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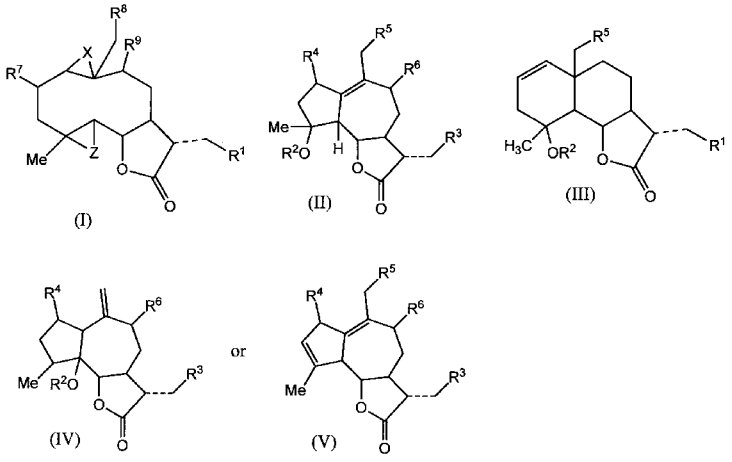
(54) **Title**: ANTI-CANCER AND ANTI-INFLAMMATORY PARTHENOLIDE COMPOUNDS



(57) **Abstract**: The invention provides compounds of formula I, formula II, formula III, formula IV, and formula V: and salts thereof wherein X, Z, ---, and R^1-R^9 have any of the values defined in the specification, as well as compositions comprising the compounds and methods for their use in therapy. The compounds are useful for the treatment of cancer, the treatment of anti-inflammatory diseases, and for the treatment of cardiovascular diseases.

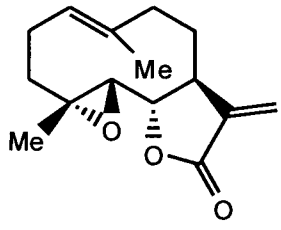
Anti-cancer and Anti-inflammatory Parthenolide Compounds

Priority of Invention

This application claims priority to United States Provisional Application Number 61/477,380 that was filed on April 20, 2011. The entire content of this provisional application is hereby incorporated herein by reference.

Background of the Invention

The natural product parthenolide (PTL, **1**):

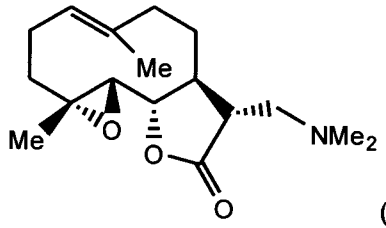


(1)

a component of traditional herbal remedy from the feverfew plant *Tanacetum parthenium*, has demonstrated cytotoxic activity against a spectrum of human cancers, including brain cancer, breast cancer, chronic lymphocytic leukemia, pancreatic cancer, and prostate cancer. See Anderson, K. N., et al. *J. Pharmacol. Sci.* **2008**, *106*, 318-320; Nakshatri, H., et al. *Oncogene* **2004**, *23*, 7330-7344; Sweeney, C. J., et al. *Mol. Cancer Ther.* **2005**, *4*, 1004-1012; Steele, A. J., et al. *Leukemia* **2006**, *20*, 1073-1079; Ramachandran, P. V., et al. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6620-6623; Sweeney, C., et al. *Clinical Cancer Research* **2004**, *10*, 5501-5507; and Shanmugam, R., et al. *Prostate* **2006**, *66*, 1498-1511.

Excitement towards the therapeutic potential of PTL was heightened in 2005 when PTL was shown to induce apoptosis in primary human acute myeloid leukemia (AML) cells and blast crisis chronic myeloid leukemia (CML) cells without targeting normal hematopoietic stem cells (HSCs) (Guzman, M. L., et al. *Blood* **2005**, *105*, 4163-4169). PTL was also shown to induce apoptosis in AML $CD34^+/CD38^-$ cells, which are AML cancer stem cells, and diminish the repopulating ability of AML in immunocompromised mice (Guzman, M. L., et al. *Blood* **2005**, *105*, 4163-4169). However, the clinical utility of PTL has been limited due to its poor water solubility and low serum bioavailability (Sweeney,

C. J., et al. *Mol. Cancer Ther.* **2005**, *4*, 1004-1012). To overcome this limitation, a prodrug of PTL, dimethylamino-parthenolide (DMAPT, **2**), has been prepared:



(2).

DMAPT (also known as LC-1) is a water-soluble analogue and a clinical drug candidate with efficacy against AML stem and progenitor cells *in vivo* (canines), and has substantially improved bioavailability as compared to PTL. Notably, a Phase I trial with DMAPT has been recently initiated in the United Kingdom for the treatment of AML (Guzman, M. L., et al. *Blood* **2007**, *110*, 4427-4435; and Neelakantan, S., et al. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4346-4349).

Despite the promising cytotoxicity of PTL, the mechanism of action by which PTL targets CSCs is unclear. Previous studies have characterized PTL as an inhibitor of NF-κB signaling via the covalent modification of IKKβ kinase and the alkylation of NF-κB p65 protein (Garcia-Pineres, A. J., et al. *J. Biol. Chem.* **2001**, *276*, 39713-39720; Hehner, S. P., et al. *J. Immunol.* **1999**, *163*, 5617-5623; and Kwok, B. H. B., et al. *Chem. Biol.* **2001**, *8*, 759-766). However, others have shown that inhibition of NF-κB signaling in primary AML cells with an IκB superrepressor allele, which abolishes NF-κB activation via production a degradation-resistant IκBα suppressor protein, fails to promote the loss of leukemia CSC viability (Guzman, M. L., et al. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 16220-16225). PTL has also been shown to affect other cellular processes, such as blocking STAT3 phosphorylation of IL-6, inhibiting c-Jun *N*-terminal kinase (JNK), depleting cellular glutathione levels, increasing cellular oxidative stress by the generation of reactive oxygen species (ROS), activation of p53 and cellular caspases, and inhibition of Hsp70. See Sobota, R., et al. *Biochem. Biophys. Res. Comm.* **2000**, *267*, 329-333; Won, Y. K., et al. *Carcinogenesis* **2004**, *25*, 1449-1458; Wen, J., et al. *J. Biol. Chem.* **2002**, *277*, 38954-38964; Zhang, S. Y, et al. *Cancer Letters* **2004**, *211*, 175-188; and Pei, S. S., et al. In *American Society of Hematology Conference Abstract 2734* 2009; Vol. 114.

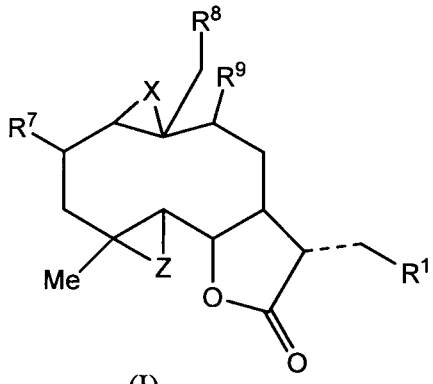
The level to which any or all of these events contribute to PTL's cytotoxicity towards AML CSCs is largely unknown. However, the feature that PTL and DMAPT (LC-1) can eradicate CSC

populations and not target normal hematopoietic stem cells make these natural products extremely promising molecules for future development.

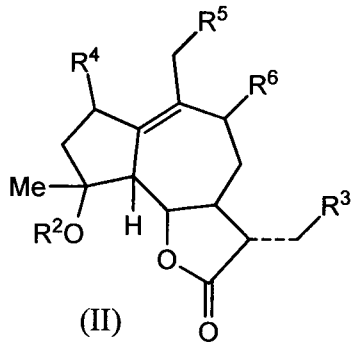
Currently, there is a need for novel anti-cancer agents, especially those agents that target differentiated as well as stem cell populations in cancer (Wang, J. C. Y. *Cell Stem Cell* **2007**, *1*, 497-501; and Park, C. Y., et al. *Mol. Ther.* **2009**, *17*, 219-230). Therapy regimens that fail to address cancer stem cell populations are predicted to fail by the cancer stem cell model (Ward, R. J., et al. *Ann. Rev. Pathol. Mech.* **2007**, *2*, 175-189). There is also an additional need for novel parthenolide compounds that can be used to study the mechanism of action of parthenolide and that have improved potency or pharmacological properties.

