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NOTICE OF ENTITLEMENT

I/We TAIHO PHARMACEUTICAL COMPANY, LIMITED

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CHIYODA-KU
TOKYO-TO
JAPAN

being the applicant(s) in respect of an application for a patent for an invention entitled COMPOSITIONS, METHODS AND KITS FOR POTENTIATING ANTITUMOR EFFECT AND FOR TREATING TUMOR (Application No. 17912/92), state the following:

1. The nominated person(s) has/have, for the following reasons, gained entitlement from the actual inventor(s):

THE NOMINATED PERSON IS THE ASSIGNEE OF THE
ACTUAL INVENTORS.

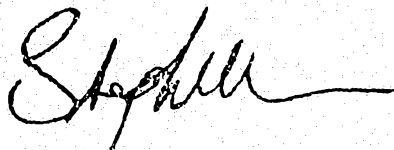
2. The nominated person(s) has/have, for the following reasons, gained entitlement from the applicant(s) listed in the declaration under Article 8 of the PCT:

THE APPLICANT AND NOMINATED PERSON IS THE
BASIC APPLICANT.

3. The basic application(s) listed in the declaration under Article 8 of the PCT is/are the first application(s) made in a Convention country in respect of the invention.

DATED: 18 January 1993

TAIHO PHARMACEUTICAL COMPANY, LIMITED
GRIFFITH HACK & CO.



Patent Attorney for and
on behalf of the applicant(s)

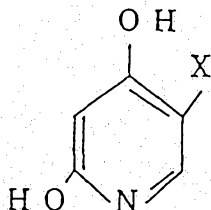


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COMPOSITION, METHOD AND KIT FOR POTENTIATING ANTITUMOR ACTIVITY AND FOR CURING TUMOR
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- (57) Claim

1. An antitumor effect-potentiating composition for potentiating the antitumor effect of an antitumor composition containing a therapeutically effective amount of tegafur while suppressing the side effects of the antitumor composition, the antitumor effect-potentiating composition being characterized in that it contains a compound of the formula



(I)

(I)

wherein X is a halogen atom or a cyano group in an amount effective for potentiating the antitumor effect, and oxonic acid or a pharmaceutically acceptable salt thereof

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in an amount effective for suppressing the side effects, as active ingredients, and a pharmaceutically acceptable carrier.

8. A method for treating a cancer in a mammal, comprising administering to the mammal a therapeutically effective amount of tegafur, an antitumor effect-potentiating effective amount of the compound of the formula (I) of claim 1, and a side effect-suppressing effective amount of oxonic acid or a pharmaceutically acceptable salt thereof.

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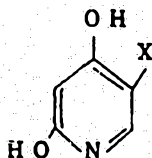
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(21) 国際出願番号 PCT/JP92/00656 (22) 国際出願日 1992年5月22日(22. 05. 92) (30) 優先権データ 特願平3/121247 1991年5月27日(27. 05. 91) JP (71) 出願人 (米国を除くすべての指定国について) 大腸薬品工業株式会社 (TAIHO PHARMACEUTICAL CO., LTD.) [JP/JP] 〒101 東京都千代田区神田錦町1-27 Tokyo, (JP) (72) 発明者; および (75) 発明者/出願人 (米国についてのみ) 白坂哲彦 (SHIRASAKA, Tetsuhiko) [JP/JP] 〒350 埼玉県川越市市場1-10-3 Saitama, (JP) 福島正和 (FUKUSHIMA, Masakazu) [JP/JP] 〒520 滋賀県大津市千町2丁目9-7 Shiga, (JP) 大下英之 (OHSHIMO, Hideyuki) [JP/JP] 〒357 埼玉県飯能市南町10-28 Saitama, (JP) 島本雄司 (SHIMAMOTO, Yuji) [JP/JP] 〒520-02 滋賀県大津市仰木の里2丁目9-11 Shiga, (JP) (74) 代理人 弁理士 三枝英二, 外 (SAEGUSA, Eiji et al.) 〒541 大阪府大阪市中央区平野町2-1-2 沢のビル Osaka, (JP)	(81) 指定国 AT (欧州特許), AU, BE (欧州特許), CA, CH (欧州特許), DE (欧州特許), DK (欧州特許), ES (欧州特許), FR (欧州特許), GB (欧州特許), GR (欧州特許), IT (欧州特許), JP, KR, LU (欧州特許), MC (欧州特許), NL (欧州特許), SE (欧州特許), US. 添付公開書類 国際調査報告書 654555	

(54) Title : COMPOSITION, METHOD AND KIT FOR POTENTIATING ANTITUMOR ACTIVITY AND FOR CURING TUMOR

(54) 発明の名称 抗腫瘍効果増強のための及び腫瘍治療のための組成物、方法及びキット



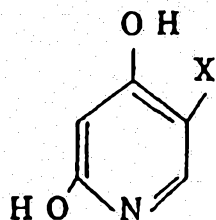
(I)

(57) Abstract

A composition for potentiating the antitumor activity of tegafur and reducing the adverse effects, comprising a compound represented by general formula (I) wherein X represents halogen or cyano and oxonic acid or a pharmaceutically acceptable salt thereof, and a method and kit therefor; and a composition for curing tumors comprising tegafur, a compound represented by formula (I) and oxonic acid or a pharmaceutically acceptable salt thereof; and a method and kit therefor.

