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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/40	A1	(11) International Publication Number: **WO 99/34796**
		(43) International Publication Date: 15 July 1999 (15.07.99)

(21) International Application Number: PCT/EP98/08159

(22) International Filing Date: 12 December 1998 (12.12.98)

(30) Priority Data:
9727524.2 31 December 1997 (31.12.97) GB

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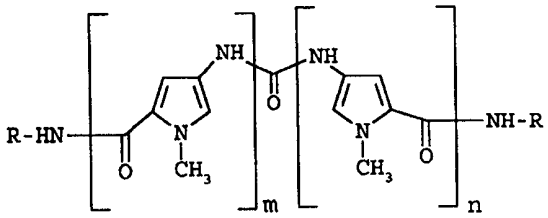
(81) Designated States: JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
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.

(54) Title: SYNERGISTIC ANTITUMOR COMPOSITION CONTAINING A NAPHTHALENSULPHONIC ACID DERIVATIVE



(I)

(57) Abstract

A pharmaceutical composition for use in antineoplastic therapy in mammals, including humans, comprising a biologically active ureido compound of formula (I), wherein each of m and n, being the same, is an integer of 1 to 3; and each of the R groups, which are the same, is a naphthyl group substituted by 1 to 3 sulfonic groups, or a pharmaceutically acceptable salt thereof, and an antineoplastic agent selected from the group consisting of an antineoplastic vinca alkaloid, an antineoplastic antibiotic, and antineoplastic antimetabolite, an antineoplastic platinum coordination complex, an antineoplastic taxane compound, an antineoplastic ceramide compound, an antineoplastic distamycin compound, an antineoplastic epidophyllotoxin compound and an antineoplastic topoisomerase (I) inhibitor, and a pharmaceutically acceptable carrier or excipient, in amounts effective to produce a synergistic antineoplastic effect, is provided herein.

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SYNERGISTIC ANTITUMOR COMPOSITION CONTAINING A NAPHTHALENSULPHONIC ACID DERIVATIVE

Field of the invention

The present invention relates in general in the field of cancer and, more particularly, provides an antitumor composition comprising a cytostatic agent and a biologically active ureido compound, having a synergistic antineoplastic effect.

Background of the invention

Neoplastic diseases in humans are recognized throughout the world as being serious and oftentimes life-threatening conditions. These neoplastic diseases, which are characterized by rapidly-proliferating cell growth, have been and continue to be the subject of worldwide research efforts directed toward the identification of therapeutic agents which are effective in the treatment of patients suffering therefrom. Effective therapeutic agents can be characterized as those which prolong the survival of the patients, which inhibit the rapidly-proliferating cell growth associated with the neoplasm, or which effect a regression of the neoplasm. Research in this area is primarily focused toward identifying agents which would be therapeutically effective in humans. Typically, compounds are tested for antineoplastic activity in small mammals, such as mice, in experiments designed to be predictive of antineoplastic activity not only in those animals but also in humans against specific neoplastic disease states.

The present invention concerns a method for treating tumors utilizing a combination of known antitumor agents which exert their efficacy through inhibition of tumor cells

proliferation (cytotoxic agents) with known not-cytotoxic ureido compounds which exert their efficacy through inhibition of blood vessel formation (angiogenesis).

It is a recognized phenomenon that angiogenesis is a fundamental requisite for solid tumor growth and metastatic spread. Angiogenesis is started when tumor cells produce angiogenic factors which stimulate quiescent endothelial cells to proliferate, destroy the basal membrane, migrate, adhere and proliferate to form new capillaries. As a consequence, inhibitors of angiogenesis will block tumor growth; although no definitive clinical response is presently available on the activity of the angiogenesis inhibitors undergoing clinical trials, experimental evidence indicates that modulation of angiogenesis alone may be insufficient to efficiently control tumor growth and metastatic spread. It is thus conceivable that combined therapy with non toxic inhibitors of angiogenesis and cytotoxic agents can represent a new effective clinical regimen.

Biologically active compounds known from WO 91/10649 inhibit angiogenesis through making a complex with growth factors and angiogenic polypeptides such as basic fibroblast growth factor, insulin growth factor-1 and hepatocyte growth factor. They do not inhibit tumor cells proliferation, and administered by intravenous (iv), intraperitoneal (ip), subcutaneous (sc) and oral route inhibit in mice angiogenesis induced by growth/angiogenic factors and the growth of transplanted human and murine tumors.