Summary of the Invention

The present invention provides novel compounds that possess anti-cancer and anti-inflammatory properties and that are useful for treating cancer and cardiovascular diseases. Accordingly there is provided a compound of the invention which is a compound of formula I, formula II, formula III, formula IV, or formula V:



(I)



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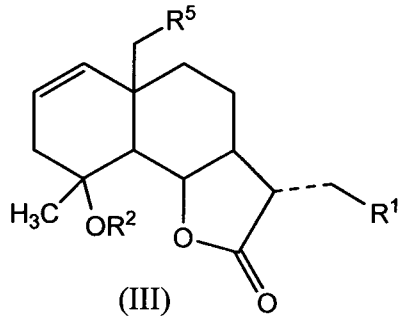

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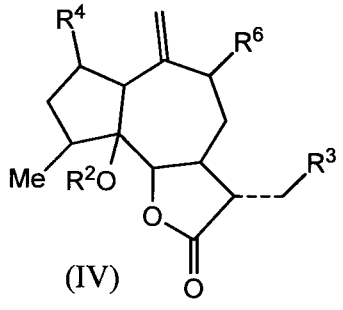

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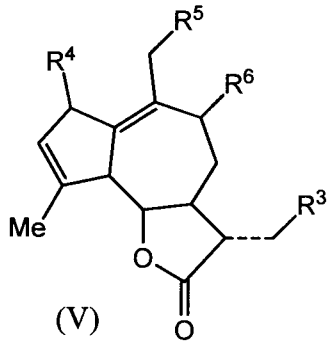
or



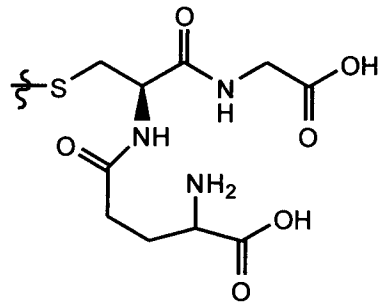
(V)

wherein:

X is O or CH_2, is absent, or taken together with the carbons to which it is attached forms a double bond;

Z is O or CH_2 or taken together with the carbons to which it is attached forms a double bond; the bond represented by --- is a single or a double bond;

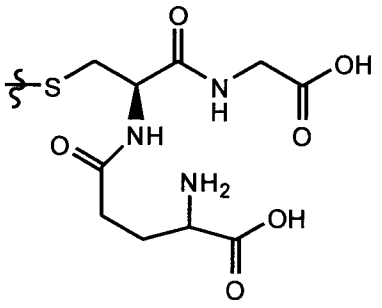
R^1 is H, halo, cyano, nitro, hydroxy, carboxy, trifluoromethyl, trifluoromethoxy, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxycarbonyl, $(C_1\text{-}C_6)$alkanoyloxy, aryl, heteroaryl, aryloxy, heteroaryloxy, a group of formula:



or $-NR^cR^d$; wherein any alkyl of R^1 is optionally substituted with one or more R^a ; and wherein any aryl, heteroaryl, or any aryl or heteroaryl portion of any aryloxy, or heteroaryloxy of R^1 is optionally substituted with one or more R^b;

R^2 is H, phosphate, trifluoromethyl, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxycarbonyl, aryl, heteroaryl, aryl$(C_1\text{-}C_6)$alkyl, or heteroaryl$(C_1\text{-}C_6)$alkyl; wherein any alkyl of R^2 is optionally substituted with one or more R^a ; and wherein any aryl, heteroaryl, or any aryl or heteroaryl portion of any aryl$(C_1\text{-}C_6)$alkyl or heteroaryl$(C_1\text{-}C_6)$alkyl of R^2 is optionally substituted with one or more R^b;

R^3 is H, halo, cyano, nitro, hydroxy, carboxy, trifluoromethyl, trifluoromethoxy, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxycarbonyl, $(C_1\text{-}C_6)$alkanoyloxy, aryl, heteroaryl, aryloxy, heteroaryloxy, a group of formula:



or $-NR^cR^d$; wherein any alkyl of R^3 is optionally substituted with one or more R^a ; and wherein any aryl, heteroaryl, or any aryl or heteroaryl portion of any aryloxy, or heteroaryloxy of R^3 is optionally substituted with one or more R^b;

R^4 is H or OR^v;

R^5 is H or OR^v;

R^6 is H or OR^v;

R^7 is H or OR^v;

R^8 is H or OR^v;

R^9 is H or OR^v;

each R^a is independently selected from halo, cyano, nitro, hydroxy, carboxy, oxo, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxycarbonyl, $(C_1\text{-}C_6)$alkanoyloxy, aryl, heteroaryl, aryloxy, heteroaryloxy, $(C_1\text{-}C_6)$alkylthio, $-OP(=O)(OH)_2$, $-S(O)R^k$, $-S(O)_2R^k$, $-S(O)_3R^k$, $-S(O)_2NR^eR^f$, and $-NR^eR^f$; wherein each aryl, heteroaryl, aryloxy, and heteroaryloxy is optionally substituted with one or more groups independently selected from halo, cyano, nitro, hydroxy, carboxy, trifluoromethyl, trifluoromethoxy, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxycarbonyl, $(C_1\text{-}C_6)$alkanoyloxy, $(C_1\text{-}C_6)$alkylthio, $-S(O)R^k$, $-S(O)_2R^k$, $-S(O)_3R^k$, $-S(O)_2NR^gR^h$, and $-NR^gR^h$;

each R^b is independently selected from halo, cyano, nitro, hydroxy, carboxy, trifluoromethyl, trifluoromethoxy, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxycarbonyl, $(C_1\text{-}C_6)$alkanoyloxy, aryl, heteroaryl, aryloxy, heteroaryloxy, $(C_1\text{-}C_6)$alkylthio, $-OP(=O)(OH)_2$, $-S(O)R^k$, $-S(O)_2R^k$, $-S(O)_3R^k$, $-S(O)_2NR^mR^n$, and $-NR^mR^n$; wherein each aryl, heteroaryl, aryloxy, and heteroaryloxy is optionally substituted with one or more groups independently selected from halo, cyano, nitro, hydroxy, carboxy, trifluoromethyl, trifluoromethoxy, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxycarbonyl, $(C_1\text{-}C_6)$alkanoyloxy, $(C_1\text{-}C_6)$alkylthio, $-S(O)R^k$, $-S(O)_2R^k$, $-S(O)_3R^k$, $-S(O)_2NR^mR^n$, and $-NR^mR^n$;

each R^c and R^d is independently selected from H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_6)$alkyl, hydroxy, aryl, heteroaryl, aryl$(C_1\text{-}C_6)$ alkyl and heteroaryl$(C_1\text{-}C_6)$ alkyl; or R^c and R^d together with the nitrogen to which they are attached form a aziridino, azetidino, morpholino, piperazino, pyrrolidino or piperidino; wherein any $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_6)$alkyl, aryl, heteroaryl, aryl$(C_1\text{-}C_6)$ alkyl or heteroaryl$(C_1\text{-}C_6)$alkyl of R^c and R^d is optionally substituted with one or more groups independently selected from hydroxy, carboxy, and NR^tR^u;

each R^e and R^f is independently selected from H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_6)$alkyl, aryl, heteroaryl, aryl$(C_1\text{-}C_6)$ alkyl and heteroaryl$(C_1\text{-}C_6)$ alkyl; or R^e and R^f together with the nitrogen to which they are attached form a aziridino, azetidino, morpholino, piperazino, pyrrolidino or piperidino; wherein any $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_6)$alkyl, aryl, heteroaryl, aryl$(C_1\text{-}C_6)$ alkyl or heteroaryl$(C_1\text{-}C_6)$alkyl of R^e and R^f is optionally substituted with one or more groups independently selected from hydroxy, carboxy, and NR^tR^u;

each R^g and R^h is independently selected from H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_6)$alkyl, aryl, heteroaryl, aryl$(C_1\text{-}C_6)$ alkyl and heteroaryl$(C_1\text{-}C_6)$ alkyl; or R^g and R^h together with the nitrogen to which they are attached form a aziridino, azetidino, morpholino, piperazino, pyrrolidino or piperidino; wherein any $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_6)$alkyl, aryl, heteroaryl, aryl$(C_1\text{-}C_6)$ alkyl or heteroaryl$(C_1\text{-}C_6)$alkyl of R^g and R^h is optionally substituted with one or more groups independently selected from hydroxy, carboxy, and NR^tR^u;

each R^k is independently selected from H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_6)$alkyl, aryl, heteroaryl, aryl$(C_1\text{-}C_6)$ alkyl and heteroaryl$(C_1\text{-}C_6)$ alkyl;

each R^m and R^n is independently selected from H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_6)$alkyl, aryl, heteroaryl, aryl$(C_1\text{-}C_6)$ alkyl and heteroaryl$(C_1\text{-}C_6)$ alkyl; or R^m and R^n together with the nitrogen to which they are attached form a aziridino, azetidino, morpholino, piperazino, pyrrolidino or piperidino; wherein any $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_6)$alkyl, aryl, heteroaryl, aryl$(C_1\text{-}C_6)$ alkyl or heteroaryl$(C_1\text{-}C_6)$alkyl of R^m and R^n is optionally substituted with one or more groups independently selected from hydroxy, carboxy, and NR^tR^u;

each R^t and R^u is independently selected from H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_6)$alkyl, aryl, heteroaryl, aryl$(C_1\text{-}C_6)$ alkyl and heteroaryl$(C_1\text{-}C_6)$ alkyl; or R^t and R^u together with the nitrogen to which they are attached form a aziridino, azetidino, morpholino, piperazino, pyrrolidino or piperidino; and

each R^v is H, $(C_1\text{-}C_6)$alkyl, phosphate, $(C_1\text{-}C_6)$alkoxycarbonyl, aryl, heteroaryl, aryl$(C_1\text{-}C_6)$alkyl, or heteroaryl$(C_1\text{-}C_6)$alkyl; wherein any alkyl of R^v is optionally substituted with one or more R^a ; and wherein any aryl, heteroaryl, or any aryl or heteroaryl portion of any aryl$(C_1\text{-}C_6)$alkyl or heteroaryl$(C_1\text{-}C_6)$alkyl of R^v is optionally substituted with one or more R^b;

or a salt thereof.

The invention also provides a pharmaceutical composition comprising a compound of formula I, formula II, formula III, formula IV, or formula V, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier.

The invention also provides a method for treating cancer in a mammal, comprising administering a compound of formula I, formula II, formula III, formula IV, or formula V, or a pharmaceutically acceptable salt thereof, to the mammal.

The invention also provides a method for treating a cardiovascular diseases (e.g. atherosclerosis) in a mammal, comprising administering a compound of formula I, formula II, formula III, formula IV, or formula V, or a pharmaceutically acceptable salt thereof, to the mammal.

The invention also provides a method for inhibiting the NF-κB signaling pathway in a cell, comprising contacting the cell *in vitro* or *in vivo* with an effective amount of a compound of formula I, formula II, formula III, formula IV, or formula V, or a pharmaceutically acceptable salt thereof.