(57) 要約

本発明は、一般式



(I)

〔Xはハロゲン原子又はシアノ基を示す〕で表わされる化合物とオキソン酸又はその薬学的に許容される塩を含む、テガフルの抗腫瘍効果を増強すると共に副作用を軽減する抗腫瘍効果増強のための組成物、方法及びキット、並びに、テガフル、上記一般式 (I) の化合物及びオキソン酸又はその薬学的に許容される塩を含む腫瘍治療のための組成物、方法及びキットを提供する。

情報としての用途のみ

PCTに基づいて公開される国際出願のパンフレット第1頁にPCT加盟国を同定するために使用されるコード

AT オーストリア
AU オーストラリア
BB バルバドス
BE ベルギー
BF ブルキナファソ
BG ブルガリア
BJ バナン
BR ブラジル
CA カナダ
CF 中央アフリカ共和国
CG コンゴ
CH スイス
CI コートジボアール
CM カメルーン
CS チェコスロバキア
DE ドイツ
DK デンマーク
ES スペイン

FI フィンランド
FR フランス
GA ガボン
GN ギニア
GB イギリス
GR ギリシャ
HU ハンガリー
IE アイルランド
IT イタリア
JP 日本
KP 朝鮮民主主義人民共和国
KR 大韓民国
LI リヒテンシュタイン
LK スリランカ
LU ルクセンブルグ
MC モナコ
MG マダガスカル
ML マリ

MN モンゴル
MR モーリタニア
MW マラウイ
NL オランダ
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NZ ニュージーランド
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TD チャード
TG トーゴ
UA ウクライナ
US 米国

DESCRIPTION

COMPOSITIONS, METHODS AND KITS FOR POTENTIATING
ANTITUMOR EFFECT AND FOR TREATING TUMOR

Technical Field

5 The present invention relates to a composition,
method and kit for potentiating the antitumor effect of
tegafur, and a composition, method and kit for treating a
tumor.

Background Art

10 Japanese Examined Patent Publication (kokoku)
No.155215/1987 reports that a kind of pyridine compound
can be used as a potentiator of antitumor effect of 5-
fluorouracil (hereinafter referred to as "5-FU") and
derivatives of 5-FU. The pyridine compound has the
15 feature of sustaining the concentration of 5-FU in the
living body. On the other hand, 5-FU is known to have the
serious problem that the prolonged presence of 5-FU in the
living body is likely to cause a disorder (inflammation)
in the oral cavity, gastrointestinal tissue and the like
20 as often experienced in continuous intravenous infusion of
5-FU alone.

 International Publication WO 90/07334 reports
that oxonic acid used in combination with 5-FU or 5-FU
derivative can inhibit the occurrence of inflammation
25 caused by 5-FU or 5-FU derivative. Yet oxonic acid in

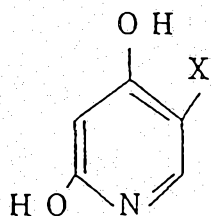


this case reduces the antitumor effect of 5-FU or 5-FU derivative. Thus oxonic acid is not satisfactory in terms of potentiation of antitumor effect and alleviation of adverse effects.

5

Disclosure of the Invention

In the above-mentioned current situation, the present inventors conducted extensive research to increase the antitumor effect of tegafur and found that when tegafur is used in combination with a compound represented
10 by the formula (I) below and oxonic acid or a pharmaceutically acceptable salt thereof, the antitumor effect of tegafur can be significantly increased while suppressing the side effects thereof such as inflammation and the like. The present invention has been accomplished
15 based on this novel finding.



(I)

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In the formula, X is a halogen atom or a cyano group.

The present invention provides an antitumor effect-potentiating composition for potentiating the antitumor effect of an antitumor composition containing a
25 therapeutically effective amount of tegafur while



suppressing the side effects of the antitumor composition,
the antitumor effect-potentiating composition being
characterized in that it contains a compound of the
formula (I) in an amount effective for potentiating the
5 antitumor effect, and oxonic acid or a pharmaceutically
acceptable salt thereof in an amount effective for
suppressing the side effects, as active ingredients, and a
pharmaceutically acceptable carrier.

The present invention also provides an antitumor
10 composition comprising a therapeutically effective amount
of tegafur, an antitumor effect-potentiating effective
amount of a compound of the formula (I) and a side effect-
suppressing effective amount of oxonic acid or a
pharmaceutically acceptable salt thereof, and a
15 pharmaceutically acceptable carrier.

The antitumor effect-potentiating composition
and the antitumor composition according to the invention
are capable of potentiating the antitumor effect of
tegafur, which is a known antitumor agent, without
20 increasing the side effects or toxicity.

Tegafur for use in the invention is a medicament
which is known to release 5-FU, i.e. an active precursor,
on activation in the living body.

Accordingly the present invention further
25 provides



a method for treating a cancer susceptible to 5-fluorouracil therapy in a mammal, comprising administering to the mammal a therapeutically effective amount of tegafur, an antitumor effect-potentiating effective amount
5 of a compound of the formula (I), and a side effect-suppressing effective amount of oxonic acid or a pharmaceutically acceptable salt thereof, and

a method for potentiating the antitumor effect of tegafur and suppressing the side effects thereof in
10 administering an antitumor composition containing a therapeutically effective amount of tegafur to a patient with a cancer susceptible to 5-fluorouracil therapy, the method being characterized by administering to the patient a compound of the formula (I) in an amount effective for
15 potentiating the antitumor effect, and oxonic acid or a pharmaceutically acceptable salt thereof in an amount effective for suppressing the side effects.

In other words, the present invention particularly provides, in a method of treating a cancer
20 susceptible to tegafur therapy in a patient in need of such treatment comprising administering to the patient a therapeutically effective amount of tegafur, the improvement comprising potentiating the antitumor effect by administering to the patient an antitumor effect-
25 potentiating effective amount of the compound of the



formula (I), while suppressing the side effects caused by administration of tegafur by administering to the patient oxonic acid or a pharmaceutically acceptable salt thereof in an amount effective for suppressing the side effects of
5 tegafur.

The tegafur for use in the invention is a known compound and can be prepared by conventional processes as disclosed, e.g. in Japanese Examined Patent Publication No.10510/1974.

10 The compounds of the formula (I) are all known and can be easily prepared by conventional processes. Examples of halogen atoms represented by X in the compound of the formula (I) are fluorine, chlorine, bromine and iodine atoms, etc. Preferred among the compounds of the
15 formula (I) are 2,4-dihydroxy-5-chloropyridine, 2,4-dihydroxy-5-cyanopyridine, etc.

