

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
22 March 2001 (22.03.2001)

PCT

(10) International Publication Number
WO 01/19399 A2

(51) International Patent Classification⁷: **A61K 45/06**,
31/335, 31/475, 31/365, 31/365, 31/40, 33/24, 38/14

(21) International Application Number: PCT/US00/25008

(22) International Filing Date:
12 September 2000 (12.09.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/396,051 15 September 1999 (15.09.1999) US

(71) Applicant: **AMERICAN HOME PRODUCTS CORPORATION** [US/US]; Five Giralda Farms, Madison, NJ 07940-0874 (US).

(72) Inventors: **GIBBONS, James, Joseph, Jr.**; 33 Terrace Drive, Westwood, NJ 07675 (US). **DUKART, Gary**; 1714 Benjamin Drive, Ambler, PA 19002 (US). **LUCAS, Judy**; 20 Azalea Drive, Nanuet, NY 10954 (US). **SPEICHER, Lisa, Anne**; 509 Covington Road, Havertown, PA 19083 (US).

(74) Agents: **MILOWSKY, Arnold, S.**; American Home Products Corporation, Patent Law Department - 2B, One Campus Drive, Parsippany, NJ 07054 et al. (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— Without international search report and to be republished upon receipt of that report.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD OF POTENTIATING CHEMOTHERAPY AND TREATING SOLID TUMORS

(57) Abstract: This invention provides a method of treating solid tumors which comprises administering an effective amount of a combination of (1) a bioresponse modifier and (2) a chemotherapeutic agent. This invention also provides a method of potentiating the effects of a chemotherapeutic regimen in a mammal in need of treatment with such regimen which comprises administering a bioresponse modifier in addition to a chemotherapeutic regimen.



WO 01/19399 A2

- 1 -

**METHOD OF POTENTIATING CHEMOTHERAPY AND
TREATING SOLID TUMORS**

5 This invention relates to the use of a combination of a bioresponse modifier and a chemotherapeutic agent in the potentiation of chemotherapy and in the treatment of solid tumors.

10 Cancer chemotherapy for solid tumors has historically been focused on cytotoxic drugs that target essential metabolic processes (anti-metabolites) or general toxins (alkylating agents) that interfere with multiple metabolic processes. Antibiotic based drugs (doxorubicin, mitoxantrone, mitomycin C, etc.) target nucleic acid replication or integrity and are, therefore, generally toxic to cells. Similarly, microtubule active (taxanes, vinca alkaloids) compounds target structurally essential components of the cell, rendering these compounds generally toxic as well.

15 The trend in recent years toward combinations of drugs with somewhat different mechanisms of action has improved the response rate and survival for some solid tumors, including breast, prostate, and small cell lung cancer. Nevertheless, most solid tumors display a poor response rate with little demonstrable effect on survival. Included in this group of cancers are non-small cell lung, head and neck, stomach, pancreatic, cervical, melanoma, adrenal cortex, and soft tissue sarcomas. For these solid tumors in particular, and for solid tumors in general, new therapies are needed.

25 U.S. Patent 5,312,831 (and EP 652228) disclose urethanes and ureas which induce cytokine production, that are useful in restoring neutrophils after cancer chemotherapy, radiation therapy, bone marrow transplantation, or infections, and are useful in the treatment of cancer, AIDS, aplastic anemia, myelodysplastic syndrome, infectious diseases, and the enhancement of the immune response.

30 U.S. Patent 4,666,890 discloses a synthetic tripeptide which has been reported to have activity as an immunomodulator, for use as an antitumor agent rather than as an adjuvant to chemotherapy. The reported cell-wall components and their synthetic analogs are all peptides incorporating a D-glutamic acid (D-Glu) moiety q-linked to

- 2 -

either lysine (Lys) or diaminopimelic acid (A2pm), with additional peptide bonds or fatty acyl groups flanking the two ends.

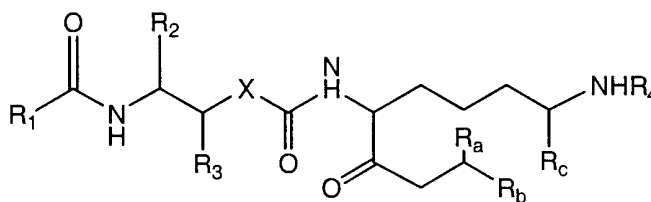
DESCRIPTION OF THE INVENTION

5 This invention provides a method of treating solid tumors which comprises administering an effective amount of a combination of (1) a bioresponse modifier and (2) a chemotherapeutic agent. This invention also provides a method of potentiating the effects of a chemotherapeutic regimen in a mammal in need of treatment with such regimen which comprises administering a bioresponse modifier in addition to a
10 chemotherapeutic regimen. As used in this invention, the term a bioresponse modifier and a chemotherapeutic agent includes the administration of one or more agents of each category; thus, for example, the term a chemotherapeutic agent can include the administration of two chemotherapeutic agents.

15 Treating is defined as providing palliative treatment, or inhibiting the growth or eradicating the solid tumor for which treatment is administered.

For the purpose of defining the scope of this invention, a bioresponse modifier is an agent which activates the body's innate immune system, and typically includes
20 cytokine inducers and immune adjuvants. Cytokine inducers are agents which induce the production of cytokines, and include cytokines such as IL-1, TNF; natural products such as muramyl dipeptide, lipopolysaccharide and beta-glucan; and synthetic cytokine inducers such as those disclosed in U.S. Patents 5,312,831, and 4,666,890, the disclosures of which are hereby incorporated by reference. Cytokine inducers are
25 the preferred bioresponse modifiers of this invention.