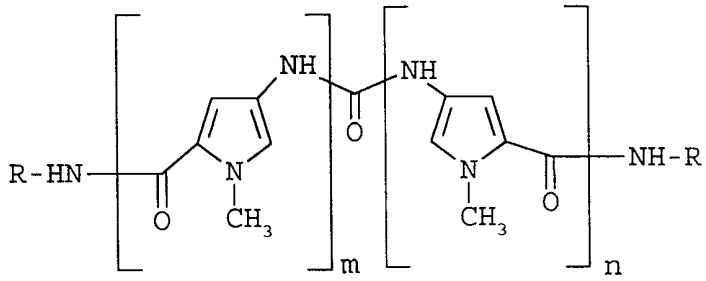
It has now been found that in treating a patient affected with certain neoplastic disease states, conjunctive therapy

with a biologically active compound known from WO 91/10649 and a cytotoxic agent, will provide a synergistic antineoplastic effect.

A synergistic effect is achieved when a greater antineoplastic effect results with a conjunctive therapy than use of either drug alone, thus giving a superadditive antineoplastic effect. One advantage of conjunctive therapy with a synergistic effect is that lower dosages of the antineoplastic agent may be used so that the therapeutic index is increased and toxic side effects are reduced.

Description of the invention

The present invention provides, in a first aspect, a pharmaceutical composition for use in antineoplastic therapy in mammals, including humans, comprising a biologically active ureido compound of formula (I)



(I)

wherein

each of m and n, being the same, is an integer of 1 to 3; and each of the R groups, which are the same, is a naphthyl group substituted by 1 to 3 sulfonic groups, or a pharmaceutically acceptable salt thereof, and an antineoplastic agent selected from the group consisting of an antineoplastic vinca alkaloid, an antineoplastic antibiotic, an antineoplastic antimetabolite, an antineoplastic platinum coordination complex, an antineoplastic taxane compound, an antineoplastic ceramide compound, an antineoplastic

distamycin compound, an antineoplastic epidophyllotoxin compound and an antineoplastic topoisomerase I inhibitor, and a pharmaceutically acceptable carrier or excipient, in amounts effective to produce a synergistic antineoplastic effect.

The present invention also provides a product comprising synergistic amounts of a biologically active ureido compound of formula (I), as defined above, or a pharmaceutically acceptable salt thereof, and an antineoplastic agent selected from the group consisting of an antineoplastic vinca alkaloid, an antineoplastic antibiotic, an antineoplastic antimetabolite, an antineoplastic platinum coordination complex, an antineoplastic taxane compound, an antineoplastic ceramide compound, an antineoplastic distamycin compound, an antineoplastic epidophyllotoxin compound and an antineoplastic topoisomerase I inhibitor, as a combined preparation for simultaneous, separate or sequential use in antitumor therapy.

A further aspect of the present invention is to provide a method of treating a mammal including humans, suffering from a neoplastic disease state comprising administering to said mammal a biologically active ureido compound of formula (I), as defined above, or a pharmaceutically acceptable salt thereof, and an antineoplastic agent selected from the group consisting of an antineoplastic vinca alkaloid, an antineoplastic antibiotic, an antineoplastic antimetabolite, an antineoplastic platinum coordination complex, an antineoplastic taxane compound, an antineoplastic ceramide compound, an antineoplastic distamycin compound, an antineoplastic epidophyllotoxin

compound and an antineoplastic topoisomerase I inhibitor, in amounts effective to produce a synergistic antineoplastic effect.

The present invention also provides a method for lowering the side effects caused by antineoplastic therapy with an antineoplastic agent in mammals, including humans, in need thereof, the method comprising administering to said mammal a combination preparation comprising an antineoplastic agent selected from the group consisting of an antineoplastic vinca alkaloid, an antineoplastic antibiotic, an antineoplastic antimetabolite, an antineoplastic platinum coordination complex, an antineoplastic taxane compound, an antineoplastic ceramide compound, an antineoplastic distamycin compound, an antineoplastic epidophyllotoxin compound and an antineoplastic topoisomerase I inhibitor, and a biologically active ureido compound of formula (I), as defined above, or a pharmaceutically acceptable salt thereof, in amounts producing a synergistic antineoplastic effect.

Preferred compounds of formula (I) are the compounds wherein m and n are each 2 and each of the R groups are as defined above, and the pharmaceutically acceptable salts thereof.

