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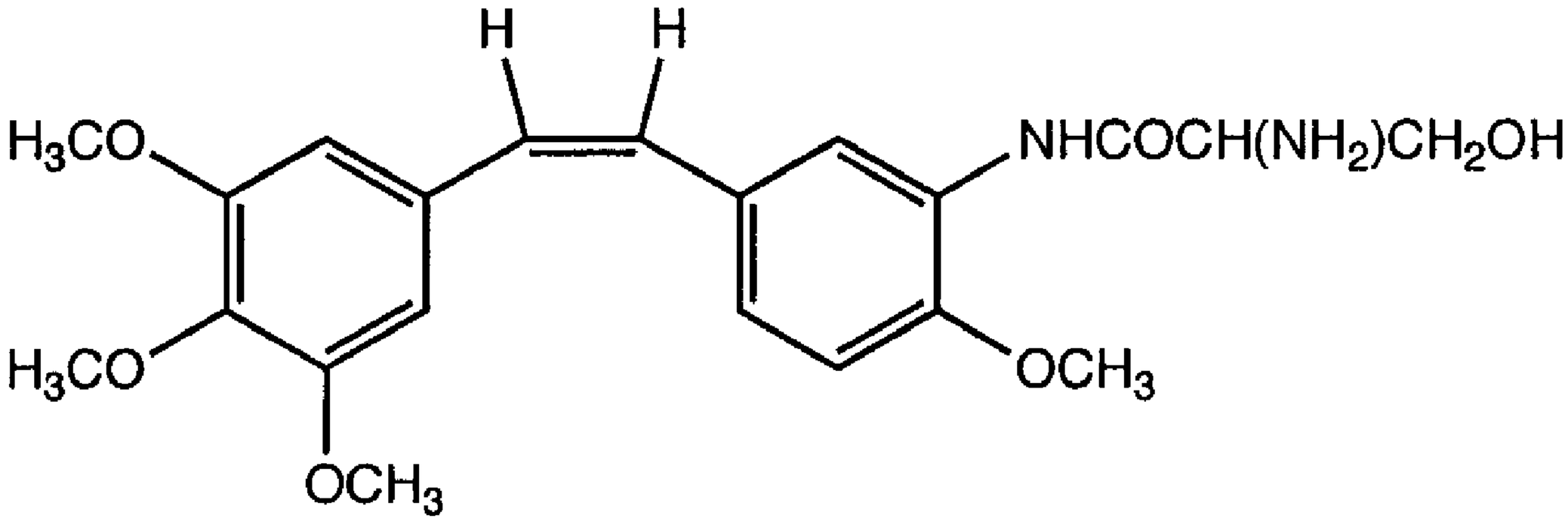
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(54) Titre : COMBINAISON COMPRENANT DE LA COMBRETASTATINE ET DES AGENTS ANTICANCEREUX
(54) Title: A COMBINATION COMPRISING COMBRETASTATIN AND ANTICANCER AGENTS



(57) Abrégé/Abstract:
An antitumor combination comprising a stilbene derivative and an anticancer compound selected from the group consisting of taxanes, alkylating agents, antimetabolites, vinca alkaloids, epidophylloptoxins, and antibiotics as the active ingredients is provided. There are also provided methods of using these pharmaceutical preparations for the treatment of solid carcinomas and the like.

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PATENT APPLICATION

A COMBINATION COMPRISING COMBRETASTATIN AND ANTICANCER AGENTS

AVENTIS PHARMA S.A.

ABSTRACT

An antitumor combination comprising a stilbene derivative and an anticancer compound selected from the group consisting of taxanes, alkylating agents, antimetabolites, vinca alkaloids, epidophylloptoxins, and antibiotics as the active ingredients is provided. There are also provided methods of using these pharmaceutical preparations for the treatment of solid carcinomas and the like.

A COMBINATION COMPRISING COMBRETASTATIN AND ANTICANCER AGENTS

The present invention relates to therapeutic combinations comprising a stilbene derivative and anticancer agents such as taxanes, alkylating agents, antimetabolites, vinca alkaloids, epidophylloptoxins, and antibiotics for the treatment for cancer.

The invention relates to the treatment of cancers, more especially solid tumors, with associations of stilbene derivatives and other anticancer drugs and the use of such associations for an improved treatment against cancers, and to uses of these effective ingredients for the treatment (therapy), suppression, and amelioration of tumors, and the like.

Today, a wide variety of chemotherapeutic agents are used for treatment, and suppression of tumors, especially malignant solid tumors. Although these agents may have a tumor reducing effect, it is often not possible for these known agents to effect a cure due to acquisition of resistance against the agent by the cancer, relapse of the tumors, and so on. Therefore, further superior antitumor agents are needed.

While stilbene derivatives, having cis-stilbene as a fundamental skeleton, are known to exhibit strong mitosis inhibitory activities and cytotoxity, most stilbene derivatives are not yet available as pharmaceutical agents because of their low solubility in water.

Recently, it has been discovered that certain stilbene derivatives having activity for inhibiting tubulin polymerization also have improved water solubility. These include the phosphorylated pro-drug of Combretastatin-A4 (See U.S. Patent No. 5,561,122), and the stilbene derivatives disclosed in US Patent 5 674 906. The clinical use of these stilbene derivatives is felt to be promising.

