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(54) Titre : METHODE DE THERAPIE DU CANCER
(54) Title: USE OF BISINDOLMALEIMIDE AND GEMCITABINE FOR THE TREATMENT OF CANCER

(57) Abrégé/Abstract:
The present invention relates to the use of a pharmaceutical combination comprising as a active ingredients a) a component consisting of pharmaceutical composition comprising a compound of formula (I) as defined in the description and claims and b) a component consisting of pharmaceutical composition comprising as an active ingredient gemcitabine for the preparation of a medicament for the treatment of patients suffering with cancer.

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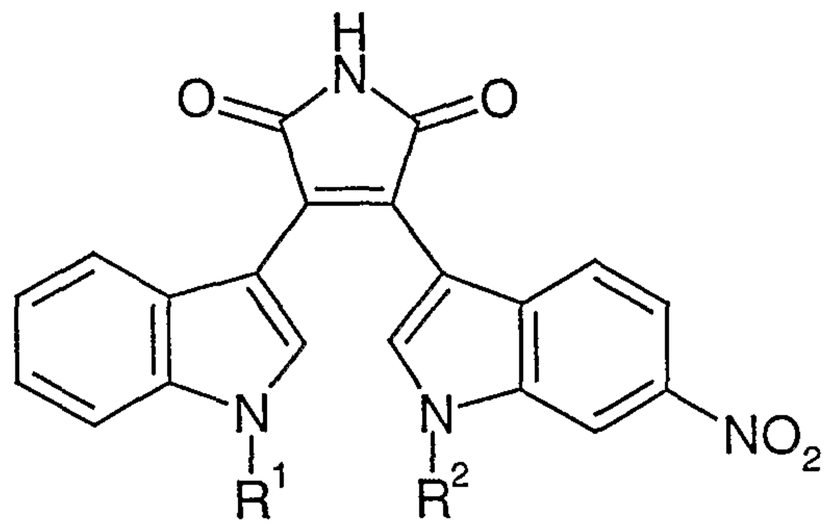
(54) Title: USE OF BISINDOLMALEIMIDE AND GEMCITABINE FOR THE TREATMENT OF CANCER

(57) Abstract: The present invention relates to the use of a pharmaceutical combination comprising as a active ingredients a) a component consisting of pharmaceutical composition comprising a compound of formula (I) as defined in the description and claims and b) a component consisting of pharmaceutical composition comprising as an active ingredient gemcitabine for the preparation of a medicament for the treatment of patients suffering with cancer.

Method for Cancer Therapy

The present invention is directed to a use of a pharmaceutical combination comprising as a active ingredients

a) a component consisting of a pharmaceutical composition comprising a compound of formula I



(I)

or a pharmaceutically acceptable salt or ester of said compound, wherein
R^1 is selected from the group consisting of -H, $-CH_3$, and $-CH_2OH$, and
R^2 is $-CH_3$; and

b) a component consisting of pharmaceutical composition comprising as an active ingredient gemcitabine gemcitabine (commercially available as Gemzar®, Lilly, Indianapolis, IN) for the preparation of a medicament for the treatment of cancer. The invention is also directed to a kit , to a method, as well as to pharmaceutical compositions.

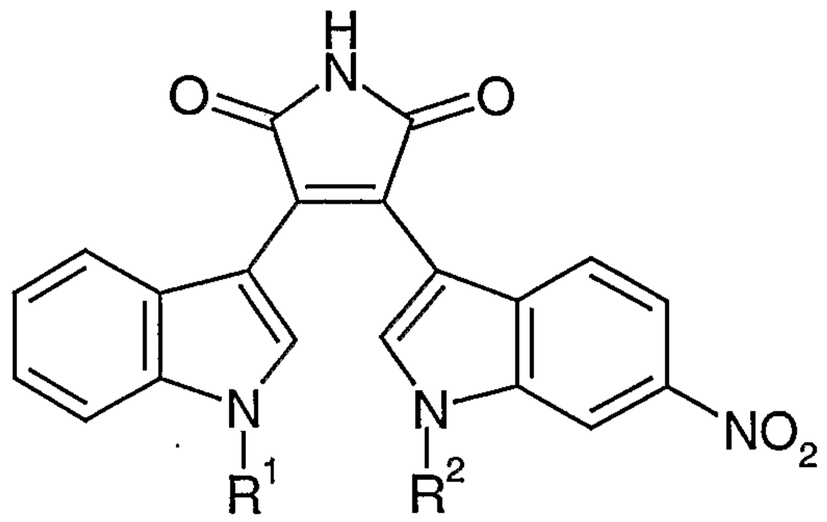
The compounds of formula I below are known to be cell cycle inhibitors and apoptosis-inducers having antiproliferative and antitumor activity against a wide range of tumors, in particular in solid tumors such as breast and colon cancers. *See, e.g.* EP 328026B1 and EP 1064279A1.

Gemcitabine is a nucleoside analog that exhibits antitumor activity by inhibiting DNA synthesis in S-phase of the cell cycle. *See, e.g., Physicians' Desk Reference* (54th Edition, 2000), pp1586 et seq.

It has now been discovered that compounds of formula I are effective in cancer therapy when administered in combination with gemcitabine without markedly increased toxicity. Moreover, because these two compounds exert antitumor effects by affecting different cellular mechanisms, a therapeutic combination of both compounds yields improved antitumor activity in certain tumors and/or prevents or delays resistance to drug therapy.

The invention also relates to a kit comprising:

a) a component comprising one or more oral unit dosage forms of an active ingredient comprising the active ingredient, wherein the active ingredient is a compound selected from formula I



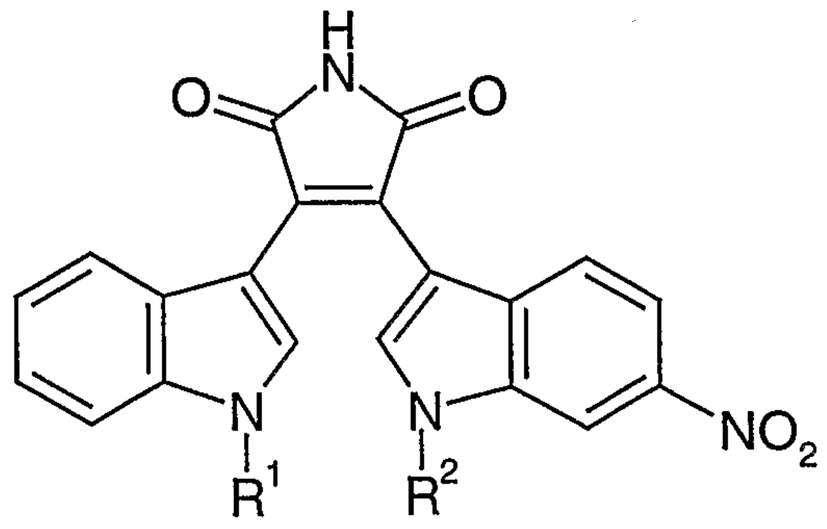
(I)

or a pharmaceutically acceptable salt or ester said compound, wherein
R^1 is selected from the group consisting of -H, $-CH_3$, and $-CH_2OH$, and
R^2 is $-CH_3$; and

b) a component containing a vial or series of vials, each vial containing a single injectable solution dose or multiple injectable solution doses, each dose comprising as an active ingredient gemcitabine.

The invention relates also a method for manufacturing a medicament for the treatment of cancer, particularly a solid cancerous tumor, using a pharmaceutical combination comprising

a) a component consisting of pharmaceutical composition comprising as an active ingredient a compound of formula I



(I)

or a pharmaceutically acceptable salt or ester of said compound, wherein
R^1 is selected from the group consisting of -H, $-CH_3$, and $-CH_2OH$, and
R^2 is $-CH_3$; and

b) a component consisting of pharmaceutical composition comprising as an active ingredient gemcitabine

Finally the present invention relates a pharmaceutical composition comprising a pharmaceutical combination comprising a component consisting of pharmaceutical composition comprising as an active ingredient a compound of formula I and a component consisting of pharmaceutical composition comprising as an active ingredient gemcitabine for the treatment of cancer, particularly a solid cancerous tumor.

It has now been discovered that the combination having a therapeutic activity is greater than the individual components of said compositions without an increase in toxicity. This combination of chemotherapeutic compounds is particularly useful in the treatment of lung, pancreatic, bladder, breast, colon, rectal, uterine and prostate cancers.

The invention permits reduction of the amount of at least one component (in comparison the amount typically given in monotherapy) while retaining a desirable therapeutic index. In preferred embodiments, the amount of both components (in comparison the amount typically given in monotherapy) is reduced affording reduced toxicity while still retaining a desirable therapeutic index.

It has now been discovered that the combination comprising an effective amount of a a compound of formula I and gemcitabine, said compositions has therapeutic benefit as compared to monotherapy.

Unless otherwise indicated, the following definitions are set forth to illustrate and defined the meaning and scope of the various terms used to describe the invention herein.

The terms "antineoplastic" or "antitumor" mean inhibiting or preventing the development, maturation or proliferation of malignant cells.

As used herein the term "concomitant" means administration of both components during the same 24 hour period, preferably within one or two hours of each other.

The term "pharmaceutically acceptable ester" of a compound of formula I means a conventionally esterified compound of formula I having a carboxyl group, which esters retain the biological effectiveness and properties of the compound of formula I.

The term "pharmaceutically acceptable salt" of a compound of formula I as used herein is any conventional salt or base addition salt that retains the biological effectiveness and properties of the compound of formula I and which is formed from a suitable non-toxic organic or inorganic acid or organic or inorganic base. Preferred salts are cationic salts, for example, of alkali metals, especially sodium salts.

As used herein "sequential" (as in sequential administration) means that one component is administered more than twenty four hours after the other component, preferably within 2-15 days of the other component.

As used herein, "therapeutically effective" or "effective amount" means an amount of drug, or combination or composition, which is effective for producing a desired therapeutic effect upon administration to a patient, for example, to stem the growth, or result in the shrinkage, of a cancerous tumor.

"Therapeutic index" is a well-recognized term of art and is an important parameter in the selection of anticancer agents for clinical trial. Therapeutic Index takes into consideration the efficacy, pharmacokinetics, metabolism and bioavailability of anticancer agents. *See, e.g.*, J. Natl. Cancer Inst. 81(13): 988-94 (July 5, 1989).

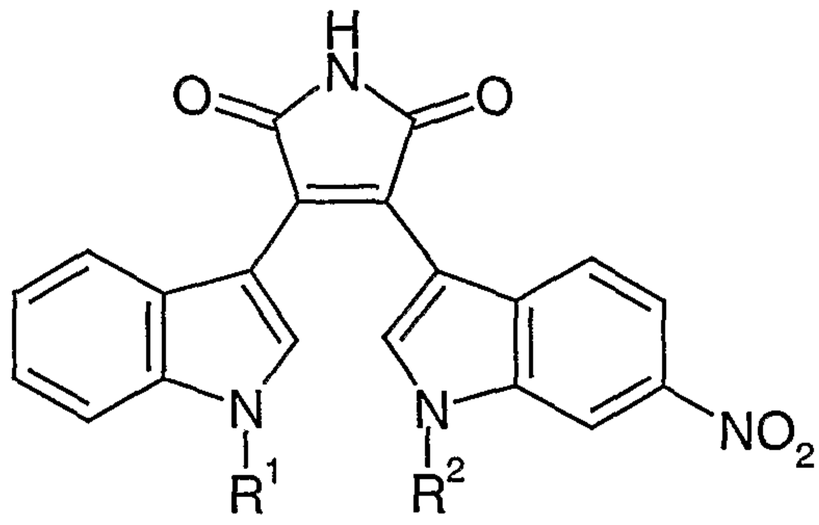
As used herein, a combination of pharmaceutical compositions exhibits a "therapeutic benefit" if it is therapeutically superior, that is less toxic and/or more

efficacious against certain tumors than either of the constituents used alone (in monotherapy) and/or prevents or delays drug resistance in certain tumors.

"Tumor control" means that the perpendicular diameters of measurable lesions has not increased by 25% or more from the last measurement. *See, e.g.*, World Health Organization ("WHO") Handbook for Reporting Results of Cancer Treatment, Geneva (1979).