Additionally, the invention provides a therapeutic method for preventing or treating a pathological condition or symptom in a mammal, such as a human, wherein the activity of the NF-κB signaling pathway is implicated and antagonism of its action is desired comprising administering to a mammal in need of such therapy, an effective amount of a compound of formula I, formula II, formula III, formula IV, or formula V, or a pharmaceutically acceptable salt thereof.

The invention provides a compound of formula I, formula II, formula III, formula IV, or formula V, or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment of cancer.

The invention provides a compound of formula I, formula II, formula III, formula IV, or formula V, or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment of a cardiovascular disease.

The invention provides a compound of formula I, formula II, formula III, formula IV, or formula V, or a pharmaceutically acceptable salt thereof, for use in medical therapy (e.g. for use in treating cancer or a cardiovascular diseases such as atherosclerosis).

The invention provides the use of a compound of formula I, formula II, formula III, formula IV, or formula V, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament useful for the treatment of cancer in a mammal, such as a human.

The invention provides the use of a compound of formula I, formula II, formula III, formula IV, or formula V, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament useful for the treatment of a cardiovascular disease (e.g. atherosclerosis) in a mammal, such as a human.

The invention also provides synthetic processes and synthetic intermediates disclosed herein that are useful for preparing compounds formula I, formula II, formula III, formula IV, or formula V, or salts thereof.

Detailed Description

The following definitions are used, unless otherwise described: halo is fluoro, chloro, bromo, or iodo. Alkyl, alkoxy, alkenyl, alkynyl, etc. denote both straight and branched groups; but reference to an individual radical such as propyl embraces only the straight chain radical, a branched chain isomer such as isopropyl being specifically referred to. Aryl denotes a phenyl radical or an ortho-fused bicyclic carbocyclic radical having about nine to ten ring atoms in which at least one ring is aromatic. Heteroaryl encompasses a radical of a monocyclic aromatic ring containing five or six ring atoms consisting of carbon and one to four heteroatoms each selected from the group consisting of non-peroxide oxygen, sulfur, and N(Y) wherein Y is absent or is H, O, $(C_1$-$C_4)$alkyl, phenyl or benzyl, as well as a radical of an ortho-fused bicyclic heterocycle of about eight to ten ring atoms comprising one to four heteroatoms each selected from the group consisting of non-peroxide oxygen, sulfur, and N(Y). As used herein (e.g. in the definition for R^2 and R^v) "phosphate" means a group $-P(=O)(OH)_2$.

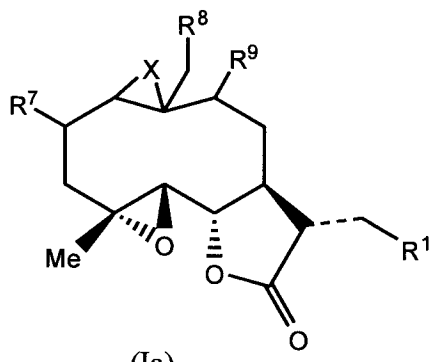
It will be appreciated by those skilled in the art that compounds of the invention having a chiral center may exist in and be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic, or stereoisomeric form, or mixtures thereof, of a compound of the invention, which possess the useful properties described herein, it being well known in the art how to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase).

Specific values listed below for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

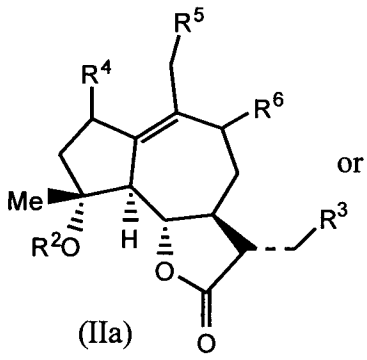
Specifically, $(C_1$-$C_6)$alkyl can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-butyl, pentyl, 3-pentyl, or hexyl; $(C_3$-$C_6)$cycloalkyl can be cyclopropyl, cyclobutyl, cyclopentyl, or

cyclohexyl; (C_1-C_6)alkoxy can be methoxy, ethoxy, propoxy, isopropoxy, butoxy, iso-butoxy, sec-butoxy, pentoxy, 3-pentoxy, or hexyloxy; (C_1-C_6)alkanoyl can be acetyl, propanoyl or butanoyl; (C_1-C_6)alkoxycarbonyl can be methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, pentoxycarbonyl, or hexyloxycarbonyl; (C_2-C_6)alkanoyloxy can be acetoxy, propanoyloxy, butanoyloxy, isobutanoyloxy, pentanoyloxy, or hexanoyloxy; aryl can be phenyl, indenyl, or naphthyl; and heteroaryl can be furyl, imidazolyl, triazolyl, triazinyl, oxazoyl, isoxazoyl, thiazolyl, isothiazoyl, pyrazolyl, pyrrolyl, pyrazinyl, tetrazolyl, pyridyl, (or its N-oxide), thienyl, pyrimidinyl (or its N-oxide), indolyl, isoquinolyl (or its N-oxide) or quinolyl (or its N-oxide).

A specific compound of the invention is a compound of formula Ia, IIa, or IIIa:

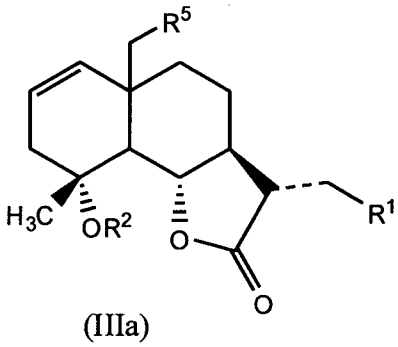


(Ia)



(IIa)

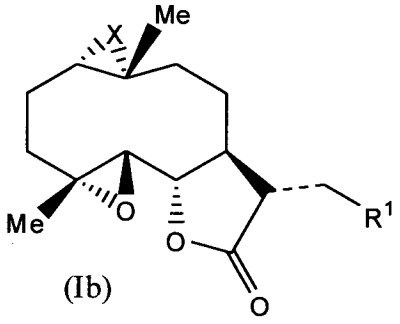
or



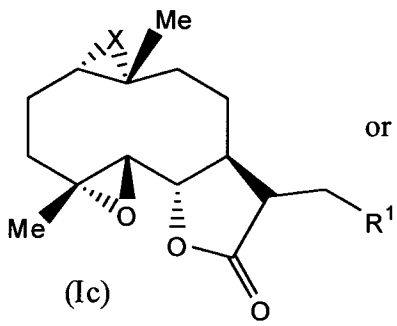
(IIIa)

or a salt thereof.

A specific compound of the invention is a compound of formula Ib, Ic, or Id:

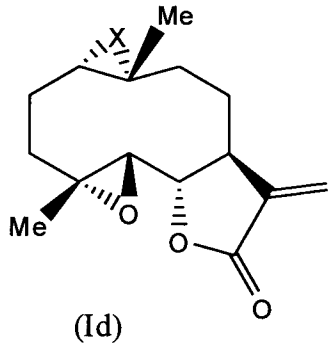


(Ib)



(Ic)

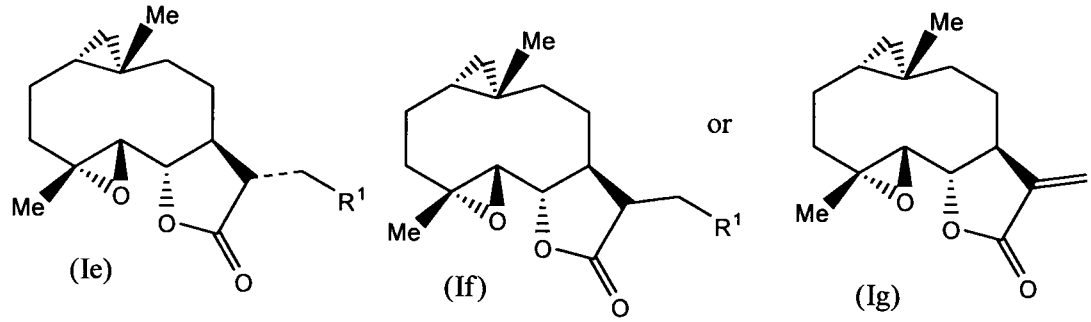
or



(Id)

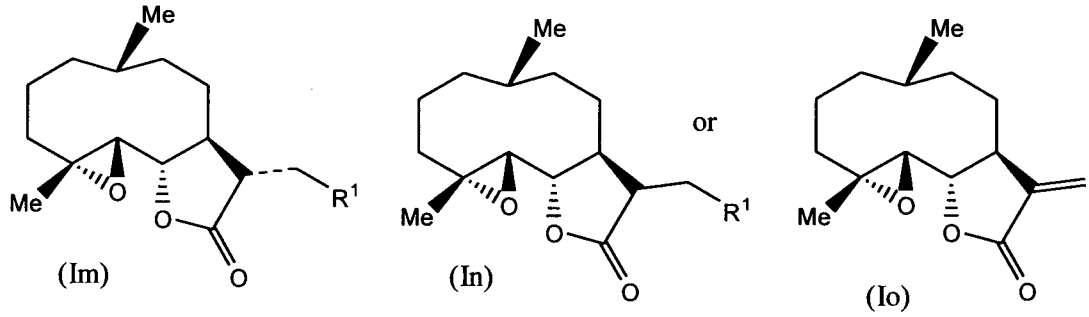
or a salt thereof.