It is an object of the present invention to develop a superior antitumor agent, specifically, to develop a pharmaceutical preparation capable of improving the efficacy of a stilbene derivative and, in particular, to develop and provide antitumor agents exhibiting superior safety and efficacy in treating malignant tumors.

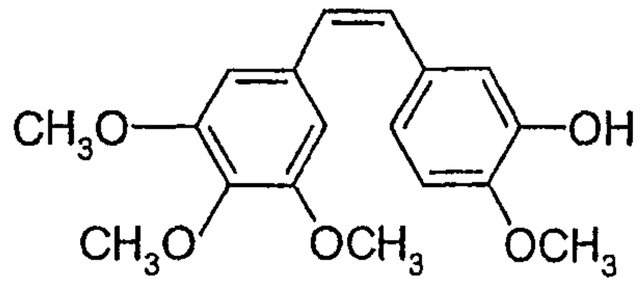
It has been found that a stilbene derivative, administered together with another anticancer agent such as a taxane, an alkylating agent, an antimetabolite, an epidophylloptoxin, an antibiotic, and a vinca alkaloid, exhibit improved therapeutic effects to inhibit tumor growth.

Among substances which may be used in association or in combination with the stilbene derivative are taxanes such as taxol, taxotere or their analogues; alkylating agents such as cyclophosphamide, isosfamide, melphalan, hexamethylmelamine, thiotepa or dacarbazine; antimetabolites such as pyrimidine analogues, for instance 5-fluorouracil, cytarabine capecitabine and gemcetabine or its analogues such as 2-fluorodeoxycytidine; folic acid analogues such as methotrexate, idatrexate or trimetrexate; spindle poisons including vinca alkaloids such as vinblastine, vincristine, vinorelbine and vindesine, or their synthetic analogues such as navelbine, or estramustine and a taxoid; epipodophyllotoxins such as etoposide or teniposide; antibiotics such as daunorubicin, doxorubicin, bleomycin or mitomycin, enzymes such as L-asparaginase, topoisomerase inhibitors such as topotecan or pyridobenzoindole derivatives; and various agents such as procarbazine, mitoxantrone, and biological response modifiers or growth factor inhibitors such as interferons or interleukins.

Taxanes such as taxol® and taxotere® and vinca alkaloids such as vincristine and vinblastine are considered antimicrotubule agents which interfere with cell division by disrupting the normal functionality of the cellular microtubules. Alkylating agents such as cyclophosphamide, isosfamide, melphalan, hexamethylmelamine, thiotepa or dacarbazine generally exert cytotoxic activity by alkylating DNA, thus directly interfering with the reproductive cycle of the cell. Antimetabolites exert cytotoxic activity by substituting fraudulent nucleotides into cellular DNA, thereby interrupting cell division or inhibiting enzymes which are necessary for DNA replication. Epidophyllotoxins such as etoposide and teniposide are topoisomerase inhibitors. Antibiotics, such as doxorubicin and daunorubicin, are also thought to work by inhibiting topoisomerase II.

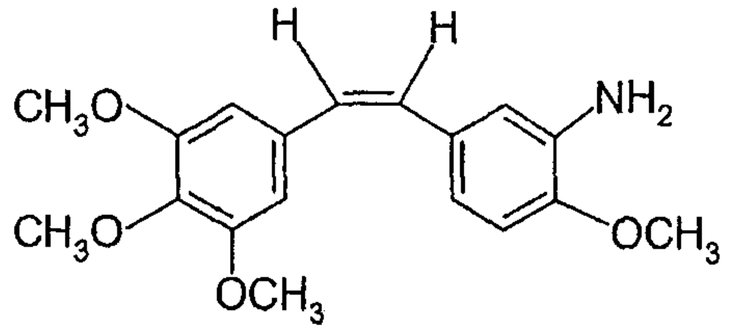
It has now been found that these various anticancer agents in combination with a stilbene derivative are especially effective in the treatment of many solid tumors. Among the effective stilbene derivatives is combretastatin A-4, and a derivative of the compound, (Z)-1-(3-amino-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene, which will be called SN38. Both of these compounds exhibit strong mitosis inhibitory activities, cytotoxicity, and inhibit tubulin polymerization.

Combretastatin A-4 has the following formula:



(I)

SN38 has the following formula:



(II)

These combretastatins are barely soluble in water and can be used in the form of a salt exemplified by hydrochloride, acetate, phosphate, methanesulfonate, and the aminoacid salt.

The manufacture of stilbene derivatives which may be in the form of pharmaceutically acceptable salts, hydrates and solvates, and the manufacture of oral and/and parenteral pharmaceutical composition containing the above compound, its inert pharmaceutically acceptable carrier(s) and/or diluent(s), are disclosed in U.S. Patent Nos. 5,525,632, 5731,353 and 5,674,906 for SN38 and prodrug. These patents disclose that stilbene derivatives, including combretastatin SN38, when used alone, have carcinostatic effects in vivo.

It has recently been discovered that the combination of combretastatin Z and an anticancer agent selected from the group consisting of taxoids, alkylating agents, antimetabolites, vinca alkaloids, epidophylloptoxins and antibiotics significantly reduces the development of tumor volume over what would be predicted from administration to tumor-infected mammals of each compound alone.

Thus, the present invention is promising as providing a novel antitumor agent, for example, a chemotherapeutic drug against cancer (cancer chemotherapy agent), comprising simultaneously or separately two types of active ingredients, namely a stilbene derivative and another anticancer compound.

