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PARENTERAL FORMULATIONS CONTAINING EPOTHILONE ANALOGS

Cross-Reference To Related Application

This application claims priority from provisional application serial number 60/264,228, filed January 25, 2001, incorporated herein by reference in its entirety.

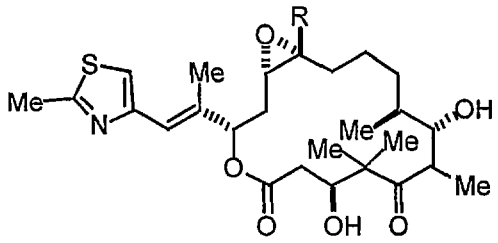
Field of the Invention

The present invention relates to an improved formulation for parenteral administration of certain epothilone analogs that are characterized by enhanced clinical efficacy.

Background of the Invention

Epothilones are macrolide compounds having utility in the pharmaceutical field. For example, Epothilones A and B having the structures:

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Epothilone A R=H

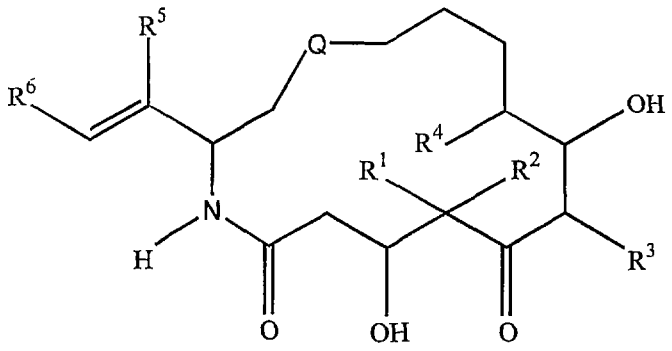
Epothilone B R=Me

may be found to exert microtubule-stabilizing effects similar to paclitaxel (TAXOL®) and hence cytotoxic activity against rapidly proliferating cells, such as, tumor cells or other hyperproliferative cellular disease, see Hofle *et al.*, Angew. Chem. Int. Ed. Engl., Vol. 35, No.13/14, 1567-1569 (1996); WO 93/10121 published May 27, 1993; and WO 97/19086 published May 29, 1997.

Derivatives and analogs of Epothilones A and B have been synthesized and may be used to treat a variety of cancers and other abnormal proliferative diseases.

Such analogs are disclosed in Hofle *et al.*, *Id.*; Nicolaou *et al.*, Angew Chem. Int. Ed. Engl., Vol. 36, No. 19, 2097-2103 (1997); and Su *et al.*, Angew Chem. Int. Ed. Engl., Vol. 36, No. 19, 2093-2097 (1997).

Analogs of the epothilones that have been found to have advantageous activity are represented by formula I:

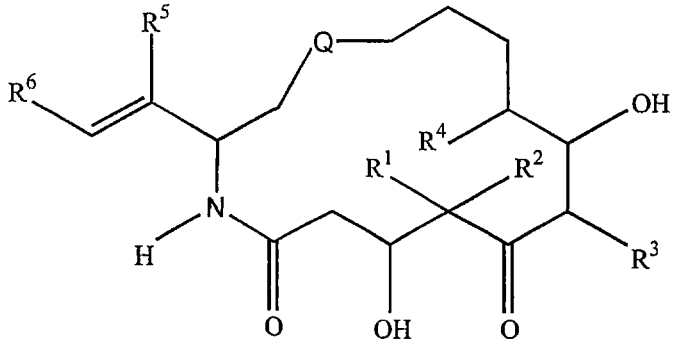


I

wherein the various symbols are as defined below. While these compounds possess significant therapeutic properties, they also present difficulties to those skilled in the art of pharmaceutical compounding, as a result of certain properties, as will be detailed hereinbelow. In accordance with the present invention, a formulation has been found whereby the epothilone analogs described above can be safely dispensed and administered via injection, without appreciable loss of potency.

Summary of the Invention

The present invention describes a formulation and the preparation thereof for epothilone analogs represented by formula I.

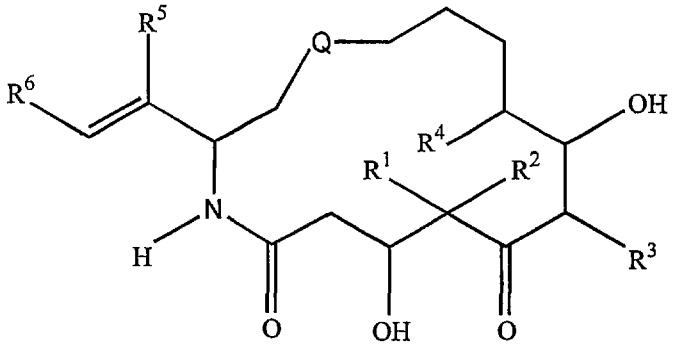


I

wherein the various symbols are as defined below. In the formulations of the present invention, the epothilone analog is initially solubilized with a mixture of tertiary-butanol and water and then lyophilized under optimized conditions. The lyophilized drug is reconstituted first with a mixture of a polyethoxylated castor oil surfactant and anhydrous ethanol, and thereafter diluted with Lactated Ringer's Injection to a concentration appropriate for administration.

