-, di- and tri-glycerides of saturated or unsaturated fatty acids having 12 to 18 carbon atoms; polyhydric alcohols such as ethylene glycols, polyethylene glycols, propylene glycol, polypropylene glycols, glycerin, batyl alcohol, pentaerythritol, sorbitol, mannitol and the like; gummy substances such as arabic gum, benzoin gum, guaiacum, tragacanth gum and the like; water-soluble natural high molecular compounds such as gelatin, starch, casein, dextrin, pectin, sodium pectate, sodium alginate, methyl cellulose, ethyl cellulose, carboxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, nitrocellulose, crystalline cellulose and the like; water-soluble synthetic high molecular compounds such as polyvinyl alcohol, poly(vinyl methyl ether), polyvinyl pyrrolidone, sodium polyacrylate, carboxyvinyl polymer, polyethyleneimine and the like; nonionic, anionic, amphoteric and cationic surfactants; ethanol, isopropanol and water, can be exemplified.

To the pharmaceutical preparations for external use, there can be added common additives such as a gelling agent, a preservative, an antioxidant, a buffer solution, a pH controlling agent, a wetting

agent, an antiseptic agent, a coloring agent, a flavoring agent, a pigment, a thickening agent, a metal chelating agent and the like.

Aerosol type preparations can be prepared generally by formulating a sterilized solution or suspension of the carbostyryl derivative of the general formula (I) with a propellant. In case of shaping in the form of a solution or suspension, any one of known diluents which are commonly used in this field can also be used, thus the diluents which are exemplified in formulating the injection preparations can be used. As to the propellant, any one of the propellants which are commonly used in this field can also be used, thus, liquefied gas propellants such as chlorofluorocarbons like Flon-12 (general term of dichlorodifluoromethane) or Flon-123 (general term of trifluorodichloroethane); compressed gas propellants such as nitrogen gas, carbon dioxide gas and the like can be exemplified. The aerosol type preparations may further contain a common solubilizing adjuvant, a buffering agent, and the like, and if necessary, a coloring agent, a preservative, a perfume, a flavoring agent, a sweetening agent may be added thereto.

The amount of the carbostyryl derivative of the general formula (I) or salt thereof to be contained in the agent for inhibiting carcinogenesis according to the present invention is not particularly restricted and can be selected from a wide range, and the amount may be

generally selected within the range of 1-70% by weight, preferably 5-50 % by weight.

Method for administering the agent of the present invention is not particularly restricted except
5 that the case selected to the specific treating purpose. The method is decided depending upon the form of preparation, the age of patient, the distinction of sex and other conditions, the degree of disease condition of the patient and others. For example, tablets, pills, a
10 liquid medicine, a suspension, an emulsion, granules, a syrup and capsules are administered orally. An injection preparation is intravenously administered singly or in combination with common auxiliary solutions such as glucose solution and/or amino acid solution, in case of
15 necessity, it is singly administered intramuscularly, intradermally, subcutaneously or intraperitoneally. A suppository is administered intrarectally. An external preparation is coated on the diseased part.

Dosage of the agent for inhibiting carcinogenesis of the present invention may be suitably
20 selected depend upon the age of patient, the distinction of sex and other conditions, as well as the degree of disease condition of the patient and other related factors, and generally the amount of carbostyryl
25 derivative of the general formula (I) or salt thereof may be 0.6 to 50 mg per 1 kg of the body weight per day. The desirable content of the effective ingredient in each unit of administration form may be 10 to 1,000 mg.

EXAMPLES

The present invention will be explained more specifically by showing Preparation Examples and Pharmacological Test.

5 Preparation Example 1

2-(4-Chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid	150 g
Avicel (trade name for microcrystalline cellulose, manufactured by Asahi Chemical Industry Co., Ltd.)	40 g
Corn starch	30 g
Magnesium stearate	2 g
Hydroxypropylmethyl cellulose	10 g
Polyethylene glycol 6000	3 g
Castor oil	40 g
Methanol	40 g

2-(4-Chlorobenzoylamino)-3-(2-quinolon-4-yl)-propionic acid, Avicel, corn starch and magnesium stearate were mixed together and ground, then the mixture was shaped into the form of tables by using a
10 conventional pounder (R 10 mm) for sugar coating. The tablets were coated with a film-coating agent consisting of hydroxypropylmethyl cellulose, propylene glycol 6000, castor oil and methanol, to prepare film-coated tablets.