A specific compound of the invention is a compound of formula Ie, If, or Ig:



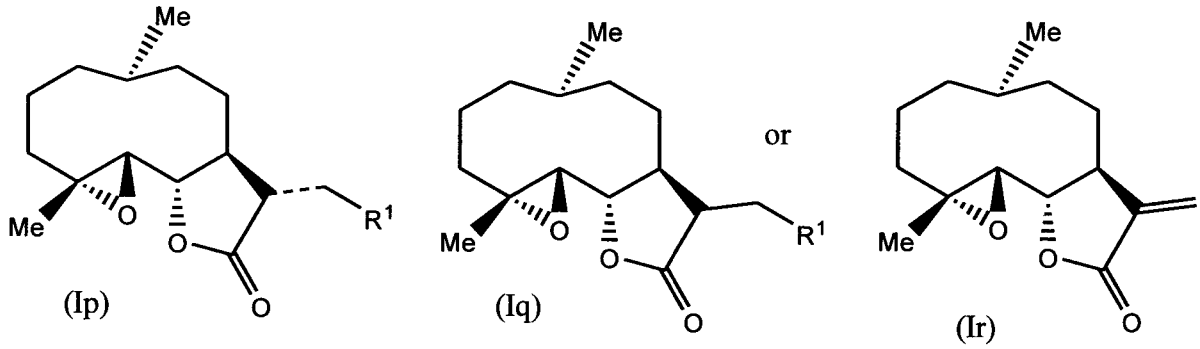
or a salt thereof.

A specific compound of the invention is a compound of formula Im, In, or Io:



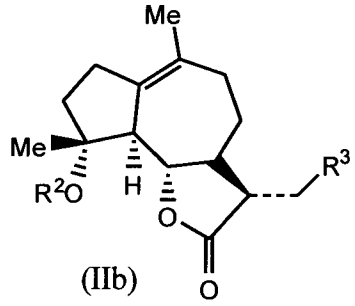
or a salt thereof.

A specific compound of the invention is a compound of formula Ip, Iq, or Ir:

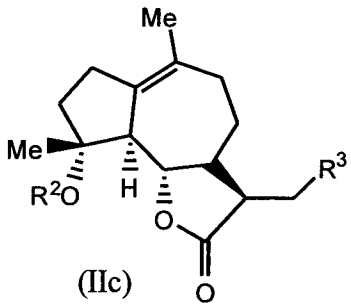


or a salt thereof.

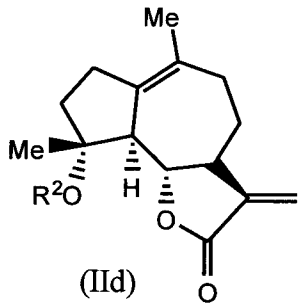
A specific compound of the invention is a compound of formula IIb, IIc, or IId:



(IIb)



(IIc)



(IId)

or a salt thereof.

A specific value for R^4 is H.

A specific value for R^5 is H.

A specific value for R^6 is H.

A specific value for R^4 is OH.

A specific value for R^5 is OH.

A specific value for R^6 is OH.

A specific value for R^7 is H.

A specific value for R^8 is H.

A specific value for R^9 is H.

A specific value for R^7 is OH.

A specific value for R^8 is OH.

A specific value for R^9 is OH.

A specific value for R^1 is H.

A specific value for R^1 is $-NR^cR^d$.

A specific value for R^2 is H.

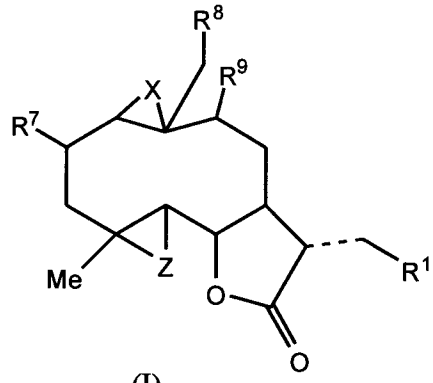
A specific value for R^2 is $(C_1\text{-}C_6)$alkyl, that is optionally substituted with one or more (e.g. 1, 2, 3, or 4) R^a.

A specific value for R^2 is $-P(=O)(OH)_2$.

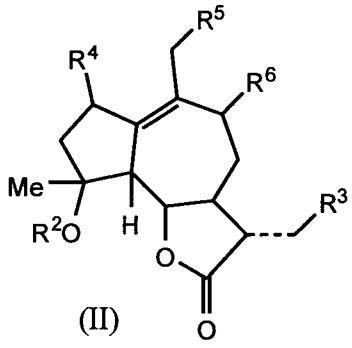
A specific value for R^3 is H.

A specific value for R^3 is $-NR^cR^d$.

A specific compound of the invention is a compound of formula I, formula II, or formula III:

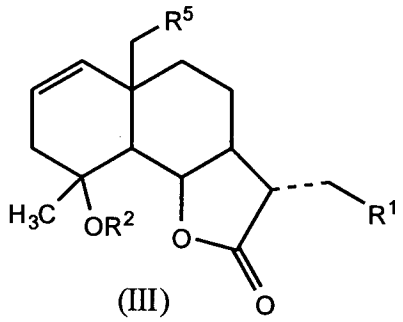


(I)



(II)

or



(III)

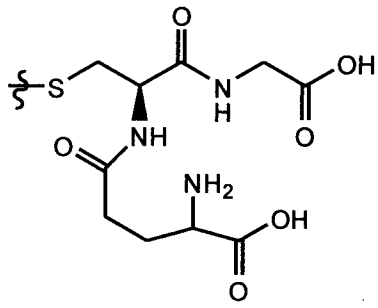
wherein:

X is O or CH_2, is absent, or taken together with the carbons to which it is attached forms a *cis*-double bond;

Z is O or CH_2 or taken together with the carbons to which it is attached forms a double bond;

the bond represented by --- is a single or a double bond;

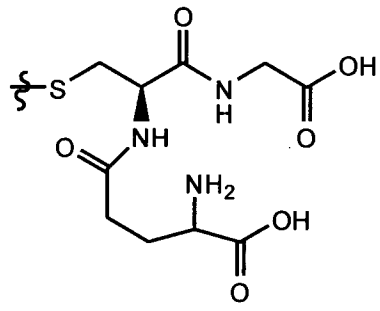
R^1 is H, halo, cyano, nitro, hydroxy, carboxy, trifluoromethyl, trifluoromethoxy, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxycarbonyl, $(C_1\text{-}C_6)$alkanoyloxy, aryl, heteroaryl, aryloxy, heteroaryloxy, a group of formula:



or $-NR^cR^d$; wherein any alkyl of R^1 is optionally substituted with one or more R^a; and wherein any aryl, heteroaryl, or any aryl or heteroaryl portion of any aryloxy, or heteroaryloxy of R^1 is optionally substituted with one or more R^b;

R^2 is H, trifluoromethyl, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxycarbonyl, aryl, heteroaryl, aryl$(C_1\text{-}C_6)$alkyl, or heteroaryl$(C_1\text{-}C_6)$alkyl; wherein any alkyl of R^2 is optionally substituted with one or more R^a; and wherein any aryl, heteroaryl, or any aryl or heteroaryl portion of any aryl$(C_1\text{-}C_6)$alkyl or heteroaryl$(C_1\text{-}C_6)$alkyl of R^2 is optionally substituted with one or more R^b;

R^3 is H, halo, cyano, nitro, hydroxy, carboxy, trifluoromethyl, trifluoromethoxy, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxycarbonyl, $(C_1\text{-}C_6)$alkanoyloxy, aryl, heteroaryl, aryloxy, heteroaryloxy, a group of formula:



or $-NR^cR^d$; wherein any alkyl of R^3 is optionally substituted with one or more R^a ; and wherein any aryl, heteroaryl, or any aryl or heteroaryl portion of any aryloxy, or heteroaryloxy of R^3 is optionally substituted with one or more R^b;

R^4 is H or OR^v;

R^5 is H or OR^v;

R^6 is H or OR^v;

R^7 is H or OR^v;

R^8 is H or OR^v;

R^9 is H or OR^v;

each R^a is independently selected from halo, cyano, nitro, hydroxy, carboxy, oxo, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxycarbonyl, $(C_1\text{-}C_6)$alkanoyloxy, aryl, heteroaryl, aryloxy, heteroaryloxy, $(C_1\text{-}C_6)$alkylthio, $-S(O)R^k$, $-S(O)_2R^k$, $-S(O)_3R^k$, $-S(O)_2NR^eR^f$, and $-NR^eR^f$; wherein each aryl, heteroaryl, aryloxy, and heteroaryloxy is optionally substituted with one or more groups independently selected from halo, cyano, nitro, hydroxy, carboxy, trifluoromethyl, trifluoromethoxy, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxycarbonyl, $(C_1\text{-}C_6)$alkanoyloxy, $(C_1\text{-}C_6)$alkylthio, $-S(O)R^k$, $-S(O)_2R^k$, $-S(O)_3R^k$, $-S(O)_2NR^gR^h$, and $-NR^gR^h$;

each R^b is independently selected from halo, cyano, nitro, hydroxy, carboxy, trifluoromethyl, trifluoromethoxy, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxycarbonyl, $(C_1\text{-}C_6)$alkanoyloxy, aryl, heteroaryl, aryloxy, heteroaryloxy, $(C_1\text{-}C_6)$alkylthio, $-S(O)R^k$, $-S(O)_2R^k$, $-S(O)_3R^k$, $-S(O)_2NR^mR^n$, and $-NR^mR^n$; wherein each aryl, heteroaryl, aryloxy, and heteroaryloxy is optionally substituted with one or more groups independently selected from halo, cyano, nitro, hydroxy,

carboxy, trifluoromethyl, trifluoromethoxy, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkanoyloxy, (C_1-C_6)alkylthio, -S(O)R^k, -S(O)$_2R^k$, -S(O)$_3R^k$, -S(O)$_2NR^mR^n$, and –NR^mR^n;

