

JOSE LLOREDA CAMACHO & CO.

ABOGADOS

Calle 72 No. 5-83 Piso 5, Bogotá, D.C. Tel: 6069700 Fax 6069701

182

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. _____ S. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-062278- -00004-0000

Fecha: 2008-06-24 16:44:01

Dep. 2020 NUECREACION

Tra. 11 PATENTEIYII

Eve: 378 FASENACIONALI

Act. 538 PETICION

Folios: 2

Re: P1.-DANA FARBER CANCER INSTITUTE.-Solicitud de Patente de Invención en Fase Nacional PCT para "COMPOSICIONES Y MÉTODOS PARA TRATAMIENTO DE ENFERMEDADES NEOPLÁSICAS".-Clase A61K 31/397.-Expediente número 07-062.278.-

1. Me refiero a mi memorial de 22 de Octubre de 2007.
2. De conformidad con lo dispuesto en el Artículo 5.2.12 de la Circular Externa No. 03 de 28 de Abril de 2003, y estando dentro del plazo de seis meses contados desde la fecha de la publicación de la solicitud en la Gaceta de la Propiedad Industrial número **587** de 18 de Enero de 2008, solicito a ese Despacho proceder a realizar el examen de patentabilidad de la presente invención.
3. Me permito recordar a usted, que tal como se informó en el Petitorio de la invención, la presente solicitud corresponde a Capítulo I.
4. Anexo me permito acompañar recibo número 08-50.024, expedido por la Superintendencia de Industria y Comercio, que acredita el pago de la tasa que dicho examen causa.

Señor Superintendente,


ALICIA LLOREDA RICAURTE
T.P. 53.215

185

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-062278- -00004-0000

Fecha: 2008-06-24 16:44:01 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 538 PETICION Folios: 2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 900176089-2

RECIBO OFICIAL DE CAJA : 08 - 50,024
: JUNIO 23 DE 2008

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LOPEZ Y CIA S. A	CONSIGNACION	BANCO DE BOGOTA	062754387	99223	23/06/2008	4,620,000.00

***** CONCEPTO *****

RENTISTICO	CONCEPTO	TOTAL CONCEPTO
50005-01-01 SOLICITUDES	85 EXAMEN DE PATENTABILIDAD DE INVEN	420,000.00
	TOTAL :	\$ 420,000.00

9911 CUATROCIENTOS VEINTE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 07-62278

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **587** DE

FECHA **18 DE ENERO DE 2008** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL **16 DE ABRIL DE 2008**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO X



Industria y Comercio
SUPERINTENDENCIA

SOLICITUD
PATENTE DE INVENCION

21. EXPEDIENTE N° 06-5363
54. TÍTULO USO DE COMPUESTOS C.2.0.1 HETEROCÍCLICOS Y
SUS ANALÓGOS PAR. EL TRATAMIENTO DE
CÁNCER, INFLAMACIÓN Y ENFERMEDADES
INFECCIOSAS
51. CLASIFICACIÓN INTERNACIONAL A61K 31/407, A61P 35/00, 35/02, 29/00
11/06, 25/00, 17/06, 9/10, 33/00, 33/02, 33/06, A61K 31/333
71. SOLICITANTE NEREUS PHARMACEUTICALS, INC.
- DOMICILIO SAN DIEGO, ESTADO DE CALIFORNIA, ESTADOS UNIDOS DE AMERICA
74. REPRESENTANTE LEGAL ALICIA LLOREDA RICAURTE
T.P. 53.215
22. BOGOTÁ, D.C. 20 ENE. 2006

PETITORIO



SUPERINTENDENCIA Y COMERCIO
Radicación: 06005363 00000000 Folios: 335
Fecha (AMB): 2006-01-20 17:36:36
Trámite: 011 PCT-PATENT 378 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO UNICO DE SOLICITUD DE PATENTE

PCT

20-01-2006

ENTRADA EN FASE I

SUPERINTENDENCIA Y COMERCIO (COPIA)

Radicación: 06005363 00000000 Folios: 335

SOLICITUD D

Fecha (AMB): 2006-01-20 17:36:36

Trámite: 011 PCT-PATENT 378 FASE NACI 411 PRESENTAC

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

①

☒ Patente de invención☒ Capítulo I.☐ Capítulo II.