Preparation Example 2

2-(4-Chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid	150.0 g
Citric acid	1.0 g
Lactose	33.5 g
Dicalcium phosphate	70.0 g
Pluronic F-68	30.0 g
Sodium lauryl sulfate	15.0 g
Polyvinyl pyrrolidone	15.0 g
Polyethylene glycol (Carbowax 1500)	4.5 g
Polyethylene glycol (Carbowax 6000)	45.0 g
Corn starch	30.0 g
Dry sodium lauryl sulfate	3.0 g
Dry magnesium stearate	3.0 g
Ethanol	A sufficient quantity

2-(4-Chlorobenzoylamino)-3-(2-quinolon-4-yl)-propionic acid, citric acid, lactose, dicalcium phosphate, Pluronic F-68 and sodium lauryl sulfate were
5 mixed together.

The mixture was sieved through a No. 60 screen. The resulting sieved mixture was wet-granulated with an ethanol solution containing polyvinyl pyrrolidone, Carbowax 1500 and Carbowax 6000. In case of
10 necessity, ethanol was added to convert the mixture into a paste-like mass. Corn starch was added, and mixing operation was continued until uniform particles were formed. The resulting particles were passed through a

No. 10 screen, then placed in a tray, and were dried in an oven at 100°C for 12-14 hours. The dried particles were sieved through a No. 16 screen. Next, dry sodium lauryl sulfate and dry magnesium stearate were added to
5 the resulting particles. The mixture was compressed into core tablets of the desired shape by using a tablet machine.

The resulting core tablets were treated with a varnish and then talc was sprayed thereon for preventing
10 from moisture absorption. On the surface of resulting core tablets, undercoat layer was coated. Sufficient number of varnish coatings were conducted to the core tablets so as to make them suitable for internal use. Formation of undercoat layer and smooth coating were
15 conducted to make the coated tablets having completely round and smooth surface. Color coating was conducted until the desired color surface was obtained. After drying, the coated tablets were polished to obtain tablets of uniform gloss.

20 Preparation Example 3

2-(4-Chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid	5.0 g
Polyethylene glycol (mol. wt.: 4000)	0.3 g
Sodium chloride	0.9 g
Polyoxyethylene sorbitan monooleate	0.4 g
Sodium metabisulfite	0.1 g
Methylparaben	0.18 g
Propylparaben	0.02 g
Distilled water for injection	10.0 ml

Parabens, sodium metabisulfite and sodium chloride were dissolved in a half volume of the above mentioned distilled water for injection at 80°C under stirring. The resulting solution was cooled to 40°C, then to this solution was added 2-(4-chlorobenzoyl-amino)-3-(2-quinolon-4-yl)propionic acid, polyethylene glycol and polyoxyethylene sorbitan monooleate and were dissolved. Next, to the resulting solution was added the remaining a half volume of the distilled water to make the solution to the final volume. Thus obtained solution was sterilized by passing through a suitable filter paper, to prepare the desired injection preparation.

Pharmacological test

Effect for inhibiting carcinogenesis of ENNG-induced cancer of the duodenum in mouse

C57/B16 strain mice of 8 week-age were used as test animals. N-Ethyl-N'-nitro-N-nitrosoguanidine (ENNG), which is known as a carcinogenic substance, was administered to the mice to produce cancer of the duodenum, then 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid (general name: Rebamipide) was administered as test compound to the test mice to examine the activity for inhibiting carcinogenesis.