Examples of specific preferred compounds of formula (I) are:
7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(3,5-naphthalendisulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(3,6-naphthalendisulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,3,5-naphthalentrisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,3,6-naphthalentrisulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,3-naphthalendisulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(2,4-naphthalendisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(2,4-naphthalendisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,3,5-naphthalentrisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(5-naphthalensulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,3-naphthalendisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(3,5-naphthalendisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,5-naphthalendisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(3-naphthalensulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1-naphthalensulfonic acid);

2,2'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,5-naphthalendisulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,6-naphthalendisulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(2,6-naphthalendisulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,5-naphthalendisulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(2,5-naphthalendisulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(2,3-naphthalendisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,6-naphthalendisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(2,6-naphthalendisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(2,5-naphthalendisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(3,6-naphthalendisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(2,3,5-naphthalentrisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,4,6-naphthalentrisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(2,4,6-naphthalentrisulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1-naphthalensulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(2-naphthalensulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(3-naphthalensulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(4-naphthalensulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,4,6-naphthalentrisulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,3,6-naphthalentrisulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(2,4,6-naphthalentrisulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(2,3,5-naphthalentrisulfonic acid);

and the pharmaceutically acceptable salts thereof.

Particularly preferred compounds of formula (I) are:

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,3-naphthalendisulfonic acid); and

2,2'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,5-naphthalendisulfonic acid);

and the pharmaceutically acceptable salts thereof.

Examples of specific antineoplastic agents, according to the invention, which are administered with a biologically active ureido compound of formula (I), are:

vincristine, vinblastine, etoposide, tallimustine-amidoxime, i.e. 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(4,N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)proprionamidoxime, (2S-RR-4E)-1,3-dihydroxy-2-tetradecanoylamido-4-octadecene, paclitaxel, docetaxel, 7-

epitaxol, 7-epitaxotere, epirubicin, idarubicin, 4'-iodoxorubicin, daunorubicin, actinomicin D, bleomycin, plycamicin, mitomycin, camptothecin, 9-aminocamptothecin, irinotecan (CPT 11), topotecan, metotrexate, cytarabine, azauridine, azarabine, fluorodeoxyuridine, deoxycoformycin, mercaptopurine, cisplatin and carboplatin.

In particular they are epirubicin, 9-aminocamptothecin and irinotecan.

As already said, the invention includes within its scope also the pharmaceutically acceptable salts of the compounds of formula (I). Examples of pharmaceutically acceptable salts are either those with inorganic bases, such as sodium, potassium, calcium and aluminum hydroxides, or with organic bases, such as lysine, arginine, N-methyl-glucamine, triethylamine, triethanolamine, dibenzylamine, methylbenzyl-amine, di-(2-ethyl-hexyl)-amine, piperidine, N-ethyl-piperidine, N,N-diethylaminoethylamine, N-ethylmorpholine, ß-phenethylamine, N-benzyl-ß-phenethylamine, N-benzyl-N,N-dimethylamine and other acceptable organic amines. Sodium and potassium salts are preferred.

Pharmacology

As stated above the present inventor has discovered that the effect of a cytotoxic agent is significantly increased, without a parallel increased toxicity, by co-administering it with a non-cytotoxic ureido derivative of the formula (1) as herein defined. The superadditive actions of the combination preparations of the present invention are shown for instance by the following *in vitro* and *in vivo* tests, which are intended to illustrate but not to limit the present invention.

Compound 7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,3-naphtalen-disulfonic acid)tetrasodium salt (internal code PNU 145156E) was chosen as a representative compound of the non-cytotoxic ureido derivatives of formula (I) as herein defined.

Five cytotoxic agents: paclitaxel (TX), cisplatin (CIS), etoposide (VP-16) and two camptothecin derivatives, irinotecan (CPT-11) and 9-aminocamptothecin (9-AC) were selected as representatives of cytotoxic agents acting *via* different modes of action:

TX is a tubulin depolymerization inhibitor, CIS is a DNA-binding agent, VP-16 is a topoisomerase II inhibitor and CPT-11 and 9AC are two semisynthetic camptothecin derivatives, which inhibit topoisomerase I.

The combinations were assayed *in vitro* on M5076 murine reticulosarcoma cells and *in vivo* on the same tumor cells implanted intramuscularly.

***IN VITRO* RESULTS**

Tumor cells were treated 72 h at 37°C, in a humidified athmosphere of 5% CO_2 with a fixed concentration of PNU 145156E and graded concentrations of cytotoxic compounds; results are reported as % cell growth, that is percentage of surviving cells vs untreated control.

Table 1 shows that the antiproliferative activity of TX, CIS, VP-16, 9-AC and SN-38 (the active metabolite of CPT-11) is unchanged in the presence of PNU 145156E.