Particularly preferred cytokine inducers are those disclosed in U.S. Patent 5,312,831(EP 652228) of Formula I, having the structure:



30

wherein

- 3 -

- R_1 is selected from the group consisting of hydrogen, a substituted or unsubstituted (C_1 - C_{20}) alkyl group, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted cycloalkylalkyl group, a vinyl group, an acetylene group, a substituted or unsubstituted amino group, a substituted or unsubstituted acylamino group, a substituted or unsubstituted aryl group, a substituted or unsubstituted aralkyl group, a substituted or unsubstituted aryl-oxy group, a substituted or unsubstituted alkoxyaryl group, a substituted or unsubstituted alkoxyaralkyl group and a substituted or unsubstituted monocyclic or bicyclic heterocyclic group containing from 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms;
- R_2 and R_3 are independently selected from hydrogen, substituted or unsubstituted (C_1 - C_6) alkyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted alkoxyaralkyl, vinyl, acetylene and a substituted or unsubstituted monocyclic or bicyclic heterocycle containing from 1 to 4 heteroatoms selected from the group consisting of nitrogen, sulfur and oxygen atoms provided that, in the case of R_3 , the hetero atoms in said heterocycle are not directly bonded to the --CH-- group of the --CH--X-- moiety;
- R_2 , R_b and R_c are independently selected from carboxy or protected carboxy, carboxy or protected carboxyloweralkyl and carboxyamide;
- X is oxygen or nitrogen;
- R_4 is H or an amino protecting group; wherein the substituents in the aforementioned substituted alkyl, cycloalkyl, cycloalkylalkyl, amino, acylamino, aryl, aralkyl, aryloxy, alkoxyaryl, alkoxyaryalkyl and heterocyclic groups are selected from the group consisting of halogen, hydroxyl, lower alkyl, lower alkoxy, aryloxy, aralkyloxy, amino, mono- or di-loweralkylamino, arylamino, aralkylamino, carboxyl, formyl, lower alkoxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl, loweralkylthio, arylthio, aralkylthio, arylsulfinyl, arylsulfinyl, aralkylsulfinyl, lower alkylsulfonyl, arylsulfonyl, aralkylsulfonyl and a monocyclic or bicyclic heterocyclic group having 1- 4 hetero atoms selected from nitrogen, sulfur and oxygen;
- or a pharmaceutically acceptable salt thereof.

- 4 -

The definitions of the substituents and methods of preparing the compounds of Formula I are provided in US Patent 5,312,831 and EP 652228. The cytokine inducers of Formula I may contain one or more asymmetric carbon atoms; in such cases, the compounds of Formula I cover the individual diastereomers, the racemates, and the individual R and S enantiomers thereof.

Particulars of the various definitions mentioned above and specific examples falling within such definitions are provided below (taken from EP 652228B):

10

a) The (C₁-C₂₀)alkyl group may be a straight chain or branched lower alkyl group having from 1 to 20 carbon atoms such as a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, an isobutyl group, a sec-butyl group, a tert-butyl group, a pentyl group, a neopentyl group, an isopentyl group, a hexyl group, an isoheptyl group and so forth.

15

b) The cycloalkyl group may be a cycloalkyl group having from 3 to 6 carbon atoms such as a cyclopropyl group, a cyclobutyl group, a cyclopentyl group or a cyclohexyl group.

20

c) The cycloalkylalkyl group may be a cycloalkylalkyl group having from 4 to 12 carbon atoms such as a cyclopropylmethyl group, a cyclobutylmethyl group, a cyclopentylmethyl group, a cyclohexylmethyl group, 1-cyclopropylethyl group, a 2-cyclopropylethyl group, a 2-cyclobutylethyl group, a 1-cyclopentylethyl group, a 2-cyclopentylethyl group, a 1-cyclohexylethyl group, a 3-cyclohexylpropyl group, a 3-cyclopentylpropyl group, a 4-cyclohexylbutyl group, a 4-cyclopentylbutyl group, a 4-cyclopentylpentyl group or 4-pentylcyclohexyl group.

25

d) The acylamino group may be an acylamino group in which the acyl moiety is derived from an acid such as organic carboxylic acid or carbonic acid, each of which more particularly includes an aliphatic, an aromatic and/or heterocyclic group in its molecule. These include aliphatic acyl groups having an acyl group derived from an aliphatic acid and includes: alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, α-ethyl-hexanoyl, heptanoyl, lauroyl, stearoyl, docosanoyl, a group of the formula: CH₃(CH₂)₃₁CO, [CH₃(CH₂)₂₁]₂CHCO,

30

35

- 5 -

[CH₃(CH₂)₁₅]₂CHCO, CH₃(CH₂)₄₁CO, etc); lower alkoxy-carbonyl (e.g methoxy-carbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, t-butoxycarbonyl, t-pentoxycarbonyl, etc.) and the like. The acyl moiety may also be an aromatic acyl meaning an acyl group derived from an acid having a substituted or unsubstituted aryl group, in which the aryl group may include phenyl, tolyl, xylyl, naphthyl and the like, and suitable examples thereof are illustrated as follows: aroyl (e.g benzoyl, toluoyl, xyloyl, naphthoyl, phthaloyl, etc.); aralkoxycarbonyl (e.g benzyloxycarbonyl, benzhydroloxycarbonyl, trityloxycarbonyl, α -naphthyl-methoxycarbonyl, etc.) and the like. The acyl moiety may also be a heterocyclic acyl group meaning an acyl group derived from an acid having a heterocyclic group and includes: heterocyclic carbonyl, in which the heterocycle moiety is 5 to 6 membered heterocycle containing at least one to four heteroatoms selected from nitrogen, oxygen and sulfur (e.g thienoyl, furoyl, pyrrolecarbonyl, 5-oxo-2-pyrrolidinecarbonyl, nicotinoyl, etc.) and the like.

15

e) The aryl group may be an aryl group having from 6 to 15 carbon atoms such as a phenyl group, a biphenyl group, a 1-naphthyl group or a 2-naphthyl group.