The test mice were classified into three groups of A, B and C (each one of the groups is con-

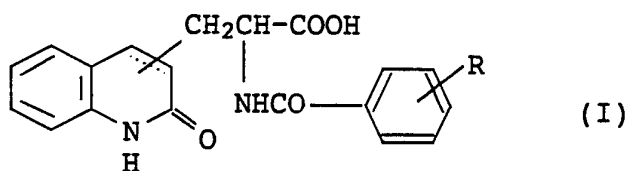
sisting of 30 mice). The all of the test mice were given freely the drinking water which contains ENNG in the concentration of 100 mg/liter for 4 weeks. Thereafter, one solid feed in which the amount of test compound of Rebamipide is controlled to keep in the rate of 20 mg/kg/day were given to the mice of Group A from 5th to 16th week, and another solid feed in which the amount of test compound of Rebamipide is controlled to keep in the rate of 50 mg/kg/day were given to the mice of Group B for from 5th to 16th week. Each one of the test mice of Groups of A, B and C were given tap water freely, then the duodenums of the test mice were sacrificed on the 16th week after the administration of the test compound, and the effect for inhibiting carcinogenesis performed by the test compound were examined.

As the result, in comparison with the incidence of carcinogenesis of 66.7% shown by test mice of Group C to which test compound of Rebamipide were not administered, while the incidence of carcinogenesis shown by test mice of Group A was 58.1% and the incidence of carcinogenesis shown by test mice of Group B was 45.2%, respectively. Thus, it can be said clearly that the carcinogenesis were inhibited by administration of carbostyryl derivative (Rebapimide) of the present invention. The average incidences of carcinogenesis (average \pm SD) were 0.84 ± 0.86 in Group A, 0.68 ± 0.87 in Group B and 1.21 ± 1.27 in Group C, respec-

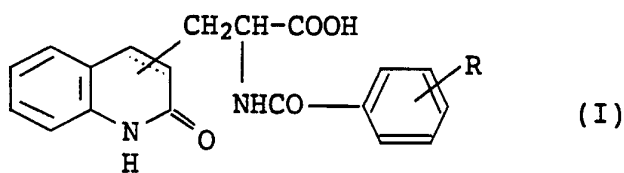
tively, thus the carcinogenesis were inhibited in the test mice of Groups A and B which were administered with carbostyryl derivative of the present invention.

CLAIMS

1. An agent for inhibiting carcinogenesis which comprises, as the active ingredient, a carbostyryl derivative represented by the general formula (I),



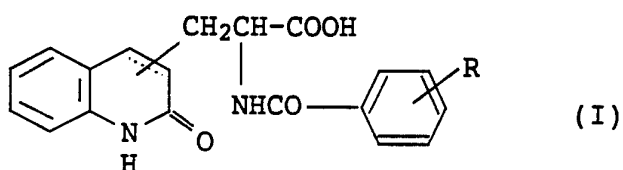
- wherein R is a halogen atom; the substituted position
 5 of the substituent in the carbostyryl skeleton is 3- or
 4-position in the carbostyryl skeleton; and the carbon-
 carbon bond between 3- and 4-positions in the
 carbostyryl skeleton is a single bond or a double bond;
 or a salt thereof.
- 10 2. An agent for inhibiting carcinogenesis of the
 digestive tract cancer which comprises, as the active
 ingredient, a carbostyryl derivative represented by the
 general formula (I),



- wherein R is a halogen atom; the substituted position
 15 of the substituent in the carbostyryl skeleton is 3- or
 4-position in the carbostyryl skeleton; and the carbon-
 carbon bond between 3- and 4-positions in the
 carbostyryl skeleton is a single bond or a double bond;

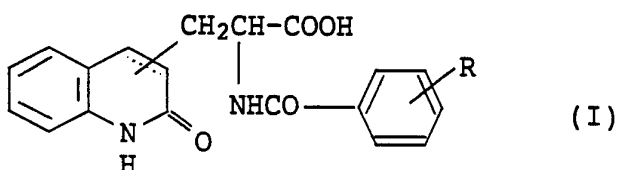
or a salt thereof.