②

SOLICITANTE
(71)

Nombre: NEREUS PHARMACEUTICALS, INC.

Dirección: 10480 Wateridge Circle, San Diego,
CA 92121, Estados Unidos de América.Nacionalidad o Domicilio: San Diego, Estado
de California, Estados Unidos de América.Lugar de Constitución: California, Estados
Unidos de América.

Teléfono: 3264270 Fax: 6069701

E-mail: jlloco@lloredacamacho.com

IDENTIFICACION

C.C. ☐ NIT ☐C.E. ☐ Otro ☐

Cual _____

Número _____

③

REPRESENTANTE
O APODERADO

Nombre: ALICIA LLORED RICAURTE

Dirección: Calle 72 No. 5-83 Piso 5º,
Bogotá- Colombia

Teléfono: 3264270 Fax: 6069701

E-mail: jlloco@lloredacamacho.com

C.C. ☒ NIT ☐C.E. ☐ Otro ☐

Cual _____

Número 39.680.713 TP 53.215

④

INVENTOR(ES)
(72)Nombre: PALLADINO, Michael; NEUTEBOOM, Saskia, Theodora, Cornelia;
MACHERLA, Venkata, Rami, Reddy y POTTS, Barbara, Christine.Dirección: 3357 Fortuna Ranch Road, Encinitas, CA 92024; 7665 Palmilla
Drive, Apt #5402, San Diego, CA 92122; 10868 Caminito Arcada, San Diego,
CA 92131 y 2029 Oro Verde Road, Escondido, CA 92027.

Nacionalidad o Domicilio: Estados Unidos de América.

⑤

PCT (88)

Solicitud Internacional No. PCT/US2004/019543

Fecha: 16/06/04

Publicación Internacional No. WO 2005/002572 A2

Fecha: 13/01/05

⑥

Título (54)

"MÉTODOS PARA UTILIZAR COMPUESTOS [3.2.0] HETEROCÍCLICOS Y
SUS ANÁLOGOS" Ver folio # 338, 360

⑦

Clasificación Internacional (51)

A61K 31/407, A61P 35/00, 35/02, 29/00, 19/02, 11/06,
25/00, 17/06, 9/10, 32/00, 32/02, 33/06, A61K 31/337

⑧

Prioridad

SI ☒ NO ☐

(33) País de Origen

US

US

(32) Fecha

20/06/03

30/04/04

(31) Número de Solicitud

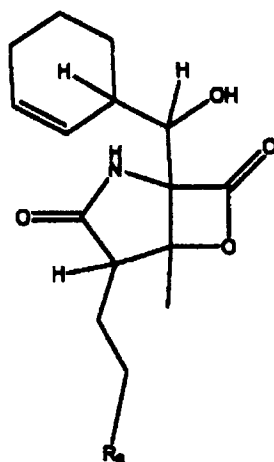
60/480,270

60/566,952

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Comprobante de Pago No. 06-3,967