each R^c and R^d is independently selected from H, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, hydroxy, aryl, heteroaryl, aryl(C_1-C_6) alkyl and heteroaryl(C_1-C_6) alkyl; or R^c and R^d together with the nitrogen to which they are attached form a aziridino, azetidino, morpholino, piperazino, pyrrolidino or piperidino; wherein any (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, aryl, heteroaryl, aryl(C_1-C_6) alkyl or heteroaryl(C_1-C_6)alkyl of R^c and R^d is optionally substituted with one or more groups independently selected from hydroxy, carboxy, and NR^tR^u;

each R^e and R^f is independently selected from H, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, aryl, heteroaryl, aryl(C_1-C_6) alkyl and heteroaryl(C_1-C_6) alkyl; or R^e and R^f together with the nitrogen to which they are attached form a aziridino, azetidino, morpholino, piperazino, pyrrolidino or piperidino; wherein any (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, aryl, heteroaryl, aryl(C_1-C_6) alkyl or heteroaryl(C_1-C_6)alkyl of R^e and R^f is optionally substituted with one or more groups independently selected from hydroxy, carboxy, and NR^tR^u;

each R^g and R^h is independently selected from H, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, aryl, heteroaryl, aryl(C_1-C_6) alkyl and heteroaryl(C_1-C_6) alkyl; or R^g and R^h together with the nitrogen to which they are attached form a aziridino, azetidino, morpholino, piperazino, pyrrolidino or piperidino; wherein any (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, aryl, heteroaryl, aryl(C_1-C_6) alkyl or heteroaryl(C_1-C_6)alkyl of R^g and R^h is optionally substituted with one or more groups independently selected from hydroxy, carboxy, and NR^tR^u;

each R^k is independently selected from H, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, aryl, heteroaryl, aryl(C_1-C_6) alkyl and heteroaryl(C_1-C_6) alkyl;

each R^m and R^n is independently selected from H, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, aryl, heteroaryl, aryl(C_1-C_6) alkyl and heteroaryl(C_1-C_6) alkyl; or R^m and R^n together with the nitrogen to which they are attached form a aziridino, azetidino, morpholino, piperazino, pyrrolidino or piperidino; wherein any (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, aryl, heteroaryl, aryl(C_1-C_6) alkyl or heteroaryl(C_1-C_6)alkyl of R^m and R^n is

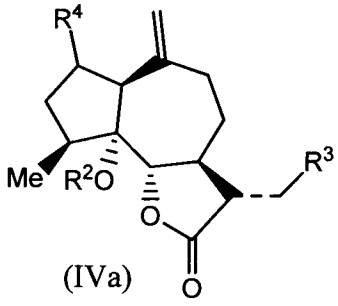
optionally substituted with one or more groups independently selected from hydroxy, carboxy, and NR^tR^u;

each R^t and R^u is independently selected from H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_6)$alkyl, aryl, heteroaryl, aryl$(C_1\text{-}C_6)$ alkyl and heteroaryl$(C_1\text{-}C_6)$ alkyl; or R^t and R^u together with the nitrogen to which they are attached form a aziridino, azetidino, morpholino, piperazino, pyrrolidino or piperidino; and

each R^v is H, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxycarbonyl, aryl, heteroaryl, aryl$(C_1\text{-}C_6)$alkyl, or heteroaryl$(C_1\text{-}C_6)$alkyl; wherein any alkyl of R^v is optionally substituted with one or more R^a ; and wherein any aryl, heteroaryl, or any aryl or heteroaryl portion of any aryl$(C_1\text{-}C_6)$alkyl or heteroaryl$(C_1\text{-}C_6)$alkyl of R^v is optionally substituted with one or more R^b;

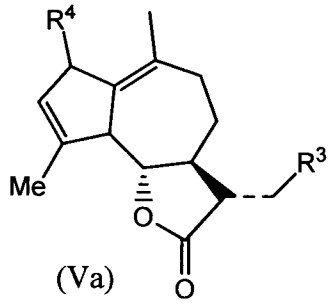
or a salt thereof.

A specific compound of the invention is a compound of formula IVa, or Va:



(IVa)

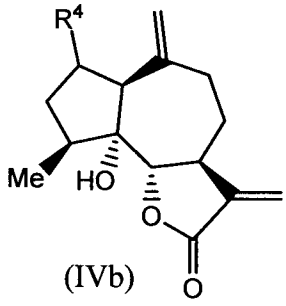
or



(Va)

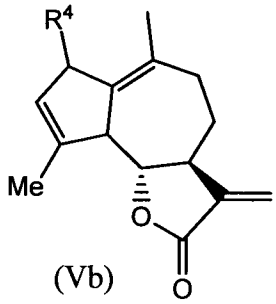
or a salt thereof.

A specific compound of the invention is a compound of formula IVb, or Vb:



(IVb)

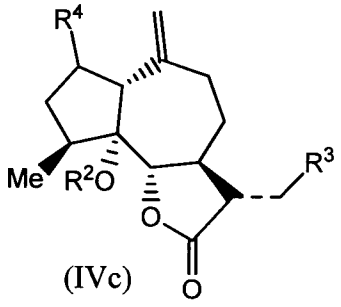
or



(Vb)

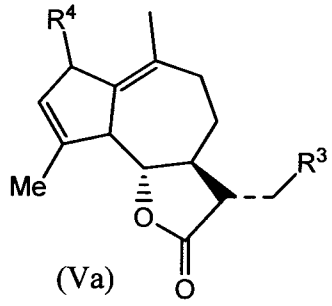
or a salt thereof.

A specific compound of the invention is a compound of formula IVc or formula Va:



(IVc)

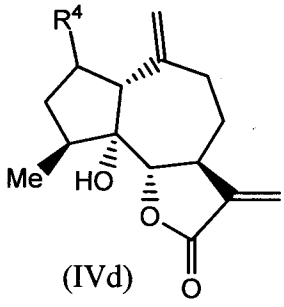
or



(Va)

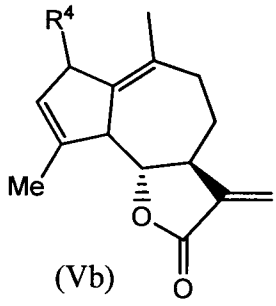
or a salt thereof.

A specific compound of the invention is a compound of formula IVd, or formula Vb:



(IVd)

or

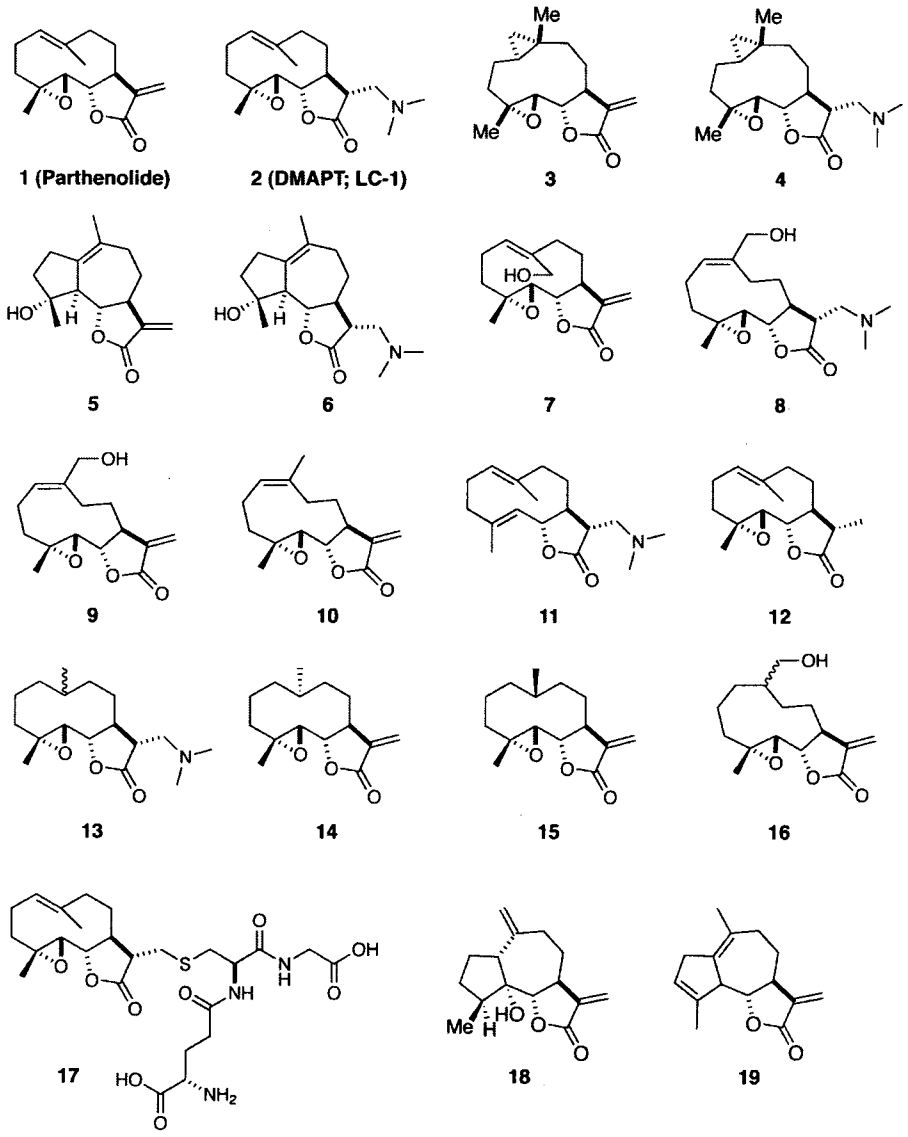


(Vb)

or a salt thereof.

In one embodiment of the invention, when a compound is shown with a wedged (up) or dashed (back) bond the compound may be enriched by about 60%, 80%, 90%, 95%, 98%, or 99% in the absolute stereoisomer represented.

A specific compound of the invention is compound **3**, **4**, **6**, **8**, **13**, **14**, **15**, or **16**, or a salt thereof.