Oxonic acid per se is a known compound. Useful pharmaceutically acceptable salts thereof include acid addition salts and basic compound salts. Examples of
20 useful acids capable of forming the acid addition salts are hydrochloric acid, sulfuric acid, phosphoric acid, hydrobromic acid and like inorganic acids, oxalic acid, succinic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, malonic acid, methanesulfonic
25 acid, benzoic acid and like organic acids. Examples of



useful basic compounds capable of forming the pharmaceutically acceptable basic compound salts are sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium carbonate, potassium hydrogencarbonate, etc.

- 5 Usable as the oxonic acid are substances capable of producing oxonic acid in the living body such as ester derivatives of oxonic acid.

The antitumor effect-potentiating composition of the present invention is obtained by formulating the
10 compound of the formula (I) and oxonic acid or a pharmaceutically acceptable salt thereof into a single preparation or into two respective separate preparations. The single preparation or two separate preparations can be administered either independently of or simultaneously
15 with tegafur which is formulated in an optional dosage form. That is, the antitumor effect-potentiating composition of the present invention can be administered at any time before, after or simultaneously with the administration of tegafur. It is preferred to administer
20 the antitumor effect-potentiating composition of the invention simultaneously with the administration of tegafur or within 4 hours before or within 4 hours after the administration of tegafur. The compound of the formula (I) and oxonic acid or a pharmaceutically
25 acceptable salt thereof may be administered simultaneously



or separately, and are in either case preferably administered simultaneously with the administration of tegafur or within 4 hours before or within 4 hours after the administration of tegafur. Generally the simultaneous
5 administration of the compound of the formula (I) and oxonic acid or a pharmaceutically acceptable salt thereof is preferred even if they are provided in the form of separate preparations.

In the composition for potentiating the
10 antitumor effect of tegafur comprising the compound of the formula (I) and oxonic acid or a pharmaceutically acceptable salt thereof as active ingredients according to the invention, it is preferable to use about 0.1 to about 10 moles, preferably about 0.5 to about 5 moles, of oxonic
15 acid or a pharmaceutically acceptable salt thereof, per mole of the compound of the formula (I).

When the antitumor effect-potentiating composition of the invention is administered independently of or simultaneously with the administration of tegafur,
20 particularly good results would be often obtained by administering the antitumor effect-potentiating composition of the invention in a manner such that about 0.1 to about 5 moles, preferably about 0.1 to about 1.5 moles, of the compound of the formula (I) and about 0.1 to
25 about 5 moles, preferably about 0.2 to about 2 moles, of



oxonic acid or a pharmaceutically acceptable salt thereof, are administered per mole of tegafur.

According to the present invention, an antitumor composition can be obtained by admixing tegafur with the antitumor effect-potentiating composition. In other words, the antitumor composition comprises three components, i.e., tegafur, a compound of the formula (I) and oxonic acid or a pharmaceutically acceptable salt thereof as active ingredients. The three active ingredients are admixed with a pharmaceutically acceptable carrier to provide a preparation in an optional unit dosage form which is then administered.

In the antitumor composition comprising tegafur, the compound of the formula (I) and oxonic acid or a pharmaceutically acceptable salt thereof as three active ingredients, it is suitable to use about 0.1 to about 5 moles, preferably about 0.1 to about 1.5 moles, of the compound of the formula (I), and about 0.1 to about 5 moles, preferably about 0.2 to about 2 moles, of oxonic acid or a pharmaceutically acceptable salt thereof, per mole of tegafur.

The proportions of the compound of the formula (I) and oxonic acid or a pharmaceutically acceptable salt thereof in this antitumor composition are not specifically limited and are suitably selected from the said range. A



good result would often be obtained by using about 0.1 to about 10 moles, preferably about 0.5 to about 5 moles, of oxonic acid or a pharmaceutically acceptable salt thereof, per mole of the compound of the formula (I).

5 The antitumor effect-potentiating composition of the invention can be prepared in various dosage forms by adding a pharmaceutically acceptable carrier to the compound of the formula (I) and oxonic acid or a pharmaceutically acceptable salt thereof. In preparing
10 the antitumor effect-potentiating composition of the invention, the compound of the formula (I) and oxonic acid or a pharmaceutically acceptable salt thereof may be provided in the form of a single preparation or two separate preparations.

15 The antitumor composition of the present invention is prepared, as described above, in the form of a single preparation containing both tegafur and the antitumor effect-potentiating composition, or in the form of two separate preparations wherein one comprises tegafur
20 and the other comprises the antitumor effect-potentiating composition.

 In either case, the foregoing pharmaceutical compositions are prepared in non-injection form by the conventional method using a suitable pharmaceutically
25 acceptable carrier. Examples of useful carriers are those



widely used in the manufacture of conventional pharmaceutical compositions, such as fillers, extenders, binders, disintegrators, surfactants, lubricants and like diluents and excipients.

5 The present invention also provides a kit comprising the compound of the formula (I) and oxonic acid or a pharmaceutically acceptable salt thereof. That is, the invention provides a kit for potentiating the antitumor effect of tegafur and suppressing the side
10 effects of tegafur, comprising

(i) the compound of the formula (I) in an amount effective for potentiating the antitumor effect of tegafur, and

(ii) oxonic acid or a pharmaceutically
15 acceptable salt thereof in an amount effective for suppressing the side effects of tegafur, the components (i) and (ii) being accommodated in separate containers.

Preferably the components (i) and (ii) are each
20 provided in the form of a preparation containing a pharmaceutically acceptable carrier.

The present invention also provides a kit comprising tegafur and the antitumor effect-potentiating composition containing the compound of the formula (I) and
25 oxonic acid or a pharmaceutically acceptable salt thereof



either in a single preparation or in two separate preparations. Stated more specifically, the present invention provides a kit for treating a cancer in a mammal, comprising

5 three components, i.e.