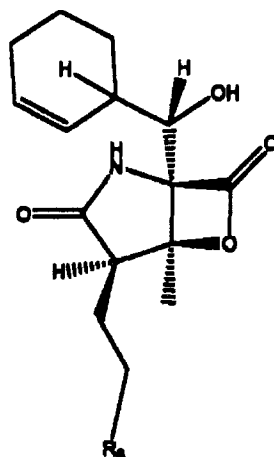
Fecha: Enero 19 de 2006



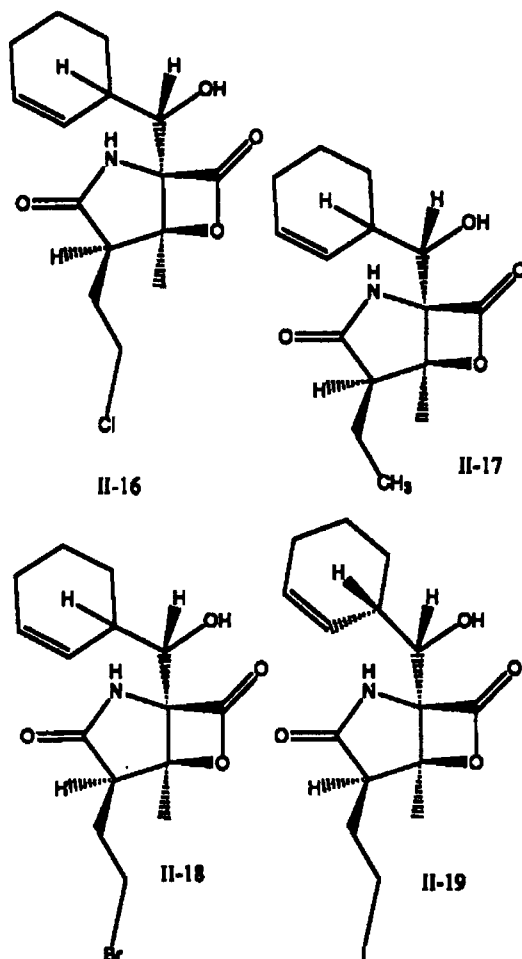
Fórmula II-15

[0145] R₆ puede incluir por ejemplo, hidrógeno, flúor, cloro, bromo y yodo.

5 [0146] Estereoquímica ejemplar puede ser como sigue:



[0147] Lo siguiente es estereoquímica ejemplar
10 para compuestos que tienen las estructuras II-16, II-17, II-18, y II-19, respectivamente:



[0148] Los compuestos de las Fórmulas II-16, II-17, II-18 y II-19 pueden obtenerse por fermentación, síntesis o semi-síntesis y aislarse/purificarse como se establece a continuación. Además, los compuestos de las Fórmulas II-16, II-17, II-18 y II-19 pueden emplearse, y se refieren como "materiales de partida" para producir otros compuestos aquí descritos.

etilendiamina o tris-(hidroximetilo)-aminometano. Con respecto a compuestos sintetizados por el método de esta modalidad que son aminas básicas, los ejemplos preferidos de sales farmacéuticamente aceptables, son sales de adición de ácido de ácidos inorgánicos u orgánicos farmacéuticamente aceptables, por ejemplo ácido hidrohálico, sulfúrico, fosfórico o ácidos carboxílicos o sulfónicos alifáticos o aromáticos, por ejemplo ácido acético, succínico, láctico, málico, tartárico, cítrico, ascórbico, nicotínico, metansulfónico, p-toluensulfónico o naftalensulfónico.

[0179] Composiciones farmacéuticas preferidas aquí descritas incluyen sales y ésteres pro-droga farmacéuticamente aceptables del compuesto de las Fórmulas I-V obtenidas y purificadas por los métodos aquí descritos. De acuerdo con esto, si la fabricación de formulaciones farmacéuticas involucra mezclado íntimo de los excipientes farmacéuticos y el ingrediente activo en su forma de sal, entonces se prefiere utilizar excipientes farmacéuticos que no son básicos, esto es ya son excipientes acídicos o neutros.

[0180] También se apreciará que la frase "Compuestos y composiciones que comprenden el compuesto" o cualquier frase semejante, se pretenden que abarquen compuestos en cualquier forma conveniente para suministro

cantidades menores de sustancias auxiliares no tóxicas tales como agentes humectantes, agentes amortiguadores de pH y semejantes. Si se desea, pueden utilizarse preparaciones que mejoran la absorción (por ejemplo liposomas).

[0243] La cantidad farmacéuticamente efectiva de la composición requerida como una dosis dependerá de la ruta de administración, el tipo de animal a tratar, y las características físicas del animal específico bajo consideración. La dosis puede ajustarse a la medida para lograr un efecto deseado, pero dependerá de factores tales como peso, dieta, medicamento concurrente y otros factores que aquellos con destreza en las técnicas médicas reconocerán.