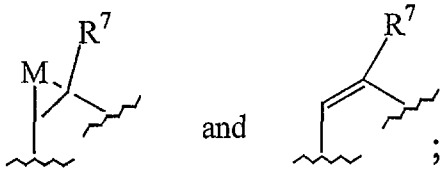
Detailed Description of the Invention

The process of the present invention provides an advantageous formulation for the administration of epothilone analogs represented by formula I:



I

As used in formula I and throughout the specification, Q is selected from the group consisting of :



;

M is selected from the group consisting of oxygen, sulfur, NR^8, and CR^9R^{10};

each R^1, R^2, R^3, R^4, R^5, R^7, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} is, independently, selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl and heterocyclo, and wherein R^1 and R^2 are alkyl, they can be joined to form cycloalkyl;

R^6 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, heterocyclo and substituted heterocyclo;

R^8 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, $R^{11}C=O$, $R^{12}OC=O$ and $R^{13}SO_2$; and

each R^9 and R^{10} is, independently, selected from the group consisting of hydrogen, halogen, alkyl, substituted alkyl, aryl, heterocyclo, hydroxy, $R^{14}C=O$, and $R^{15}OC=O$.

The following are definitions of various terms used herein to describe the present invention. These definitions apply to the terms as they are used throughout this specification, unless otherwise limited in specific instances, either individually or as part of a larger group.

The term "alkyl" refers to optionally substituted straight- or branched-chain saturated hydrocarbon groups having from 1 to about 20 carbon atoms, preferably from 1 to about 7 carbon atoms. The expression "lower alkyl" refers to optionally substituted alkyl groups having from 1 to about 4 carbon atoms.

The term "substituted alkyl" refers to an alkyl group substituted by, for example, one to four substituents, such as, halo, trifluoromethyl, trifluoromethoxy, hydroxy, alkoxy, cycloalkyoxy, heterocylooxy, oxo, alkanoyl, aryl, aryloxy, aralkyl, alkanoyloxy, amino, alkylamino, arylamino, aralkylamino, cycloalkylamino, heterocycloamino, disubstituted amino in which the two substituents on the amino group are selected from alkyl, aryl, aralkyl, alkanoylamino, aroylamino, aralkanoylamino, substituted alkanoylamino, substituted arylamino, substituted

aralkanoylamino, thiol, alkylthio, arylthio, aralkylthio, cycloalkylthio, heterocyclothio, alkylthiono, arylthiono, aralkylthiono, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, sulfonamido (*e.g.*, SO_2NH_2), substituted sulfonamido, nitro, cyano, carboxy, carbamyl (*e.g.*, $CONH_2$), substituted carbamyl (*e.g.*, CONH alkyl, CONH aryl, CONH aralkyl or instances where there are two substituents on the nitrogen selected from alkyl, aryl or aralkyl), alkoxycarbonyl, aryl, substituted aryl, guanidino and heterocyclos, such as, indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like. Wherein, as noted above, the substituents themselves are further substituted, such further substituents are selected from the group consisting of halogen, alkyl, alkoxy, aryl and aralkyl. The definitions given herein for alkyl and substituted alkyl apply as well to the alkyl portion of alkoxy groups.

The term "halogen" or "halo" refers to fluorine, chlorine, bromine and iodine.

The term "ring system" refers to an optionally substituted ring system containing one to three rings and at least one carbon to carbon double bond in at least one ring. Exemplary ring systems include, but are not limited to, an aryl or a partially or fully unsaturated heterocyclic ring system, which may be optionally substituted.

The term "aryl" refers to monocyclic or bicyclic aromatic hydrocarbon groups having from about 6 to about 12 carbon atoms in the ring portion, for example, phenyl, naphthyl, biphenyl and diphenyl groups, each of which may be substituted.

The term "aralkyl" refers to an aryl group bonded to a larger entity through an alkyl group, for example, a benzyl group.

The term "substituted aryl" refers to an aryl group substituted by, for example, one to four substituents such as alkyl; substituted alkyl, halo, trifluoromethyl, trifluoromethoxy, hydroxy, alkoxy, cycloalkyloxy, heterocyclooxy, alkanoyl, alkanoyloxy, amino, alkylamino, dialkylamino, aralkylamino, cycloalkylamino, heterocycloamino, alkanoylamino, thiol, alkylthio, cycloalkylthio, heterocyclothio, ureido, nitro, cyano, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, alkylthiono, arylthiono, alkysulfonyl, sulfonamido, aryloxy and the like. The substituent may be further substituted by one or more members selected from the group consisting of halo, hydroxy, alkyl, alkoxy, aryl, substituted alkyl, substituted aryl and aralkyl.

The term "cycloalkyl" refers to optionally substituted saturated cyclic hydrocarbon ring systems, preferably containing 1 to 3 rings and 3 to 7 carbons per

ring, which may be further fused with an unsaturated C_3-C_7 carbocyclic ring. Exemplary groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl, cyclododecyl, and adamantyl. Exemplary substituents include one or more alkyl groups as described above, or one or more of the groups described above as substituents for alkyl groups.