Table 1

% CELL GROWTH ± S.E.			
		PNU 145156E 0 ng/ml	PNU 145156E 50000 ng/ml
PACLITAXEL ng/ml	100 25 6.25 0	1 ± 1 50 ± 7 89 ± 1 100	2 ± 0 43 ± 1 87 ± 14 85 ±0
CIS ng/ml	200 40 8 0	9 ± 5 52 ± 7 91 ± 3 100	4 ± 1 46 ± 3 83 ± 7 88 ± 3
VP16 ng/ml	100 20 4 0	15 ± 7 77± 5 96± 8 100	9 ± 4 66 ± 8 91 ± 2 92 ± 5
9-AC ng/ml	40 10 2.5 0	7 ± 2 28 ± 2 88 ± 10 100	8 ± 3 29 ± 9 76 ± 6 92 ± 14
SN-38 ng/ml	35 12.5 6.5 0	5 ±1 19 ± 2 75 ± 5 100	5 ± 2 25 ± 7 74 ± 7 89 ± 19

***IN VIVO* RESULTS**

Mice C57BL/6 were implanted with M5076 murine reticulosarcoma cells. PNU 145156E was administered ip 2h prior to cytotoxic drugs administered iv starting treatment 24h after tumor implant. Treatments were performed at days 1, 4, 7 and 11.

The antitumor activity was calculated in terms of:

% AUC: inhibition of tumor growth

T/C %: percentage of median increase in survival time

TGD: tumor growth delay

The A.U.C. (area under the curve) of the tumor growth was calculated by using the trapezoidal method, and is referred to the measurement of tumor growth performed one week after the last treatment. The percentage of inhibition (% A.U.C.) was calculated using the following formula:

$$100 - \frac{\text{A.U.C. tumor growth treated mice}}{\text{A.U.C. tumor growth control mice}} \times 100$$

The percentage of increase in survival time (T/C%) was calculated using the following formula:

$$\frac{\text{median survival time treated mice}}{\text{median survival time control mice}} \times 100$$

Mice were monitored according to guidelines and sacrificed when tumor weight exceeded 10% body weight. Tumor growth delay (TGD) is the time, in days, to reach one gram of tumor weight in treated animals as compared to control animals.

The toxicological evaluation was performed in terms of body weight loss and spleen and liver reduction.

Evaluation of statistical significance was performed as follows: Student's Test for cytotoxic activity, Two-Way Anova for increase in survival time (T/C %) with combined treatment in comparison to the increase exerted separately by the two drugs, Tukey Test for tumor weight reduction

(AUC % inhibition) with combined treatment in comparison to the reduction exerted separately by the two drugs.

The criterion for statistical significance was the 0.01 level (^).

Results in Table 2 indicate that the combined treatment with TX and PNU 145156E results into 100 % AUC inhibition of tumor growth and increased TGD (18-23 days).

At both doses of TX, the reduction of tumor weight is statistically significant. Marginal effect is observed in terms of increased survival time. No increased toxicity is observed.

Table 2: combination with TX

Treatment group	Tumor weight (gr)	A.U.C. % inhib.	TGD	T/C%	Toxic/ total mice
TX 33 mg/kg	2.34 ± 0.9	77	8	108	0/10
TX 40 mg/kg	1.3 ± 0.7	93	9	118	0/10
PNU 145156E 100 mg/kg	1.45 ± 0.7	88	9	121	0/10
PNU 145156E + TX 33 mg/kg	0.07 ± 0.005^	100	18	134	0/10
PNU 145156E + TX 40 mg/kg	0.01 ± 0.001^	100	23	143	0/10

Results in Table 3 indicate that the combined treatment with CIS and PNU results into a statistically significant

reduction of tumor weight and increased TGD (32 days). No increased toxicity is observed.

Table 3 :combination with CIS

Treatment group	Tumor weight (gr)	A.U.C. %inhib.	TGD	T/C%	Toxic/ total mice
CIS 6 mg/kg	1.1 ± 0.1	75	11	130	0/10
PNU 145156E 100 mg/kg	2.63 ± 0.8	85	10	141	0/10
PNU 145156E + CIS	0.35± 0.07^	100	32	173	0/11

Results in Table 4 indicate that the combination with VP-16 results into a statistically significant reduction of tumor weight and increased TGD (28 days). Statistically significant effect is also observed in terms of increased survival time (195). No increased toxicity is observed.