20

f) The aralkyl group may be an aralkyl group having from 7-15 carbon atoms such as a benzyl group, a 1-naphthylmethyl group, a 2-naphthylmethyl group, a 5,6,7,8-tetrahydro-1-naphthyl group, a 5,6,7,8-tetrahydro-2-naphthyl group, a phenethyl group, a 3-phenylpropyl group or a 4-phenylbutyl group.

25

g) The aryloxy group may be an aryloxy group having from 6-15 carbon atoms such as a phenoxy group, a biphenyloxy group, a 1-naphthyloxy group, or a 2-naphthyloxy group.

30

h) The alkoxyaryl or alkoxyaralkyl group may be an alkoxyaryl or alkoxyaralkyl group having from 6 to 21 carbon atoms such as a benzoyl group, or an alkoxyphenylmethyl group.

35

i) The monocyclic or bicyclic heterocyclic group containing from 1 to 4 heteroatoms selected from the group consisting of nitrogen, sulfur and oxygen atoms, may be a heterocyclic group having from 4-15 carbon atoms such as a pyrrolyl group, a furyl group, a thienyl group, a pyridyl group, an imidazolyl group, a pyrazolyl group, a thiazolyl group, an isothiazolyl group, an isoxazolyl group, an oxazolyl group, a

- 6 -

pyrazinyl group, a pyrimidinyl group, a pyridazinyl group, an indolyl group, a quinolyl group, an isoquinolyl group, a phthalazinyl group, a naphthidinyl group, a quinoxalinyl group, a quinazolinyl group, a 1,4-benzodioxanyl group, a 1,3-benzodioxanyl group, a 1,2,3-triazolyl group, a 1,3,4-triazolyl group, a 1,3,4-thiadiazolyl group, a 1,2,3-thiadiazolyl group, a tetrazolyl group, a tetrahydrofuranyl group, a tetrahydrothienyl group, a pyrrolidinyl group, an imidazolidinyl group, a 2-imidazolinyl group, a morpholino group, a piperazine N-oxide group, a piperazine N-oxide group, a morpholine N-oxide group, a lower alkyl morpholino group such as an N-methylmorpholino group, an N-ethylmorpholino group or an N-propylmorpholino group, a piperazinyl group, a piperidino group, a piperidinyl group, a thiomorpholino group or a thiomorpholinyl group.

The substituents in the aforementioned groups (a)-(i) may be halogen atom such as a chlorine atom, a fluorine atom or a bromine atom, a hydroxyl group; a lower alkyl group such as a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, an isobutyl group, a sec-butyl group or a tert-butyl group; a lower alkoxy group such as a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, a butoxy group, an isobutoxy group, a sec-butoxy group or a tert-butoxy group; an aryloxy group such as a phenoxy group, as 1-naphthyloxy group or a 2-naphthyloxy group; an aralkyloxy group such as a benzyloxy group, a phenethyloxy group, a 1-naphthylmethyloxy group or a 2-naphthylmethyloxy group; an amino group; a mono- or di-lower alkylamino group such as a methylamino group, an ethylamino group, a propylamino group, an isopropylamino group, a butylamino group, a sec-butylamino group, an isobutylamino group, a tert-butylamino group, a tert-butylamino group, a dimethylamino group or a diethylamino group; an arylamino group such as a phenylamino group, a 1-naphthylamino group or a 2-naphthylamino group; an aralkylamino group such as a benzylamino group, a phenethylamino group, a 1-naphthylmethylanino group or a 2-naphthylmethylanino group; a carboxyl group; a formyl group; a lower alkoxycarbonyl group such as a methoxycarbonyl group, an ethoxycarbonyl group, an ethoxycarbonyl group, a propoxycarbonyl group, an isopropoxycarbonyl group, a butoxycarbonyl group, a sec-butoxycarbonyl group, an isobutoxycarbonyl group or a tert-butoxycarbonyl group; an aryloxy carbonyl group such as a phenoxycarbonyl group, a 1-naphthyloxy-carbonyl group or a 2-naphthyloxy-carbonyl group; an aralkyloxycarbonyl group such as a benzyloxycarbonyl group, a phenethyloxycarbonyl group, a 1-naphthylmethyloxycarbonyl group or a 2-naphthylmethyloxycarbonyl group; a mercapto group; a

- 7 -

lower alkylthio group such as a methylthio group, an ethylthio group, a propylthio group, an isopropylthio group, a butylthio group, a sec-butylthio group, an isobutylthio group or a tert-butylthio group; an arylthio group such as a phenylthio group, a 1-naphthylthio group or a 2-naphthylthio group; an aralkylthio group such as a benzylthio group, a phenethylthio group, a 1-naphthylmethylthio group or a 2-naphthylmethylthio group; an arylsulfinyl group such as a phenylsulfinyl group, a 1-naphthylsulfinyl group or a 2-naphthylmethylthio group; an arylsulfinyl group such as a phenylsulfinyl group, a 1-naphthylsulfinyl group or a 2-naphthylsulfinyl group; an aralkylsulfinyl group such as a benzylsulfinyl group, a phenethylsulfinyl group, a 1-naphthylmethylsulfinyl group or a 2-naphthylmethylsulfinyl group; a lower alkylsulfonyl group such as a mesyl group, an ethylsulfonyl group, a propylsulfonyl group, an isopropylsulfonyl group, a butylsulfonyl group, an isobutylsulfonyl group, a sec-butylsulfonyl group or a tert-butylsulfonyl group; an arylsulfonyl group such as a phenylsulfonyl group, a 1-naphthylsulfonyl group or a 2-naphthylsulfonyl group; an aralkylsulfonyl group such as a benzylsulfonyl group, a phenethylsulfonyl group, a 1-naphthylmethylsulfonyl group or a 2-naphthylmethylsulfonyl group; or a monocyclic or bicyclic heterocyclic group having 4-15 carbon atoms and 1-4 hetero atoms selected from oxygen, nitrogen and sulfur such as a pyrrolyl group, a furyl group, a thienyl group, a pyridyl group, an imidazolyl group, a pyrazolyl group, a thiazolyl group, an isothiazolyl group, an isoxazolyl group, an oxazolyl group, a pyrazinyl group, a pyrimidinyl group, a pyridazinyl group, an indolyl group, a quinolyl group, an isoquinolyl group, a phthalazinyl group, a naphthidinyl group, a quinoxalinyl group, a quinazolinyl group, a 1,4-benzodioxanyl group, a 1,3-benzodioxanyl group, a 1,2,3-triazolyl group, a 1,3,4-triazolyl group, a 1,3,4-thiadiazolyl group, a 1,2,3-thiadiazolyl group, a tetrazolyl group, a tetrahydrofuranyl group, a tetrahydrothienyl group, a pyrrolidinyl group, an imidazolidinyl group, a 2-imidazolinyl group, a morpholinyl group, a morpholino group, a morpholine N-oxide group, a lower alkyl morpholino group such as an N-methylmorpholino group, and N-ethylmorpholino group or an N-propylmorpholino group, a piperazinyl group, a piperidino group, a piperidinyl group, a thiomorpholino group or a thiomorpholinyl group.