The terms "heterocycle", "heterocyclic" and "heterocyclo" refer to an optionally substituted, unsaturated, partially saturated, or fully saturated, aromatic or nonaromatic cyclic group, for example, which is a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic ring system, which has at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2 or 3 heteroatoms selected from nitrogen atoms, oxygen atoms and sulfur atoms, where the nitrogen and sulfur heteroatoms may also optionally be oxidized and the nitrogen heteroatoms may also optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom.

Exemplary monocyclic heterocyclic groups include pyrrolidinyl, pyrrolyl, indolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxazepinyl, azepinyl, 4-piperidonyl, pyridyl, N-oxo-pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothiopyranyl sulfone, morpholinyl, thiomorpholinyl, thiomorpholinyl sulfoxide, thiomorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1, 1-dioxothienyl, dioxanyl, isothiazolidinyl, thietanyl, thiiranyl, triazinyl, and triazolyl, and the like.

Exemplary bicyclic heterocyclic groups include benzothiazolyl, benzoxazolyl, benzothienyl, quinuclidinyl, quinolinyl, quinolinyl-N-oxide, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, chromonyl, coumarinyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,1-b]pyridinyl] or furo[2,3-b]pyridinyl), dihydroisoindolyl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl), benzisothiazolyl, benzisoxazolyl, benzodiazinyl, benzofurazanyl, benzothiopyranyl, benzotriazolyl,

benzpyrazolyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, dihydrobenzopyranyl, indolinyl, isochromanyl, isoindolinyl, naphthyridinyl, phthalazinyl, piperonyl, purinyl, pyridopyridyl, quinazolinyl, tetrahydroquinolinyl, thienofuryl, thienopyridyl, thienothienyl, and the like.

Exemplary substituents for the terms "ring system," "heterocycle," "heterocyclic," and "heterocyclo" include one or more substituent groups as described above for substituted alkyl or substituted aryl, and smaller heterocyclos, such as, epoxides, aziridines and the like.

The term "alkanoyl" refers to -C(O)-alkyl.

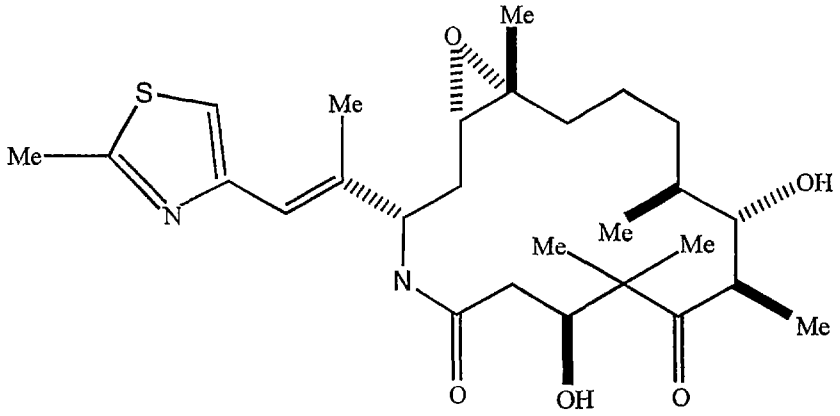
The term "substituted alkanoyl" refers to -C(O)-substituted alkyl.

The term "heteroatoms" shall include oxygen, sulfur and nitrogen.

The compounds represented by formula I form salts with a variety of organic and inorganic acids. Such salts include those formed with hydrogen chloride, hydrogen bromide, methanesulfonic acid, hydroxyethanesulfonic acid, sulfuric acid, acetic acid, trifluoroacetic acid, maleic acid, benzenesulfonic acid, toluenesulfonic acid and various others as are recognized by those of ordinary skill in the art of pharmaceutical compounding. Such salts are formed by reacting a compound represented by formula I in an equivalent amount of the acid in a medium in which the salt precipitates or in an aqueous medium followed by evaporation.

In addition, zwitterions ("inner salts") can be formed and are included within the term salts as used herein.

A particularly preferred epothilone analog within those represented by formula I is [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-7-oxabicyclo[14.1.0]heptadecane-5,9-dione represented by formula II



II

The compounds represented by formulae I and II above and their preparation are described in U.S. patent application Serial No. 09/170,582, filed October 13, 1998, the disclosure of which is incorporated herein by reference. The compounds represented by formulae I and II above may exist as multiple optical, geometric, and stereoisomers. While the compounds shown herein are depicted for one optical orientation, included within the present invention are all isomers and mixtures thereof.