The present invention is directed to an antitumor agent comprising a stilbene derivative and an anticancer agent.

The present invention also encompasses a combination therapy wherein the stilbene derivative and another anticancer agent are prepared as two separate

pharmaceutical preparations and administered to a patient in need thereof, simultaneously, semi-simultaneously, separately or spaced out over time.

The tumor against which the antitumor agents of the present invention are administered encompasses all sorts of tumors occurring in an animal, especially in a human being. Preferably, the antitumor agents of the present invention may be used for inhibiting proliferation of tumor cells in a human being. The antitumor agents of the present invention are pharmaceutical preparations wherein at least two compounds are used to cure (treat), or suppress tumors.

There is no particular limitation to the form of administration of the antitumor agents. Anticancer agents are routinely administered intravenously, parenterally, and orally. The present invention also encompasses an antitumor agent consisting in the combination of two compounds having distinct forms of administration.

The stilbene derivative used in the present invention has cis-stilbene as a fundamental skeleton and exhibits *in* vivo tubulin polymerization inhibiting activity and/or an antitumor activity. The stilbene derivatives of the present invention also include prodrugs which may be converted *in vivo* into a stilbene derivative. All forms of suitable pharmaceutically allowable derivatives, such as salts, esters, amides, solvates (solvation products) and hydrates thereof, may be used as the stilbene derivatives in the present invention, provided that the derivatives exhibit antitumor activity when used *in vivo*.

Prodrugs of product of formula (II) are preferably aminoacid salts.

Representative stilbene derivatives are shown by one of the following general formula (I) or (II).

The amino acids may be enumerated by α-amino acids, β-amino acids and γ-amino acids. Examples of preferred amino acids include glycine, alanine, leucine, serine, lysine, glutamic acid, asparatic acid, threonine, valine, isoleucine, ornithine, glutamine, asparagine, tyrosine, phenylalanine, cysteine, methionine, arginine, -alanine, tryptophan, proline, histidine, etc. In particular, threonine and serine are preferred in view of pharmaceutical effects and safety. Although any one of these amino acids may be of the L-, D- or DL-form, the L-form. is preferred.

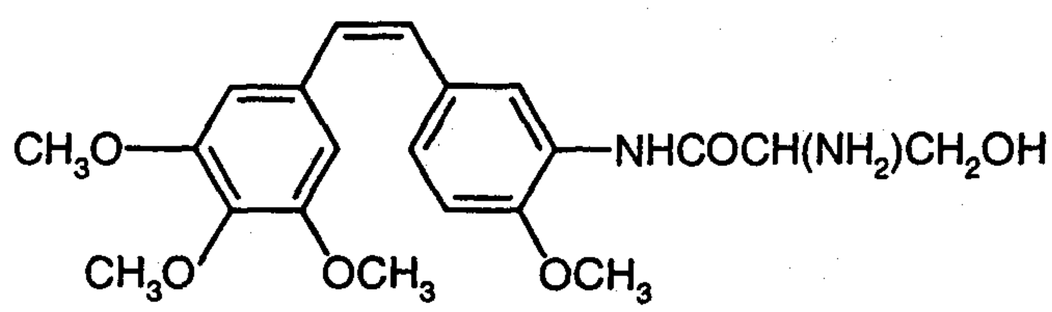
As described above, the stilbene derivative of the present invention is a compound having a cis-stilbene skeleton in its structure and exhibits tubulin polymerization inhibiting activity and/or an antitumor activity. Such stilbene derivatives are exemplified by combretastatin-A4 and product of formula (II) disclosed in prior art publications, such as the U.S. Patent Nos. 4,996,237, 5,561,122 and 5,430,062, The prior

art stilbene derivatives, described in these patent publications and combrestatin of formula (II) described in U.S. Patent Nos. 5,525,632 and 5,731,353, can be used for the stilbene derivatives of the present invention, insofar as they meet the definition for the stilbene derivatives in the present invention.

The above mentioned stilbene derivatives may be manufactured by the routine technique including the method disclosed in the above mentioned known publications.

Among the stilbene derivatives of the present invention, there are salts, esters, and other derivatives of stilbene, and derivatives which may be converted *in vivo* into the stilbene derivatives, insofar as the stilbene derivatives manifest the above-mentioned objective activities in an animal body.

Among the compounds represented by the above general formula (II), are compounds represented by the following formula (IIa):



(IIa)

Compound of formula (IIa) is soluble in water and may be in the form of a salt exemplified by hydrochloride, acetate, methanesulfonate and the like.

When the antitumor agent of the present invention is to be used, a stilbene derivative in an amount sufficient to inhibit tumor proliferation may be combined with a compound chosen from the group consisting of taxanes, alkylating agents, antimetabolites, vinca alkaloids, epidophylloptoxins, and antibiotics and administered to the subject, an animal, especially a human being, in need of curing, alleviation of tumors, especially a human being suffering from proliferation of tumor cells, to inhibit the proliferation of said tumor cells.

The present invention also relates to pharmaceutical compositions containing the combinations according to the invention.

The products of which the combination are composed may be administered simultaneously, separately or spaced out over a period of time so as to obtain the maximum efficacy of the combination; it being possible for each administration to vary in its duration from a rapid administration to a continuous perfusion.