Table 4: combination with VP-16

Treatment group	Tumor weight (gr)	A.U.C. %inhib.	TGD	T/C%	Toxic/ total mice
VP-16 15 mg/kg	2.86 ± 0.8	90	12	130	0/9
PNU 145156E 100 mg/kg	1.4 ± 0.7	90	16	148	0/9
PNU 145156E + P-16	0.45 ± 0.2^	100	28	195^	0/9

Results in Table 5 indicate that the combination with 9AC results into a statistically significant increased reduction of tumor weight and increased TGD (13-15 days). No increased toxicity is observed.

Table 5: combination with 9AC

Treatment group	Tumor weight (gr)	A.U.C. % inhib.	TGD	T/C%	Toxic/ total mice
9AC 2.5 mg/kg	2. 4 ± 0.9	45	5	121	0/10
9AC 3 mg/kg	2.13 ± 0.8	48	6	125	0/10
9AC 3.5 mg/kg	1.58 ± 0.6	68	8	128	1/10
PNU 145156E 100 mg/kg	1.4 ± 0.7	75	9	121	0/10
PNU 145156E + 9AC 2.5 mg/kg	0.2 ± 0.01^	96	13	140	0/10
PNU 145156E + 9AC 3 mg/kg	0.14 ± 0.07^	100	14	147	1/9
PNU 145156E + 9AC 3.5 mg/kg	0.05+- 0.001^	100	15	140	1/9

Results in Table 6 indicate that the combination with CPT-11 results into a statistically significant reduction of tumor weight and increased TGD (>45 days). Statistically significant effect is also observed in terms of increased survival time (>250). No increased toxicity is observed.

Table 6: combination with CPT-11					
Treatment group	**Tumor weight (gr)**	**A.U.C. % inhib.**	**TGD**	**T/C%**	**Toxic/ total mice**
CPT-11 60 mg/kg	0.05 ± 0.2	100	34	215	0/8
PNU 145156E 100 mg/kg	1.7 ± 0.65	90	16	148	0/8
PNU 145156E + CPT-11	0 ± 0^	100	>45	>250^	0/8

From the above test data the following facts can be appreciated:

The combined treatment of PNU 145156E with the five tested drugs is associated in all combinations with higher tumor growth inhibition and increased tumor growth delay in respect to treatment with one drug alone, with a significant increase in survival time in the combination with VP-16 and CPT-11.

The synergistic activity observed *in vivo* is clearly not related to any interference of PNU 145156E on the antiproliferative effect of the cytotoxic drugs, as evidenced by results showing that *in vitro* the cytotoxic activity of the five tested drugs is unchanged in the presence of PNU 145156E.

It is of note that no obvious increased general toxicity was ever observed with the combinations, as evaluated in

terms of early deaths or gross pathological findings at necropsy.

These results support the utilization of an ureido compound of formula (I), as herein defined, in therapy in combination with cytotoxic drugs.

In the combination preparations, pharmaceutical compositions and method of treatment, according to the present invention, one or more biologically active ureido compounds of formula (I) may be used at the same time, however only one compound of formula (I), or a pharmaceutically acceptable salt thereof, is preferably used.

The term "antineoplastic agent" as used herein refers both to a single antitumor drug and "cocktails" i.e. a mixture of such drugs according to the clinical practice.

The combination preparation according to the invention can also include combination packs or compositions in which the constituents are placed side by side and can therefore be administered simultaneously, separately or sequentially to one and the same mammal, including humans.

The term "neoplastic disease state" as used herein refers to an abnormal state or condition characterized by rapidly proliferating cell growth or neoplasm. Neoplastic disease states for which conjunctive therapy according to the present invention will be particularly useful include: Leukemias such as, but not limited to, acute lymphoblastic, chronic lymphocytic, acute myoblastic and chronic mylocytic; Carcinomas, such as, but not limited to, those of the cervix, oesophagus, stomach, such as, but not limited to, oesteroma, oesterosarcoma, lepoma, liposarcoma,

hemangioma and hemangiosarcoma; Melanomas, including amelanotic and melanotic; and mixed types of neoplasias such as, but not limited to, carcinosarcoma, lymphoid tissue type, follicular reticulum, cell sarcoma, and Hodgkins Disease. Of course, one skilled in the art will recognize that not every combination of conjunctive therapy according to the present invention will be equally effective against each of the neoplastic disease states. Selection of the most appropriate combination is within the ability of one of ordinary skill in the art and will depend on a variety of factors including assessment of results obtained in standard animal cancer models and the effectiveness of the individual agents as monotherapy in treating particular neoplastic disease states. Conjunctive therapy may result in lowered doses of one or more of the antineoplastic agents.