The compounds represented by formulae I and II above are microtubule-stabilizing agents. They are thus useful in the treatment of a variety of cancers and other proliferative diseases including, but not limited to, the following:

carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, ovary, pancreas, stomach, cervix, thyroid and skin, including squamous cell carcinoma;

hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma and Burketts lymphoma;

hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias and promyelocytic leukemia;

tumors of mesenchymal origin, including fibrosarcoma and rhabdomyoscarcoma;

other tumors, including melanoma, seminoma, teratocarcinoma, neuroblastoma and glioma;

tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma, and schwannomas;

tumors of mesenchymal origin, including fibrosarcoma, rhabdomyoscaroma, and osteosarcoma; and

other tumors, including melanoma, xeroderma pigmentosum, keratoacanthoma, seminoma, thyroid follicular cancer and teratocarcinoma.

The compounds represented by formulae I and II above will also inhibit angiogenesis, thereby affecting the growth of tumors and providing treatment of tumors and tumor-related disorders. Such anti-angiogenesis properties of the compounds represented by formulae I and II will also be useful in the treatment of other conditions responsive to anti-angiogenesis agents including, but not limited to, certain forms of blindness related to retinal vascularization, arthritis, especially inflammatory arthritis, multiple sclerosis, restinosis and psoriasis.

Compounds represented by formulae I and II will induce or inhibit apoptosis, a physiological cell death process critical for normal development and homeostasis. Alterations of apoptotic pathways contribute to the pathogenesis of a variety of human diseases. Compounds represented by formulae I and II, as modulators of apoptosis, will be useful in the treatment of a variety of human diseases with aberrations in apoptosis including, but not limited to, cancer and precancerous lesions, immune response related diseases, viral infections, degenerative diseases of the musculoskeletal system and kidney disease.

Each of the compounds represented by formulae I and II may also be formulated or co-administered with other therapeutic agents that are selected for their particular usefulness in administering therapies associates with the aforementioned conditions. For example, each of the compounds of formulae I and II may be formulated with agents to prevent nausea, hypersensitivity, and gastric irritation, such as anti-emetics, and H_1 and H_2 antihistamines. The above therapeutic agents, when employed in combination with the compound of formulae I or II, may be used in

those amounts indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

Furthermore, compounds of formulae I or II may be administered in combination with other anti-cancer and cytotoxic agents and treatments useful in the treatment of cancer or other proliferative diseases. Especially useful are anti-cancer and cytotoxic drug combinations wherein the second drug chosen acts in a different manner or different phase of the cell cycle, *e.g.*, S phase, than the present compounds of formula I and II which exert their effects at the G_2-M phase. Example classes of anti-cancer and cytotoxic agents include, but are not limited to, alkylating agents, such as nitorgen mustards, alkyl sulfonates, nitrosoureas, ethylenimines, and triazenes; antimetabolites, such as folate antagonists, purine analogues, and pyrimidine analogues; antibiotics, such as anthracyclines, bleomycins, mitomycin, dactinomycin, and plicamycin; enzymes, such as L-asparaginase; farnesyl-protein transferase inhibitors; hormonal agents, such as glucocorticoids, estrogens/antiestrogens, androgens/antiandrogens, progestins, and luteinizing hormone-releasing hormone anatagonists, octreotide acetate; microtubule-disruptor agents, such as ecteinascidins or their analogs and derivatives; microtubule-stabilizing agents such as paclitaxel (Taxol®), docetaxel (Taxotere®); plant-derived products, such as vinca alkaloids, epipodophyllotoxins, taxanes; and topoisomerase inhibitors; prenyl-protein transferase inhibitors; and miscellaneous agents such as, hydroxyurea, procarbazine, mitotane, hexamethylmelamine, platinum coordination complexes such as cisplatin and carboplatin; and other agents used as anti-cancer and cytotoxic agents such as biological response modifiers, growth factors; immune modulators, and monoclonal antibodies. Compounds represented by formulae I and II may also be used in conjunction with radiation therapy.

Representative examples of these classes of anti-cancer and cytotoxic agents include, but are not limited to, mechlorethamine hydrochlordie, cyclophosphamide, chlorambucil, melphalan, ifosfamide, busulfan, carmustin, lomustine, semustine, streptozocin, thiotepa, dacarbazine, methotrexate, thioguanine, mercaptopurine, fludarabine, pentastatin, cladribin, cytarabine, fluorouracil, doxorubicin hydrochloride, daunorubicin, idarubicin, bleomycin sulfate, mitomycin C, actinomycin D, safracins, saframycins, quinocarcins, discodermolides, vincristine,

vinblastine, vinorelbine tartrate, etoposide, teniposide, paclitaxel, tamoxifen, estramustine, estramustine phosphate sodium, flutamide, buserelin, leuprolide, pteridines, diyneses, levamisole, aflacon, interferon, interleukins, aldesleukin, filgrastim, sargramostim, rituximab, BCG, tretinoin, irinotecan hydrochloride, betamethosone, gemcitabine hydrochloride, altretamine, and topoteca and any analogs or derivatives thereof.

Preferred members of these classes include, but are not limited to, paclitaxel, cisplatin, carboplatin, doxorubicin, carminomycin, daunorubicin, aminopterin, methotrexate, methopterin, mitomycin C, ecteinascidin 743, porfiromycin, 5-fluorouracil, 6-mercaptopurine, gemcitabine, cytosine arabinoside, podophyllotoxin or podophyllotoxin derivatives such as etoposide, etoposide phosphate or teniposide, melphalan, vinblastine, vincristine, leurosidine, vindesine, and leurosine.