As used herein, "lower alkyl" means a C₁-C₆ alkyl group.

A protecting group for the protected carboxy or protected carboxyloweralkyl include any conventional protecting groups for carboxy groups as routinely used by

- 8 -

those skilled in the art of peptide and amino acid chemistry such as those found in T. Green, "Protecting Groups in Organic Synthesis", J Wiley and Sons, 1981. These include silyl esters, aliphatic esters, and aromatic esters such as trimethylsilyl, t-butyldimethylsilyl, acetyl, benzoyl, and the like.

5

A protecting group for the protected amino group includes any conventional protecting group for amino groups as routinely used by those skilled in the art of peptide and amino acid chemistry such as those found in T. Green, supra pp 218-287. A suitable protecting group is chosen such that conditions for its removal are compatible with other structural features of the compound. Suitable protecting groups include acyl groups such as tert-butoxycarbonyl or benzyloxycarbonyl and the like.

10

Relative to the above generic description, compounds of Formula I which are preferred are those in which:

15

R_1 is selected from the group consisting of a substituted or unsubstituted (C_1 - C_{20}) alkyl group, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted cycloalkylalkyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted aralkyl group, a substituted or unsubstituted aryloxy group, a substituted or unsubstituted alkoxyaryl group, and a substituted or unsubstituted alkoxyaralkyl group wherein the aryl moiety in the foregoing groups is selected from substituted or unsubstituted phenyl;

20

R_a and R_b are independently selected from hydrogen, and substituted or unsubstituted (C_1 - C_6)alkyl;

25

R_2 , R_b and R_c are independently selected from carboxy or protected carboxy, carboxy or protected carboxylower alkyl and carboxamide;

X is oxygen or nitrogen; and

R_4 is H or an amino protecting group.

30

Furthermore, most preferred compounds of Formula I according to the present invention are those of Formula I in which

R_1 is selected from the group consisting of a (C_4 - C_{14})alkyl group, a cycloalkyl group, a (C_2 - C_8)alkyl substituted cycloalkyl group, a phenyl group, a benzyl group, a (C_4 - C_8)alkylphenyl group, and a (C_1 - C_6)alkyl- or alkoxy-phenylmethyl group;

35

R_a and R_b are independently selected from hydrogen and (C_1 - C_6)alkyl;

- 9 -

R_2 , R_b and R_c are independently selected from carboxy or protected carboxy, carboxy or protected carboxyloweralkyl and carboxyamide;
 X is oxygen or nitrogen; and
 R_4 is H or an amino protecting group.

5

Compounds of the Formula I which are most particularly preferred are those in which:

R_1 is selected from the group consisting of an n-hexyl group, a 4-n-pentylcyclohexyl group;

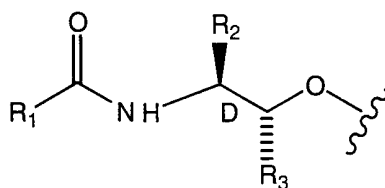
R_1 and R_3 are independently selected from hydrogen or methyl;

10 R_2 , R_b and R_c are carboxy;

X is oxygen or nitrogen; and

R_4 is H.

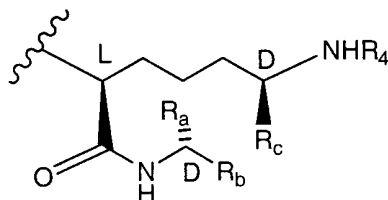
Particularly preferred are those compounds of Formula I have the D-allo-
 15 threonine configuration as follows:



wherein R_3 is methyl, and R_1 and R_2 are hereinbefore defined.

20

Also particularly preferred are those compounds having the following stereochemistry in the diaminopimelyl-alanine portion of the molecule:

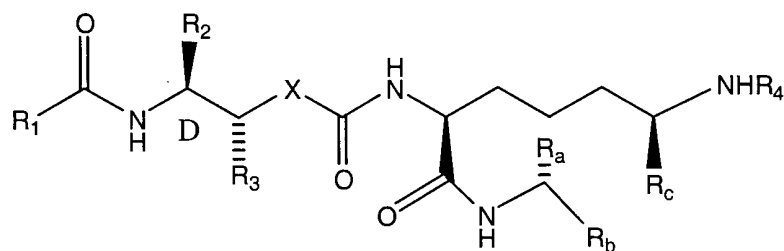


wherein R_1 is methyl, and R_b , R_c and R_4 are as hereinbefore defined.

25

With respect to stereochemistry, the following compounds of Formula I are most particularly preferred:

- 10 -



wherein R_3 and R_1 are methyl, X is oxygen, R_b , R_c , R_1 , R_2 , R_4 are hereinbefore defined.