As a result, for the purposes of the present invention, the combinations are not exclusively limited to those which are obtained by physical association of the

constituents, but also encompass those which permit a separate administration, which can be simultaneous or spaced out over a period of time.

One of the preferred embodiments in the present invention is to use compound IIa in an amount effective to inhibit proliferation of tumor cells in combination with taxotere, doxorubicin, or vincristine to inhibit proliferation of tumor cells.

The inhibition of proliferation of tumor cells means inhibition of proliferation of the tumor cells sensitive to therapy including administration of an effective amount of the stilbene derivatives, such as combretastatin IIa, and taxoid compounds, such as taxol, taxotere and their derivatives to, *e.g.*, a human being suffering from proliferation of tumor cells. In an acceptable case, this administration suppresses proliferation of tumor cells or diminishes the measurable size of the tumors. In an optimum case, the tumor undergoes regression completely.

As described above, there is no particular limitation to the method of administering the antitumor agent of the present invention to the human being, such that it may be administered orally or parenterally, by intravenous, subcutaneous or intramuscular route. For prompt efficacy, parenteral administration, by intravenous and subcutaneous administration, i.e., by infusion, etc. is preferred. In the method for administering the pharmaceutical preparation according to the present invention, the stilbene derivative may be administered simultaneously with the taxoid compound or the two may be sequentially administered in an optional order. The practically desirable method and sequence for administration are varied depending on the individual preparation of the stilbene derivative used and the individual preparation of the other anticancer compound used, e.g., taxotere, doxorubicin or a vinca alkaloid, the individual tumor cells being cured, and the individual hosts being treated. The optimum method and sequence for administration of the stilbene derivative and the auxiliary anticancer compound under preset given conditions may be suitably selected by those skilled in the art with the aid of the routine technique and the information contained in the present specification.

The antitumor agent of the present invention is sufficient to be a pharmaceutical preparation comprising the two active ingredients of the present invention contained separately in distinct pharmaceutical preparations used in combination. It is noted that such a pharmaceutical preparation containing other agents (third and fourth medical ingredients and so on) such as other antitumor agents, may naturally be encompassed by the present invention, insofar as the effective ingredients used in the present invention are contained in the pharmaceutical preparation.

As the suitable pharmaceutically acceptable carriers and diluents, used in the antitumor agent of the present invention, those carriers etc., known to those skilled in the art of preparation of pharmaceutical preparations, may be used as appropriate. The antitumor agents of the present invention may be administered parenterally, as discussed above. In this case, the antitumor agent is prepared into an intravenous infusion bag, along with pharmaceutically acceptable carriers by variable methods known to those skilled in the art. Preferably, the pharmaceutical agent is manufactured by a routine technique in *e.g.*, a unit dosage form and in the form of a freeze-dried preparation, and is reprepared in water or other suitable liquid infusion in administration.

The ratio of the two ingredients for the pharmaceutical preparation for the antitumor agent of the present invention may be varied in a wide range, depending on a number of factors, such as a desired amount of administration and on the pharmaceutically acceptable carrier in use. As for the amounts or combination in administering the stilbene derivative in the pharmaceutical preparation as the antitumor agent of the present invention, the stilbene derivative of approximately 0.01 to 1000 and, in particular, approximately 0.1 to 100 parts by weight of the stilbene derivative, to 1 part by weight of the auxiliary anticancer compound present in the pharmaceutical preparation as the antitumor agent of the present invention, are preferably employed. So, when the pharmaceutical preparation in the present invention containing two active ingredients is to be administered to the patient, it is administered in an amount which will give the above-defined administration range.

If the pharmaceutical preparation is to be administered stepwise, the above-defined administration range can be set as the average ratio for the separate pharmaceutical preparations.

The present invention is now explained in more detail with reference to preferred embodiments thereof. It is to be noted that these are given only as an example and are not intended to limit the invention.

The efficacy of a combination may be demonstrated by determination of its therapeutic synergy. A combination manifests therapeutic synergy if it is therapeutically superior to one or other of the constituents used at its optimum dose (T.H. Corbett et al., Cancer Treatment Reports, 66, 1187 (1982)).

The efficacy of a combination may also been demonstrated by comparison of the maximum tolerated dose of the combination with the maximum tolerated dose of each of the separate constituents in the study in question. This efficacy may be quantified, for example by the $\log_{10}$ cell kill, which is determined by the following formula:

$$\log_{10} \text{cells killed} = \text{T-C(days)}/3.32 \times T_d$$

in which T-C represents the time taken for the cells to grow, which is the mean time in days for the tumors of the treated group (T) to reach a predetermined value (1 g for example) and the tumors of the control group (C) to reach the same value, and T_d represents the time in days needed for the volume of the tumors in the control group to double. (T.H. Corbett et al., Cancer, 40, 2660.2680 (1977); F.M. Schabel et al., Cancer Drug Development, Part B, Methods in Cancer Research, 17, 3-51, New York, Academic Press Inc. (1979)). A product is considered to be active if the $\log_{10}$ cell kill is greater than or equal to 0.7. A product is considered to be very active if the $\log_{10}$ cell kill is greater than 2.8.

The combination, used at its own maximum tolerated dose, in which each of the constituents will be present at a dose generally not exceeding its maximum tolerated dose, will manifest therapeutic synergy when the $\log_{10}$ cells killed is greater than the value of the $\log_{10}$ cells killed of the best constituent when it is administered alone.