Examples of anti-cancer and other cytotoxic agents include the following: cyclin dependent kinase inhibitors as found in WO 99/24416; and prenyl-protein transferase inhibitors as found in WO 97/30992 and WO 98/54966.

Without being bound by any theory regarding mechanism or morphology, the compounds represented by formulae I and II may also be used to treat conditions other than cancer or other proliferative diseases. Such conditions include, but are not limited to viral infections such as herpesvirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus; autoimmune diseases such as systemic lupus erythematosus, immune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel diseases and autoimmune diabetes mellitus; neurodegenerative disorders such as Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy and cerebellar degeneration; AIDS; myelodysplastic syndromes; aplastic anemia; ischemic injury associated myocardial infarctions; stroke and reperfusion injury; restenosis; arrhythmia; atherosclerosis; toxin-induced or alcohol induced liver diseases; hematological diseases such as chronic anemia and aplastic anemia; degenerative diseases of the musculoskeletal system such as osteoporosis and arthritis; aspirin-sensitive rhinosinusitis; cystic fibrosis; multiple sclerosis; kidney diseases; and cancer pain.

The effective amount of a compound represented by formulae I and II may be determined by one of ordinary skill in the art, and includes exemplary dosage amounts for a human of from about 0.05 mg/kg/day to about 200 mg/kg/day, which may be administered in a single dose or in the form of individual divided doses, such as from 1 to about 4 times per day. Preferably, the compounds are administered in a dosage of less than about 100 mg/kg/day, in a single dose or in about 2 to about 4 divided doses. It will be understood that the specific dose level and frequency of dosage for any particular subject may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition. Preferred subjects for treatment include animals, most preferably mammalian species such as humans, and domestic animals such as dogs, cats and the like, subject to the aforementioned disorders.

The compounds represented by formulae I and II, particularly the latter, are disadvantageous from the viewpoint of compounding a suitable formulation for administration in that they possess very low solubility in aqueous media, rapidly degrade in contact with aqueous media, are sensitive to low pH when in solution, are light sensitive, are "Class D" cytotoxic and have exceptionally poor wetting characteristics. Any one or two of these characteristics might be compensated for in compounding a pharmaceutical formulation for intravenous administration, but the combination of all of them presents a formidable challenge to the pharmaceutical compounding chemist. Given the constraint that materials to be utilized in compounding an intravenous formulation must be approved for intravenous administration, the formulation provided in accordance with the present invention unexpectedly was found to be suitable for overcoming the disadvantageous properties of the subject epothilone analogs as noted above. Initially, because of the fact that the subject epothilone analogs are poorly soluble in aqueous media and, in fact, rapidly degrade in contact therewith, it was decided that they should be formulated in lyophilized form.

It has been found that a suitable media to form a solution of the subject compounds for lyophilization is a mixture of tertiary-butanol and water for injection. This mixture must be at least about 50% v/v, preferably from about 50% to about 80% v/v tertiary butanol to prevent degradation of the subject epothilone analogs. Further, due to the exceptionally poor wetting characteristics of the subject epothilone analogs, the initial solution must be effected utilizing a mixture of at least about 60% v/v, preferably from about 60% to about 95 % v/v, tertiary butanol and water. Once the solution is made, the requisite amount of water or tertiary-butanol-water mixture can be added to achieve the final concentration for lyophilization as stated above.

It has unexpectedly been found that the stability of the subject epothilone analogs can be significantly enhanced by carrying out the preparation of the solution at a temperature below ambient, preferably from about 5°C to about 15°C, more preferably about 5°C. Further, both the process of forming the solution and subsequent lyophilization are to be carried out in vessels such that the epothilone analogs are protected from exposure to light. It is also beneficial to carry out the lyophilization in comparatively small batches so that the epothilone analogs are exposed to an aqueous medium for a minimum amount of time.

The primary drying stage of lyophilization of the solution formed as described above is carried out at temperatures from about -10°C to about -40°C, preferably about -25°C, under high vacuum, *i.e.*, from about 50 millitorr to about 300 millitorr, preferably about 200 millitorr, for an extended period, *i.e.*, from about 24 hours to about 96 hours, preferably about 48 hours. Lyophilization in this temperature range produces an amorphous product which is desirable for an intravenous preparation. Those of ordinary skill in the art will appreciate that conventional procedures, such as powder X-ray diffraction, can be utilized to confirm the amorphous nature of the lyophilized product.

The residual solvents in the product are removed by a secondary drying stage that is carried out at comparatively low temperatures, *i.e.*, from about 10°C to about 30°C, preferably about 25°C, under high vacuum, *i.e.*, from about 50 millitorr to about 300 millitorr, preferably about 150 millitorr for an extended period, *i.e.*, from about 24 hours to about 96 hours, preferably about 48 hours.