The present invention is directed to an use of a pharmaceutical combination comprising as an active ingredients

a) a component consisting of a pharmaceutical composition comprising a compound of formula I



(I)

or a pharmaceutically acceptable salt or ester of said compound, wherein
R^1 is selected from the group consisting of -H, $-CH_3$, and $-CH_2OH$, and
R^2 is $-CH_3$; and

b) a component consisting of pharmaceutical composition comprising as an active ingredient gemcitabine

for the preparation of a medicament for the treatment of cancer.

In the use according to the present invention both compounds may be administered concomitantly or, alternatively, sequentially.

The amount of each component in the combination is such that the combination is therapeutically effective to treat or ameliorate a cancerous tumor. The amount of each component administered according to the present invention may, but does not have to be therapeutically effective by itself. That is, this invention specifically contemplates combinations wherein the amount of compound I and/or the amount of gemcitabine in the combination is less than a therapeutically effective amount as judged by the amounts recommended in monotherapy (i.e. a "suboptimal" amount).

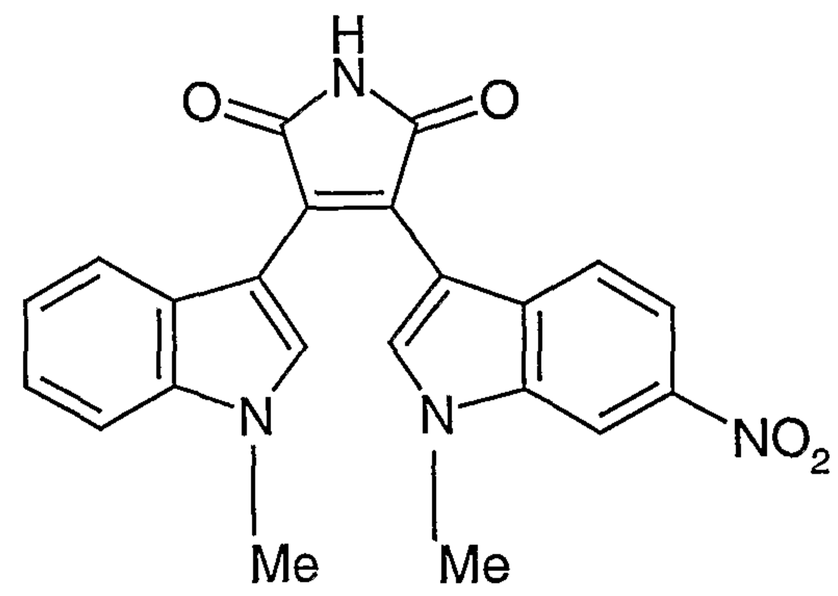
The two components of the invention, that is a pharmaceutical composition containing a compound of formula I and a pharmaceutical composition containing gemcitabine, may be administered concomitantly or sequentially over such period of time so as to obtain maximum therapeutic effect. As is demonstrated below, when the components are administered sequentially, either component may be administered first. In a preferred embodiment, both components are administered concomitantly.

In accordance with the present invention, administration of the two components, concomitantly or sequentially, enhances the treatment of cancer as compared to administering each component independently in monotherapy. The combination effect results in an improved therapeutic index as compared to either agent alone while toxicity remains acceptable.

Preferably, the compound of formula I is administered to the patient in an oral unit dosage form, more preferably in capsule or tablet form. The other one, gemcitabine, is administered by parenteral, preferably by intravenous administration, in association with a compound of formula I as described herein.

The two components of the present invention are administered in any amount and for any duration that is effective to maintain or decrease tumor size.

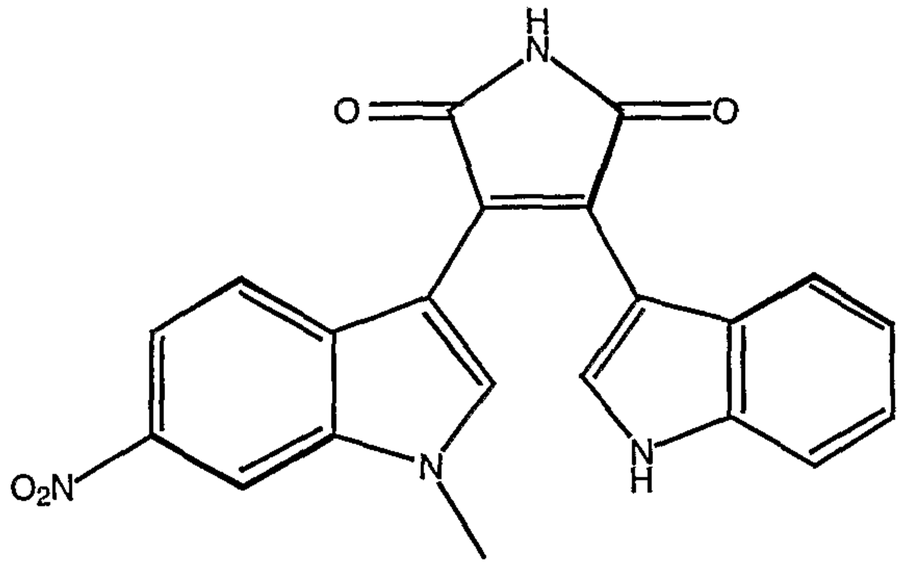
A preferred compound of formula (I) is:



(II) .

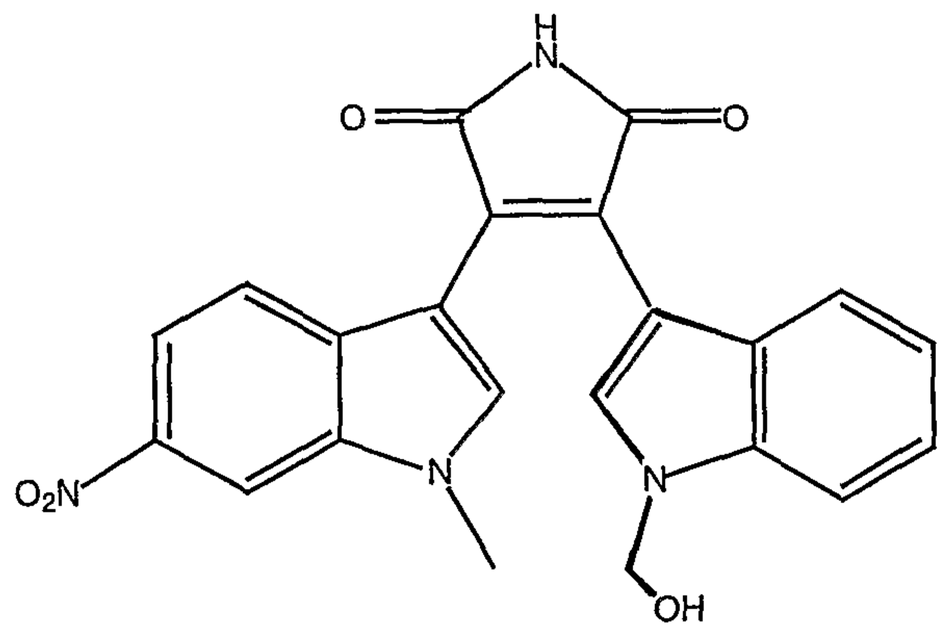
This is a known compound. *See* EP 328023B1, which is incorporated herein by reference.

Other preferred compounds of formula (I) are



(III)

and



(IV)

Compounds (III) and (IV) above are also known compounds. *See* EP 1064279A1, which is incorporated herein by reference.

The determination of tumor control (also referred to as "maintenance") or shrinkage (also referred to as "regression") is made by known processs. For example, by evaluation of patient symptoms, physical examination, X-ray, MRI or CAT scan or other commonly accepted evaluation modalities.

In a preferred embodiment, administration of the composition containing a compound of formula I and the composition containing gemcitabine occur on the first day of a 21-28 days cycle (that is, a 3 to 4 weeks repeating cycle). The composition containing a compound of formula I is administered daily for up to about 14 days, preferably for about 7 days, and more preferably for about 4 days. The composition containing gemcitabine is administered preferably on days 1, 8 and 15 of a 21-28 days cycle, more preferably days 1 and 8 of a 21-28 days cycle, repeated for a total of up to about 16-24 doses.

In a preferred embodiment of the present invention, the amount of the compound of formula I is from about 1040 mg/m^2 to about 3000 mg/m^2 , more preferably from about 1480 mg/m^2 to about 2360 mg/m^2, and is administered over a period of up to about 14 days.

In another preferred embodiment of the present invention, the amount of the compound of formula I, over a period of about 7 days, is from about 1040 mg/m^2 to about 3000 mg/m^2 , more preferably from about 1480 mg/m^2 to about 2360 mg/m^2.

In another preferred embodiment of the present invention, the amount of the compound of formula I, over a period of about 4 days, is from about 780 mg/m^2 to about 2250 mg/m^2., more preferably from about 1110 mg/m^2 to about 1770 mg/m^2

In a preferred embodiment of the invention, the dose intensity of the compound of formula I is from about 260 mg/m^2/week to about 750 mg/m^2/week and more preferably from about 370 mg/m^2/week to about 590 mg/m^2/week.

In a preferred embodiment, the composition containing gemcitabine is administered on the first day of a 21-days cycle, preferably within about 16 hours after the administration of the composition containing a compound of formula I.

In another preferred embodiment, the composition containing a compound of formula I is administered on the first day of a 21-days cycle, preferably within about 8 hours after administration of the composition containing gemcitabine.

The course of a preferred cycle is 21 or 28 days, though cycles anywhere between about 21 to about 28 days are also effective and contemplated. When the composition containing a compound of formula I is administered for about 4 to about 7 days, a 21 days treatment cycle is preferred. When the composition containing a compound of formula I is administered for about 14 days, a 28 days treatment cycle is preferred. At the end of the 21-28 days of each cycle, the cycle of dosing is repeated for as long as clinically tolerated and the tumor is under control or until tumor regression. Tumor "control" is a well recognized clinical parameter, as defined above. In a preferred embodiment, the cycle of dosing is repeated for up to about 16 cycles.

In an alternative preferred embodiment, the composition containing gemcitabine is administered on days 1 and 8 of a 3 weeks (21 days) or 4 weeks (28 days) cycle, preferably a 3 weeks cycle.

The dose intensity of compound of formula I is from about 260 mg/m^2/week to about 750 mg/m^2/week. The total overall dosage for the compound of formula I for a period of up to about 21-28 days is from about 780 mg/m^2 to about 3000 mg/m^2. A patient's body measurement in square meters ("m^2"), this is a "BSA (body surface area") measurement", typically ranges from about 1.4 m^2 to about 2.2 m^2. Thus, the total amount of compound of formula I to be delivered in a treatment cycle (mg) is calculated as follows:

[Dose intensity(mg/m^2/week)] x [BSA(m^2)] x [number of weeks in treatment cycle]

The foregoing amount of compound of formula I is divided, preferably into equal doses (though this is not required), and administered daily, as a single dose or divided into two or more doses daily, preferably twice per day, most preferably at 12 hour intervals ("Q12" or "BID"). The length of preferred treatment cycle is from about 3 to about 4 weeks.

Preferably, the compound of formula I is administered twice daily over a period of about 1-14 days. Preferred therapeutic regimens for administration of compounds of formula I are summarized in Tables 1A-1C below.

TABLE 1A

PREFERED DOSAGE REGIMENS OF COMPOUNDS OF FORMULA 1:

THREE WEEK CYCLE

	Dose Intensity (mg/m^2/week)	Range Total Dose/Cycle (mg/m^2)	BSA Range (m^2)	No. of days of Dosing	Individual Dose (mg/m^2 BID)
Desired	260-750	780-2250	1.4-2.2	4	95-285
Preferred	370-590	1110-1770	1.4-2.2	4	135-225

TABLE 1B

PREFERED DOSAGE REGIMENS OF COMPOUNDS OF FORMULA 1:

FOUR WEEK CYCLE

	Dose Intensity (mg/m^2/week)	Range Total Dose/Cycle (mg/m^2)	BSA Range (m^2)	No. of days of Dosing	Individual Dose (mg/m^2 BID)
Desired	260-750	1040-3000	1.4-2.2	7	70-215
Preferred	370-590	1480-2360	1.4-2.2	7	100-170

TABLE 1C

PREFERED DOSAGE REGIMENS OF COMPOUNDS OF FORMULA 1:

FOUR WEEK CYCLE

	Dose Intensity (mg/m^2/week)	Range Total Dose/Cycle (mg/m^2)	BSA Range (m^2)	No. of days of Dosing	Individual Dose (mg/m^2 BID)
Desired	260-750	1040-3000	1.4-2.2	14	35-110
Preferred	370-590	1480-2360	1.4-2.2	14	50-85

In a preferred embodiment of the invention, the amount of gemcitabine is from about 1200 mg/m^2 to about 2400 mg/m^2 administered over a period of up to about 8 days, and, more preferrably, from about 1600 mg/m^2 to about 2000 mg/m^2.