(i) a therapeutically effective amount of tegafur,

(ii) the compound of the formula (I) in an amount effective for potentiating the antitumor effect of
10 tegafur, and

(iii) oxonic acid or a pharmaceutically acceptable salt thereof in an amount effective for suppressing the side effects of tegafur; and

two or three containers holding the components
15 (i), (ii) and (iii), the tegafur (i) being contained in a container different from the container(s) for the components (ii) and (iii). In the kit, the components (ii) and (iii) may be accommodated in separate containers, or a mixture of the components (ii) and (iii) may be held
20 in a single container.

The components (i), (ii) and (iii) are preferably each in the form of a preparation containing a pharmaceutically acceptable carrier.

In the kits of the invention, the components may
25 be administered simultaneously, or one or two components



may be administered at any time before or after the administration of the other one component. Preferably the components may be administered simultaneously, or one or two components may be administered within 4 hours before or within 4 hours after the administration of the other one component. More preferably the components may be administered simultaneously, or one or two components may be administered within 2 hours before or within 2 hours after the administration of the other one component.

10 According to the kit of the invention, the antitumor effect of the antitumor composition containing tegafur as the active ingredient is significantly increased by the antitumor effect-potentiating composition comprising the compound of the formula (I) and oxonic acid or a pharmaceutically acceptable salt thereof in a single preparation or separate preparations, without increasing the level of toxicity such as gastrointestinal toxicity.

20 The present invention also provides the use of a combination of tegafur, a compound of the formula (I) and oxonic acid or a pharmaceutically acceptable salt thereof for preparing a composition for treating a cancer in a mammal with increased antitumor activity and suppressed side effects, and the use of a combination of the compound of the formula (I) and oxonic acid or a pharmaceutically acceptable salt thereof for preparing a composition for

25



potentiating the antitumor effect of tegafur and suppressing the side effects of tegafur.

There is no particular restriction on the unit dosage form which can be adopted for the antitumor effect-
5 potentiating composition or antitumor composition of the invention in the treatment of malignant tumors in mammals inclusive of human beings insofar as it is non-injection form. Thus, optional desired unit dosage form can be selected according to the purpose of treatment. Examples
10 thereof are oral dosage forms such as tablets, coated tablets, pills, powders, granules, capsules, solutions, suspensions, emulsions, etc. and parenteral dosage forms such as suppositories, ointments, plasters, etc. These dosage forms can be manufactured by conventional
15 pharmaceutical procedures known in this field.

As the carrier for shaping into the form of tablets, there can be employed various excipients such as lactose, sucrose, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose, silicic
20 acid, etc.; binders such as simple syrup, glucose solution, starch solution, gelatin solution, carboxymethylcellulose, shellac, methylcellulose, potassium phosphate, polyvinylpyrrolidone, etc.; disintegrators such as dry starch, sodium alginate, agar
25 powder, laminaran powder, sodium hydrogen carbonate,



calcium carbonate, polyoxyethylene-sorbitan fatty acid esters, sodium lauryl sulfate, stearic acid monoglyceride, starch, lactose, etc.; antidisintegrators such as sucrose, stearic acid, cacao butter, hydrogenated oil, etc.;

5 absorption promoters such as quaternary ammonium bases, sodium lauryl sulfate, etc.; humectants such as glycerol, starch, etc.; adsorbents such as starch, lactose, kaolin, bentonite, colloidal silicic acid, etc.; and lubricants such as purified talc, stearic acid salts, boric acid
10 powder, polyethylene glycol, etc. Where necessary, the tablets may be in the form of coated tablets such as sugar-coated tablets, gelatin-coated tablets, enteric-coated tablets, film-coated tablets, or double or multi-layer tablets, etc.

15 The carrier for shaping into the form of pills includes, for example, various excipients such as glucose, lactose, starch, cacao butter, hardened vegetable oil, kaolin, talc, etc.; binders such as gum arabic powder, gum tragacanth powder, gelatin, etc.; and disintegrators such
20 as laminaran, agar, etc.

The carrier for shaping into the form of suppositories includes, for example, polyethylene glycol, cacao butter, higher alcohols, esters of higher alcohols, gelatin, semi-synthetic glycerides, etc.

25 Capsules are manufactured by mixing the



antitumor effect-potentiating composition, either alone or together with tegafur, with any of the carriers mentioned above and encapsulating the mixture in hard gelatin capsule, soft capsule or other capsules.

5 For manufacturing in the form of pastes, creams, and gels, there is employed a diluent such as, for example, white petrolatum, paraffin, glycerol, cellulose derivatives, polyethylene glycols, silicone, bentonite, etc.

10 When required, the above preparations may contain coloring agents, preservatives, perfumes, flavors, sweeteners, other medicament, etc.

 The amounts of the compound of the formula (I) and oxonic acid or a pharmaceutically acceptable salt thereof, which are the active ingredients of the antitumor effect-potentiating composition of the present invention, and the amounts of tegafur, the compound of the formula (I) and oxonic acid or a pharmaceutically acceptable salt thereof, which are the active ingredients of the antitumor composition of the invention are dependent on the dosage form, route of administration, dosing schedule, etc. and can be appropriately chosen without specific limitation. Generally, however, the total amount of active ingredients in the dosage form may range from about 1 to about 70 percent by weight.

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The route of administration of the antitumor effect-potentiating composition or antitumor composition of the present invention is not specifically limited insofar as it is non-injection route and may be, for
5 example, intestinal, oral, rectal, stomatic, percutaneous or the like and can be selected according to the dosage form, the patient's age, sex and other factors, the severity of the symptom of the patient and so on. By way of example, tablets, pills, solutions, suspensions,
10 emulsions, granules and capsules are orally administered. Suppositories are inserted into the rectum. Ointments are applied to the skin, the intraoral mucosa or the like.

In the present invention, the dosage of each active ingredient in each pharmaceutical composition can
15 be selected according to the method of administration, the patient's age, sex and other factors, the degree of disease and so on. In the case of oral administration, the standard dosage for a human adult is usually about 0.1 to about 100 mg/kg/day, preferably about 1 to about 30
20 mg/kg/day, for tegafur, about 0.1 to about 100 mg/kg/day, preferably about 1 to about 50 mg/kg/day, for the compound of the formula (I) and about 0.1 to about 100 mg/kg/day, preferably about 1 to about 40 mg/kg/day, for oxonic acid or a pharmaceutically acceptable salt thereof. The
25 compositions of the invention can each be administered



daily in a single dose or in 2 to 4 divided doses. In the case of suppositories, for human adults, the equivalent of about 1 to 100 mg/kg of tegafur is administered into the rectum once or twice a day at an interval of 6 to 12
5 hours.