It has unexpectedly been found that the stability of lyophilized epothilone analogs described herein are not enhanced by excipients commonly utilized for such purposes, such as lactose, mannitol, dextran and the like. Certain of these excipients may actually have a negative effect on the stability of the lyophilized product (lyophile). Hence, the epothilone analogs formulated in accordance with the present invention are lyophilized neat, *i.e.*, without any excipient.

The lyophilized epothilone analogs represented by formulae I and II are reconstituted with a mixture of equal parts by volume of Dehydrated Alcohol, USP and a nonionic surfactant, preferably a polyoxyethylated castor oil surfactant available from GAF Corporation, Mount Olive, New Jersey, under the trademark, Cremophor EL. The lyophilized product and vehicle for reconstitution are packaged separately in appropriately light-protected vials. To minimize the amount of surfactant in the reconstituted solution, only a sufficient amount of the vehicle is provided to form a solution having a concentration of about 2 mg/mL to about 4 mg/mL of the epothilone analog. Once dissolution of the drug is achieved, the resulting solution is further diluted prior to injection with a suitable parenteral diluent. Such diluents are well known to those of ordinary skill in the art. These diluents are generally available in clinical facilities. It is, however, within the scope of the present invention to package the subject epothilone analogs with a third vial containing sufficient parenteral diluent to prepare the final concentration for administration. A preferred diluent is Lactated Ringer's Injection. The final concentration for administration would preferably contain from about 0.1 mg/mL to about 0.9 mg/mL of the epothilone analog.

The final dilution of the reconstituted epothilone analog in the formulation of the invention may be carried out with other preparations having similar utility, for example, 5% Dextrose Injection, Lactated Ringer's and Dextrose Injection, Sterile Water for Injection, and the like. However, because of its narrow pH range, pH 6.0 to 7.5, Lactated Ringer's Injection is preferred. Per 100 mL, Lactated Ringer's Injection contains Sodium Chloride USP 0.6 g, Sodium Lactate 0.31 g, Potassium chloride USP 0.03 g and Calcium Chloride·$2H_2O$ USP 0.02g. The osmolarity is 275 mOsmol/L, which is very close to isotonicity.

The constituted preparation according to the present invention, *i.e.*, the solution of the epothilone analog in the alcohol-surfactant vehicle, can be stored for up to about 24 hours before being further diluted for administration. It has been found that the incidence of allergic reactions encountered due to the presence of the surfactant in the formulation is minimized by keeping its concentration at the minimum necessary to effect solution of the epothilone analog. Further, the incidence of such reactions is about the same as has been experienced with other parenterally administered pharmaceuticals containing it, such as cyclosporine. This observed level of allergic reaction with the present formulation is significantly lower that has been experienced with certain other oncology agents, such as Paclitaxel. The final dilution is administered by intravenous infusion, typically over a period of up to an hour.

The following non-limiting example serves to illustrate the practice of the present invention.

Example

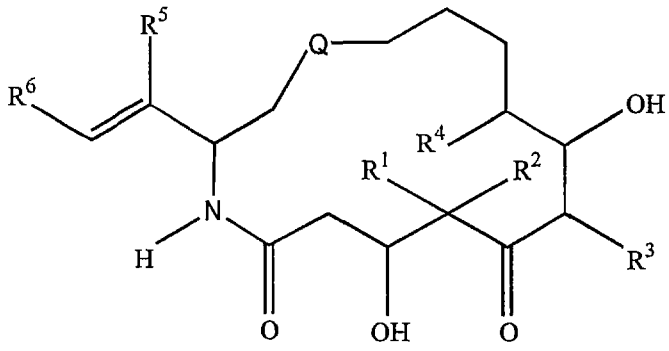
[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione, 9.86 g, was wetted/partially dissolved with 600 mL of a 9:1 mixture of tertiary butanol and Water for Injection USP which had been pre-cooled to 5°C. Once the drug powder had become completely wetted, dissolution was completed by the addition of 600 mL of a 1:9 mixture of tertiary butanol and Water for Injection and 766 mL of a 1:1 mixture of tertiary butanol and Water for Injection which likewise had been pre-cooled to 5°C thereby making the final solution a 1:1 mixture. The dissolution was carried out under protection from light.

The solution formed above was promptly lyophilized in a Virtis INOTOP lyophilizer at -16°C under light protectant conditions over a period of 48 hours. The resultant lyophilized product (lyophile) was then further dried at 15°C under high vacuum for 48 hours. No detectable degradation of the drug was observed during these procedures. The lyophile was packaged under sterile conditions into 30 mL vials, each containing 10 mg of drug and standard excess to allow for vial/needle/syringe loss.

The lyophile is reconstituted with 5.5 mL of a 1:1 volume mixture of Dehydrated Alcohol USP and Cremophor EL®, which typically will be supplied with the drug in a separate vial, to achieve a final drug concentration of 2 mg/mL. Once dissolution is effected by gently swirling the vial, the resultant solution is diluted to achieve a concentration of 0.2 mg/mL by the addition of 9 mL of Lactated Ringer's for Injection for each milliliter of constituted drug product.