In the present invention, a stilbene derivative, such as combretastatin, in an amount sufficient to inhibit tumor proliferation may be used with another anticancer agent such as taxoids, alkylating agents, antimetabolites, vinca alkaloids, epidophylloptoxins, and antibiotics and administered to a mammal, in need of curing, alleviation, or prevention of tumors, especially a human being suffering from proliferation of tumor cells, in order to inhibit the growth of the tumor cells.

The inhibition of proliferation of tumor cells means inhibition of those tumor cells sensitive to therapy including administration of an effective amount of combretastatin and an effective amount of a second anticancer compound as described below to a human being suffering from proliferation of tumor cells. In an acceptable case, this administration suppresses proliferation of tumor cells or diminishes the measurable size of the tumors. In an optimum case, the tumor undergoes regression completely.

As described above, there is no particular limitation to the method of administering the antitumor agents of the present invention to the mammal being treated. They may be administered orally or parenterally, such as by intravenous, subcutaneous or intramuscular route. For prompt efficacy, parenteral administration of combretastatin, such as by intravenous and subcutaneous administration, by infusion, etc. is preferred. In the method for administering the pharmaceutical preparation according to the present invention, combretastatin may be administered simultaneously with another anticancer

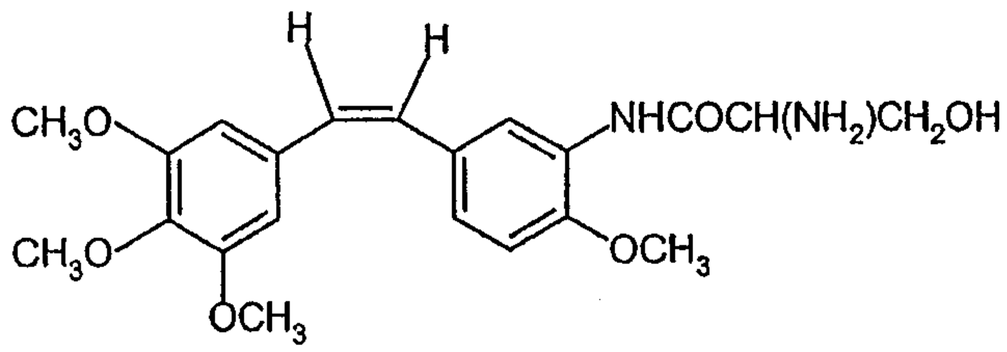
agent or the two may be sequentially administered in an optional order. In practice, the method and sequence for administration are varied depending on the individual preparation of combretastatin, the individual preparation of the second anticancer agent, the individual tumor cells being cured, and the individual hosts being treated. The optimum method and sequence for administration of combretastatin and the second anticancer agent may be suitably selected by those skilled in the art with the aid of routine technique and the information contained in the present specification.

An efficacious tumor proliferation inhibiting amount of the combretastatin and an anticancer agent selected from the group consisting of taxoids, alkylating agents, antimetabolites, vinca alkaloids, epidophylloptoxins, and antibiotics means a curative unit inhibiting proliferation of the tumor cells sensitive to administration in the human being suffering from proliferation of tumor cells. The practically desirable curative unit is varied depending on the individual dosage forms of combretastatin used, the individual dosage forms of the auxiliary anticancer agent used, the individual tumor cells being cured and the individual hosts being treated. The optimum curative units for preset given conditions may be suitably selected by those skilled in the art with the aid of the curative test units and the information contained in the present specification.

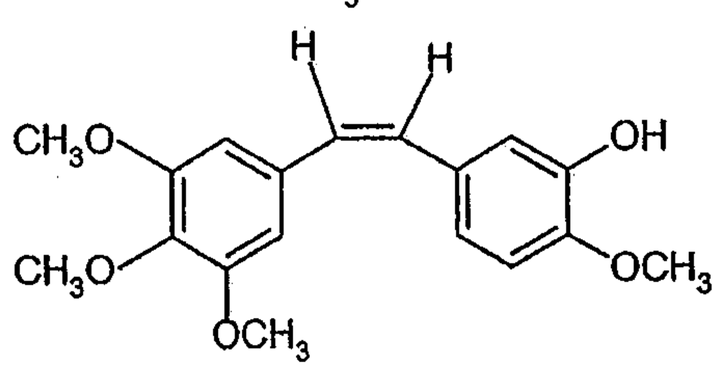
The antitumor agent of the present invention is a pharmaceutical preparation comprising at least combretastatin and one of the anticancer compounds as described above, such that the two active ingredients may be contained as a mixture in a pharmaceutical preparation. However, the two active ingredients in the present invention may also be contained separately in distinct pharmaceutical preparations to be used sequentially and in combination. It is noted that such a pharmaceutical preparation containing other agents (third and fourth medical ingredients and so on) such as other antitumor agents, may naturally be encompassed by the present invention, insofar as the effective ingredients used in the present invention are contained in the pharmaceutical preparation. Moreover, it is possible for carriers, diluents and other substances, pharmaceutically acceptable for any of the pharmaceutical preparations in the present invention (a sole pharmaceutical preparation containing both ingredients in the present invention and separate pharmaceutical preparations separately each containing one of the two ingredients for use in combination) to be contained in the antitumor agent of the present invention.

The present invention is now explained in more detail with reference to preferred embodiments thereof. It is to be noted that these are given only as an examples and are not intended to limit the invention.