The malignant tumors which can be treated with the compositions of the invention may be any of the tumors susceptible to 5-FU which is the active precursor. Among them are cancers of the head and neck, stomach, colon,
10 rectum, liver, gallbladder-bile duct, pancreas, lung, breast, urinary bladder, prostate, uterine cervix and so on.

Examples

The present invention will be described in more
15 detail with reference to pharmacological tests, examples illustrating the preparation of antitumor effect-potentiating compositions of the invention and examples illustrating the preparation of antitumor compositions of the invention comprising the antitumor effect-potentiating
20 composition and tegafur.

Pharmacological Test 1

(a) Preparation I of Test Suspensions

Tegafur (hereinafter referred to as "FT") and 2,4-dihydroxy-5-chloropyridine (hereinafter referred to as
25 "ClDU") were suspended at concentrations of 2.0 mg/ml and



0.73 mg/ml, respectively, in a 1% solution of hydroxypropylmethylcellulose. The suspension was stirred by a stirrer at room temperature for about 20 minutes and subjected to ultrasonic treatment with ice-cooling for 5 minutes, giving a FT-ClDU mixed suspension (test suspension (1)). Two test suspensions (2) and (3) were prepared by adding a 1% solution of hydroxypropylmethylcellulose to test suspension (1) to give FT concentrations of 1.0 and 0.5 mg/ml, respectively.

10 (b) Preparation II of Test Suspensions

FT, ClDU and potassium oxonate were suspended at concentrations of 2.0 mg/ml, 0.73 mg/ml and 1.95 mg/ml, respectively, in a 1% solution of hydroxypropylmethylcellulose. The suspension was stirred by a stirrer at room temperature for about 20 minutes and subjected to ultrasonic treatment with ice-cooling for 5 minutes, giving a FT-ClDU-potassium oxonate mixed suspension (test suspension (4)). Test suspensions (5) and (6) were prepared by adding a 1% solution of hydroxypropylmethylcellulose to test suspension (4) to give FT concentrations of 1.0 and 0.5 mg/ml, respectively.

(c) Preparation III of Test Suspensions

Test suspensions (7) to (12) were prepared in the same manner as in Preparations I and II with the



exception of using 1.46 mg/ml of ClDU.

(d) Preparation IV of Test Suspensions

"UFT" (product of Taiho Pharmaceutical Co., Ltd. containing uracil and FT in a molar ratio of 4:1) was
5 suspended in a 1% solution of hydroxypropylmethyl-
cellulose to obtain three suspensions each having FT
concentrations of 1, 2 and 3 mg/ml, respectively. To the
suspensions were added potassium oxonate to concentrations
of 0.975 mg/ml, 1.95 mg/ml and 2.93 mg/ml, respectively.
10 The suspensions were stirred by a stirrer at room
temperature for about 20 minutes and subjected to
ultrasonic treatment with ice-cooling, giving UFT-
potassium oxonate mixed suspensions (test suspensions (13)
to (15)).

15 (e) Preparation V of Test Suspensions

Test suspensions (16) to (21) were prepared in
the same manner as in Preparations I and II with the
exception of using 0.58 mg/ml of ClDU.

(f) Anti-cancer Experiment

20 Yoshida sarcoma cells were subcutaneously
transplanted in an amount of 2×10^4 each into the back of
5-week-old Donryu-strain male rats. Then, 24 hours after
the transplantation, each of the test suspensions (1) to
(21) was orally administered to the rats at a dose of 1.0
25 ml per 100 g of body weight once a day. The



administration was conducted for 7 consecutive days. A 1% solution of hydroxypropylmethylcellulose alone was orally administered to the cancer-bearing control rats.

The rats were sacrificed on day 8 after the
5 transplantation of the tumor, and the tumor and
gastrointestinal tissues were removed from the rats. The
weight of tumor was measured and the tumor decrease ratio
(%) was calculated from the following equation:

$$\text{Tumor decrease ratio} = [1 - (T/C)] \times 100$$

10 wherein T is the weight (g) of tumor of the group to which
the test suspension was administered and C is the weight
(g) of tumor of the control group.

Section samples were obtained from the digestive
tract removed from the rats and observed under an optical
15 microscope to check the sections for the degree of
occurrence of inflammation of the digestive tract. The
degree of occurrence of inflammation was evaluated
according to the number of inflammatory sites and rated
into 4 grades with (-) for no inflammation, (+) for a
20 slight degree of inflammation, (++) for a medium degree of
inflammation, and (+++) for a high degree of inflammation.
The tissue samples were obtained by cutting open the
removed digestive tract, washing them with a physiological
saline and dipping them in a 10% neutral buffer formalin
25 solution for fixation.



The body weight of the rats was measured with time to determine the body weight change (BWC) from the body weights measured before the transplantation of tumor and on day 8 after the transplantation. The therapeutic index (TI) was given by the following equation:

$$TI = BWC_{50} / ED_{50}$$

wherein BWC_{50} is the concentration of FT at which increase in body weight becomes 50% compared with the control group and ED_{50} is the concentration of FT at which increase in tumor weight becomes 50% compared with the control group.

The results are shown in Table 1 below. By the administration of UFT + potassium oxonate, increase in tumor weight did not become 50% or less compared with the control group, and therefore the ED_{50} value was not obtained. In Table 1, "oxo" represents potassium oxonate.