For example, conjunctive therapy with an ureido compound of formula (I) and vinblastin will be particularly effective in the treatment of a patient afflicted with leukemia, carcinoma, lymphoma or osteosarcoma.

Conjunctive therapy with an ureido compound of formula (I) and cisplatin will be particularly effective in the treatment of a patient afflicted with carcinoma, testicular teratoma or ovarian carcinoma.

Conjunctive therapy with an ureido compound of formula (I) and epirubicin will be particularly effective in the treatment of a patient afflicted with breast carcinoma, leukemia, lymphoma or ovarian carcinoma.

Conjunctive therapy with an ureido compound of formula (I) and cytarabine will be particularly effective in the treatment of a patient afflicted with leukemia.

Conjunctive therapy with an ureido compound of formula (I)

and CPT-11 or 9-aminocamptothecin will be particularly effective in the treatment of advanced colon and ovarian cancer.

As used herein, the term "effective antineoplastic amount" refers to an amount which is effective, upon single or multiple dose administration to the patient, in controlling the growth of the neoplasm or in prolonging the survivability of the patient beyond that expected in the absence of such treatment. As used herein, "controlling the growth" of the neoplasm refers to slowing, interrupting, arresting or stopping its growth and does not necessarily indicates a total elimination of the neoplasm.

An effective antineoplastic amount of an ureido compound of formula (I) is expected to vary from about 0.5 to about 1000 mg pro dose 1-4 times a day

The effective antineoplastic amounts of the various cytotoxic agents are well known and appreciated in the art. For example, an effective antineoplastic amount of vinblastine is expected to vary from about 3 $mg/m^2/day$ to about 10 $mg/m^2/day$. An effective antineoplastic amount of cisplatin is expected to vary from about 20 $mg/m^2/day$ to about 50 $mg/m^2/day$. An effective antineoplastic amount of cytarabine is expected to vary from about 1 $mg/m^2/day$ to about 200 $mg/m^2/day$. An effective antineoplastic amount of 9-aminocamptothecin is expected to vary from about 0.5 $mg/m^2/day$ to about 10 $mg/m^2/day$. An effective antineoplastic amount of irinotecan is expected to vary from about 50 $mg/m^2/day$ to about 500 $mg/m^2/day$.

In effecting treatment of a patient afflicted with a disease state described above an ureido derivative of

formula (I) can be administered in any form or mode which makes the compound bioavailable in effective amounts, including oral and parenteral routes. For example, it can be administered orally, subcutaneously, intraperitoneally, intramuscularly, intravenously, transdermally, intranasally, rectally, and the like. Oral administration is generally preferred. One skilled in the art of preparing formulations can readily select the proper form and mode of administration depending upon the particular circumstances, including the disease state to be treatment, the stage of the disease, the form of administration of the selected cytotoxic agent and the manner of co-administration selected.

For example, WO 91/10649 discloses the preparation of pharmaceutical compositions comprising an ureido compound of formula (I) and a suitable carrier or excipient.

The selected antineoplastic agent can be administered in a manner as is well known and accepted for the particular agent. For example, vincristine, vinblastine, etoposide, tallimustine-amidoxime, i.e. 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(4,N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)proprionamidoxime, (2S-RR-4E)-1,3-dihydroxy-2-tetradecanoylamido-4-octadecene, paclitaxel, docetaxel, 7-epitaxol, 7-epitaxotere, epirubicin, idarubicin, 4'-iodoxorubicin, daunorubicin, actinomicin D, bleomycin, plycamicin, mitomycin, camptothecin, 9-aminocamptothecin, irinotecan (CPT 11), topotecan, metotrexate, cytarabine, azauridine, azarabine, fluorodeoxyuridine, deoxycoformycin, mercaptopurine, cisplatin and carboplatin, can be administered intravenously.

Irinotecan, 9-aminocamptothecin and topotecan can also be administered by oral route.