5 It is particularly preferred that the cytokine inducer is [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy]carbonyl]-L-lysyl]-alanine or a pharmaceutically acceptable salt thereof (a compound of Formula I), which is disclosed as Example 28 of U.S. Patent 5,312,831.

10 U.S. Patent 5,312,831 discloses several standard pharmacologic test procedures which will enable one skilled in the art to evaluate whether compounds are bioresponse modifiers. For example, the test procedures in col. 16-17, evaluate the induction of IL-6, CSF, and G-CSF production.

15 It is preferred that the chemotherapeutic agent is a microtubular agent or a macrophage activating agent. Microtubular active compounds are defined as compounds that destabilize microtubules either by preventing polymerization of the protein tubulin (e.g., vincristine) or by preventing the depolymerization of tubulin (e.g., taxanes). The assembly and disassembly of microtubules is a dynamic process
 20 influenced by tubulin binding proteins and protein phosphorylation (kinases). Microtubular active compounds include taxanes, such as paclitaxel or docetaxel, vincristine, vinblastine, vinorelbine, and the like. Macrophage activating agents are those compounds which activate macrophage activity, such as adriamycin, doxorubicin, and similar anthracenediones and anthracyclines, cisplatin, carboplatin,
 25 mitomycin C, bleomycin, and the like. It is preferred that the chemotherapeutic agent is paclitaxel or carboplatin, or a combination of both. The microtubular agents or macrophage activating agents of this invention are either commercially available or can be prepared by standard procedures in the published literature.

- 11 -

The potentiating effect of bioresponse modifiers on chemotherapeutic agents was evaluated in an in vivo standard pharmacological test procedure in which a human non small cell type lung cancer (NSCLC) cell line was engrafted onto the flanks of immunodeficient nude mice. The following briefly describes the test procedure used and results obtained. [R-(R*,R*)]-N-[(R)-6-Carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy]carbonyl]-L-lysyl]-alanine was used as a representative bioresponse modifier and paclitaxel was used a representative chemotherapeutic agent.

Balb-c nu/nu female mice were obtained from Charles River Laboratories at 6-8 weeks of age and used experimentally at 8-10 weeks of age. The human non small-cell lung carcinoma (NSCLC) line H-157 was obtained from the American tissue culture collection (ATCC) (Bethesda, MD). Cells were grown in RPMI medium with 10% fetal bovine serum.

Mice were injected subcutaneously with 7.5×10^6 H-157 NSCLC tumor cells. Tumors were allowed to develop until they reached a size of 80-150 mg. Tumor size was determined using vernier calipers to measure length (l) and width (w). The tumor volume was estimated using the formula $l \times w^2/2$. The volume in mm³ can be converted to milligrams directly assuming unit density. Seven days after injection, mice were randomized (day 0) into groups of 10 with a mean tumor mass of 100 mg. Treatment groups received paclitaxel (30 mg/kg) on day 0 and either vehicle or [R-(R*,R*)]-N-[(R)-6-Carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy]carbonyl]-L-lysyl]-alanine (100 µg/kg) on days 1 and 8.

On days 7 and 14, tumor growth in groups receiving paclitaxel plus [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy]carbonyl]-L-lysyl]-alanine was significantly inhibited versus untreated controls or groups receiving paclitaxel only. Paclitaxel alone inhibited tumor cell growth measured on day 7 ($p \leq 0.05$ by student's t test) and the degree of suppression was significantly enhanced by treatment with [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy]carbonyl]-L-lysyl]-alanine one day after paclitaxel administration. By day 14, tumor growth in the paclitaxel only group was not significantly suppressed versus control; however, the group receiving paclitaxel on day 0 and [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-

- 12 -

[(1-oxoheptyl)amino]ethoxy carbonyl]-L-lysyl]-alanine on days 1, 8 was still significantly suppressed when compared either to untreated controls or the paclitaxel only group. The results obtained are shown below in Table 1. In the below table, [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy] carbonyl]-L-lysyl]-alanine is referred to as CI.

TABLE 1. The Effect of CI on Paclitaxel Mediated Inhibition of Tumor Cell Growth in Nude Mice Xenografts

Treatment Group	^a Tumor size (mg) Day 7	% Suppression	Tumor size (mg) Day 14	% Suppression
untreated control	410 ± 99	-	1234 ± 354	-
Paclitaxcel	^c 289 ± 108	30	866 ± 348	30
Paclitaxel + CI	^b 182 ± 69	56	^b 491 ± 151	60

^a data are from 5 independent evaluations (mean ± standard deviation) in which there were 10 mice/group in each evaluation. Treatment groups received paclitaxel (30 mg/kg) on day 0 and either vehicle or CI (100 µg/kg) on day 1 and day 8.

^b P ≤ 0.05 versus the untreated group or the paclitaxel only group (Student's t test).

^c P ≤ 0.05 versus the untreated control.

15

Several evaluations were performed in which tumor bearing mice received only [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy] carbonyl]-L-lysyl]-alanine (100 µg/kg) on days 1 and 8 after staging (data not shown). In none of these evaluations did [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy] carbonyl]-L-lysyl]-alanine by itself inhibit tumor cell growth in nude mice. [R-(R*,R*)]-N-[(R)-6-Carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy] carbonyl]-L-lysyl]-alanine does not directly inhibit tumor cell growth *in vitro* nor does it potentiate the growth inhibitory effect of paclitaxel in cell culture.