Table 1

Test suspension	Drug (Molar ratio)	Dose (*) (mg/kg)	Tumor decrease ratio (%)	Therapeutic index BWC ₅₀ /ED ₅₀	Digestive tract disorder
3	FT+C1DU (1:0.5)	5	16	1.28	-
2		10	73		+
1		20	100		++
6	FT+Oxo+C1DU (1:1:0.5)	5	36	2.50	-
5		10	65		-
4		20	99		-
9	FT+C1DU (1:1)	5	12	1.07	-
8		10	90		+
7		20	100		+++
12	FT+Oxo+C1DU (1:1:1)	5	30	1.84	-
11		10	86		-
10		20	99		-
13	UFT+Oxo (1:1)	10	0	-	-
14		20	42		-
15		30	24		-
18	FT+C1DU (1:0.4)	5	28	0.76	-
17		10	20		+
16		20	100		++
21	FT+Oxo+C1DU (1:1:0.4)	5	0	>2.35	-
20		10	72		-
19		20	99		-

(*) Amount of FT



Pharmacological Test 2

(a) Preparation I of Test Suspension

FT and 2,4-dihydroxy-5-cyanopyridine
(hereinafter referred to as "CNDU") were suspended at
5 concentrations of 3.0 mg/ml and 1.02 mg/ml, respectively,
in a 1% solution of hydroxypropylmethylcellulose. The
suspension was stirred by a stirrer at room temperature
for about 20 minutes and subjected to ultrasonic
treatment with ice-cooling for 5 minutes, giving a FT-
10 CNDU mixed suspension (test suspension (1)).

(b) Preparation II of Test Suspension

FT, CNDU and potassium oxonate were suspended
at concentrations of 3.0 mg/ml, 1.02 mg/ml and 2.93
mg/ml, respectively, in a 1% solution of
15 hydroxypropylmethyl- cellulose. The suspension was
stirred by a stirrer at room temperature for about 20
minutes and subjected to ultrasonic treatment with ice-
cooling for 5 minutes, giving a FT-CNDU-potassium oxonate
mixed suspension (test suspension (2)).

20 (c) Anti-cancer Experiment

Sarcoma S-180 cells were subcutaneously
transplanted in an amount of 1×10^7 each into the back
of 4-week-old ICR strain male mice. Then, 24 hours after
the transplantation, each of the test suspensions (1) and
25 (2) was orally administered to the mice at a dose of 1.0



ml per 100 g of body weight once a day. The administration was conducted for 7 consecutive days. A 1% solution of hydroxypropylmethylcellulose alone was orally administered to the cancer-bearing control mice.

5 The mice were sacrificed on day 10 after the transplantation of the tumor, and the tumor was removed from the mice to measure the weight of tumor. The tumor decrease ratio (%) was calculated from the following equation.

10
$$\text{Tumor decrease ratio} = [1 - (T/C)] \times 100$$

wherein T is the weight (g) of tumor of the group to which the test suspension was administered and C is the weight (g) of tumor of the control group.

15 The body weight of the mice was measured with time, and the body weight gain was determined from the body weights of mice measured before the trasplantation of tumor and 10 days after the transplantation to obtain a percent body weight change (%) according to the following equation:

20
$$\text{Percent body weight change} = (TBI/CBI) \times 100$$

wherein TBI is the body weight gain (g) of the group to which the test suspension was administered and CBI is the body weight gain (g) of the control group.

25 Table 2 below shows the results. In Table 2 "oxo" represents potassium oxonate.



Table 2

Test suspension	Drug (Molar ratio)	Dose(*) (mg/kg)	Tumor decrease ratio (%)	Percent body weight change (%)
1	FT+CNDU (1:0.5)	30	58	56
2	FT+Oxo+CNDU (1:1:0.5)	30	62	89

(*) Amount of FT

Pharmacological Test 3

(a) Preparation I of Test Drug

FT and ClDU were used in amounts of 6 mg and 1.74 mg, respectively, per kg of body weight of a beagle dog. These two components were encapsulated in gelatin capsules for animals (No.13, 1/8 ounce), and mixed with thorough shaking, giving a FT-ClDU mixture (test drug (1)).

(b) Preparation II of Test Drug

FT, ClDU and potassium oxonate were used in amounts of 6 mg, 1.74 mg and 5.88 mg, respectively, per kg of body weight of a beagle. These components were



encapsulated in gelatin capsules for animals (No.13, 1/8 ounce), and mixed with thorough shaking, giving a FT-ClDU-potassium oxonate mixture (test drug (2)).

(c) Preparation III of Test Drug

5 FT and uracil were used in amounts of 20 mg and 44.8 mg, respectively, per kg of body weight of a beagle dog. The two components were encapsulated in gelatin capsules for animals (No.13, 1/8 ounce), and mixed with thorough shaking, giving a FT-uracil mixture (test drug
10 (3)).

(d) Pharmacological Test

Each of test drugs (1) to (3) was forcibly administered to male beagle dogs weighing 9 to 10 kg through oral route. Test drugs (1) and (2) were
15 administered once a day for 5 consecutive days. The test drug (3) was administered once a day for 4 consecutive days.

During the above oral administration period, the dogs were observed every day for occurrence of vomiting
20 and diarrhea (digestive tract disorder). The degree of diarrhea was rated (-) when the stool was normal to loose stool, and rated (+) when the stool was mucous stool or liquid stool. Observation was continued until the day following the day of final administration to count the
25 number of dogs with which vomiting or diarrhea (+) was



observed at least once during the period of observation.

Table 3 shows the results. In Table 3, "oxo" denotes potassium oxonate.





Table 3

Test drug	Drug (Molar ratio)	Dose (*) (mg/kg)	Number of adminis- tration	Number of animals	Occurrence of vomiting	Occurrence of diarrhea
1	FT+ClDU (1:0.4)	6	5	11	7/11	10/11
2	FT+Oxo+ClDU (1:1:0.4)	6	5	11	1/11	1/11
3	FT+Uracil (1:4)	20	4	6	6/6	0/6

(*) Amount of FT

Formulation Example 1: Tablet

	CIDU	41 mg
	Potassium oxonate	60 mg
	Starch	112 mg
5	Magnesium stearate	17 mg
	<u>Lactose</u>	<u>45 mg</u>
	Total	275 mg

Using the conventional procedure, tablets each weighing 275 mg were prepared according to the above
10 formula.