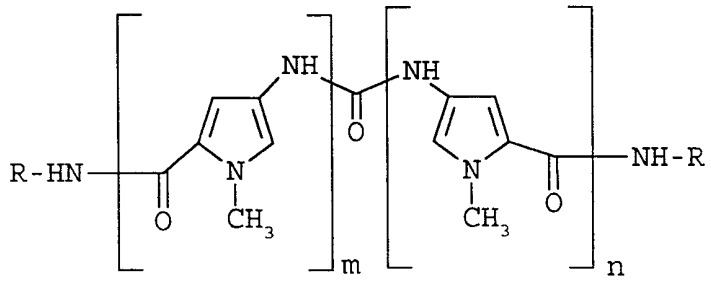
Formulation Example 1

Intramuscular injection 40 mg/ml

An injectable pharmaceutical preparation can be manufactured by dissolving 40 g of 7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonylimino(N-methyl-4,2-pyrrole)carbonylimino)-bis(1,3-naphthalenedisulfonic acid)tetrasodium salt in water for injection (1000 ml) and sealing ampoules of 1-10 ml.

CLAIMS

1. A pharmaceutical composition for use in antineoplastic therapy in mammals, including humans, comprising a biologically active ureido compound of formula (I)



(I)

wherein

each of m and n, being the same, is an integer of 1 to 3; and each of the R groups, which are the same, is a naphthyl group substituted by 1 to 3 sulfonic groups, or a pharmaceutically acceptable salt thereof, and an antineoplastic agent selected from the group consisting of an antineoplastic vinca alkaloid, an antineoplastic antibiotic, an antineoplastic antimetabolite, and antineoplastic platinum coordination complex, an antineoplastic taxane compound, an antineoplastic ceramide compound, an antineoplastic distamycin compound, an antineoplastic epidophyllotoxin compound and an antineoplastic topoisomerase I inhibitor, and a pharmaceutically acceptable carrier or excipient, in amounts effective to produce a synergistic antineoplastic effect.

2. A product comprising synergistic amounts of a biologically active ureido compound of formula (I), as defined in claim 1, or a pharmaceutically acceptable salt thereof, and an antineoplastic agent selected from the group

consisting of an antineoplastic vinca alkaloid, an antineoplastic antibiotic, an antineoplastic antimetabolite, an antineoplastic platinum coordination complex, an antineoplastic taxane compound, an antineoplastic ceramide compound, an antineoplastic distamycin compound, an antineoplastic epidophyllotoxin compound and an antineoplastic topoisomerase I inhibitor, as a combined preparation for simultaneous, separate or sequential use in antitumor therapy.

3. A method of treating a mammal including humans, suffering from a neoplastic disease state comprising administering to said mammal a biologically active ureido compound of formula (I), as defined in claim 1, or a pharmaceutically acceptable salt thereof, and an antineoplastic agent selected from the group consisting of an antineoplastic vinca alkaloid, an antineoplastic antibiotic, an antineoplastic antimetabolite, an antineoplastic platinum coordination complex, an antineoplastic taxane compound, an antineoplastic ceramide compound, an antineoplastic distamycin compound, an antineoplastic epidophyllotoxin compound and an antineoplastic topoisomerase I inhibitor, in amounts effective to produce a synergistic antineoplastic effect.

4. A method for lowering the side effects caused by antineoplastic therapy with an antineoplastic agent in mammals, including humans, in need thereof, the method comprising administering to said mammal a combination preparation comprising an antineoplastic agent selected from the group consisting of an antineoplastic vinca alkaloid, an antineoplastic antibiotic, an antineoplastic

antimetabolite, an antineoplastic platinum coordination complex, an antineoplastic taxane compound, an antineoplastic ceramide compound, an antineoplastic distamycin compound, an antineoplastic epidophyllotoxin compound and an antineoplastic topoisomerase I inhibitor, and a biologically active ureido compound of formula (I), as defined in claim 1, or a pharmaceutically acceptable salt thereof, in amounts producing a synergistic antineoplastic effect.

5. A pharmaceutical composition according to claim 1, wherein in the ureido compound of formula (I) m and n are each 2 and each of the R groups are as defined in claim 1.

6. A pharmaceutical composition according to claim 1, wherein the ureido compound of formula (I) is selected from:

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(3,5-naphthalendisulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(3,6-naphthalendisulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,3,5-naphthalentrisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,3,6-naphthalentrisulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,3-naphthalendisulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(2,4-naphthalendisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(2,4-naphthalendisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,3,5-naphthalentrisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(5-naphthalensulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,3-naphthalendisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(3,5-naphthalendisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,5-naphthalendisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(3-naphthalensulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1-naphthalensulfonic acid);

2,2'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,5-naphthalendisulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,6-naphthalendisulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(2,6-naphthalendisulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,5-naphthalendisulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(2,5-naphthalendisulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(2,3-naphthalendisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,6-naphthalendisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(2,6-naphthalendisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(2,5-naphthalendisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(3,6-naphthalendisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(2,3,5-naphthalentrisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,4,6-naphthalentrisulfonic acid);