A specific compound of the invention is compound **3**, **4**, **14**, or **15**, or a salt thereof.

In one embodiment of the invention, the compound of the invention is not compound **1**, **2**, **5**, **7**, **9**, **10**, **11**, **12**, **17**, **18**, or **19**, or a salt thereof.

In cases where compounds are sufficiently basic or acidic, a salt of a compound of formula I, formula II, formula III, formula IV, or formula V can be useful as an intermediate for isolating or purifying a compound of formula I. Additionally, administration of a compound of formula I, formula II, formula III, formula IV, or formula V as a pharmaceutically acceptable acid or base salt may be appropriate. Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids which form a physiological acceptable anion, for example, tosylate, methanesulfonate, fumarate,

acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, α-ketoglutarate, and α-glycerophosphate. Suitable inorganic salts may also be formed, including hydrochloride, sulfate, nitrate, bicarbonate, and carbonate salts.

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example calcium) salts of carboxylic acids can also be made.

The compounds of formula I, formula II, formula III, formula IV, or formula V can be formulated as pharmaceutical compositions and administered to a mammalian host, such as a human patient in a variety of forms adapted to the chosen route of administration, i.e., orally or parenterally, by intravenous, intramuscular, topical or subcutaneous routes.

Thus, the present compounds may be systemically administered, e.g., orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2% to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as

preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

The active compound may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active compound or its salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

For topical administration, the present compounds may be applied in pure form, i.e., when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or

formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers.

Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

Examples of useful dermatological compositions which can be used to deliver the compounds to the skin are known to the art; for example, see Jacquet et al. (U.S. Pat. No. 4,608,392), Geria (U.S. Pat. No. 4,992,478), Smith et al. (U.S. Pat. No. 4,559,157) and Wortzman (U.S. Pat. No. 4,820,508).

Useful dosages of the compounds can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949.

The amount of the compound, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.

In general, however, a suitable dose will be in the range of from about 0.5 to about 100 mg/kg, e.g., from about 10 to about 75 mg/kg of body weight per day, such as 3 to about 50 mg per kilogram body weight of the recipient per day, preferably in the range of 6 to 90 mg/kg/day, most preferably in the range of 15 to 60 mg/kg/day.

The compound is conveniently formulated in unit dosage form; for example, containing 5 to 1000 mg, conveniently 10 to 750 mg, most conveniently, 50 to 500 mg of active ingredient per unit dosage form. In one embodiment, the invention provides a composition comprising a compound of the invention formulated in such a unit dosage form.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator or by application of a plurality of drops into the eye.

Compounds of the invention can also be administered in combination with other therapeutic agents, for example, other agents that are useful for the treatment of cancer. Accordingly, in one embodiment the invention also provides a composition comprising a compound of the invention, or a pharmaceutically acceptable salt thereof, at least one other therapeutic agent, and a pharmaceutically acceptable diluent or carrier. The invention also provides a kit comprising a compound of the invention, or a pharmaceutically acceptable salt thereof, at least one other therapeutic agent, packaging material, and instructions for administering the compound of the invention or the pharmaceutically acceptable salt thereof and the other therapeutic agent or agents to an animal to treat cancer.

The cytotoxicity of a compound of the invention may be determined using pharmacological models which are well known, or using Test A described below.

Test A.

Mammalian Cell Culture. Cell lines were maintained in a humidified 5% CO_2 environment at 37 °C. CCRF-CEM acute lymphoblastic leukemia cells (ATCC, CCL-119) were cultured in RPMI-1640 media (ATCC, 30-2001) supplemented with 10% fetal bovine serum (FBS, Gibco), penicillin (100 I.U./mL), and streptomycin (100 µg/mL) (ATCC, 30-2300) at a density of 2 10^5 - 2 10^6 cells/mL. HL-60 acute promyelocytic leukemia cells (ATCC, CCL-240) were cultured in IMDM media (ATCC, 30-2005) supplemented with 10% FBS, penicillin (100 I.U./mL), and streptomycin (100 µg/mL) at a density of 1 10^5 - 1 10^6 cells/mL. DU-145 prostate cancer cells (ATCC, HTB-81) were cultured in EMEM media (ATCC, 30-2003) supplemented with 10% FBS, penicillin (100 I.U./mL), and streptomycin (100 µg/mL). U-87 MG glioblastoma cells (ATCC, HTB-14) were cultured in EMEM media (ATCC, 30-2003) supplemented with 10% FBS, penicillin (100 I.U./mL), and streptomycin (100 µg/mL). GBM6 primary glioblastoma cells (a gift from Professor John Ohlfest, University of Minnesota) were cultured under serum-free conditions utilizing Neural Stem Cell (NSC) complete growth media. This media was prepared by treating a 500 mL bottle of DMEM/F12 (1:1) media containing L-glutamine (ThermoSci. SH3027101) with B-27 supplement without Vitamin A (10 mL of a 50X solution; Gibco 12587-010), N-2 supplement (5 mL of a 100X solution; Gibco 17502-048), normocin (100 µg/mL; Invivogen ant-nr-1), penicillin (50 I.U./mL; Cellgro 30-001-CI), and

streptomycin (50 μg/mL; Cellgro 30-001-CI). In addition, cytokines, human EGF (20 ng/μL in 0.1% BSA/PBS solution; PeptroTech; 100-15) and human FGF-basic (20 ng/μL in 0.1% BSA/PBS solution; PeproTech; 100-18B), were added to aliquots of the NSC media prior to splitting and plating the cell cultures. Trypsinization of GBM6 cells was achieved with the use of TrypLE Express solution (Gibco 12604013) in place of trypsin.

Mammalian Cytotoxicity Assays. CCRF-CEM and HL-60 cells were seeded at a density of 10,000 cells/well in cell culture media (50 μL) in standard 96-well plates (Costar) 24 h prior to treatment. DU-145, U87-MG, and GBM6 cells were seeded at a density of 5,000 cells/well in cell culture media (50 μL) in standard 96-well plates (Costar). Blank (no cells) wells and control (vehicle control treated) wells were prepared with each experiment. Compounds were serially diluted in pre-warmed media and dosed to cells (final volume/well = 100 μL; final DMSO concentration = 0.5%). Approximately 2 h before the end of the treatment period (48 h), Alamar Blue (Invitrogen) cell viability reagent was added to each well (10 μL). This procedure yields a quantitative measure of cell viability by evaluating the ability of metabolically active cells (which are proportional to the number of living cells) to convert resazurin (non-fluorescent dye) to red-fluorescent resorufin. Fluorescence data were obtained on either a Molecular Devices SpectraMax M2 plate reader or an LJL BioSystems HT Analyst plate reader. Background fluorescence (no cell controls) was subtracted from each well and cellular viability values following compound treatment were normalized to vehicle-only treated wells (control wells only treated with aqueous DMSO, which were arbitrarily assigned 100% viability). Individual IC_{50} curves were generated by fitting data to the sigmoidal (dose response) function of varied slope in GraphPad Prism (v. 5.0) software. Only curve fits with $r^2 > 0.95$ were deemed sufficient. Each experiment was performed in biological triplicate and mean IC_{50} values (with standard deviation) were calculated from the individual IC_{50} values obtained from each replicate.

Murine Cytotoxicity Assays. The anti-leukemic activities of **1-19** were studied in murine cell culture models of drug-resistant acute myeloid leukemia (AML). The cell lines used are B117P, B117H, B140P and B140H. B117P and B140P are murine AML cell lines derived from a BXH-2 strain of mice that develop AML (*J. Virol* **1995**, *69*, 5095). These cell lines are *cytarabine-sensitive* models of AML. Continuous low-dose culturing of B117P and B140P cell lines with cytarabine yielded B117H and B140H, respectively, which can tolerate cytarabine concentrations 500-1000 times greater than the

parental cell lines (*Exp. Hematol.* **2006**, *34*, 631). These cell lines are *cytarabine-resistant* models of AML and are excellent tools for studying drug resistant disease. Importantly, the B117P cells display phenotypic markers consistent with stem cells or early progenitors, such as CD34 and c-kit, while the B140P cells do not. This diversity between the cell lines, plus the abundance of knowledge already accumulated, makes these lines a valuable tool for studying drug responses in AML. Cell viability against these cell lines was measured by standard MTS colorimetric assay.

Data for representative compounds of the invention are shown in the following tables.