Pharmaceutical preparations for infusion were prepared in accordance with the following composition using the compounds, combretastatins Z and A-4, shown by the following chemical formulas (1) and (2) respectively:



(IIa)



(I)

Compound (I) (as phosphate)	10 mg
Tween® 80	0.5 ml and
physiological saline water	9.5 ml
Compound (IIa) (as hydrochloride)	5 mg
Tween® 80	0.5 ml and
physiological saline water	9.5 ml

The preparation of taxol, taxotere and their derivatives form the subject, for example, of European Patents EP 0,253,738 and EP 0,253,739 and International Application PCT WO 92/09,589.

Generally, the doses of the taxane used, which depend on factors distinctive to the subject to be treated, are between 1 and 10 mg/kg administered intraperitoneally or between 1 and 3 mg/kg administered intravenously.

Antitumor Effect and Tests on Safety

The efficacy of the combinations on solid tumors may be determined experimentally in the following manner:

The animals subjected to the experiment, generally mice, are subcutaneously grafted bilaterally with 30 to 60 mg of a tumor fragment on day 0. The animals bearing tumors are mixed before being subjected to the various treatments and controls. In the case of treatment of advanced tumors, tumors are allowed to develop to the desired size,

and animals having insufficiently developed tumors are eliminated. The selected animals are distributed at random to undergo the treatments and controls. Animals not bearing tumors may also be subjected to the same treatments as the tumor-bearing animals in order to be able to dissociate the toxic effect from the specific effect on the tumor. Chemotherapy generally begins from 3 to 22 days after grafting, depending on the type of tumor, and the animals are observed every day. The different animal groups are weighed 3 or 4 times a week until the maximum weight loss is attained, and the groups are then weighed at least one a week until the end of the trial.

The tumors are measured 2 or 3 times a week until the tumor reaches approximately 2 g, or until the animal dies if this occurs before the tumor reaches 2 g. The animals are autopsied when sacrificed.

The antitumor activity is determined in accordance with different parameters recorded such as dose (mg/kg), mode of administration, time of administration, cytotoxicity, toxicity and log cell kill.

For a study of the combinations on leukemias, the animals are grafted with a particular number of cells, and the antitumour activity is determined by the increase in the survival time of the treated mice relative to the controls. The product is considered to be active if the increase in survival time is greater than 27 %, and is considered to be very active if it is greater than 75 % in the case of P388 leukemia.

The results obtained with combinations of combretastatin and various chemotherapeutic agents, such as taxotere (taxane), doxorubicin (antibiotic) and vincristine (vinca alkaloid), the combinations being used at their optimum dose, will be reported.

IN VIVO EVALUATION OF COMPOUND (IIA) (AS HYDROCHLORIDE) AND CISPLATINUM COMBINATION

Agent	Tumor	Schedule days	HNTD Dose mg/kg	T-C days	LcK	RR PR	RR CR	RR TFS
Single agents:								
COMPOUND (IIA) (as hydrochloride)	C51	12,16	116	10	1.2	6/6	0/6	0/6
CDDP		12,16	6.2	16.5	1.9	5/6	0/6	0/6
Combination:								
- simultaneous								
COMPOUND (IIA) (as hydrochloride) 1st		12,16	116	NA	NA	6/6	6/6	6/6
CDDP		12,16	10					
- sequential								
COMPOUND (IIA) (as hydrochloride)		14	58	51	5.9	5/5	5/5	0/5
CDDP		15,19	10					

BCM-1209 (09.20.00-01.29.01)

Abbreviations used:
HNTD = highest nontoxic dose; T-C = tumor growth delay; LcK = log cell kill; RR = response rate; PR = partial response; CR = complete response, TFS = tumor free survivors.

Conclusion: The combination of COMPOUND (IIA) (as hydrochloride) and cisplatinum is synergistic.

IN VIVO EVALUATION OF COMPOUND (IIA) (AS HYDROCHLORIDE) AND VINORELBINE COMBINATION

Agent	Tumor	Schedule days	HNTD Dose mg/kg	T-C days	LcK	RR PR	RR CR	RR TFS
Single agents:								
COMPOUND (IIA) (as hydrochloride)	MA13/C	15,25	150	5	0.5	0/5	0/5	0/5
Vinorelbine		15,25	19.8	45.5	4.6	5/5	5/5	0/5
Combination – sequential								
COMPOUND (IIA) (as hydrochloride) 1st		14	75	84.7	8.5*	5/5	5/5	2/5
Vinorelbine 2nd		15,25	32					

BCM-1234 (11.23.00-05.10.01)

*log cell kill evaluated on the limited number of mice that developed tumor, the other mice in the group being tumor free survivors.

Abbreviations used:
HNTD = highest nontoxic dose; T-C = tumor growth delay; LcK = log cell kill; RR = response rate; PR = partial response; CR = complete response, TFS = tumor free survivors.

Conclusion: The combination of COMPOUND (IIA) (as hydrochloride) and vinorelbine is synergistic.