3. A method for inhibiting carcinogenesis comprising by administering to a patient in need thereof an agent for inhibiting carcinogenesis which comprises, as the active ingredient, in an effective amount for inhibiting carcinogenesis of a carbostyryl derivative represented by the general formula (I),



wherein R is a halogen atom; the substituted position of the substituent in the carbostyryl skeleton is 3- or 4-position in the carbostyryl skeleton; and the carbon-carbon bond between 3- and 4-positions in the carbostyryl skeleton is a single bond or a double bond; or a salt thereof.

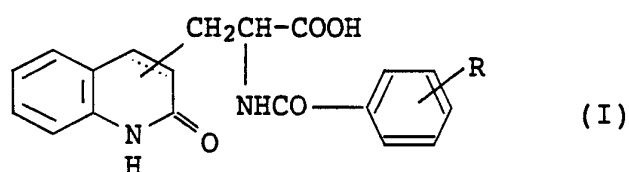
4. A method for inhibiting carcinogenesis of the digestive tract cancer by administering to a patient in need thereof an agent for inhibiting carcinogenesis of the digestive cancer which comprises, as the active ingredient, in an effective amount for inhibiting carcinogenesis of the digestive cancer of a carbostyryl derivative represented by the general formula (I),



wherein R is a halogen atom; the substituted position

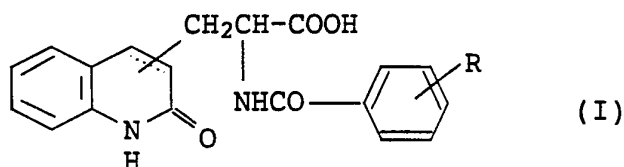
of the substituent in the carbostyryl skeleton is 3- or 4-position in the carbostyryl skeleton; and the carbon-carbon bond between 3- and 4-positions in the carbostyryl skeleton is a single bond or a double bond; or a salt thereof.

5. Use of a compound for the production of a medicament for inhibiting carcinogenesis which comprises, as the active ingredient, a carbostyryl derivative represented by the general formula (I),



10 wherein R is a halogen atom; the substituted position of the substituent in the carbostyryl skeleton is 3- or 4-position in the carbostyryl skeleton; and the carbon-carbon bond between 3- and 4-positions in the carbostyryl skeleton is a single bond or a double bond; or a salt thereof.

6. Use of a compound for the production of a medicament for inhibiting carcinogenesis of the digestive tract cancer, which comprises as the active ingredient, a carbostyryl derivative represented by the
20 general formula (I),



wherein R is a halogen atom; the substituted position

of the substituent in the carbostyryl skeleton is 3- or 4-position in the carbostyryl skeleton; and the carbon-carbon bond between 3- and 4-positions in the carbostyryl skeleton is a single bond or a double bond; or a salt thereof.

7. The agent for inhibiting carcinogenesis according to Claim 1, wherein the active ingredient is 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid or a salt thereof.

8. The agent for inhibiting carcinogenesis of the digestive tract cancer according to Claim 2, wherein the active ingredient is 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid or a salt thereof.

9. The method for inhibiting carcinogenesis by administering the agent for inhibiting carcinogenesis according to Claim 3, wherein the active ingredient is 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid or a salt thereof.

10. The method for inhibiting carcinogenesis of the digestive tract cancer by administering the agent for inhibiting carcinogenesis of the digestive tract cancer according to Claim 4, wherein the active ingredient is 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid or a salt thereof.

11. The use of compound for the production of a medicament for inhibiting carcinogenesis according to Claim 5, wherein the active ingredient is 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid or a

salt thereof.

12. The use of compound for the production of a medicament for inhibiting carcinogenesis of the digestive tract cancer according to Claim 6, wherein the
5 active ingredient is 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid or a salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 96/02319

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 23043 A (OTSUKA PHARMACEUTICAL COMPANY LTD.) 25 November 1993 cited in the application see page 5, paragraph 1; claims ---	1-12
X	WO 94 12182 A (OTSUKA PHARMACEUTICAL CO., LTD) 9 June 1994 cited in the application see claims ---	1,2,7,8
A	EP 0 552 373 A (OTSUKA PHARMACEUTICAL CO., LTD.) 28 July 1993 see claims 1,2 ---	1-12
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