In a second preferred embodiment of the invention, the amount of gemcitabine is from about 1800 mg/m^2 to about 3600 mg/m^2 administered over a period of up to about 15 days, and , more preferably, from about 2400 mg/m^2 to about 300 mg/m^2.

In a preferred embodiment of the invention, the dose intensity of gemcitabine is from about 460 mg/m^2/week to about 800 mg/m^2/week and, more preferably, from about 530 mg/m^2/week to about 670 mg/m^2/week.

The dose intensity of gemcitabine is from about 300 mg/m^2/week to about 900 mg/m^2/week. The overall dosage of the gemcitabine is from about 1200 mg/m^2 to about 3600 mg/m^2, administered over a 21-28 days period. In a preferred embodiment, the gemcitabine is given as an i.v. infusion on days 1 and 8 of a 21 days cycle, and the regimen is then repeated for up to about 8 cycles.

In a second preferred embodiment, the gemcitabine is given as an i.v. infusion on days 1 and 8 of a 28 days cycle, and the regimen is then repeated for up to about 8 cycles.

In a third preferred embodiment, the gemcitabine is given as an i.v. infusion on days 1, 8, and 15 of a 28 days cycle, and the regimen is then repeated for up to about 8 cycles

While the doses of gemcitabine do not have to be equal, they typically are. In a most preferred embodiment, the total dose of gemcitabine is administered to the patient on days 1 and 8 of a 21 days cycle by approximately a short i.v. infusion, typically over a period of about 30 minutes.

Preferred therapeutic regimens for administration of gemcitabine are summarized in Tables 2A-2C below.

TABLE 2A

PREFERED DOSAGE REGIMENS OF GEMCITABINE: 3 WEEK CYCLE

	Dose Intensity (mg/m^2/week)	Range Total Dose/Cycle (mg/m^2)	BSA Range (m^2)	No. of days of Dosing	Individual Dose (mg/m^2)
Desired	460-800	1400-2400	1.4-2.2	2 (days 1,8)	700-1200
Preferred	530-670	1600-2000	1.4-2.2	2 (days 1,8)	800-1000

TABLE 2B

PREFERED DOSAGE REGIMENS OF GEMCITABINE: 4 WEEK CYCLE

	Dose Intensity (mg/m^2/week)	Range Total Dose/Cycle (mg/m^2)	BSA Range (m^2)	No. of days of Dosing	Individual Dose (mg/m^2)
Desired	300-600	1200-2400	1.4-2.2	2 (days 1,8)	600-1200
Preferred	400-500	1600-2000	1.4-2.2	2 (days 1,8)	800-1000

TABLE 2C

PREFERED DOSAGE REGIMENS OF GEMCITABINE: 4 WEEK CYCLE

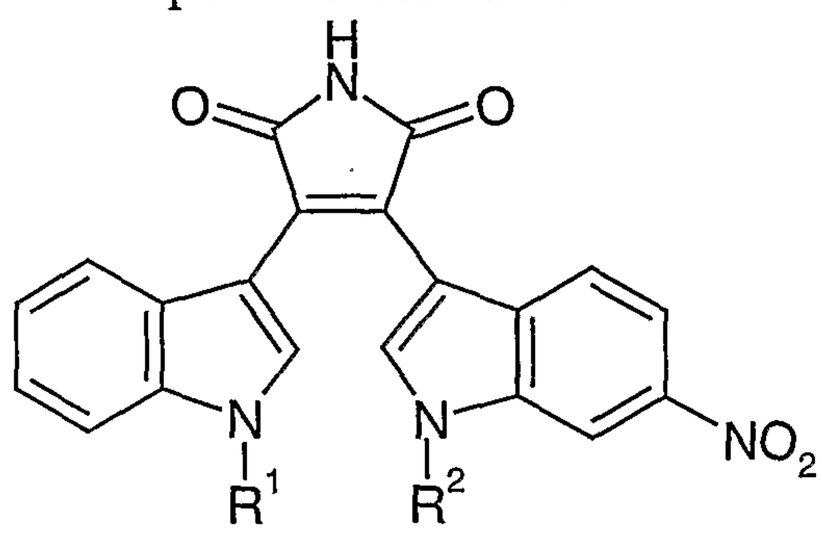
	Dose Intensity (mg/m^2/week)	Range Total Dose/Cycle (mg/m^2)	BSA Range (m^2)	No. of days of Dosing	Individual Dose (mg/m^2)
Desired	450-900	1800-3600	1.4-2.2	3 (days 1,8,15)	600-1200
Preferred	600-750	2400-3000	1.4-2.2	3 (days 1,8,15)	800-1000

The dosage levels of each of the components may be modified by the physician to be lower or higher than that stated herein depending on the needs of the patient, and the reaction of the patient to the treatment. The dosages may be administered according to any dosage schedule determined by the physician in accordance with the requirements of the patient. For example, the dosages of each of the two components may be administered in single or in divided doses over a period of several days, or alternating daily schedules.

Preferably, four days treatment schedules are repeated every twenty one days, or as soon as permitted by recovery from toxicity, for so long as the tumor is under control and the patient tolerates the regimen or tumor regression. Seven, fourteen and fifteen day treatment schedules are preferably repeated every twenty eight days. Preferably, these treatment cycles are repeated for a total of up to about eight cycles (that is a total of about twenty four or about thirty two weeks).

In a particular embodiment, the present invention relates to a use of a pharmaceutical combination comprising

a) a component consisting of a pharmaceutical composition comprising as an active ingredient a compound of formula :



(I)

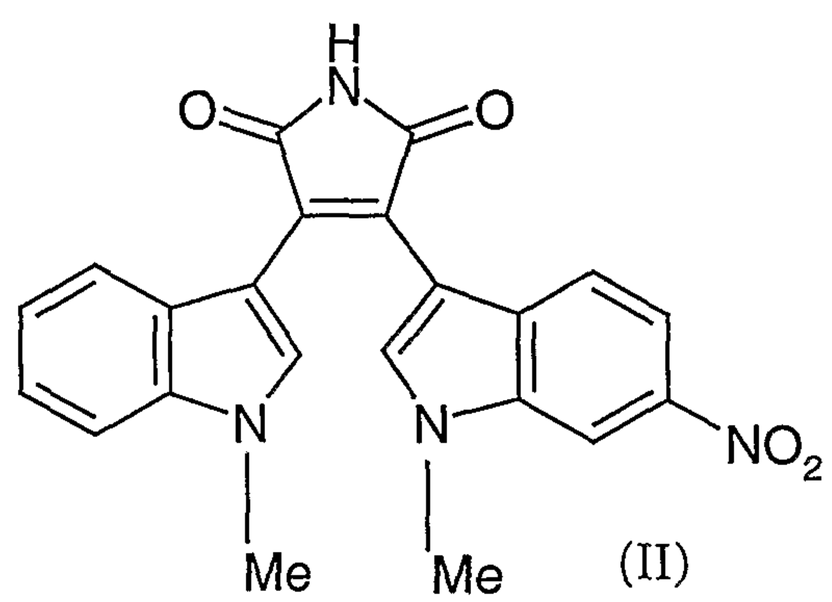
or a pharmaceutically acceptable salt or ester of said compound,
wherein
R^1 is selected from the group consisting of -H, $-CH_3$, and $-CH_2OH$, and
R^2 is $-CH_3$, and
wherein the active ingredient of the component is administered daily as an oral sustained release formulation for an administration period of up to about 14 days, in a total amount of from about 780 mg/m^2 to about 3000 mg/m^2 divided over the administration period; and

b) a component consisting of a pharmaceutical composition comprising as an active ingredient gemcitabine, wherein the gemcitabine is administered in a total amount of from about 1200 mg/m^2 to about 3600 mg/m^2, over about 15 days, beginning on the first day of the 21-28 days cycle; said treatment cycle being optionally repeated every 21-28 days;

for the treatment of cancer, particularly a solid cancerous tumor. The 21-28 days cycle may be repeated for as long as the tumor remains under control and the regimen is clinically tolerated.

In another embodiment, the present invention relates to a use of a pharmaceutical combination comprising

a) a component consisting of a pharmaceutical composition comprising as an active ingredient a compound of formula :



(II)

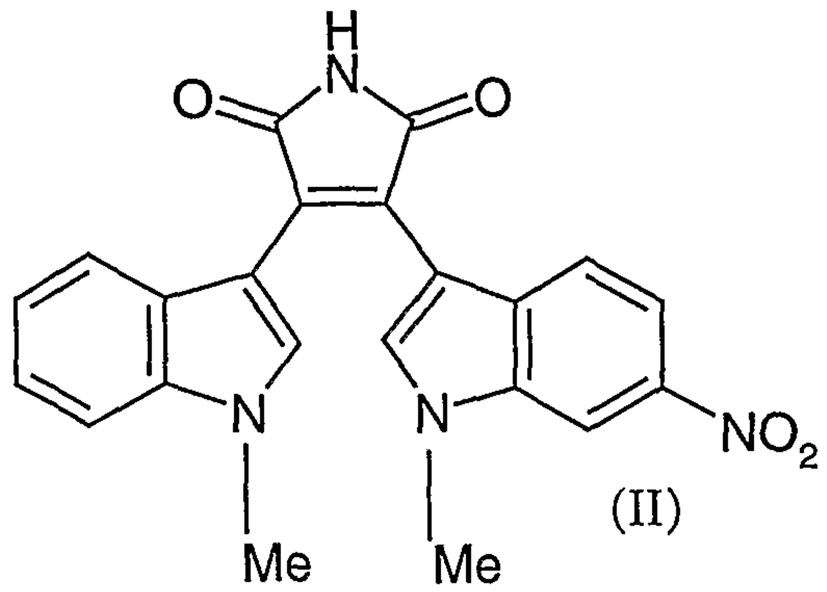
or a pharmaceutically acceptable salt or ester of said compound,
wherein the compound of formula II is administered in an amount of from about 70 mg/m^2 per day to about 220 mg/m^2 per day for up to about 14 days starting on the first day of a 28 days cycle, and

b) a component consisting of an injection solution comprising as an active ingredient gemcitabine which is administered in amount of from about 800 mg/m^2 to about 1000 mg/m^2 on the first, eighth and fifteenth day of a 28 days cycle, said 28 days cycle being optionally repeated;

for the treatment of cancer, particularly a solid cancerous tumor. The 28 days cycle may be repeated as long as the tumor remains under control.