8,8'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(2,4,6-naphthalentrisulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1-naphthalensulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(2-naphthalensulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(3-naphthalensulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(4-naphthalensulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,4,6-naphthalentrisulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,3,6-naphthalentrisulfonic acid);

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(2,4,6-naphthalentrisulfonic acid); and

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(2,3,5-naphthalentrisulfonic acid); or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition according to claim 1, wherein the ureido compound of formula (I) is selected from:

7,7'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,3-naphthalendisulfonic acid); and

2,2'-(carbonyl-bis(imino-N-methyl-4,2-pyrrolecarbonyl-imino(N-methyl-4,2-pyrrole)carbonylimino))bis(1,5-naphthalendisulfonic acid); or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition according to claim 1, wherein the antineoplastic agent is selected from:

vincristine, vinblastine, etoposide, tallimustine-amidoxime, (2S-RR-4E)-1,3-dihydroxy-2-tetradecanoylamido-4-octadecene, paclitaxel, docetaxel, 7-epitaxol, 7-epitaxotere, epirubicin, idarubicin, 4'-iodoxorubicin, daunorubicin, actinomicin D, bleomycin, plycamicin, mitomycin, camptothecin, 9-aminocamptothecin, irinotecan (CPT 11), topotecan, metotrexate, cytarabine, azauridine, azarabine, fluorodeoxyuridine, deoxycoformycin, mercaptopurine, cisplatin and carboplatin.

INTERNATIONAL SEARCH REPORT

Intern. nal Application No
PCT/EP 98/08159

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/40

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,P	SOLA F ET AL: "The antitumor efficacy of cytotoxic drugs is potentiated by treatment with PNU 145156E, a growth-factor-complexing molecule." CANCER CHEMOTHER PHARMACOL, 1999, 43 (3) P241-6, XP002104215 GERMANY see abstract ---	1-8
X	SOLA F ET AL: "Treatment with FCE 26644, a growth factor complexing molecule and antiproliferative compound: increased antitumor activity with no increased toxicity (Meeting abstract)." PROC ANNU MEET AM ASSOC CANCER RES;36:A621 1995, XP002104216 see abstract ---	1-8

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° 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 when the document is taken alone

"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.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 June 1999	11/06/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gonzalez Ramon, N

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern. ..nal Application No
PCT/EP 98/08159

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	SOLA F ET AL: "ANTITUMOR ACTIVITY OF FCE 26644. A NEW GROWTH-FACTOR COMPLEXING MOLECULE" CANCER CHEMOTHERAPY AND PHARMACOLOGY, vol. 36, no. 200, 1 January 1995, pages 217-222, XP000572595 see discussion see page 222; figure 1 ---	1-8
X	ZOU J. P. ET AL: "Distamycin A derivatives potentiate tumor-necrosis factor activity via the modulation of tyrosine phosphorylation" INT J. CANCER, vol. 72, 1997, pages 810-814, XP002104217 see abstract see page 813, column 2, paragraph 2 ---	1-8
X	EP 0 583 161 A (ERBA CARLO SPA) 16 February 1994 see page 5, line 45 - page 6, line 5; claim 11 ---	1-8
X	WO 94 20095 A (ERBA CARLO SPA) 15 September 1994 see page 11, line 20-27; claim 9 ---	1-8
E	WO 99 00363 A (CIOMEI MARINA ;ALBANESE CLARA (IT); CRUGNOLA ANGELO (IT); MONGELLI) 7 January 1999 see page 5 - page 7 see page 13, line 5-30 ---	1-8
A	ZAMAI MORENO VALERIA R_(A): "Antiangiogenic naphthalene sulfonic distamycin-A derivatives tightly interact with human basic fibroblast growth factor." MEDICINAL CHEMISTRY RESEARCH, 1997, XP002104218 SEE SCHEME 1 see abstract see page 43 ---	1-8
A	ARMAND J.P.: "New anticancer drugs in Europe" JAPANESE JOURNAL OF CANCER AND CHEMOTHERAPY_(_JPN. J. CANCER CHEMOTHER._), 24/SUPPL. 1 (70-93), XP002104437 Japan see page 85 see the whole document -----	1-8

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 98/08159

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 3, 4
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
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. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] 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 claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. nal Application No
PCT/EP 98/08159

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		JP 6184098 A	05-07-1994
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WO 9420095 A	15-09-1994	AU 669269 B	30-05-1996
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