What is claimed is:

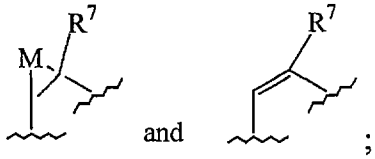
1. A process for formulating, for parenteral administration, an epothilone analog represented by formula I:



I

wherein:

Q is selected from the group consisting of:



;

M is selected from the group consisting of oxygen, sulfur, NR^8, and CR^9R^{10};

each R^1, R^2, R^3, R^4, R^5, R^7, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} is, independently, selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl and heterocyclo, and wherein R^1 and R^2 are alkyl, they can be joined to form cycloalkyl;

R^6 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, heterocyclo and substituted heterocyclo;

R^8 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, $R^{11}C=O$, $R^{12}OC=O$ and $R^{13}SO_2$; and

each R^9 and R^{10} is, independently, selected from the group consisting of hydrogen, halogen, alkyl, substituted alkyl, aryl, heterocyclo, hydroxy, $R^{14}C=O$, and $R^{15}OC=O$;

and any salts, solvates, or hydrates thereof, comprising the following steps carried out under protection from light:

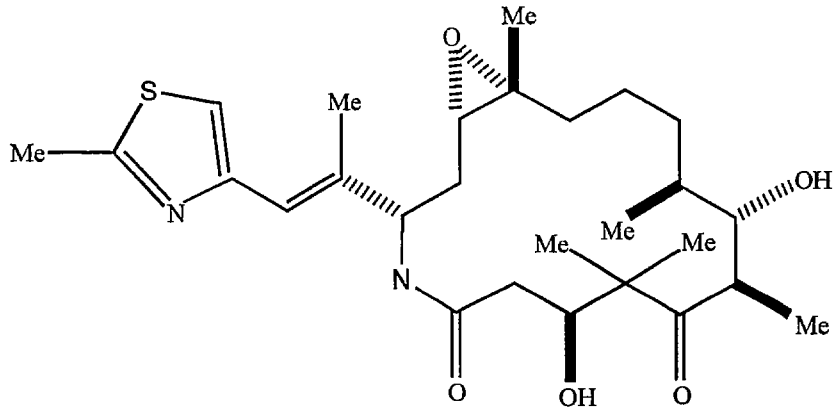
a) dissolving said epothilone analog in a mixture of at least about 50% by volume tertiary-butanol in water to form a solution;

b) performing primary drying of said solution at a temperature of from about -10°C to about -40°C under high vacuum of from about 50 millitorr to about 300 millitorr for from about 24 hours to about 96 hours to form a lyophilized product;

c) performing secondary drying of the resultant lyophilized product at a temperature of from about 10 °C to about 30°C under high vacuum of from about 50 millitorr to about 300 millitorr for from 24 hours to about 96 hours; and

d) packaging said lyophilized product in a first vial in combination with a second vial containing a sufficient quantity of an equal mixture by volume of a suitable nonionic surfactant and anhydrous ethanol to effect solution thereof.

2. The process of claim 1 wherein said epothilone analog is represented by formula II:



II

3. The process of claims 1 or 2 wherein in step a) said analog is first wetted with a mixture of at least about 60% tertiary-butanol in water, and then sufficient water, or a mixture of tertiary-butanol and water, is added thereto so that the resulting solution contains from about 2 mg/mL to about 30 mg/mL of said analog in a mixture of from about 50% to about 80% by volume tertiary-butanol in water.

4. The process of claim 3 wherein in step a) said analog is initially wetted with a mixture of from about 60% to about 95% by volume tertiary-butanol in water.

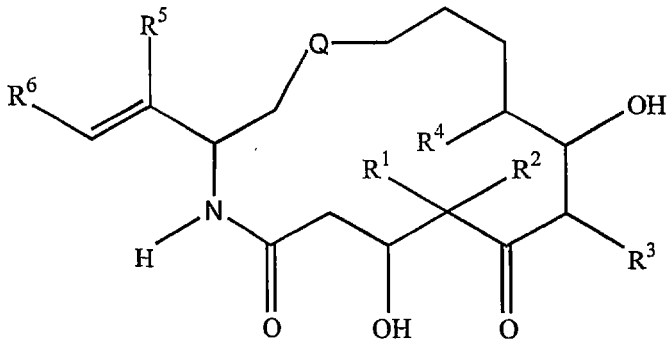
5. The process of claims 1 or 2 wherein said primary drying in step b) is carried out at a temperature of about -25°C and a pressure of about 200 millitorr for about 48 hours.

6. The process of claims 1 or 2 wherein said secondary drying in step c) is carried out at a temperature of about 25°C and a pressure of about 150 millitorr for about 48 hours.

7. The process of claims 1 or 2 wherein said surfactant is polyethoxylated castor oil.

8. The process of claim 7 wherein said second vial contains an amount of said mixture sufficient to form a solution of from about 2 mg/mL to about 4 mg/mL of said analog therein.