In another embodiment, the present invention relates to a use of a pharmaceutical combination comprising

a) a component consisting of a pharmaceutical composition comprising as an active ingredient a compound of formula :



(II)

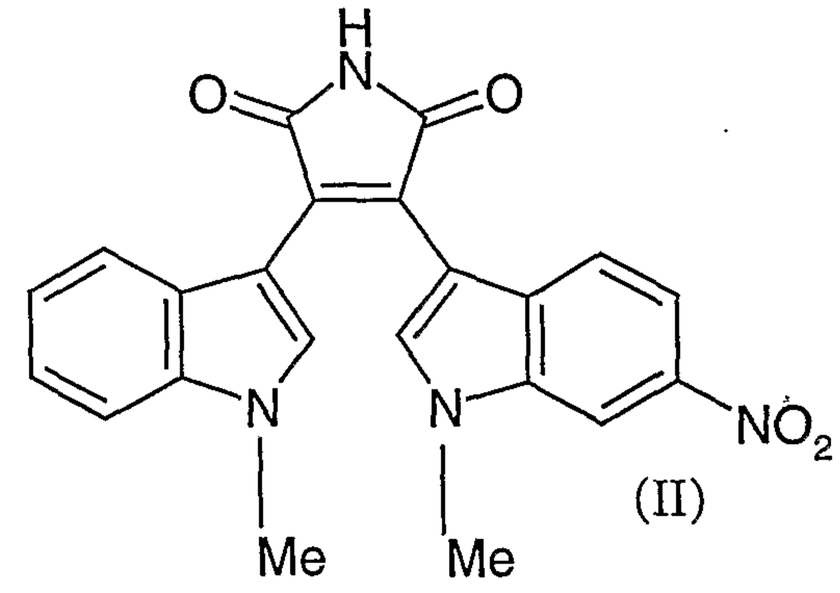
or a pharmaceutically acceptable salt or ester of said compound,
wherein the compound of formula II is administered in an amount of from about 200 mg/m^2 per day to about 340 mg/m^2 per day for up to about 7 days starting on the first day of a 28 days cycle, and

b) a component consisting of an injection solution comprising as an active ingredient gemcitabine which is administered in amount of from about 600 mg/m^2 to about 1200 mg/m^2 on the first and eighth day of a 28 days cycle, and said 28 days cycle being optionally repeated;

for the treatment of cancer, particularly a solid cancerous tumor. The 28 days cycle may be repeated as long as the tumor remains under control

In another embodiment, the present invention a use of a pharmaceutical combination comprising

a) a component consisting of a pharmaceutical composition comprising as an active ingredient a compound of formula :



(II)

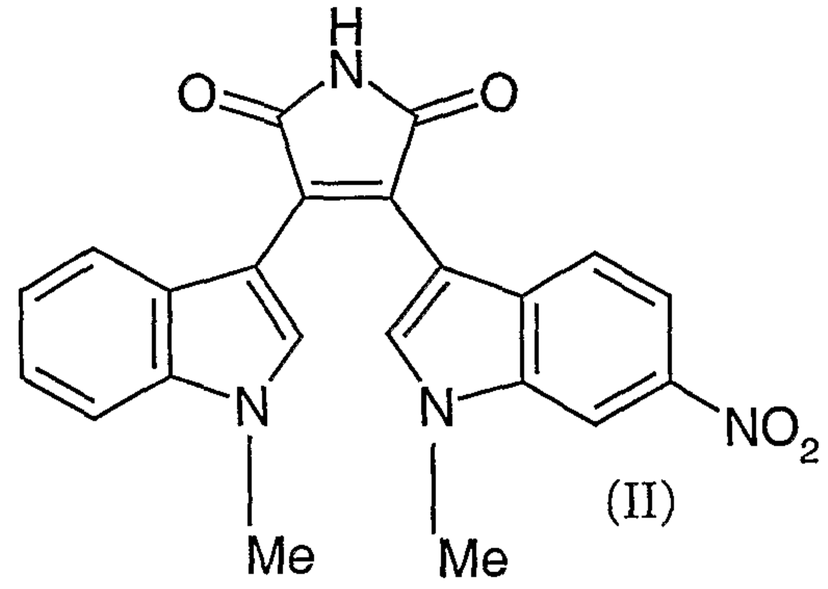
or a pharmaceutically acceptable salt or ester of said compound,
wherein the compound of formula II is administered in an amount of from about 270 mg/m^2 per day to about 450 mg/m^2 per day for up to about 4 days starting on the first day of a 21 days cycle, and

b) a component consisting of an injection solution comprising as an active ingredient gemcitabine which is administered in amount of from about 800 mg/m^2 to about 1000 mg/m^2 on the first and eighth day of a 21 days cycle, and said 21 days cycle being optionally repeated;

for the treatment of cancer, particularly a solid cancerous tumor. The 21 days cycle may be repeated as long as the tumor remains under control

In another specific embodiment, the present invention relates to a use of a pharmaceutical combination comprising

a) a component consisting of a pharmaceutical composition comprising as an active ingredient a compound of formula :



(II)

or a pharmaceutically acceptable salt or ester of said compound,
wherein the compound of formula II is administered in an amount of from about 190 mg/m^2 per day to about 570 mg/m^2 per day for up to about 4 days starting on the first day of a 21 days cycle, and

b) a component consisting of an injection solution comprising as an active ingredient gemcitabine which is administered in amount of from about 700 mg/m^2 to about 1200 mg/m^2 on the first and eighth day of a 21 days cycle, said 21 days cycle being optionally repeated;

for the treatment of cancer, particularly a solid cncerous tumor. The 21 days cycle is repeated as long as the tumor remains under control

In a most preferred embodiment, from about 95 mg/m^2 to about 285 mg/m^2 of Compound II are administered twice daily (total daily dose of from about 190 mg/m^2 to about 570 mg/m^2) for 4 consecutive days commencing on day 1 of a 21 day cycle. Also on day 1 of the cycle, preferably starting at about the same time as the first dose of Compound II, from about 700 mg/m^2 to about 1200 mg/m^2 of gemcitabine are administered as an i.v. infusion. The gemcitabine dose is repeated on day 8 of the cycle. This treatment is repeated every twenty one days, or as soon as permitted by recovery from toxicity, for so long as the tumor is under control and the patient tolerates the regimen or tumor regression. Preferably, the cycles are repeated for a total of up to 8 cycles (that is twenty four weeks).

In another most preferred embodiment, from about 135 mg/m^2 to about 225 mg/m^2 of Compound II are administered twice daily (total daily dose of from about 270 mg/m^2 to about 450 mg/m^2) for 4 consecutive days commencing on day 1 of a 21 day cycle. Also on day 1 of the cycle, preferably starting at the about the same time as the first dose of Compound II, from about 800 mg/m^2 to about 1000 mg/m^2 of gemcitabine are administered as an i.v. infusion. The gemcitabine dose is repeated on day 8 of the cycle. This treatment is repeated every twenty one days, or as soon as permitted by recovery from toxicity, for so long as the tumor is under control and the patient tolerates the regimen or tumor regression. Preferably, the cycles are repeated for a total of up to 8 cycles (that twenty four weeks).

In another most preferred embodiment, from about 70 mg/m^2 to about 215 mg/m^2 of Compound II are administered twice daily (total daily dose of from about 200 mg/m^2 to about 340 mg/m^2) for 7 consecutive days commencing on day 1 of a 28 day cycle. Also on day 1 of the cycle, preferably starting at the about the same time as the first dose of Compound II, from about 600 mg/m^2 to about 1200 mg/m^2 of gemcitabine are administered as an i.v. infusion. The gemcitabine dose is repeated on day 8 of the cycle. This treatment is repeated every 28 days, or as soon as permitted by recovery from toxicity, for so long as the tumor is under control and the patient tolerates the regimen or tumor regression. Preferably, the cycles are repeated for a total of up to 8 cycles (that is thirty two weeks).

In another most preferred embodiment, from about 100 mg/m^2 to about 170 mg/m^2 of Compound II are administered twice daily (total daily dose of from about 200 mg/m^2 to about 340 mg/m^2) for 7 consecutive days commencing on day 1 of a 28 day cycle. Also on day 1 of the cycle, preferably starting at the about the same time as the first dose of Compound II, from about 800 mg/m^2 to about 1000 mg/m^2 of gemcitabine are administered as an i.v. infusion. The gemcitabine dose is repeated on day 8 of the cycle.

This treatment is repeated every 28 days, or as soon as permitted by recovery from toxicity, for so long as the tumor is under control and the patient tolerates the regimen or tumor regression. Preferably, the cycles are repeated for a total of up to 8 cycles (that is thirty two weeks).

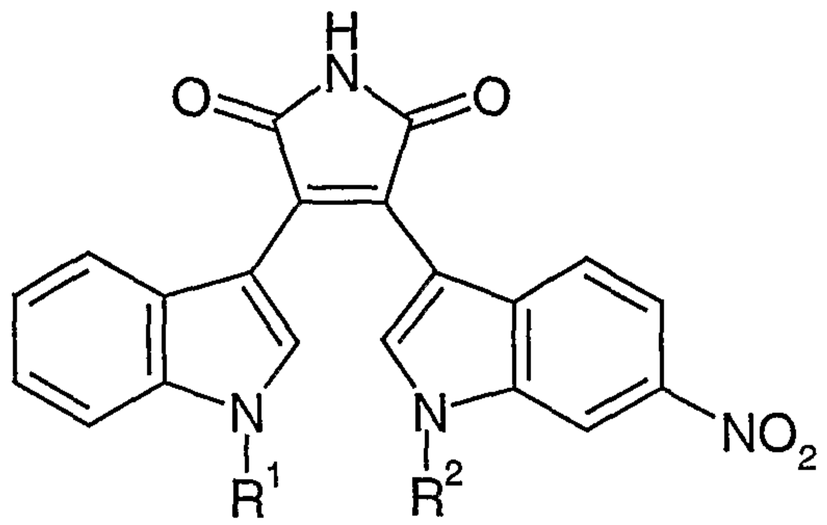
In another most preferred embodiment, from about 35 mg/m^2 to about 110 mg/m^2 of Compound II are administered twice daily (total daily dose of from about 70 mg/m^2 to about 220 mg/m^2) for 14 consecutive days commencing on day 1 of a 28 day cycle. Also on day 1 of the cycle, preferably starting at the about the same time as the first dose of Compound II, from about 800 mg/m^2 to about 1000 mg/m^2 of gemcitabine are administered as an i.v. infusion. The gemcitabine dose is repeated on days 8 and 15 of the cycle. This treatment is repeated every 28 days, or as soon as permitted by recovery from toxicity, for so long as the tumor is under control and the patient tolerates the regimen or tumor regression. Preferably, the cycles are repeated for a total of up to 8 cycles (that is thirty two weeks).

In another most preferred embodiment, from about 50 mg/m^2 to about 85 mg/m^2 of Compound II are administered twice daily (total daily dose of from about 100 mg/m^2 to about 170 mg/m^2) for 14 consecutive days commencing on day 1 of a 28 day cycle. Also on day 1 of the cycle, preferably starting at the about the same time as the first dose of Compound II, from about 800 mg/m^2 to about 1000 mg/m^2 of gemcitabine are administered as an i.v. infusion. The gemcitabine dose is repeated on days 8 and 15 of the cycle. This treatment is repeated every 28 days, or as soon as permitted by recovery from toxicity, for so long as the tumor is under control and the patient tolerates the regimen or tumor regression. Preferably, the cycles are repeated for a total of up to 8 cycles (that is thirty two weeks).

The present invention relates also to a kit comprising:

a) a component comprising one or more oral unit dosage forms of an active ingredient, each unit comprising about 50 mg to about 200 mg of the active ingredient, wherein the active ingredient is a compound selected from formula

I



(I)

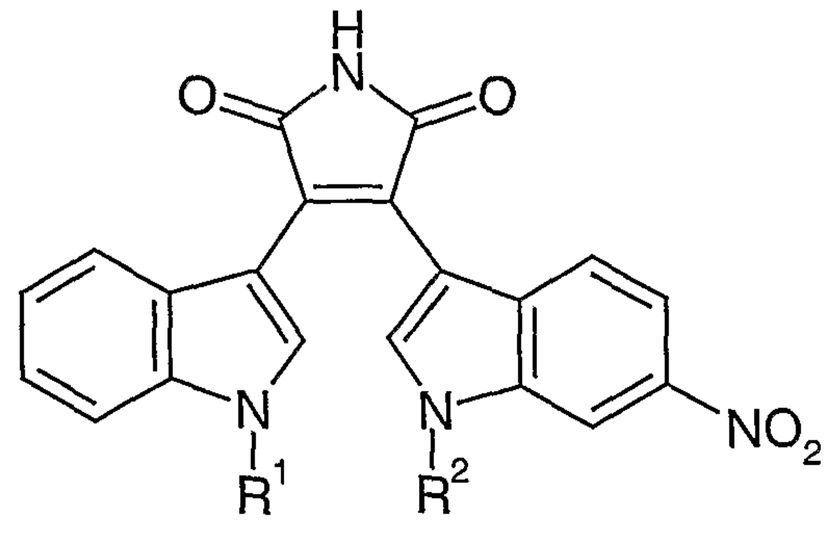
or a pharmaceutically acceptable salt or ester said compound, wherein
R^1 is selected from the group consisting of -H, $-CH_3$, and $-CH_2OH$, and
R^2 is $-CH_3$; and

b) a component containing a vial or series of vials, each vial containing a single injectable solution dose or multiple injectable solution doses, each dose comprising as an active ingredient about 200 mg to about 1 g of gemcitabine.