Formulation Example 2: Tablet

	Tegafur	30 mg
	CIDU	20 mg
	Potassium oxonate	30 mg
15	Starch	110 mg
	Magnesium stearate	17 mg
	<u>Lactose</u>	<u>43 mg</u>
	Total	250 mg

Using the conventional procedure, tablets each weighing 250 mg were prepared according to the above
20 formula.

Formulation Example 3: Tablet

	CNDU	16 mg
	Potassium oxonate	50 mg
25	Lactose	45 mg



	Crystalline cellulose	20 mg
	Magnesium stearate	5 mg
	Talc	4 mg
	<u>Methylcellulose</u>	<u>10 mg</u>
5	Total	150 mg

Using the conventional procedure, tablets each weighing 150 mg were prepared according to the above formula.

Formulation Example 4: Tablet

10	Tegafur	40 mg
	CNDU	10 mg
	Potassium oxonate	38 mg
	Lactose	54 mg
	Crystalline cellulose	20 mg
15	Magnesium stearate	5 mg
	Talc	3 mg
	<u>Methylcellulose</u>	<u>10 mg</u>
	Total	180 mg

Using the conventional procedure, tablets each weighing 180 mg were prepared according to the above formula.

Formulation Example 5: Granule

	C1DU	50 mg
	Potassium oxonate	150 mg
25	Lactose	340 mg



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Corn starch	450 mg
<u>Hydroxypropylmethylcellulose</u>	<u>10 mg</u>
Total	1000 mg

Using the conventional procedure, granules were
5 prepared according to the above formula.

Formulation Example 6: Granule

	Tegafur	200 mg
	ClDU	50 mg
	Potassium oxonate	150 mg
10	Lactose	340 mg
	Corn starch	450 mg
	<u>Hydroxypropylmethylcellulose</u>	<u>10 mg</u>
	Total	1200 mg

Using the conventional procedure, granules were
15 prepared according to the above formula.

Formulation Example 7: Suppository

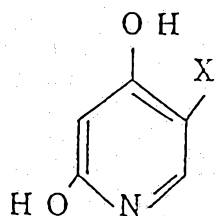
	Tegafur	300 mg
	ClDU	300 mg
	Potassium oxonate	400 mg
20	<u>Witepsol W-35</u>	<u>900 mg</u>
	Total	1900 mg

Using the conventional procedure, suppositories
were prepared according to the above formula.



CLAIMS

1. An antitumor effect-potentiating composition for potentiating the antitumor effect of an antitumor composition containing a therapeutically effective amount
5 of tegafur while suppressing the side effects of the antitumor composition, the antitumor effect-potentiating composition being characterized in that it contains a compound of the formula



(I)

(I)

- 10 wherein X is a halogen atom or a cyano group in an amount effective for potentiating the antitumor effect, and oxonic acid or a pharmaceutically acceptable salt thereof in an amount effective for suppressing the side effects, as active ingredients, and a pharmaceutically acceptable
15 carrier.

2. An antitumor effect-potentiating composition according to claim 1 which contains about 0.1 to about 10 moles of oxonic acid or a pharmaceutically acceptable salt thereof per mole of the compound of the formula (I) of
20 claim 1.

3. An antitumor effect-potentiating composition



according to claim 1 which contains about 0.5 to about 5 moles of oxonic acid or a pharmaceutically acceptable salt thereof per mole of the compound of the formula (I) of claim 1.

5 4. An antitumor composition comprising a therapeutically effective amount of tegafur, an antitumor effect-potentiating effective amount of a compound of the formula (I) of claim 1, a side effect-suppressing effective amount of oxonic acid or a pharmaceutically
10 acceptable salt thereof, and a pharmaceutically acceptable carrier.

5. An antitumor composition according to claim 4 which contains, per mole of tegafur, about 0.1 to about 5 moles of the compound of the formula (I) of claim 1, and
15 about 0.1 to about 5 moles of oxonic acid or a pharmaceutically acceptable salt thereof.

6. An antitumor composition according to claim 4 which contains about 0.1 to about 1.5 moles of the compound of the formula (I) of claim 1 per mole of
20 tegafur.

7. An antitumor composition according to claim 4 which contains about 0.2 to about 2 moles of oxonic acid or a pharmaceutically acceptable salt thereof per mole of tegafur.

25 8. A method for treating a cancer in a mammal,



comprising administering to the mammal a therapeutically effective amount of tegafur, an antitumor effect-potentiating effective amount of the compound of the formula (I) of claim 1, and a side effect-suppressing effective amount of oxonic acid or a pharmaceutically acceptable salt thereof.

9. A method for potentiating the antitumor effect of tegafur and suppressing the side effects thereof in administering an antitumor composition containing a therapeutically effective amount of tegafur to a patient with a cancer susceptible to 5-fluorouracil therapy, the method being characterized by administering to the patient a compound of the formula (I) of claim 1 in an amount effective for potentiating the antitumor effect, and oxonic acid or a pharmaceutically acceptable salt thereof in an amount effective for suppressing the side effects.

10. A method according to claim 9 wherein an antitumor effect-potentiating effective amount of the compound of the formula (I) of claim 1 and a side effect-suppressing effective amount of oxonic acid or a pharmaceutically acceptable salt thereof are administered to the patient within 4 hours before or within 4 hours after the administration of the antitumor composition.

11. A method according to claim 9 wherein an antitumor effect-potentiating effective amount of the



compound of formula (I) of claim 1 and a side effect-suppressing effective amount of oxonic acid or a pharmaceutically acceptable salt thereof are administered to the patient simultaneously with the administration of the antitumor composition.

DATED THIS 14TH DAY OF SEPTEMBER 1994

TAIHO PHARMACEUTICAL CO. LTD.