IN VIVO EVALUATION OF COMPOUND (IIA) (AS HYDROCHLORIDE) AND DOCETAXEL COMBINATION

Agent	Tumor	Schedule days	HNTD Dose mg/kg	T-C days	LcK	PR	RR CR	TFS
Single agents:								
Docetaxel	MA13/C	17,24	68	26.7	3.2*	6/6	4/6	3/6
COMPOUND (IIA) (as hydrochloride)		17,24 (2x/d)	242	10.8	1.3	1/6	1/6	0/6
Combination - sequential								
COMPOUND (IIA) (as hydrochloride)		16,23 (2x/d)	150	74.8	6.0*	6/6	6/6	4/6
Docetaxel		17,24	109.6					

BCM-1269 (09.04.01-03.08.02)

*log cell kill evaluated on the limited number of mice that developed tumor, the other mice in the group being tumor free survivors.

Abbreviations used:
HNTD = highest nontoxic dose; T-C = tumor growth delay; LcK = log cell kill; RR = response rate; PR = partial response; CR = complete response, TFS = tumor free survivors.

Conclusion: The combination of COMPOUND (IIA) (as hydrochloride) and docetaxel is synergistic.

IN VIVO EVALUATION OF COMPOUND (IIA) (AS HYDROCHLORIDE) AND DOXORUBICIN COMBINATION

Agent	Tumor	Schedule days	HNTD Dose mg/kg	T-C days	LcK	RR PR	CR	TFS
Single agents:								
Doxorubicin	MA13/C	15,22	17.4	53.5	4.5	4/6	4/6	0/6
COMPOUND (IIA) (as hydrochloride)		15,22	186.0	30.2	1.3	0/6	0/6	0/6
Combination – sequential								
COMPOUND (IIA) (as hydrochloride)		15,21	139.6	80.6	11*	7/7	7/7	2/7
Doxorubicin		16,22	17.4					

BCM-1262 (07.23.01-02.14.02)

*log cell kill evaluated on the limited number of mice that developed tumor, the othermice in the group being tumor free survivors.

Abbreviations used:
HNTD = highest nontoxic dose; T-C = tumor growth delay; LcK = log cell kill; RR = response rate; PR = partial response; CR = complete response, TFS = tumor free survivors.

Conclusion: The combination of COMPOUND (IIA) (as hydrochloride) and doxorubicin is synergistic.

IN VIVO EVALUATION OF COMPOUND (IIA) (AS HYDROCHLORIDE) AND CPT-11 COMBINATION

Agent	Tumor	Schedule days	HNTD Dose mg/kg	T-C days	LcK	PR	RR CR	TFS
Single agents:								
COMPOUND (IIA) (as hydrochloride)	C51	13-17 (2x/d)	116:5	10.3	1.3	5/5	0/5	0/5
CPT-11 (oral)		14-17	400.0	8.7	1.1	0/5	0/5	0/5
Combination - sequential								
CPT-11 (oral) COMPOUND (IIA) (as hydrochloride)		13-16 17	400 36	15.1	1.9	5/5	3/5	0/5

BCM-1182 (06.06.00-07.24.00)

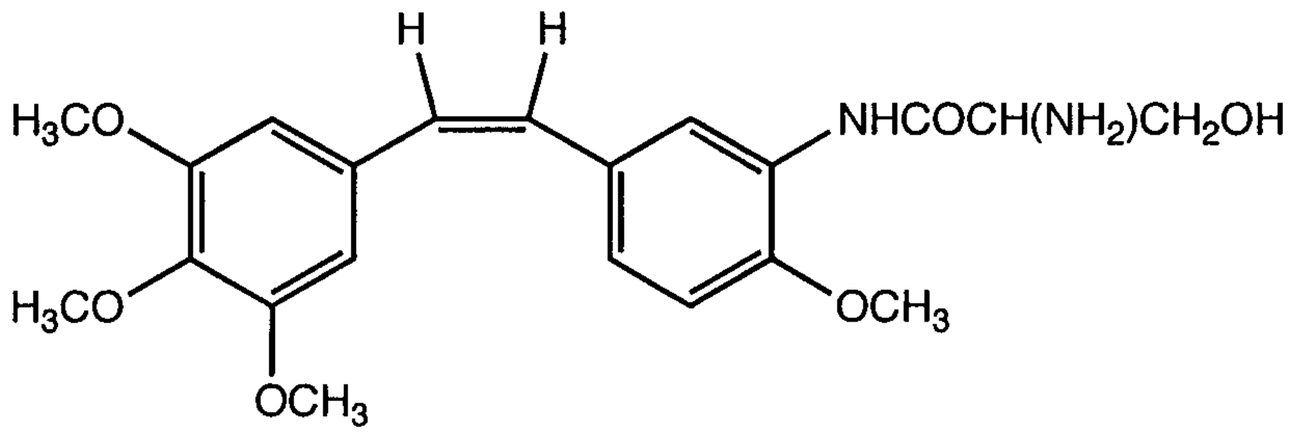
Abbreviations used:
HNTD = highest nontoxic dose; T-C = tumor growth delay; LcK = log cell kill; RR = response rate; PR = partial response; CR = complete response, TFS = tumor free survivors.

Conclusion: The combination of COMPOUND (IIA) (as hydrochloride) and CPT-11 induces a greater number of complete responses and a higher log cell kill.

The antitumor agent according to the present invention, comprising a stilbene derivative and an auxiliary anticancer compound, such as taxanes, alkylating agents, antimetabolites, vinca alkaloids, epidophylloptoxins, and antibiotics, in combination or as a mixture, can be used as a cancer chemotherapeutic drug, which may be highly effective in treating, suppressing and preventing tumors, especially solid carcinomas, due to the therapeutic and sometimes synergistic effect derived from the combination of a stilbene such as combrestatin Z with another anticancer agent as described above.