[0244] Los productos o composiciones de la modalidad, como se describió anteriormente pueden ser empleados solos o en combinación entre sí, o en combinación con otros agentes terapéuticos o de diagnóstico. Estos productos pueden utilizarse *in vivo* o *in vitro*. Las dosis útiles y los modos de administración más útiles variarán dependiendo de la edad, peso y animal tratado, los compuestos particulares empleados y el uso específico para el cual se emplean esta composición o composiciones. La magnitud de una dosis en el tratamiento o manejo de un desorden particular variará con la



US 20040138196A1

02 193

(19) **United States**(12) **Patent Application Publication** (10) **Pub. No.: US 2004/0138196 A1****Fenical et al.**(43) **Pub. Date: Jul. 15, 2004**(54) **SALINOSPORAMIDES AND METHODS FOR USE THEREOF****Publication Classification**(76) Inventors: **William Fenical**, Del Mar, CA (US);
Paul Jensen, San Diego, CA (US);
Tracy Mincer, San Diego, CA (US);
Robert H.R. Felling, Wiesbaden (DE)(51) **Int. Cl.⁷** **A61K 31/43**; A61K 31/424;
A61K 31/397; A61K 31/407
(52) **U.S. Cl.** **514/192**; 514/210.06; 514 210.09;
540/304; 540/347

Correspondence Address:

GRAY CARY WARE & FREIDENRICH LLP
4365 EXECUTIVE DRIVE
SUITE 1100
SAN DIEGO, CA 92121-2133 (US)(57) **ABSTRACT**

The present invention is based on the discovery that certain fermentation products of the marine actinomycete strains CNB392 and CNB476 are effective inhibitors of hyperproliferative mammalian cells. The CNB392 and CNB476 strains lie within the family Micromonosporaceae, and the generic epithet *Salinospora* has been proposed for this obligate marine group. The reaction products produced by this strain are classified as salinosporamides, and are particularly advantageous in treating neoplastic disorders due to their low molecular weight, low IC_{50} values, high pharmaceutical potency, and selectivity for cancer cells over fungi.

(21) Appl. No.: **10/600,854**(22) Filed: **Jun. 20, 2003****Related U.S. Application Data**

(60) Provisional application No. 60/391,314, filed on Jun. 24, 2002.

and "substituted heterocyclic" refers to heterocyclic groups further bearing one or more substituents as set forth above.

[0044] In certain embodiments, there are provided compounds of structure I wherein E_1 , E_3 , and E_4 are —O, and E_2 is —NH.

[0045] In certain embodiments, there are provided compounds of structure I wherein R_1 and R_2 are —H, alkyl, or substituted alkyl, and R_3 is hydroxy or alkoxy. In some embodiments, R_1 is substituted alkyl. Exemplary substituted alkyls contemplated for use include halogenated alkyls, such as for example chlorinated alkyls.

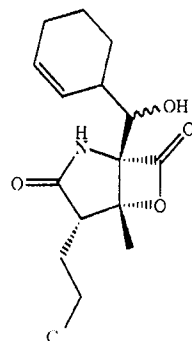
[0046] The compounds of the invention may be formulated into pharmaceutical compositions as natural or salt forms. Pharmaceutically acceptable non-toxic salts include the base addition salts (formed with free carboxyl or other anionic groups) which may be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, 2-ethylamino-ethanol, histidine, procaine, and the like. Such salts may also be formed as acid addition salts with any free cationic groups and will generally be formed with inorganic acids such as, for example, hydrochloric, sulfuric, or phosphoric acids, or organic acids such as acetic, p-toluenesulfonic, methanesulfonic acid, oxalic, tartaric, mandelic, and the like. Salts of the invention include amine salts formed by the protonation of an amino group with inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like. Salts of the invention also include amine salts formed by the protonation of an amino group with suitable organic acids, such as p-toluenesulfonic acid, acetic acid, and the like. Additional excipients which are contemplated for use in the practice of the present invention are those available to those of ordinary skill in the art, for example, those found in the United States Pharmacopeia Vol. XXII and National Formulary Vol. XVII, U.S. Pharmacopeia Convention, Inc., Rockville, Md. (1989), the relevant contents of which is incorporated herein by reference.