Preferably, the first component contains a sufficient number of units so that a patient can administer up to about 600 mg per day of the active ingredient for a period of about four to 14 days and the second component contains a sufficient number of doses so that a patient can administer up to 2600 mg per day for a period of about 3 days.

Another embodiment of the present invention is a method for manufacturing a medicament for the treatment of cancer, particularly a solid cancerous tumor using a pharmaceutical combination comprising

a) a component consisting of pharmaceutical composition comprising as an active ingredient a compound of formula :



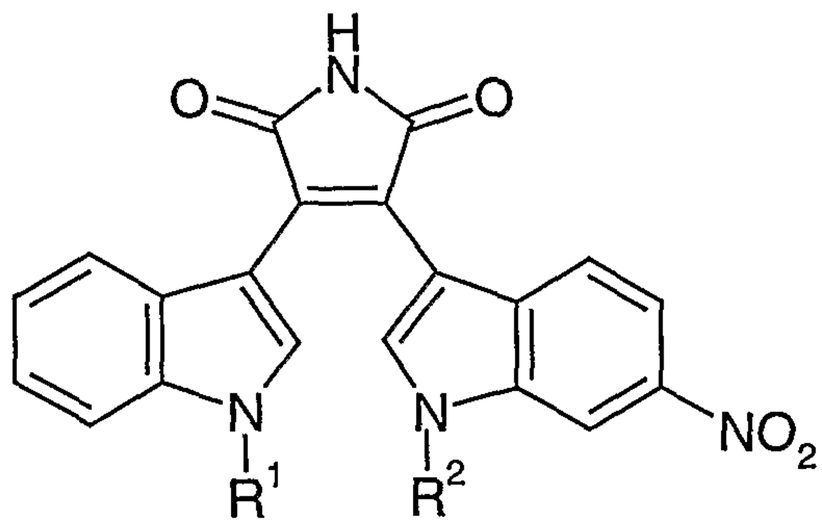
(I)

or a pharmaceutically acceptable salt or ester of said compound, wherein
R^1 is selected from the group consisting of -H, $-CH_3$, and $-CH_2OH$, and
R^2 is $-CH_3$; and

b) a component consisting of pharmaceutical composition comprising as an active ingredient gemcitabine.

The present invention relates also to a pharmaceutical composition comprising a pharmaceutical combination comprising

a) a component consisting of pharmaceutical composition comprising as an active ingredient a compound of formula I



(I)

or a pharmaceutically acceptable salt or ester of said compound, wherein R^1 is selected from the group consisting of -H, $-CH_3$, and $-CH_2OH$, and R^2 is $-CH_3$; and

b) a component consisting of pharmaceutical composition comprising as an active ingredient gemcitabine

for the treatment of cancer, particularly a solid cncerous tumor.

According to the present invention, in the pharmaceutical composition, the antineoplastic combination is in combination with radiotherapy or alternatively together with another anticancer agent.

The present invention may be exemplified by the Examples below, which illustrate the invention without limitation.

EXAMPLES

The efficacy of the combinations of the present invention on solid tumors is demonstrated by the following experiments:

Example 1: *In Vitro* Assay

Description of Tumor Cell Lines and Cultures:

H1299 cells were obtained from the National Cancer Institute. A549 cells were purchased from ATCC. The cells were grown in a subconfluent condition to maintain a logarithmic growth phase. The cells were dislodged for passage using trypsin-EDTA (0.05% and 0.53 mM, respectively).

Tetrazolium dye proliferation assay:

Cellular proliferation was evaluated by the tetrazolium dye assay. Cells from exponentially growing cultures were plated at the appropriate seeding density in the optimal medium to give logarithmic growth over the course of the assay. Plates were incubated overnight at 37°C in a humidified CO_2 atmosphere to allow for recovery from trypsinization before beginning the assay. Compound II stock solution was prepared in DMSO (dimethyl sulfoxide) and aliquots were stored at -20°C. Purified gemcitabine was diluted in sterile saline. Each drug was diluted to eight times the final concentration in media containing 0.4% DMSO. One eighth final well volume of each dilution was added in triplicate to plates containing cells. An equal volume of 0.4% DMSO in media was added to single drug wells and twice the volume of 0.4% DMSO in media was added to a row of control wells so that the final concentration of DMSO in all wells was 0.2%. The plates were returned to 37°C and assayed for proliferation by MTT (3-(4,5-dimethyl-thiazole-2-yl)-2,5-diphenyl-2H-tetrazolium bromide at time points that would allow for at least three population doublings in the untreated control cultures. MTT was added to each well to yield a final concentration of 1 mg/ml and the plates were returned to 37°C for 2.5 hours. Following incubation, the MTT-containing medium was removed by aspiration and the resulting formazan metabolite was solubilized in 50 µl ethanol. Absorbances were read at a

wavelength of 570 nm with a 650 nm reference. Percent inhibition was calculated using the formula:

$$\text{Percent Inhibition} = 1 - \left[\frac{\text{Mean Absorbance of Experimental Wells}}{\text{Mean Absorbance of Control Wells}}\right] \times 100$$

Findings:

The antiproliferative activity of Compound II in combination with gemcitabine was evaluated *in vitro* using a tetrazolium dye assay in two different tumor cell lines derived from non-small cell lung cancers. Table 3 below shows that in cell culture studies with A549 (non-small cell lung carcinoma) and H1299 (non-small cell lung carcinoma) tumor cells, Compound II in combination with gemcitabine produced a statistically significant greater growth inhibitory effect than that produced by either compound alone at the same concentrations. The *in vitro* studies demonstrate dose combinations of Compound II with gemcitabine that provide superior antiproliferative activity compared to corresponding doses of these same agents in monotherapy.

TABLE 3

Statistical comparisons for various combinations of Compound II in combination with Gemcitabine in vitro

Cell line	Percent Inhibition In Compound II Treated Cultures	Percent Inhibition In Gemcitabine Treated Cultures	Percent Inhibition In Combination Treated Cultures	Compound II vs Combination p value*	Gemcitabine vs Combination p value
H1299	38.9 ± 5.10	43.0 ± 0.09	81.6 ± 8.16	0.002	0.001
	38.9 ± 5.10	43.5 ± 2.30	68.9 ± 2.75	<0.001	<0.001
	40.0 ± 1.36	43.0 ± 0.09	82.2 ± 7.80	<0.001	<0.001
A549	44.2 ± 1.24	42.0 ± 0.88	65.1 ± 7.94	0.011	0.007
	44.2 ± 1.24	40.2 ± 1.81	55.3 ± 1.71	<0.001	<0.001
	47.9 ± 1.44	42.0 ± 0.88	63.9 ± 1.47	<0.001	<0.001

*P values for various combinations of Compound II and gemcitabine were determined using the unpaired t-test (SigmaStat) to compare triplicate values of Compound II-treated

cultures to triplicate values of combination-treated cultures and triplicate values of gemcitabine-treated cultures to triplicate values of combination-treated cultures.

Example 2: *In Vivo* Assay

In Vivo Implantation:

For implantation in mice, A549 cells were dislodged with trypsin-EDTA, washed with 1x D-PBS, and resuspended in serum-free media. Tumor cells were implanted subcutaneously in mice using a 27 gauge needle and 1 ml syringe. Tumors were allowed to establish until they were palpable and of an appropriate tumor volume (based on previous tumorigenicity studies) before initiation of treatment. Animals were randomly assigned to groups according to initial tumor volume, and the day of tumor cell inoculation was considered to be study day 0.

Mice:

Female BALB/c nu/nu mice were obtained from Charles River Laboratories (Wilmington, MA). The mice were housed in an AALAC approved facility and received standard care in accordance with institutional policy (fully compliant with both NIH and Roche Animal Care and Use Committee guidelines).

Drug Preparation and Treatment:

Compound II was microprecipitated with an ionic polymer, Eudragit L-100-55, using a solvent extraction process. Eudragit L100-55 (described in USP/NF as "Methacrylic Acid Copolymer") is an anionic copolymer based on methacrylic acid and ethyl acrylate. The ratio of drug to polymer in the final formulation was 50% w/w Compound II and 50% w/w Eudragit L100-55. For oral administration, the formulated Compound II or pure Eudragit L100-55 (administered to vehicle control groups) was suspended in 0.2% CMC (carboxy-methyl cellulose) solution (Aqualon Hercules, Inc., Parlin, NJ). The CMC solution was added immediately prior to dosing to animals. Gemzar® (Lilly, Indianapolis, IN) was applied to a 40 micron high performance Whatman C-18 column. The column was eluted

at 60ml/min for 50 minutes with water, followed by elution with 40% CH_3CN/water until UV clear. The solution was then evaporated and lyophilized. The purified gemcitabine had identical potency to Gemzar® in MTT assay using H1299 cells (IC_{50} 3.8nM/IC_{90} 5.9nM for Gemzar® versus IC_{50} 3.8nM/IC_{90} 6.0nM for purified gemcitabine).

Measurements and Statistical Analysis:

Weight loss was graphically represented as percent change in mean group body weight, using the formula:

$((W - W_0)/W_0) \times 100$,

where 'W' represents mean body weight of the treated group at a particular day, and 'W_0' represents mean body weight of the same treated group at initiation of treatment. Maximum weight loss was also represented using the above formula, and indicated the maximum percent body weight loss that was observed at any time during the entire experiment for a particular group.

Efficacy data was graphically represented as the mean tumor volume ± standard error of the mean (SEM). Tumor volumes of treated groups were presented as percentages of tumor volumes of the control groups (%T/C), using the formula:

$$100 \times ((T - T_0)/(C - C_0)),$$

where 'T' represented mean tumor volume of a treated group on a specific day during the experiment, 'T_0' represented mean tumor volume of the same treated group on the first day of treatment; 'C' represented mean tumor volume of a control group on a specific day during the experiment, and 'C_0' represented mean tumor volume of the same treated group on the first day of treatment.

Tumor volume (mm^3) was calculated using the ellipsoid formula:

$$(D \times (d^2))/2,$$

where 'D' represents the large diameter of the tumor, and 'd' represents the small diameter. In some cases, tumor regression and/or percent change in tumor volume was calculated using the formula:

$$((T - T_0)/T_0) \times 100,$$

where 'T' represents mean tumor volume of the treated group at a particular day, and 'T_0' represents mean tumor volume of the same treated group at initiation of treatment.

Statistical analysis was determined by the rank sum test (SigmaStat, v.2.0, Jandel Scientific, San Francisco, CA). Differences between control and experimental groups were considered to be significant when the probability value (p) was ≤ 0.05.

Findings:

Table 4 below shows that significant efficacy (tumor growth inhibition) was produced by combining low doses of Compound II and gemcitabine which were less effective as single agents. This particular combination was well tolerated, showing little evidence of enhanced toxicity. The *in vivo* studies demonstrate dose combinations of Compound II with gemcitabine that provide superior therapeutic index compared to corresponding regimens using these same agents in monotherapy.