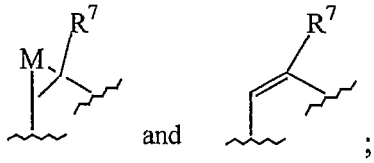
9. A pharmaceutical preparation comprising, in separate vials, a lyophilized epothilone analog and a quantity of a solvent therefor such that when the contents of said vials are combined, the resulting solution contains from about 2 mg/mL to about 4 mg/mL of said analog, said solvent comprising a mixture of about equal parts by volume of dehydrated ethanol and a suitable nonionic surfactant, said analog being represented by formula I:



I

wherein:

Q is selected from the group consisting of



;

M is selected from the group consisting of oxygen, sulfur, NR^8, and CR^9R^{10};

each R^1, R^2, R^3, R^4, R^5, R^7, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} is, independently, selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl and heterocyclo, and wherein R^1 and R^2 are alkyl, they can be joined to form cycloalkyl;

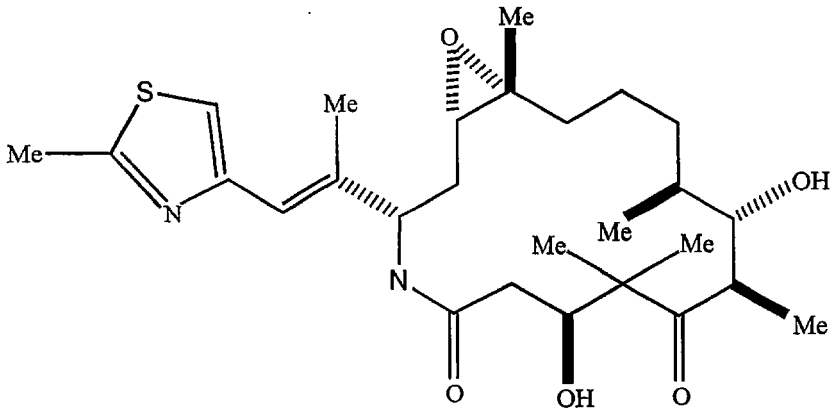
R^6 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, heterocyclo and substituted heterocyclo;

R^8 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, $R^{11}C=O$, $R^{12}OC=O$ and $R^{13}SO_2$; and

each R^9 and R^{10} is, independently, selected from the group consisting of hydrogen, halogen, alkyl, substituted alkyl, aryl, heterocyclo, hydroxy, $R^{14}C=O$, and $R^{15}OC=O$;

and any salts, solvates, or hydrates thereof.

10. The pharmaceutical preparation of claim 9 wherein said epothilone analog is represented by formula II:



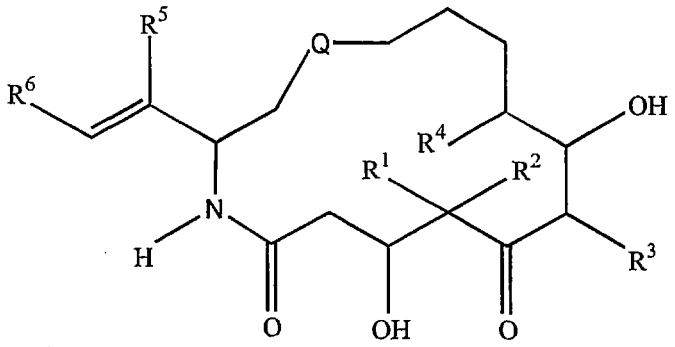
II

11. The pharmaceutical preparation of claim 9 wherein said nonionic surfactant is polyethoxylated castor oil.

12. A process for forming a pharmaceutical composition for parenteral administration comprising mixing the contents of the vials of the pharmaceutical preparation of any of claims 9, 10 and 11 to effect solution of said lyophilized epothilone analog and diluting the resultant solution with a quantity of a suitable parenteral diluent such that the concentration of said analog therein will be from about 0.1 mg/mL to about 0.9 mg/mL.

13. The process of claim 12 wherein said diluent is Lactated Ringer's Injection.

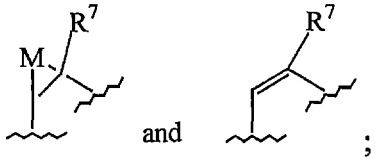
14. A process for treating a patient in need of treatment with an epothilone analog represented formula I:



I

wherein:

Q is selected from the group consisting of



;

M is selected from the group consisting of oxygen, sulfur, NR^8, and CR^9R^{10};

each R^1, R^2, R^3, R^4, R^5, R^7, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} is, independently, selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl,

substituted aryl and heterocyclo, and wherein R^1 and R^2 are alkyl, they can be joined to form a cycloalkyl;

R^6 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, heterocyclo and substituted heterocyclo;

R^8 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, $R^{11}C=O$, $R^{12}OC=O$ and $R^{13}SO_2$; and

each R^9 and R^{10} is, independently, selected from the group consisting of hydrogen, halogen, alkyl, substituted alkyl, aryl, heterocyclo, hydroxy, $R^{14}C=O$, and $R^{15}OC=O$;

and any salts, solvates, or hydrates thereof, comprising administering to said patient, by intravenous injection, an effective amount of a pharmaceutical composition of claim 12.

15. The process of claim 14 wherein said diluent is Lactated Ringer's Injection.