25

The effects of a bioresponse modifier and a chemotherapeutic agent were also evaluated in a clinical study. [R-(R*,R*)]-N-[(R)-6-Carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy]carbonyl]-L-lysyl]-alanine was used as a representative bioresponse modifier, and paclitaxel and carboplatin were used as representative chemotherapeutic agents. In this study, cancer patients with late stage

30

- 13 -

disease were given a dose of [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy]carbonyl]-L-lysyl]-alanine (cycle 0) approximately 7 days before the first round of chemotherapy (carboplatin and paclitaxcel). Patients received a second round of chemotherapy approximately 21 days later and on days 1 and 8 after this 2nd chemotherapy treatment patients received [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy] carbonyl]-L-lysyl]-alanine at the doses indicated in table below. Sixty-nine percent of patients showed some clinical benefit either in the form of complete or partial reduction in tumor mass or stabilization of disease. Of the 16 patients treated, 6 had a presumed diagnosis of NSCLC. In this group, there were 3 complete responses, 1 partial response, one stabilization of disease and only 1 patient with progressive disease. Inasmuch as the expected complete response rate with the standard chemotherapy regimen (paclitaxel and carboplatin) is approximately 5%, the finding that 3 of 6 treated patients showed a complete response was completely unexpected. In this treatment regimen, the dose of paclitaxel was 175-200 mg/m² and the dose of carboplatin was the dose at which the area under the curve (AUC) equals 6 mg/ml x min. The results from the clinical trial are summarized in the table below. In the Table below, [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy] carbonyl]-L-lysyl]-alanine is referred to as CI.

TABLE 2. Treatment of Advanced Cancer Patients with a Combination of Paclitaxcel, Carboplatin and CI.

			*Tumor Response			
	# Patients treated	Dose (μg/kg) ^b	Complete	Partial	Stable	Progressive
	3	0.1	2	1		
	6	0.2		1	2	3
	4	0.266	1	1	1	1
	3	0.4	1		1	1
Total	16		4	3	4	5

^a Complete - no evidence of disease

Partial - ≥ 50% decrease in tumor mass

Stable - no further progression of disease

Progressive - disease progressed

^bDose of CI.

The results of the in vivo standard pharmacological test procedure and clinical trial using representative bioresponse modifiers and chemotherapeutic agents demonstrate that the combination of a bioresponse modifier with a chemotherapeutic agent is useful in potentiating standard chemotherapeutic regimens and is useful in
5 treating solid tumors. In particular, the combination of this invention is useful in treating non-small cell lung carcinoma, glioma, cancers of the ovary, breast, prostate, head and neck, kidney, pancreas, liver, and colon, and soft tissue sarcoma.

As used in this invention, the combination regimen can be given
10 simultaneously or can be given in a staggered regimen, with the bioresponse modifier being given at a different time during the course of chemotherapy. Therefore, the term combination does not necessarily mean administered at the same time or as a unitary dose. For example, the regimen in the clinical study typifies a therapeutically useful regimen, in which patients received a bioresponse modifier before receiving
15 the first course of chemotherapy. As typical for chemotherapeutic regimens, the course of chemotherapy is repeated several weeks later, and in this case, the bioresponse modifier was administered one or more days after the administration of the second course of chemotherapy. This course of staggered administration can be continued throughout the treatment period.

20

The components of the combination can be formulated into a unitary dosage form, for simultaneous administration, however, it is anticipated that the components of the combinations will be formulated for separate administration.

Formulations for specific chemotherapeutic agents are well known in the art
25 (and most used will typically be commercially available or already formulated for use in clinical trials), with such agents typically administered intravenously or orally; however, as each agent and patient varies, the chemotherapeutic agents may also be administered by parenteral injection, rectally, vaginally, transdermally, subcutaneously, topically, intranasally, or by direct infusion to the site of the lesion.

30 The bioresponse modifiers of this invention may also be administered orally, intravenously, parenterally, rectally, vaginally, transdermally, subcutaneously, topically, intranasally, or by direct infusion to the site of the lesion. The bioresponse modifiers can be formulated according to standard literature methodology. For

- 15 -

example, formulations for the compounds of Formula I and [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy] carbonyl]-L-lysyl]-alanine are provided in U.S. Patent 5,312,831.

Bioresponse modifiers and chemotherapeutic agents which are not
5 commercially available or available in clinical trials (or in which it is undesirable to use such existing formulations) may be formulated neat or may be combined with one or more pharmaceutically acceptable carriers for administration. For example, solvents, diluents and the like, and may be administered orally in such forms as tablets, capsules, dispersible powders, granules, or suspensions containing, for
10 example, from about 0.05 to 5% of suspending agent, syrups containing, for example, from about 10 to 50% of sugar, and elixirs containing, for example, from about 20 to 50% ethanol, and the like, or parenterally in the form of sterile injectable solution or suspension containing from about 0.05 to 5% suspending agent in an isotonic medium. Such pharmaceutical preparations may contain, for example, from about
15 0.05 up to about 90% of the active ingredient in combination with the carrier, more usually between about 5% and 60% by weight.

Formulation for tablet or capsule administration may include solid carriers including starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include sterile water, polyethylene glycols, non-ionic
20 surfactants and edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvants customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as flavoring agents, coloring agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

25 These components of the combination may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary
30 conditions of storage and use, these preparation contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of

- 16 -

sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

It is anticipated that the dosage of chemotherapeutic agents and bioresponsive modifiers will be adjusted during the course of treatment, according to patient response to treatment and toxicity inherent in standard chemotherapeutic regimens. For example, the dosage of chemotherapeutic agents is typically lowered upon observation of myelosuppression or impaired hepatic function. As a starting dosage, it is anticipated that the initial dosages of chemotherapeutic agents will be the dosages which would be used absent combination with a bioresponse modifier. For example, for a regimen consisting of paclitaxel, carboplatin and [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy] carbonyl]-L-lysyl]-alanine, it is anticipated that the dosage of paclitaxel would be 135-225 mg/m², with 175-200 mg/m² being preferred, and the dose of carboplatin would be the dose at which the area under the curve (AUC) equals 5-7 mg/ml x min, with 6 mg/ml x min being preferred. Projected dosages of the bioresponse modifiers will vary according to their potency in inducing the immune system; for cytokine inducers, their potency in inducing the production of cytokines. For [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy]carbonyl]-L-lysyl]-alanine it is anticipated that the initial dosage will range from 0.005 - 2 µg/kg, with 0.01 - 1 µg/kg being preferred.