DU-145 Prostate Cancer Cells

Compound	DU-145 IC_{50} (uM) ± S.D.
1	8.89 ± 4.60
2	3.26 ± N/A
3	16.93 ± 2.75
4	10.10 ± N/A
5	11.40 ± N/A
8	24.93 ± N/A
11	16.14 ± 2.34
12	> 100
13	13.67 ± 2.46
14	5.49 ± 1.51
15	6.19 ± 2.82
17	> 100

CCRF-CEM T-Cell Leukemia Cells

Compound	CCRF-CEM IC_{50} (μM) ± S.D.
1	2.86 ± N/A
2	1.87 ± 0.36
3	0.92 ± 0.10
4	1.80 ± N/A
5	2.70 ± 1.08
6	15.31 ± N/A
7	2.55 ± N/A
8	4.71 ± N/A
9	5.50 ± 1.23
10	2.73 ± N/A
11	2.89 ± N/A
12	> 100
13	5.23 ± 2.23
14	2.54 ± 2.09
15	1.62 ± 0.35
16	3.67 ± N/A
17	7.38 ± N/A
18	4.83 ± 1.54
19	9.98 ± 0.61

HL-60 Acute Myelogenous Leukemia Cells

Compound	HL-60 IC_{50} (μM) ± S.D.
1	9.26 ± 3.84
2	6.10 ± N/A
3	4.40 ± 1.31
4	6.51 ± 2.69
5	9.16 ± 2.20
6	> 50
7	21.62 ± N/A
8	23.2 ± N/A
12	> 100
14	7.86 ± N/A
15	7.35 ± N/A
16	41.8 ± N/A
18	11.58 ± 0.31
19	15.86 ± 4.36

U-87 MG Glioblastoma Cells

Compound	U-87 MG IC_{50} (μM) ± S.D.
1	5.79 ± 2.29
2	8.84 ± 1.90
9	22.88 ± N/A
11	22.34 ± 4.80
12	> 100
13	22.49 ± 4.54
14	7.50 ± 0.40
15	7.74 ± 1.13
16	26.82 ± 2.33
17	> 100

GBM6 Primary Glioblastoma Cells

Compound	GBM6 IC_{50} (μM) ± S.D.
1	3.39 ± 1.09
2	3.47 ± 1.05
3	1.59 ± 0.34
4	3.00 ± N/A
5	8.15 ± N/A
6	34.68 ± N/A
8	8.63 ± 2.41
9	3.51 ± N/A
11	11.57 ± 0.83
12	> 100
13	8.26 ± N/A
14	2.00 ± 0.32
15	2.04 ± 0.26
16	17.12 ± N/A
17	> 100
18	8.41 ± 1.83
19	9.38 ± 0.35

Screening in Murine AML Cell lines B117P, B117H, B140P, and B140H

Compound	B117P IC_{50} (μM) ± S.D.	B117H IC_{50} (μM) ± S.D.	B140P IC_{50} (μM) ± S.D.	B140H IC_{50} (μM) ± S.D.
1	1.1 ± 0.2	2.0 ± 0.1	2.9 ± 0.6	3.6 ± 0.9
2	1.5 ± 0.4	2.8 ± 1.8	4.1 ± 1.2	5.7 ± 1.8
4	1.9 ± 1.8	4.4 ± 0.7	4.2 ± 1.2	4.1 ± 1.3
5	6.4 ± 1.0	8.8 ± 1.7	10.0 ± 0.4	9.3 ± 1.5

AML Colony Forming Assay. AML proliferation is dependent on the existence of the cancer stem cell population, and drug-mediated elimination of AML CSCs will prohibit colony formation (*Nat. Immunol.* **2004**, *5*, 738). A colony-forming assay with **5** was performed. A low concentration of primary murine leukemia cells (harboring *Mll/AF9* and $NRAS^{G12V}$ transgenes) were treated with vehicle control or 38 μM **5** and then plated in methylcellulose semi-solid media containing IL-3, IL-6, GM-CSF, and SCF. As a result, individual cells were suspended in the media, and therefore, resulting colonies represent the outgrowth from single cells with replicative capacity (stem cells). Colonies were then counted for both vehicle control and **5**. Dosing of the vehicle control yields approximately 26 colonies per 10,000 nucleated cells in this assay. Repeating this experiment with **5** revealed no colony formation, suggesting the AML CSC population was eradicated by the compound.

Compound	Dose (μM)	Colonies/10k nucleated cells
Vehicle	N/A	26
5	38	0

The pharmacokinetic properties of a compound of the invention may be determined using pharmacological models which are well known, or using Test B described below.

Test B. **Pharmacokinetics (PK) Studies in Mice**

Pharmacokinetics of 2 and 4. A pharmacokinetics study was performed with compounds **2** and **4** in CD1 male mice. Both compounds **2** and **4** were synthesized as their mono-fumarate salts. Testing was performed at Apredica in Watertown, MA by contract service. Details of the PK experiment are as follows:

LC/MS/MS Method development. The signal was optimized for each compound by ESI positive or negative ionization mode. An MS2 scan or a SIM scan was used to optimize the fragmenter voltage

and a product ion analysis was used to identify the best fragment for analysis, and the collision energy was optimized using a product ion or MRM scan. An ionization ranking was assigned indicating the compound's ease of ionization.

Analysis. Samples were analyzed by LC/MS/MS using an Agilent 6410 mass spectrometer coupled with an Agilent 1200 HPLC and a CTC PAL chilled autosampler, all controlled by MassHunter software (Agilent). After separation on a C18 reverse phase HPLC column (Agilent, Waters, or equivalent) using an acetonitrile-water gradient system, peaks were analyzed by mass spectrometry (MS) using ESI ionization in MRM mode.

Sample preparation. Plasma and brain samples were thawed on ice and kept at 4 °C during processing. Brain tissues were homogenized in 50 mM potassium phosphate, pH 7.4. An aliquot of plasma or brain homogenate sample or calibration sample were mixed with three volumes of methanol containing internal standard, incubated on ice for 5 min, and centrifuged. The protein-free supernatant was used for analysis.

Calibration samples. A working dilution of test agent in DMSO at 50 times the final concentration was prepared and serially diluted samples were prepared. These samples were diluted 50-fold into Mouse plasma or brain homogenate and processed as above.

Animals. Species and sex: Mouse, male. Strain: CD1. Number: 12. All procedures in this protocol are in compliance with the Animal Welfare Act, the Guide for the Care and Use of Laboratory Animals, and the Office of Laboratory Animal Welfare. In the opinion of the Sponsor and Principal Investigator, this study did not unnecessarily duplicate any previous work.

Study Design. Test Article Formulation: Test articles were formulated in 0.5% methylcellulose; the dosing solution was freshly made on the dosing day and dosed the animals immediately: PO at 100 mg/Kg, (10 mg/mL, 10 mL/kg). The following is the study table:

Molecule Tested	Route	Type of Mouse	# of animals	Dose (mg/Kg)	Sample Collected	Collection time points
4	PO	CD-1	3	100	Plasma	1, 4 hours
4	PO	CD-1	3	100	Brain	1, 4 hours
2	PO	CD-1	3	100	Plasma	1, 4 hours
2	PO	CD-1	3	100	Brain	1, 4 hours

Test Article administration. Mice were provided a single dose by body weight via oral gavage at 100 mg/Kg (10 mg/mL, 10 mL/kg)

Sampling. Blood samples were collected into K_2EDTA microtainer tubes for plasma separation. Blood samples were centrifuged at 4 °C at 6,000 RPM for 5 minutes. Decanted plasma samples were stored at -80 °C until analysis. Brains were perfused and collected for the oral study. The tissue samples were stored at -80 °C until analysis.

Clinical Observations. There were no clinical observations to report as all the mice were normal.

Results. The following tables show the results from the PK study of **2** and **4**.

Compound 2 Measured in Mouse Plasma:

Mouse ID	Dosage	Time (hr)	Compound **2** in plasma (ng/mL)	Compound **1** in plasma (ng/mL)
1-1	PO (100 mg/kg)	1	2329	1516
1-2	PO (100 mg/kg)	1	3600	2768
1-4	PO (100 mg/kg)	4	116	195
1-4	PO (100 mg/kg)	4	113	195
1-4	PO (100 mg/kg)	4	--	243

Compound 2 Measured in Mouse Brain:

Mouse ID	Dosage	Time (hr)	Compound **2** in brain (ng/g)	Compound **1** in brain (ng/g)
1-1	PO (100 mg/kg)	1	4996	2129
1-2	PO (100 mg/kg)	1	7505	2676
1-4	PO (100 mg/kg)	4	240	74.7
1-4	PO (100 mg/kg)	4	204	66.1
1-4	PO (100 mg/kg)	4	581	197

Compound 4 Measured in Mouse Plasma:

Mouse ID	Dosage	Time (hr)	Compound **4** in plasma (ng/mL)	Compound **3** in plasma (ng/mL)
1-1	PO (100 mg/kg)	1	525	106
1-2	PO (100 mg/kg)	1	368	103
1-4	PO (100 mg/kg)	4	10.0	16.2
1-4	PO (100 mg/kg)	4	5.3	15.8
1-4	PO (100 mg/kg)	4	7.6	1.7

Compound 4 Measured in Mouse Brain:

Mouse ID	Dosage	Time (hr)	Compound **4** in brain (ng/g)	Compound **3** in brain (ng/g)
1-1	PO (100 mg/kg)	1	1763	118
1-2	PO (100 mg/kg)	1	869	94.9
1-4	PO (100 mg/kg)	4	27	--
1-4	PO (100 mg/kg)	4	29	--
1-4	PO (100 mg/kg)	4	22	--

The above results demonstrate that representative compounds of the invention (compounds **2** and **4**) accumulate to micromolar levels in serum and, therefore, reach efficacious levels with respect to their IC_{50} anticancer activties as determined by cell culture experiments. Therefore, biologically relevant levels of these molecules can be achieved in serum. Additionally, both compounds **2** and **4** are highly brain penetrant and accumulate to higher levels in brain tissue than serum. The ratio of brain/serum levels (about 2:1) surpasses that observed with temozolomide (about 1:2.5), which is the front-line small molecule used to treat glioblastomas. Since most small molecules against brain tumors fail due to inability to cross the blood-brain barrier (or are rapidly removed by efflux mechanisms), the feature that these molecules accumulate to high levels in brain tissue is significant.

The invention will now be illustrated by the following non-limiting Examples.