Table 4: Efficacy and Toxicity of Compound II in Combination with Gemcitabine in the A549 NSCLC Xenograft Model

Group	n	Route	Tumor Volume (Mean+SEM) mm 3 (Day 30)	Tumor Volume (Mean+SEM) mm 3 (Day 47)	% T/C* (Day 47)	p values (Day 47)	Change in Body Weight (Day 47) (%)	Maximum Weight Loss (%)	Drug Related Deaths (%)
SINGLE AGENTS									
Vehicle (Eudragit/CMC)	9	PO	110+16	337+82	-	-	2	0	0
CII**: 50 mg/kg	9	PO	104+18	217+32	50	0.470	5	0	0
CII: 100 mg/kg	9	PO	148+28	213+35	29	0.121	6	0	0
CII: 200 mg/kg	9	PO	99+17	141+21	18	0.008	4	0	0
Vehicle (Saline)	9	IP	117+23	273+62	-	-	6	0	0
G***:30 mg/kg	10	IP	97+15	210+44	72	0.427	5	0	0
G:60 mg/kg	10	IP	111+17	188+27	49	0.206	6	0	0
G:120 mg/kg	10	IP	98+20	193+36	61	0.253	7	0	0

	SIMULTANEOUS COMBINATION								
	Vehicle (Eudragit/CMC & Saline)	9	PO/IP	106+21	243+42	-	-	2	0	0
	CII: 50 mg/kg & G:30 mg/kg	0	PO/IP	142+24	217+42	55	0.111	5	0	0
5	CII: 100 mg/kg & G:30 mg/kg	0	PO/IP	115+9	192+28	57	0.094	6	0	0
	CII: 100 mg/kg & G:60 mg/kg	0	PO/IP	125+26	190+30	48	0.037	5	0	0
	CII: 200 mg/kg & G:120 mg/kg	0	PO/IP	119+17	146+20	19	0.002	-8	-13 (Day 45)	0
	FORWARD SEQUENCE COMBINATIONS (*Compound II followed by Gemcitabine*)									
10	Vehicle (Eudragit/CMC & Saline)	9	PO/IP	106+21	243+42	-	-	2	0	0
	CII: 50 mg/kg & G:30 mg/kg	0	PO/IP	98+12	182+42	62	0.361	7	0	0
	CII:100 mg/kg & G:30 mg/kg	0	PO/IP	101+16	142+27	30	0.006	7	-1 (Day 32)	0
	CII:100 mg/kg & G:60 mg/kg	0	PO/IP	110+16	134+15	18	0.001	7	0	0
	CII:200 mg/kg & G:120 mg/kg	0	PO/IP	125+22	175+55	36	0.017	-5	-13 (Day 38)	50

REVERSE SEQUENCE COMBINATIONS

(Gemcitabine followed by Compound II)

	Vehicle (Eudragit/CMC & Saline)	9	PO/IP	106+21	243+42	-	-	2	0	0
5	G:30 mg/kg & CII:50 mg/kg	0	IP/PO	122+24	144+28	16	0.005	3	-1 (Day 32)	0
	G:30 mg/kg & CII:100 mg/kg	0	IP/PO	120+17	155+26	25	0.005	3	0	0
	G:60 mg/kg & CII:100 mg/kg	0	IP/PO	102+17	130+27	21	0.010	1	-3 (Day 44)	0
	G:120 mg/kg & CII:200 mg/kg	0	IP/PO	97+8	137+17	29	0.014	-4	-18 (Day 43)	20

10 * %T/C values were compared to the appropriate vehicle group.

**CII = Compound II

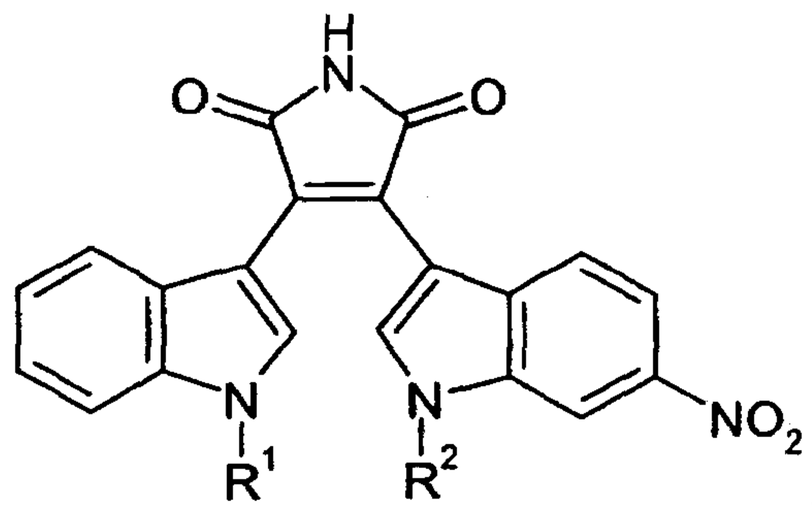
*** G = Gemcitabine

The above *in vitro* and *in vivo* data identify dose combinations of Compound II and gemcitabine that are efficacious with minimal toxicity, and that are statistically superior in terms of antiproliferative activity and/or efficacy to corresponding doses of each agent used in monotherapy.

Claims

1. Use of a pharmaceutical combination comprising as active ingredients

a) a component consisting of a pharmaceutical composition comprising a compound of formula I



(I)

or a pharmaceutically acceptable salt or ester of said compound, wherein R^1 is selected from the group consisting of -H, $-CH_3$, and $-CH_2OH$, and R^2 is $-CH_3$ and

b) a component consisting of a pharmaceutical composition comprising as an active ingredient gemcitabine,

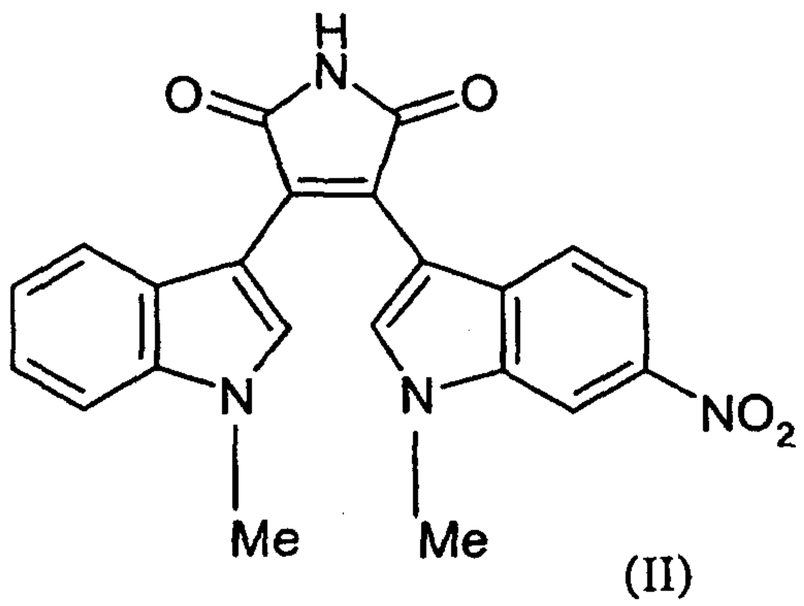
for the preparation of a medicament for the treatment of cancer, wherein the component consisting of a pharmaceutical composition comprising a compound of formula I is administered over a treatment cycle of 21 to 28 days in a total amount from about 780 mg/m^2 to about 3000 mg/ m^2, and wherein the component consisting of a pharmaceutical composition comprising as an active ingredient gemcitabine is administered over the treatment cycle of 21 to 28 days in a total amount of from about 1200 mg/m^2 to about 3600 mg/m^2.

2. The use of claim 1, wherein both compounds are administered concomitantly.

3. The use of claim 1, wherein both compounds are administered sequentially.

4. The use of any one of claims 1 to 3, wherein a component consisting of pharmaceutical composition comprising a compound of formula I is an an oral unit dosage form.

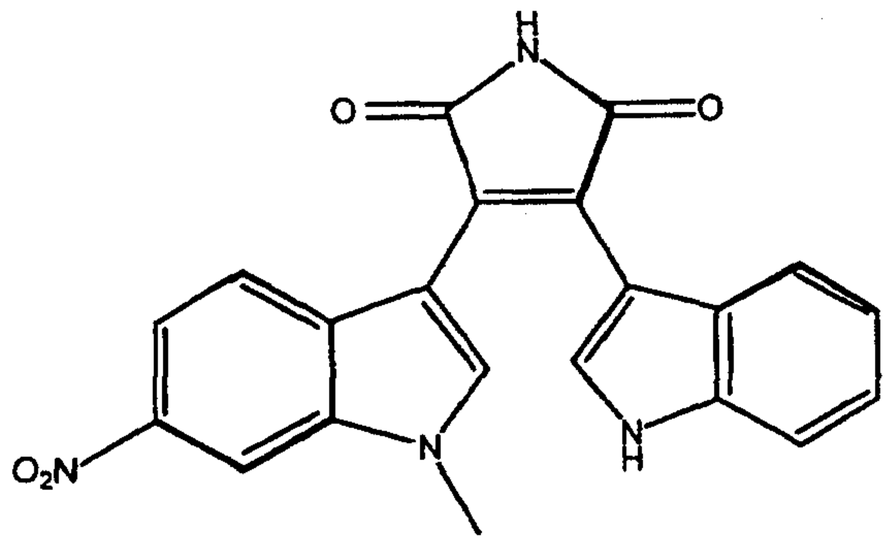
5. The use of any one of claims 1 to 4, wherein the compound of formula I is a compound of the formula:



(II)

or a pharmaceutically acceptable salt or ester thereof.

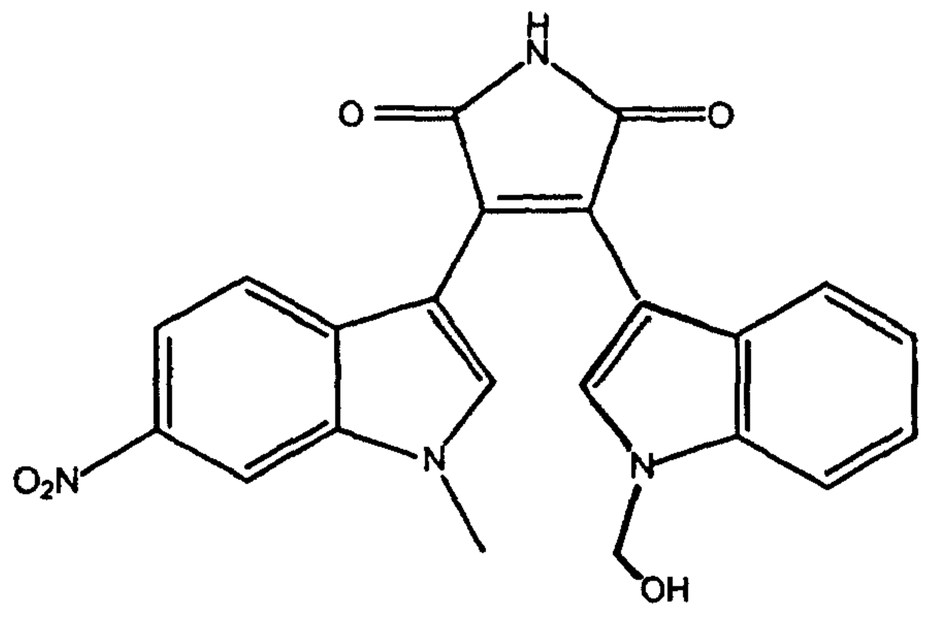
6. The use of any one of claims 1 to 4, wherein the compound of formula I is a compound of the formula:



(III)

or a pharmaceutically acceptable salt or ester thereof.

7. The use of any one of claims 1 to 4, wherein the compound of formula I is a compound of the formula:



(IV)

or a pharmaceutically acceptable salt or ester thereof.

8. The use of any one of claims 1 to 6 wherein the amount of the compound of formula I is from about 1040 mg/m^2 to about 3000 mg/m^2 administered over a period of up to about 14 days.

9. The use of claim 8 wherein the amount of the compound of formula I is from about 1480 mg/m^2 to about 2360 mg/m^2.

10. The use of any one of claims 1 to 6 wherein the amount of the compound of formula I is from about 1040 mg/m^2 to about 3000 mg/m^2 over a period of about 7 days.

11. The use of claim 10 wherein the amount of the compound of formula I is from about 1480 mg/m^2 to about 2360 mg/m^2.

12. The use of any one of claims 1 to 6 wherein the amount of the compound of formula I is from about 780 mg/m^2 to about 2250 mg/m^2 over a period of about 4 days.

13. The use of claim 12 wherein the amount of the compound of formula I is from about 1110 mg/m^2 to about 1770 mg/m^2 over a period of about 4 days.

14. The use of any one of claims 1 to 6 wherein the dose intensity of the compound of formula I is from about 260 mg/m^2/week to about 750 mg/m^2/week.

15. The use of claim 14 wherein the dose intensity of the compound of formula I is from about 370 mg/m^2/week to about 590 mg/m^2/week.

16. The use of any one of claims 1 to 6 wherein the amount of gemcitabine is from about 1200 mg/m^2 to about 2400 mg/m^2 administered over a period of up to about 8 days.