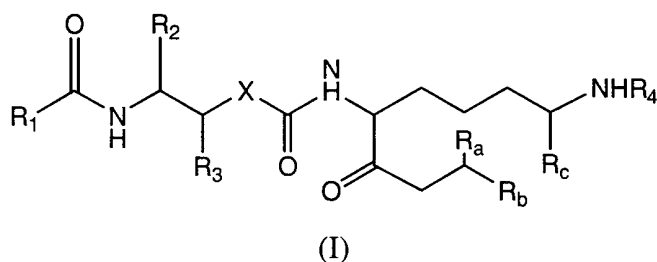
CLAIMS

1. A method of treating solid tumor in a mammal which comprises administering to said mammal an effective amount of a combination of a bioresponse
5 modifier and a chemotherapeutic agent.

2. Use of a bioresponse modifier and a chemotherapeutic agent in the preparation of a medicament for the treatment of solid tumour in a mammal.

10 3. A method or use according to Claim 1 or Claim 2 wherein the bioresponse modifier is a cytokine inducer.

4. A method or use according to Claim 3 wherein the cytokine inducer is a compound of formula I, having the structure
15



wherein

R₁ is selected from the group consisting of hydrogen, a substituted or unsubstituted
20 (C₁-C₂₀) alkyl group, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted cycloalkylalkyl group, a vinyl group, an acetylene group, a substituted or unsubstituted amino group, a substituted or unsubstituted acylamino group, a substituted or unsubstituted aryl group, a substituted or unsubstituted aralkyl group, a substituted or unsubstituted
25 aryloxy group, a substituted or unsubstituted alkoxyaryl group, a substituted or unsubstituted alkoxyaralkyl group and a substituted or unsubstituted monocyclic or bicyclic heterocyclic group containing from 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms;

R_a and R₃ are independently selected from hydrogen, substituted or unsubstituted
30 (C₁-C₆) alkyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl,

- 18 -

substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted alkoxyaralkyl, vinyl, acetylene and a substituted or unsubstituted monocyclic or bicyclic heterocycle containing from 1 to 4 heteroatoms selected from the group consisting of nitrogen, sulfur and oxygen atoms provided that, in the case of R₃, the hetero atoms in said heterocycle are not directly bonded to the --CH-- group of the --CH--X-- moiety;

R₂, R_b and R_c are independently selected from carboxy or protected carboxy, carboxy or protected carboxyloweralkyl and carboxamide;

X is oxygen or nitrogen;

R₄ is H or an amino protecting group; wherein the substituents in the aforementioned substituted alkyl, cycloalkyl, cycloalkylalkyl, amino, acylamino, aryl, aralkyl, aryloxy, alkoxyaryl, alkoxyaryalkyl and heterocyclic groups are selected from the group consisting of halogen, hydroxyl, lower alkyl, lower alkoxy, aryloxy, aralkyloxy, amino, mono- or di-loweralkylamino, arylamino, aralkylamino, carboxyl, formyl, lower alkoxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl, loweralkylthio, arylthio, aralkylthio, arylsulfinyl, aralkylsulfinyl, lower alkylsulfonyl, arylsulfonyl, aralkylsulfonyl and a monocyclic or bicyclic heterocyclic group having 1- 4 hetero atoms selected from nitrogen, sulfur and oxygen;

or a pharmaceutically acceptable salt thereof.

5. A method or use according to Claim 4, in which the compound of formula I is [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy]carbonyl]-L-lysyl]-alanine or a pharmaceutically acceptable salt thereof.

6. A method or use according to any one of Claims 1 to 5 wherein the chemotherapeutic agent is a microtubular agent or a macrophage activating agent.

7. A method or use according to Claim 6 wherein the microtubular agent or macrophage activating agent is selected from paclitaxel, docetaxel, vincristine, vinblastine, vinorelbine, adriamycin, doxorubicin, cisplatin, carboplatin, mitomycin C, and bleomycin.

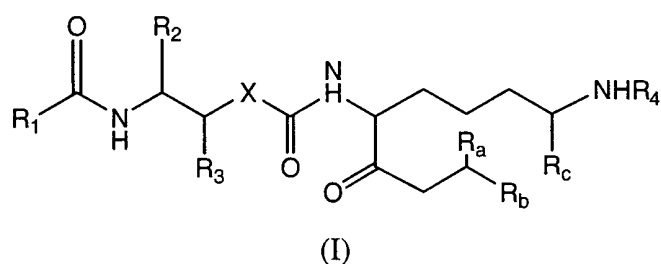
- 19 -

8. A method or use according to Claim 7 wherein the microtubular agent or macrophage activating agents are paclitaxel and carboplatin.

9. A method of potentiating the effects of a chemotherapeutic regimen in a mammal in need of treatment with such regimen which comprises administering a bioresponse modifier in addition to a chemotherapeutic regimen.

10. The method according to Claim 9 wherein the bioresponse modifier is a cytokine inducer.

11. The method according to Claim 10 wherein the cytokine inducer is a compound of formula I, having the structure



wherein

R₁ is selected from the group consisting of hydrogen, a substituted or unsubstituted (C₁-C₂₀) alkyl group, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted cycloalkylalkyl group, a vinyl group, an acetylene group, a substituted or unsubstituted amino group, a substituted or unsubstituted acylamino group, a substituted or unsubstituted aryl group, a substituted or unsubstituted aralkyl group, a substituted or unsubstituted aryloxy group, a substituted or unsubstituted alkoxyaryl group, a substituted or unsubstituted alkoxyaralkyl group and a substituted or unsubstituted monocyclic or bicyclic heterocyclic group containing from 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms;

R_a and R₃ are independently selected from hydrogen, substituted or unsubstituted (C₁-C₆) alkyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted alkoxyaralkyl, vinyl, acetylene and a substituted or unsubstituted