[0047] The compounds according to this invention may contain one or more asymmetric carbon atoms and thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. The term "stereoisomer" refers to chemical compounds which differ from each other only in the way that the different groups in the molecules are oriented in space. Stereoisomers have the same molecular weight, chemical composition, and constitution as another, but with the atoms grouped differently. That is, certain identical chemical moieties are at different orientations in space and, therefore, when pure, have the ability to rotate the plane of polarized light. However, some pure stereoisomers may have an optical rotation that is so slight that it is undetectable with present instrumentation. All such isomeric forms of these compounds are expressly included in the present invention.

[0048] Each stereogenic carbon may be of R or S configuration. Although the specific compounds exemplified in this application may be depicted in a particular configuration, compounds having either the opposite stereochemistry at any given chiral center or mixtures thereof are also envisioned. When chiral centers are found in the derivatives of this invention, it is to be understood that this invention

encompasses all possible stereoisomers. The terms "optically pure compound" or "optically pure isomer" refers to a single stereoisomer of a chiral compound regardless of the configuration of the compound.

[0049] An exemplary invention compound of structure I is salinosporamide A (1), shown below:



[0050] Salinosporamide A (1) exhibits a molecular structure having a variety of functional groups (lactone, alkyl-halide, amide, hydroxide) that can be chemically modified to produce synthetic derivatives. Accordingly, exemplary invention compound salinosporamide A (1) provides an excellent lead structure for the development of synthetic and semisynthetic derivatives. Indeed, salinosporamide A (1) can be derivatized to improve pharmacokinetic and pharmacodynamic properties, which facilitate administration and increase utility of the derivatives as anti-neoplastic agents. Procedures for chemically modifying invention salinosporamide compounds to produce additional compounds within the scope of the present invention are available to those of ordinary skill in the art.

[0051] Salinosporamide A (1) shows strong cytotoxic activity against human colon cancer cells in the HTC-116 cell assays. The IC_{50} of 11 ng/mL exceeds the activity of etoposide (see FIG. 3, IC_{50} 828 ng/mL), an anticancer drug used for treatment of a number of cancers, by almost two orders of magnitude (see FIG. 4). This high activity makes invention salinosporamides excellent candidates for use in the treatment of various human cancers, especially slow growing, refractile cancers for which there are no therapies. Salinosporamide A (1) is specific to inhibition of mammalian cells and shows little antifungal activity against *Candida albicans* (IC_{50} 250 μ g/mL) and no antibacterial activity (*Staphylococcus aureus*, *Enterococcus faecium*). The IC_{50} of salinosporamide A (1) is far lower than the strongest chemotherapeutic agents currently in use or in clinical trials.

[0052] Salinosporamide A (1) is a fermentation product of the marine actinomycete strains CNB392 and CNB476. These strains are members of the order Actinomycetales, which are high G+C gram positive bacteria. The novelty of CNB392 and CNB476 is at the genus level. Invention compounds set forth herein are produced by certain "Salinospora" sp. In some embodiments, invention compounds are produced by "Salinospora" sp. strains CNB392 and CNB476. To that end, the CNB392 and CNB476 strains of "Salinospora" sp. were deposited on Jun. 20, 2003, pursuant to the Budapest Treaty on the International Deposit of Microorganisms for the Purposes of Patent Procedure with

by the methods of the invention include disorders characterized by the formation of neoplasms. As such, invention compounds are anti-neoplastic agents. As used herein, "neoplastic" pertains to a neoplasm, which is an abnormal growth, such growth occurring because of a proliferation of cells not subject to the usual limitations of growth. As used herein, "anti-neoplastic agent" is any compound, composition, admixture, co-mixture or blend which inhibits, eliminates, retards or reverses the neoplastic phenotype of a cell. In certain embodiments, the neoplasms are selected from mammary, small-cell lung, non-small-cell lung, colorectal, leukemia, melanoma, pancreatic adenocarcinoma, central nervous system (CNS), ovarian, prostate, sarcoma of soft tissue or bone, head and neck, gastric which includes thyroid and non-Hodgkin's disease, stomach, myeloma, bladder, renal, neuroendocrine which includes thyroid and non-Hodgkin's disease and Hodgkin's disease neoplasms. In one embodiment, the neoplasms are colorectal.