17. The use of claim 16 wherein the amount of gemcitabine is from about 1600 mg/m^2 to about 2000 mg/m^2 administered over a period of up to about 8 days.

18. The use of any one of claims 1 to 6 wherein the amount of gemcitabine is from about 1800 mg/m^2 to about 3600 mg/m^2 administered over a period of up to about 15 days.

19. The use of claim 18 wherein the amount of gemcitabine is from about 2400 mg/m^2 to about 300 mg/m^2 administered over a period of up to about 15 days.

20. The use of any one of claims 1 to 6 wherein the gemcitabine is administered on days 1 and 8 of a 21-days treatment cycle.

21. The use of claim 20 wherein the dose intensity of gemcitabine is from about 460 mg/m^2/week to about 800 mg/m^2/week.

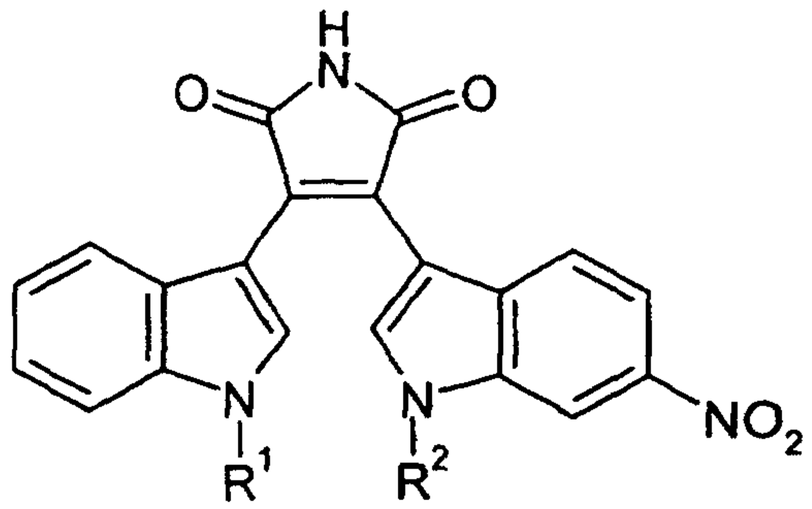
22. The use of claim 21 wherein the dose intensity of gemcitabine is from about 530 mg/m^2/week to about 670 mg/m^2/week.

23. The use of any one of claims 1 to 6 wherein the gemcitabine is administered on days 1 and 8 of a 21-28 days treatment cycle.

24. The use of any one of claims 1 to 6 wherein the gemcitabine is administered on days 1, 8 and 15 of a 28-days treatment cycle.

25. Use of a pharmaceutical combination comprising

a) a component consisting of a pharmaceutical composition comprising as an active ingredient a compound of formula :



(I)

or a pharmaceutically acceptable salt or ester of said compound,
wherein
R^1 is selected from the group consisting of -H, $-CH_3$, and $-CH_2OH$, and
R^2 is $-CH_3$, and

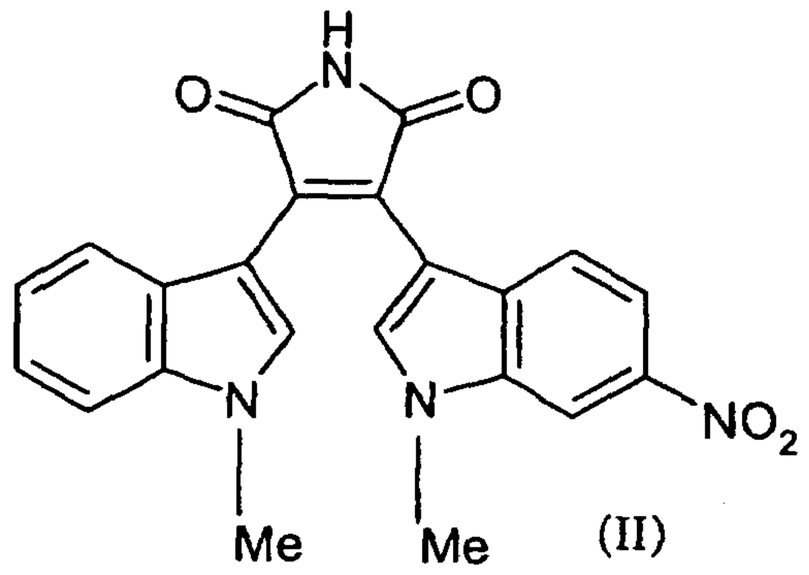
wherein the active ingredient of the component is administered daily as an oral sustained release formulation for an administration period of up to about 14 days, in a total amount of from about 780 mg/m^2 to about 3000 mg/m^2 divided over the administration period; and

b) a component consisting of a pharmaceutical composition comprising as an active ingredient gemcitabine, wherein the gemcitabine is administered in a total amount of from about 1200 mg/m^2 to about 3600 mg/m^2, over about 15 days, beginning on the first day of the 21-28 days cycle; said treatment cycle being otionally repeated every 21-28 days;

for the treatment of cancer, particularly a solid cancerous tumor.

26. Use of a pharmaceutical combination comprising

a) a component consisting of a pharmaceutical composition comprising as an active ingredient a compound of formula :



(II)

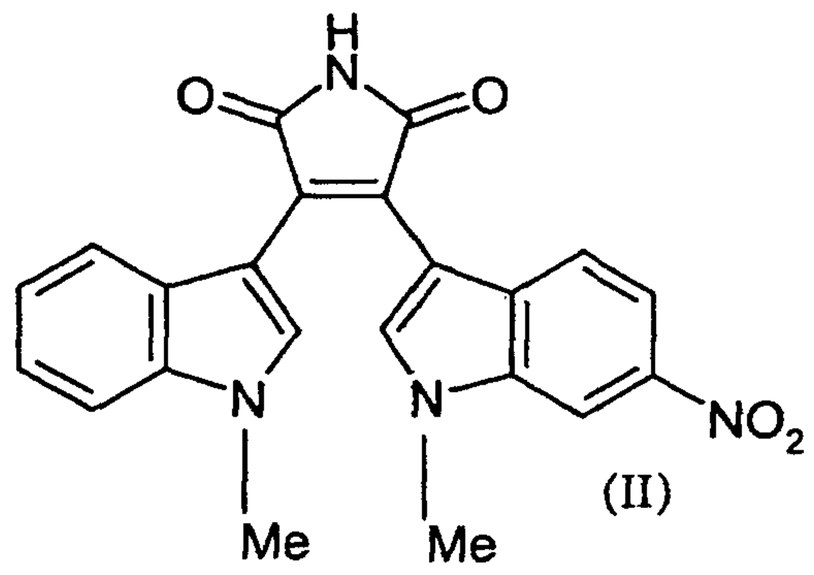
or a pharmaceutically acceptable salt or ester of said compound,
wherein the compound of formula II is administered in an amount of from about 70 mg/m^2 per day to about 220 mg/m^2 per day for up to about 14 days starting on the first day of a 28 days cycle, and

b) a component consisting of an injection solution comprising as an active ingredient gemcitabine which is administered in amount of from about 800 mg/m^2 to about 1000 mg/m^2 on the first, eighth and fifteenth day of a 28 days cycle, said 28 days cycle being optionally repeated;

for the treatment of cancer, particularly a solid cancerous tumor.

27. Use of a pharmaceutical combination comprising

a) a component consisting of a pharmaceutical composition comprising as an active ingredient a compound of formula :



(II)

or a pharmaceutically acceptable salt or ester of said compound,

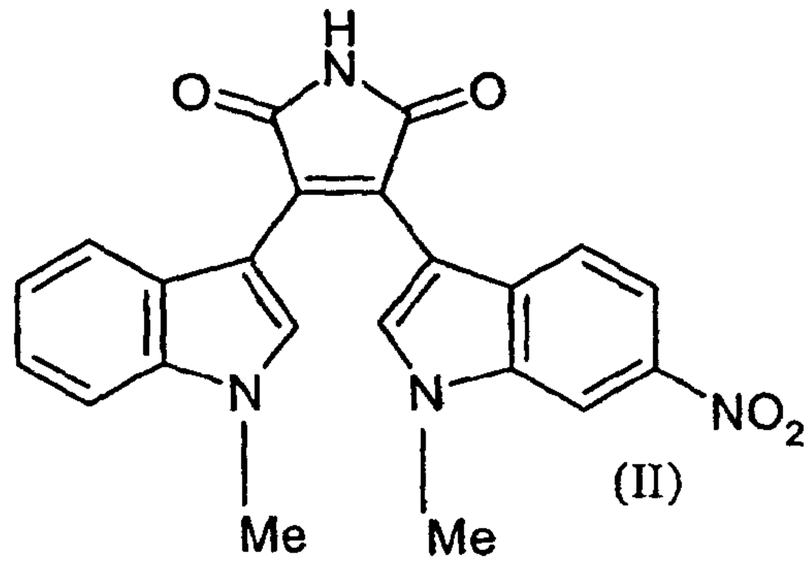
wherein the compound of formula II is administered in an amount of from about 200 mg/m^2 per day to about 340 mg/m^2 per day for up to about 7 days starting on the first day of a 28 days cycle, and

b) a component consisting of an injection solution comprising as an active ingredient gemcitabine which is administered in amount of from about 600 mg/m^2 to about 1200 mg/m^2 on the first and eighth day of a 28 days cycle, and said 28 days cycle being optionally repeated;

for the treatment of cancer, particularly a solid cancerous tumor.

28. Use of a pharmaceutical combination comprising

a) a component consisting of a pharmaceutical composition comprising as an active ingredient a compound of formula :



(II)

or a pharmaceutically acceptable salt or ester of said compound,

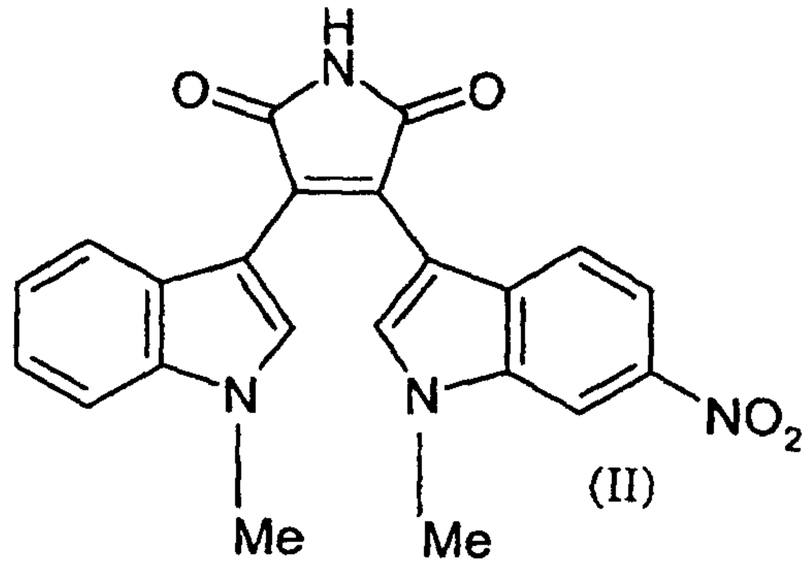
wherein the compound of formula II is administered in an amount of from about 270 mg/m^2 per day to about 450 mg/m^2 per day for up to about 4 days starting on the first day of a 21 days cycle, and

b) a component consisting of an injection solution comprising as an active ingredient gemcitabine which is administered in amount of from about 800 mg/m^2 to about 1000 mg/m^2 on the first and eighth day of a 21 days cycle, and said 21 days cycle being optionally repeated;

for the treatment of cancer, particularly a solid cancerous tumor.