By its Patent Attorneys:

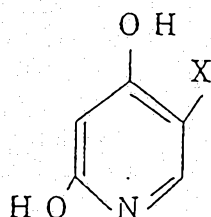
GRIFFITH HACK & CO

Fellows Institute of Patent
Attorneys of Australia.



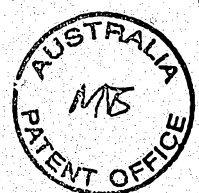
ABSTRACT

This invention provides a composition, method and kit for potentiating the antitumor effect of tegafur and reducing the side effects of tegafur, comprising a compound of the formula



(I)

wherein X is a halogen atom or a cyano group and oxonic acid or a pharmaceutically acceptable salt thereof, and also provides a composition, method and kit for treating a tumor, comprising tegafur, a compound of the formula (I) and oxonic acid or a pharmaceutically acceptable salt thereof.



INTERNATIONAL SEARCH REPORT

International Application No PCT/JP92/00656

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int. Cl. ⁵ A61K31/53// (A61K31/53, A61K31:44, A61K31:505)		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
IPC	A61K31/53, A61K31/505, A61K31/44	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	JP, A, 56-2913 (Setsuro Fujii), January 13, 1981 (13. 01. 81)	1-7, 12-15
A	JP, A, 55-111420 (Setsuro Fujii), August 28, 1980 (28. 08. 80)	1-7, 12-15
A	JP, A, 62-155215 (Otsuka Pharmaceutical Co., Ltd.), July 10, 1987 (10. 07. 87)	1-7, 12-15
¹⁰ Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "Z" document member of the same patent family		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
August 4, 1992 (04. 08. 92)		August 25, 1992 (25. 08. 92)
International Searching Authority		Signature of Authorized Officer
Japanese Patent Office		

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 8-11 because they relate to subject matter not required to be searched by this Authority, namely:

Claims 8 to 11 pertain to a medical treatment of the human body by curing.

2. ☐ Claim numbers ... because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers ... because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

国 際 調 査 報 告

国際出願番号PCT/JP 9 2/ 0 0 6 5 6

I. 発明の属する分野の分類		
国際特許分類 (IPC) Int. Cl. A 6 1 K 3 1 / 5 3 // (A 6 1 K 3 1 / 5 3 , A 6 1 K 3 1 : 4 4 , A 6 1 K 3 1 : 5 0 5)		
II. 国際調査を行った分野		
調 査 を 行 っ た 最 小 限 資 料		
分 類 体 系	分 類 記 号	
IPC	A 6 1 K 3 1 / 5 3 , A 6 1 K 3 1 / 5 0 5 , A 6 1 K 3 1 / 4 4	
最小限資料以外の資料で調査を行ったもの		
III. 関連する技術に関する文献		
引用文献の カテゴリー※	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	請求の範囲の番号
A	JP, A. 56-2913 (藤 井 節 郎), 13. 1月. 1981 (13. 01. 81)	1-7, 12-15
A	JP, A. 55-111420 (藤 井 節 郎), 28. 8月. 1980 (28. 08. 80)	1-7, 12-15
A	JP, A. 62-155215 (大塚製薬株式会社), 10. 7月. 1987 (10. 07. 87)	1-7, 12-15
※引用文献のカテゴリー 「A」特に関連のある文献ではなく、一般的技術水準を示すもの 「E」先行文献ではあるが、国際出願日以後に公表されたもの 「L」優先権主張に疑義を提起する文献又は他の文献の発行日若しくは他の特別な理由を確立するために引用する文献 (理由を付す) 「O」口頭による開示、使用、展示等に言及する文献 「P」国際出願日前で、かつ優先権の主張の基礎となる出願の日の後に公表された文献 「T」国際出願日又は優先日の後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの 「X」特に関連のある文献であって、当該文献のみで発明の新規性又は進歩性がないと考えられるもの 「Y」特に関連のある文献であって、当該文献と他の1以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの 「&」同一パテントファミリーの文献		
IV. 認 証		
国際調査を完了した日 0 4 . 0 8 . 9 2	国際調査報告の発送日 25.08.92	
国際調査機関 日本国特許庁 (ISA/JP)	権限のある職員 特許庁審査官 佐 伯 と も 子	4 C 7 2 5 2

第2ページから続く情報

V. ☒ 一部の請求の範囲について国際調査を行わないときの意見

次の請求の範囲については特許協力条約に基づく国際出願等に関する法律第8条第3項の規定によりこの国際調査報告を作成しない。その理由は、次のとおりである。

1. ☒ 請求の範囲 8-11 は、国際調査をすることを要しない事項を内容とするものである。

請求の範囲 8-11 は、人の身体の治療による処置方法である。

2. ☐ 請求の範囲 _____ は、有効な国際調査をすることができる程度にまで所定の要件を満たしていない国際出願の部分に係るものである。

3. ☐ 請求の範囲 _____ は、従属請求の範囲でありかつ PCT 規則 6.4(a)第2文の規定に従って起草されていない。

VI. ☐ 発明の単一性の要件を満たしていないときの意見

次に述べるようにこの国際出願には二以上の発明が含まれている。

1. ☐ 追加して納付すべき手数料が指定した期間内に納付されたので、この国際調査報告は、国際出願のすべての調査可能な請求の範囲について作成した。
2. ☐ 追加して納付すべき手数料が指定した期間内に一部分しか納付されなかったので、この国際調査報告は、手数料の納付があった発明に係る次の請求の範囲について作成した。
請求の範囲 _____
3. ☐ 追加して納付すべき手数料が指定した期間内に納付されなかったので、この国際調査報告は、請求の範囲に最初に記載された発明に係る次の請求の範囲について作成した。
請求の範囲 _____
4. ☐ 追加して納付すべき手数料を要求するまでもなく、すべての調査可能な請求の範囲について調査することができたので、追加して納付すべき手数料の納付を命じなかった。

追加手数料異議の申立てに関する注意

- ☐ 追加して納付すべき手数料の納付と同時に、追加手数料異議の申立てがされた。
- ☐ 追加して納付すべき手数料の納付に際し、追加手数料異議の申立てがされなかった。