[0062] Chemotherapy, surgery, radiation therapy, therapy with biologic response modifiers, and immunotherapy are currently used in the treatment of cancer. Each mode of therapy has specific indications which are known to those of ordinary skill in the art, and one or all may be employed in an attempt to achieve total destruction of neoplastic cells. Chemotherapy utilizing one or more invention salinosporamide compounds is provided by the present invention. Moreover, combination chemotherapy, chemotherapy utilizing invention salinosporamide compounds in combination with other neoplastic agents, is also provided by the invention as combination therapy is generally more effective than the use of single anti-neoplastic agents. Thus, a further aspect of the present invention provides compositions containing a therapeutically effective amount of at least one invention salinosporamide compound in combination with at least one other anti-neoplastic agent. Such compositions can also be provided together with physiologically tolerable liquid, gel or solid carriers, diluents, adjuvants and excipients. Such carriers, diluents, adjuvants and excipients may be found in the United States Pharmacopeia Vol. XXII and National Formulary Vol. XVII, U.S. Pharmacopeia Convention, Inc., Rockville, Md. (1989), the contents of which are herein incorporated by reference. Additional modes of treatment are provided in AHFS Drug Information, 1993 ed. by the American Hospital Formulary Service, pp. 522-660, the contents of which are herein incorporated by reference.

[0063] Anti-neoplastic agents which may be utilized in combination with an invention salinosporamide compound include those provided in The Merck Index, 11th ed. Merck & Co., Inc. (1989) pp. 16-17, the contents of which are hereby incorporated by reference. In a further embodiment of the invention, anti-neoplastic agents may be antimetabolites which may include, but are not limited to, methotrexate, 5-fluorouracil, 6-mercaptopurine, cytosine arabinoside, hydroxyurea, and 2-chlorodeoxyadenosine. In another embodiment of the present invention, the anti-neoplastic agents contemplated are alkylating agents which may include, but are not limited to, cyclophosphamide, melphalan, busulfan, paraplalin, chlorambucil, and nitrogen mustard. In a further embodiment of the invention, the antineoplastic agents are plant alkaloids which may include, but are not limited to, vincristine, vinblastine, taxol, and etoposide. In a further embodiment of the invention, the anti-neoplastic agents contemplated are antibiotics which may include, but are not limited to, doxorubicin (adriamycin),

daunorubicin, mitomycin c, and bleomycin. In a further embodiment of the invention, the anti-neoplastic agents contemplated are hormones which may include, but are not limited to, calusterone, diomostavolone, propionate, epitostanol, mepitiostane, testolactone, tamoxifen, polyestradiol phosphate, megestrol acetate, flutamide, nilutamide, and trilostane. In a further embodiment of the invention, the anti-neoplastic agents contemplated include enzymes which may include, but are not limited to, L-Asparaginase or aminoacridine derivatives which may include, but are not limited to, amsacrine. Additional anti-neoplastic agents include those provided in Skeel, Roland T., "Antineoplastic Drugs and Biologic Response Modifier: Classification, Use and Toxicity of Clinically Useful Agents," Handbook of Cancer Chemotherapy (3rd ed.), Little Brown & Co. (1991), the contents of which are herein incorporated by reference.

[0064] In addition to primates, such as humans, a variety of other mammals can be treated according to the method of the present invention. For instance, mammals including, but not limited to, cows, sheep, goats, horses, dogs, cats, guinea pigs, rats or other bovine, ovine, equine, canine, feline, rodent or murine species can be treated.

[0065] The term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician, e.g., lessening of the effects/symptoms of cell proliferative disorders.

[0066] By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[0067] The terms "administration of" and or "administering a" compound should be understood to mean providing a compound of the invention to the individual in need of treatment. Administration of the invention compounds can be prior to, simultaneously with, or after administration of another therapeutic agent or other anti-neoplastic agent.

[0068] The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases.

[0069] The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs.

[0070] Compositions intended for oral use may be prepared according to any method E known to the art for the manufacture of pharmaceutical compositions and such com-