29. Use of a pharmaceutical combination comprising

a) a component consisting of a pharmaceutical composition comprising as an active ingredient a compound of formula :



(II)

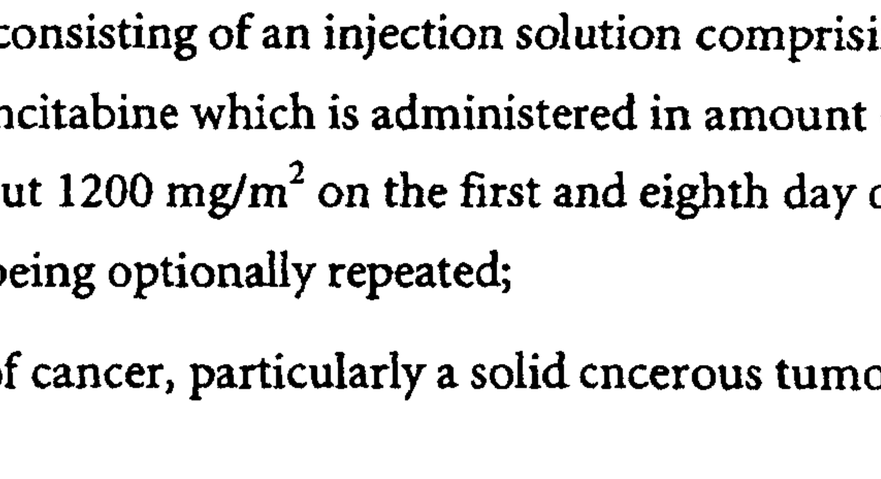
or a pharmaceutically acceptable salt or ester of said compound,
wherein the compound of formula II is administered in an amount of from about 190 mg/m^2 per day to about 570 mg/m^2 per day for up to about 4 days starting on the first day of a 21 days cycle, and

b) a component consisting of an injection solution comprising as an active ingredient gemcitabine which is administered in amount of from about 700 mg/m^2 to about 1200 mg/m^2 on the first and eighth day of a 21 days cycle, said 21 days cycle being optionally repeated;

for the treatment of cancer, particularly a solid cncerous tumor.

30. A kit comprising:

a) a component comprising one or more oral unit dosage forms of an active ingredient, each unit comprising about 50 mg to about 200 mg of the active ingredient, wherein the active ingredient is a compound selected from formula I



(I)

or a pharmaceutically acceptable salt or ester said compound, wherein
R^1 is selected from the group consisting of -H, $-CH_3$, and $-CH_2OH$, and
R^2 is $-CH_3$; and

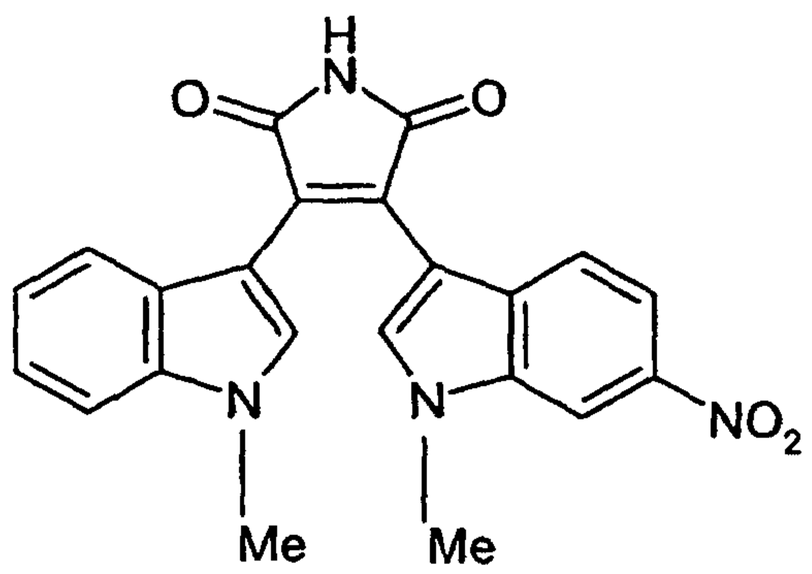
b) a component containing a vial or series of vials, each vial containing a single injectable solution dose or multiple injectable solution doses, each dose comprising as an active ingredient about 200 mg to about 1 g of gemcitabine.

31. The kit according to claim 30, comprising

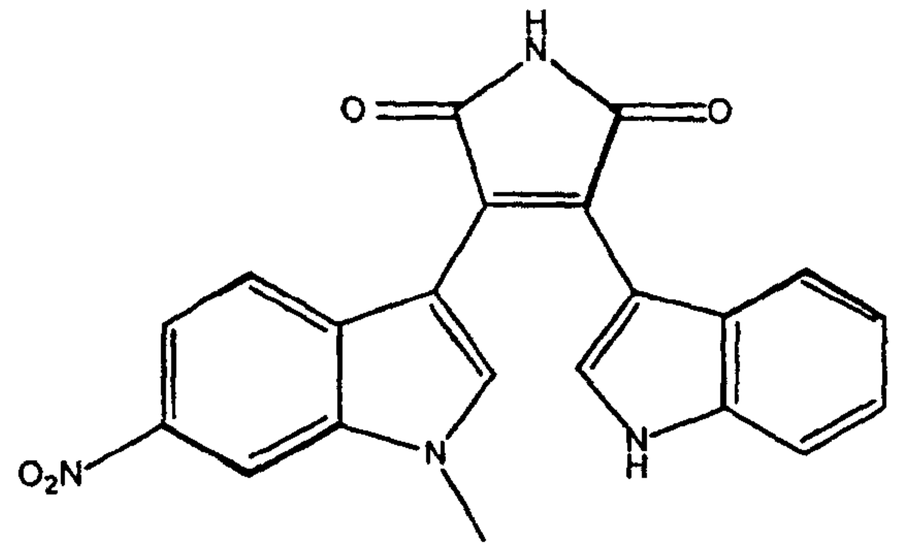
a) the component such as comprising a sufficient number of units so that a patient can administer about 600 mg per day of the compound of formula I or a pharmaceutically acceptable salt or ester of said compound for a period of about 4 to about 14 days and

b) the component such as comprsing a sufficient number of doses so that a patient can administer about 2600 mg per day of gemcitabine for a period of about three days.

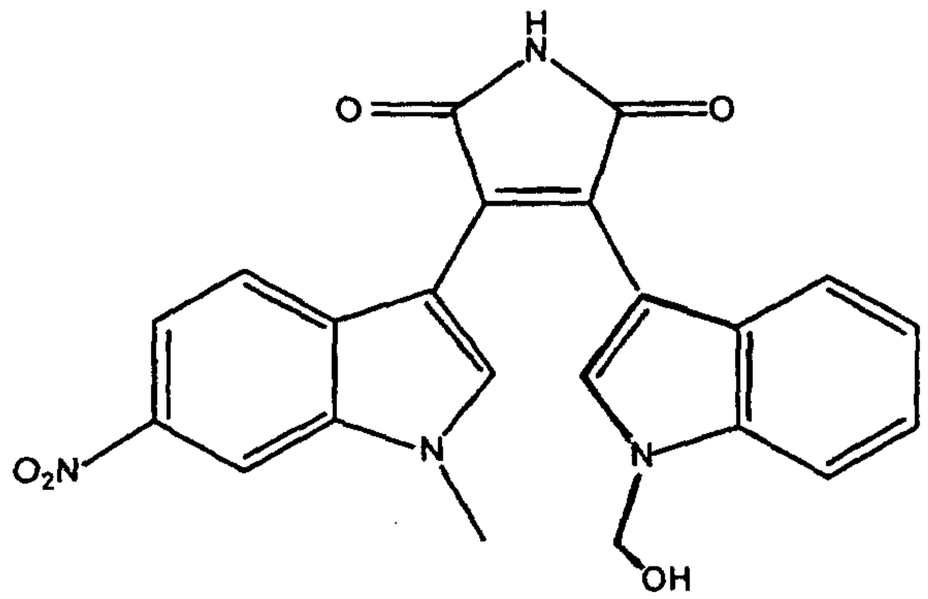
32. The kit according to claims 30 or 31 wherein the active ingredient selected from formula I is



33. The kit according to claims 30 or 31 wherein the active ingredient selected from formula I is

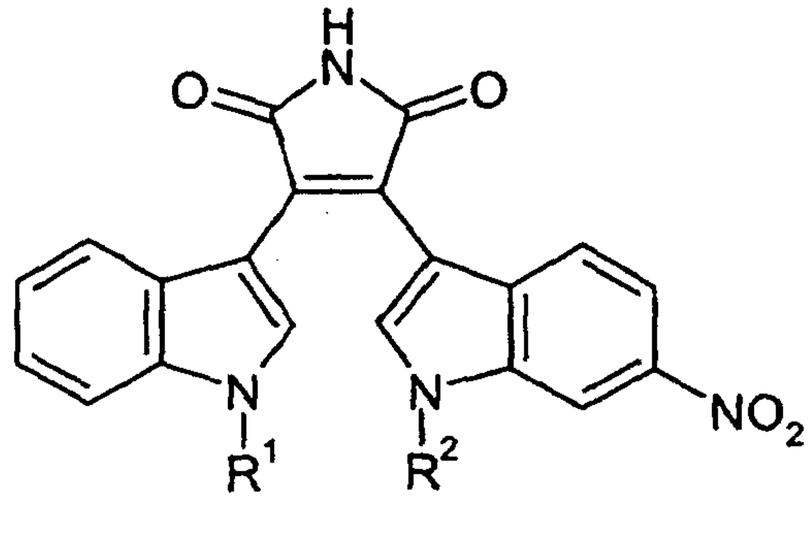


34. The kit according to claims 30 or 31, wherein the active ingredient selected from formula I is



35. Method for manufacturing a medicament for the treatment of cancer, particularly a solid cancerous tumor characterised in that a pharmaceutical combination comprising

a) a component consisting of pharmaceutical composition comprising as an active ingredient a compound of formula :



(I)

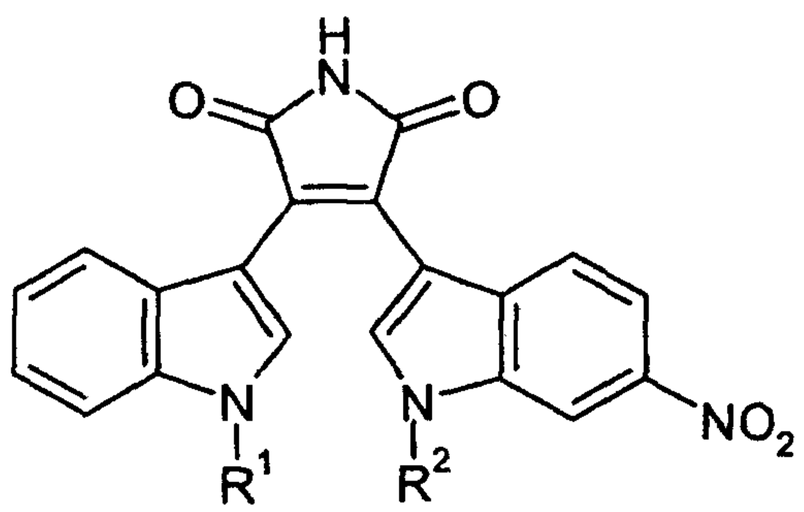
or a pharmaceutically acceptable salt or ester of said compound which is administerable over a treatment cycle of 21 to 28 days in a total amount from

about 780 mg/m^2 to about 3000 mg/m^2, wherein R^1 is selected from the group consisting of -H, -CH_3, and -CH_2OH, and R^2 is -CH_3; and

b) a component consisting of pharmaceutical composition comprising as an active ingredient gemcitabine which is administerable over the treatment cycle of 21 to 28 days in a total amount of from about 1200 mg/m^2 to about 3600 mg/m^2, is used.

36. A pharmaceutical composition comprising a pharmaceutical combination comprising

a) a component consisting of pharmaceutical composition comprising as an active ingredient a compound of formula I



(I)

or a pharmaceutically acceptable salt or ester of said compound which is administered over a cycle of 21 to 28 days in a total amount from about 780 mg/m^2 to about 3000 mg/m^2, and wherein R^1 is selected from the group consisting of -H, -CH_3, and -CH_2OH, andR^2 is -CH_3; and,

b) a component consisting of pharmaceutical composition comprising as an active ingredient gemcitabine which is administered over a cycle of 21 to 28 days in a total amount of from about 1200 mg/m^2 to about 3600 mg/m^2,

for the treatment of cancer, particularly a solid cncerous tumor.

37. The pharmaceutical composition according to claim 36 wherein the pharmaceutical combination is in combination with radiotherapy or alternatively together with another anticancer agent.

38. Novel uses, kit and method pharmaceutical as well as compositions as described herein before.