- 20 -

monocyclic or bicyclic heterocycle containing from 1 to 4 heteroatoms selected from the group consisting of nitrogen, sulfur and oxygen atoms provided that, in the case of R₃, the hetero atoms in said heterocycle are not directly bonded to the --CH-- group of the --CH--X-- moiety;

- 5 R₂, R_b and R_c are independently selected from carboxy or protected carboxy, carboxy or protected carboxyloweralkyl and carboxyamide;

X is oxygen or nitrogen;

- R₄ is H or an amino protecting group; wherein the substituents in the aforementioned substituted alkyl, cycloalkyl, cycloalkylalkyl, amino, acylamino, aryl, aralkyl, 10 aryloxy, alkoxyaryl, alkoxyaryalkyl and heterocyclic groups are selected from the group consisting of halogen, hydroxyl, lower alkyl, lower alkoxy, aryloxy, aralkyloxy, amino, mono- or di-loweralkylamino, arylamino, aralkylamino, carboxyl, formyl, lower alkoxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl, loweralkylthio, arylthio, aralkylthio, arylsulfinyl, arylsulfinyl, aralkylsulfinyl, 15 lower alkylsulfonyl, arylsulfonyl, aralkylsulfonyl and a monocyclic or bicyclic heterocyclic group having 1- 4 hetero atoms selected from nitrogen, sulfur and oxygen;

or a pharmaceutically acceptable salt thereof.

- 20 12. The method according to Claim 11, in which the compound of formula I is [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxo-heptyl)amino]ethoxy]carbonyl]-L-lysyl]-alanine or a pharmaceutically acceptable salt thereof.

- 25 13. The method according to any one of Claims 9 to 12 wherein the chemotherapeutic agent is a microtubular agent or a macrophage activating agent.

14. The method according to Claim 13 wherein the microtubular agent or macrophage activating agent is selected from the group consisting of paclitaxcel, 30 docetaxel, vincristine, vinblastine, vinorelbine, adriamycin, doxorubicin, cisplatin, carboplatin, mitomycin C, and bleomycin.

- 21 -

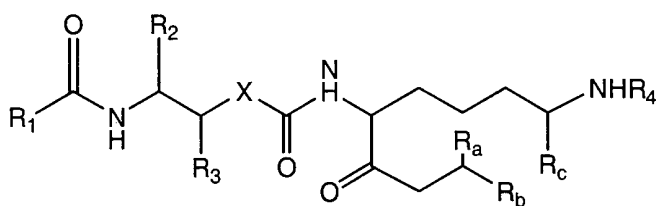
15. The method according to Claim 14 wherein the microtubular agent or macrophage activating agents are paclitaxel and carboplatin.

16. A product containing a bioresponse modifier and a chemotherapeutic agent as a combined preparation for simultaneous, separate or sequential use in the treatment of solid tumors.

17. A product according to claim 16 wherein the bioresponse modifier is a cytokine inducer.

10

18. A product according to claim 17 wherein the cytokine inducer is a compound of formula I, having the structure



15

(I)

wherein

R_1 is selected from the group consisting of hydrogen, a substituted or unsubstituted (C_1 - C_{20}) alkyl group, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted cycloalkylalkyl group, a vinyl group, an acetylene group, a substituted or unsubstituted amino group, a substituted or unsubstituted acylamino group, a substituted or unsubstituted aryl group, a substituted or unsubstituted aralkyl group, a substituted or unsubstituted aryloxy group, a substituted or unsubstituted alkoxyaryl group, a substituted or unsubstituted alkoxyaralkyl group and a substituted or unsubstituted monocyclic or bicyclic heterocyclic group containing from 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms;

R_a and R_b are independently selected from hydrogen, substituted or unsubstituted (C_1 - C_6) alkyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl,

30

- 22 -

substituted or unsubstituted alkoxyaralkyl, vinyl, acetylene and a substituted or unsubstituted monocyclic or bicyclic heterocycle containing from 1 to 4 heteroatoms selected from the group consisting of nitrogen, sulfur and oxygen atoms provided that, in the case of R₃, the hetero atoms in said heterocycle are not directly bonded to the --CH-- group of the --CH--X-- moiety;

R₂, R_b and R_c are independently selected from carboxy or protected carboxy, carboxy or protected carboxyloweralkyl and carboxyamide;

X is oxygen or nitrogen;

R₄ is H or an amino protecting group; wherein the substituents in the aforementioned substituted alkyl, cycloalkyl, cycloalkylalkyl, amino, acylamino, aryl, aralkyl, aryloxy, alkoxyaryl, alkoxyaryalkyl and heterocyclic groups are selected from the group consisting of halogen, hydroxyl, lower alkyl, lower alkoxy, aryloxy, aralkyloxy, amino, mono- or di-loweralkylamino, arylamino, aralkylamino, carboxyl, formyl, lower alkoxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl, loweralkylthio, arylthio, aralkylthio, arylsulfinyl, arylsulfinyl, aralkylsulfinyl, lower alkylsulfonyl, arylsulfonyl, aralkylsulfonyl and a monocyclic or bicyclic heterocyclic group having 1- 4 hetero atoms selected from nitrogen, sulfur and oxygen;

or a pharmaceutically acceptable salt thereof.

19. A product according to Claim 18, in which the compound of formula I is [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]-ethoxy]carbonyl]-L-lysyl]-alanine or a pharmaceutically acceptable salt thereof.

20. A product according to any one of Claims 16 to 19 wherein the chemotherapeutic agent is a microtubular agent or a macrophage activating agent.

21. A product according to Claim 20 wherein the microtubular agent or macrophage activating agent is selected from paclitaxel, docetaxel, vincristine, vinblastine, vinorelbine, adriamycin, doxorubicin, cisplatin, carboplatin, mitomycin C, and bleomycin.

22. A product according to Claim 20 wherein the microtubular agent or macrophage activating agents are paclitaxel and carboplatin.