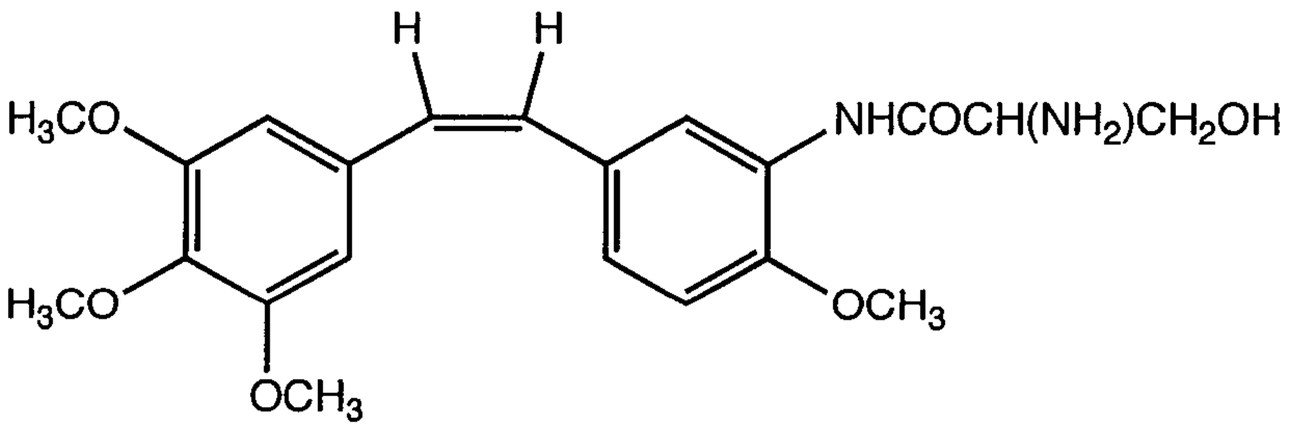
THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A pharmaceutical combination comprising an effective amount of doxorubicin in combination with an effective amount of combretastatin for the treatment of solid tumours, wherein said combretastatin has the following formula:

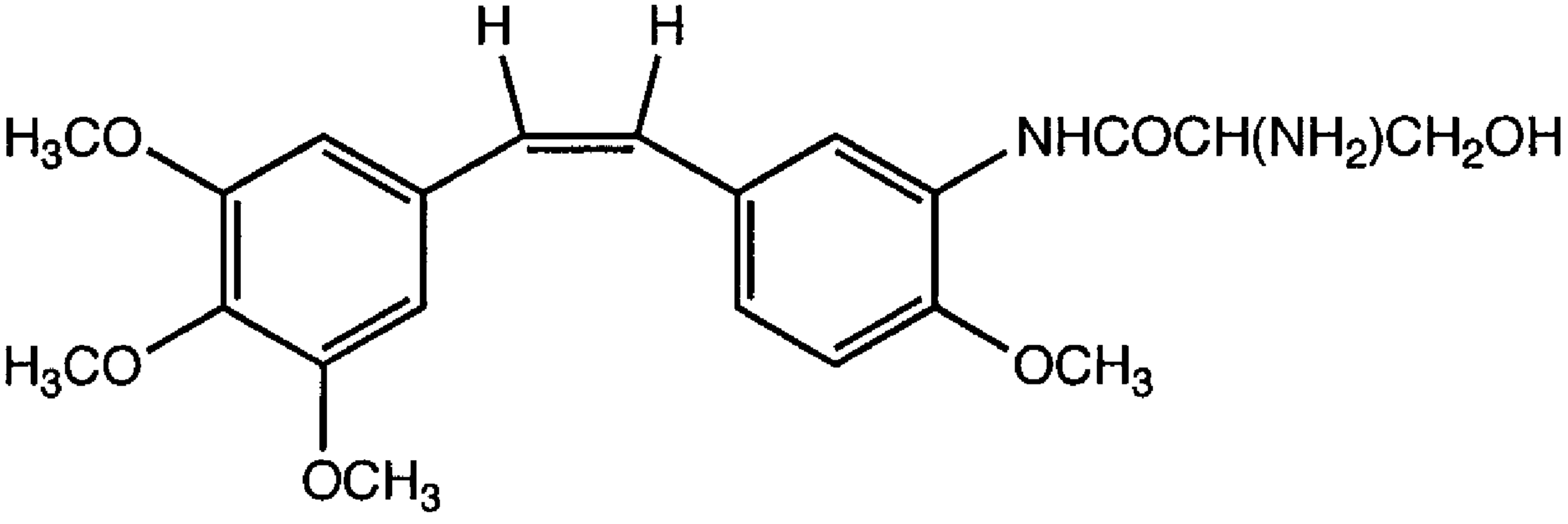


2. The combination according to claim 1, wherein said combretastatin is in the form of a hydrochloride salt.

3. A pharmaceutical combination comprising an effective amount of vinorelbine in combination with an effective amount of combretastatin for the treatment of solid tumours, wherein said combretastatin has the following formula:



4. The combination according to claim 3, wherein said combretastatin is in the form of a hydrochloride salt.


H
H
H3CO
H3CO
OCH3
NHCOCH(NH2)CH2OH
OCH3