EXAMPLES

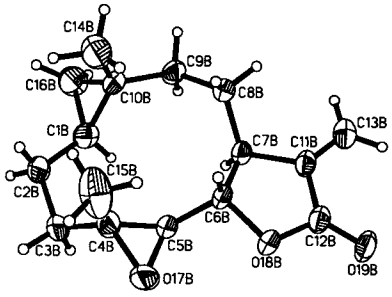
General. Chemical reagents were typically from Aldrich or Acros and were used without additional purification unless explicitly noted. Solvents were from Fisher Scientific. Parthenolide (**1**) was purchased from Enzo Life Sciences and repurified by SiO_2 chromatography before use. Unless otherwise noted, reactions were performed under an atmosphere of dry nitrogen. MPLC chromatography was preformed on a Teledyne-Isco Combiflash Rf-200 instrument utilizing Redisep Rf Gold High Performance silica gel columns or self-packed columns with SiliCycle SiliaFlash 60Å silica gel. Preparative HPLC purifications were performed on an Agilent 1200 series instrument equipped with a Zorbax SB-C18 column (21.2 x 250 mm, 7 μm; Agilent Technologies). Nuclear magnetic resonance (NMR) spectroscopy employed a Bruker Avance 400 MHz (for ^1H) instrument. Chemical shifts were normalized to internal solvent peaks or tetramethylsilane. X-ray crystal structures were solved by Victor G. Young, Jr. at the X-Ray Crystallographic Laboratory, University of Minnesota, Department of Chemistry.

Dimethylamino parthenolide (DMAPT; LC-1; compound 2) was prepared as previously described (*Bioorg. Med. Chem. Lett.* **2009**, *19*, 4346).

Example 1. Preparation of Compound **3**

A 0.20 M solution of $Zn(CH_2I)_2 \cdot DME$ complex was made in the following manner: diethyl zinc (1.0 M solution in hexanes, 4.0 mL, 4 mmol) was added to CH_2Cl_2 (20 mL) and DME (0.50 mL) at 0 °C under N_2. Diiodomethane (0.80 mL, 9.92 mmol) was added and the mixture was stirred for 10 minutes. This material was added dropwise over 10 minutes to a solution of parthenolide (**1**, 90 mg, 0.36 mmol) in CH_2Cl_2 (2 mL) at 0 °C. The mixture was stirred for 1 hour at 0 °C, and the stirring was continued overnight with gradual warming to room temperature. The crude material was quenched by pouring into NH_4Cl (saturated, aq., 20 mL) and then extracted with CH_2Cl_2 (20 mL, 4x). The combined organic layers were washed with $NaHCO_3$ (saturated, aq., 20 mL), brine (saturated, aq., 20 mL) and then dried over Na_2SO_4. The crude material was MPLC purified using SiO_2 (10-30% EtOAc in hexanes over 15 minutes) to yield compound **3** (36 mg, 40%) as a colorless oil and recovered **1** (37 mg, 41%). ^1H NMR (400 MHz, $CDCl_3$) δ: 6.28 (d, J = 3.5 Hz, 1H), 5.57 (d, J = 3.3 Hz, 1H), 3.96 (t, J = 3.3 Hz, 1H), 2.98 (d, J = 9.0 Hz, 1H), 2.67 (ddd, J = 9.1, 5.9, 2.8 Hz, 1H), 2.39 (dd, J = 14.7, 7.9 Hz, 1H), 2.19 (dd, J = 8.3, 2.3 Hz, 1H), 2.00 – 1.88 (m, 2H), 1.70 (ddd, J = 15.9, 10.7, 5.8 Hz, 1H), 1.40 (s, 3H), 1.30 -1.24 (m, 2H), 1.09 (s, 3H), -0.08 (dd, J = 5.7, 4.4 Hz, 1H), 0.39 (dd, J = 9.5 4.3 Hz, 1H), 0.64 (td, J =

9.5, 5.9 Hz, 1H), 0.85 (dd, J = 14.6, 11.0 Hz, 1H),. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.4, 139.86, 120.5,. 82.7, 65.5, 60.6, 48.0, 42.3, 38.4, 25.7, 24.5, 22.3, 20.5, 18.8, 18.5, 17.1. The structure of **3** (shown below) was further confirmed by small molecule X-ray crystallography.



Example 2. Preparation of Compound **4**

Cyclopropyl parthenolide (**3**, 35.0 mg, 0.134 mmol) was dissolved in anhydrous MeOH (1 mL). Dimethylamine (2.0 M solution in methanol, 100.0 µL, 0.200 mmol) was added and the mixture was allowed to stir overnight at room temperature. The solvent and excess dimethylamine were removed *in vacuo*, and the crude material was MPLC purified using SiO_2 (5-30% MeOH in CH_2Cl_2 over 15 minutes) to afford **4** (34.0 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.94 (t, J = 9.4 Hz, 1H), 2.93 (d, J = 9.0 Hz, 1H), 2.73 (dd, J = 13.0, 5.3, 1H), 2.59 (dd, J = 13.3, 5.3 Hz, 1H), 2.40 (dt, J = 12.3, 5.5 Hz, 1H), 2.33 - 2.21 (m, 7H), 2.20 - 2.07 (m, 2H), 1.97 - 1.95 (m, 1H), 1.83 (dd, J = 15.6, 8.8 Hz, 1H), 1.64 (ddd, J = 16.3, 9.8, 6.0 Hz, 1H), 1.40 (s, 3H), 1.30 - 1.24 (m, 2H), 1.07 (s, 3H), 0.81 (dd, J = 14.8, 10.3 Hz, 1H), 0.64 (td, J = 9.8, 6.0 Hz, 1H), 0.37 (dd, J = 9.4, 4.1 Hz, 1H),-0.10 (dd, J = 5.8, 4.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.5, 82.4, 65.38, 60.6, 57.5, 48.3, 47.0, 45.9, 42.2, 38.6, 25.3, 24.4, 22.6, 20.3, 18.8, 18.5, 17.1. The fumarate salt of compound **4** was also prepared using standard procedures. The fumarate salt of compound **4** is also a representative compound of the invention.

Example 3. Preparation of Compound **5**

This compound was synthesized by a modification to the procedure reported in *J. Nat. Prod.* **1993**, *59*, 90. In brief, parthenolide (**1**, 20 mg, 0.08 mmol) was dissolved in toluene (0.8 mL) and $BF_3 \cdot Et_2O$ (5 uL, 0.048 mmol) was added to the solution at 0 °C. The reaction was stirred at room temperature for 1 hour and quenched by the addition of $NaHCO_3$ (saturated, aq., 20 mL). The crude material was diluted with CH_2Cl_2 (20 mL) and then extracted with CH_2Cl_2 (20 mL, 4x). The combined

organic layers were washed with $NaHCO_3$ (saturated, aq., 20 mL), brine (saturated, aq., 20 mL) and then dried over Na_2SO_4. The crude material was MPLC purified on SiO_2 (10-35% EtOAc in hexanes over 14 min) to yield compound **5** (11 mg, 55%). ^1H NMR (400 MHz, $CDCl_3$) δ: 6.21 (d, J = 3.3 Hz, 1H), 5.50 (d, J = 3.0 Hz, 1H), 3.81 (t, J = 10.3 Hz, 1H), 2.74 - 2.62 (m, 3H), 2.39 (dd, J = 16.2, 8.4 Hz, 1H), 2.27 - 2.23 (m, 2H), 2.13 - 2.05 (m, 1H), 1.88 - 1.72 (m, 2H), 1.69 (s, 3H), 1.63 (br. s., 1H), 1.42 - 1.29 (m, 4H).

Example 4. Preparation of Compound **6.**

This compound was prepared from **5**, followed by installation of the dimethylamino group as described in the synthesis of **4**. ^1H NMR (400 MHz, $CDCl_3$) δ: 3.83 (t, J = 10.4 Hz, 1H), 2.76 (dd, J = 12.8, 5.2 Hz, 1H), 2.63 (m, 2H), 2.45 - 2.35 (m, 3H), 2.30 (s, 6H), 2.17 - 1.98 (m, 5H), 1.84 - 1.72 (m, 2H), 1.67 (s, 3H), 1.31 - 1.25 (m, 4H).

Example 5. Preparation of Compound **7**.

This molecule was synthesized from melampomagnolide B (**9**) by photochemical isomerization of the C1-C10 olefin. A protocol for this reaction is described for a related molecule in *Eur. J. Org. Chem.* **2003,** 2003, 3969.

Example 6. Preparation of Compound **8**.

This molecule was synthesized from melampomagnolide B (**9**) by incorporation of the dimethylamino group as described in the synthesis of **4**.

Example 7. Preparation of Compound **9**.

This compound is melampomagnolide B and was prepared from parthenolide (**1**) according to the method described in *Phytochemistry* **1984,** *23*, 2372. ^1H NMR (400 MHz, $CDCl_3$) δ: 6.32 (d, J = 3.6 Hz, 1H), 5.61 (d, J = 3.6 Hz, 1H), 5.20 (dd, J = 12.1 Hz, 2.4 Hz, 1H), 3.85 (t, J = 8.6 Hz, 1H), 2.79 - 2.76 (m, 2H), 2.43 (dd, J = 13.7, 5.2 Hz, 1H), 2.37 (dd, J = 13.0, 5.2 Hz, 1H), 2.20 - 2.11 (m, 4H), 1.76 – 1.67 (m, 4H), 1.29 - 1.19 (m, 4H).

Example 8. Preparation of Compound **10**.

This molecule is the C1-C10 isomer of parthenolide and was prepared according to the known method in *Eur. J. Org. Chem.* **2003,** 2003, 3969. HRMS calcd for $(C_{17}H_{27}NO_4 + H)^+$ 310.2018, found 310.2019

Example 9. Preparation of Compound **11**.

This molecule is dimethylamino costunolide. It was synthesized by addition of a dimethylamino group to costunolide (commercial) according to the method described in the synthesis of **4**.

Example 10. Preparation of Compound **12.**

This molecule was synthesized as previously described (*Bioorg. Med. Chem.* **2006,** *14*, 83). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.17 (d, J = 12.0 Hz, 1H), 3.80 (t, J = 9.2 Hz, 1H), 2.69 (d, J = 8.8 Hz, 1H), 2.79 - 2.76 (m, 2H), 2.39 - 2.26 (m, 3H), 2.18 - 2.01 (m, 3H), 1.83 – 1.92 (m, 2H), 1.69 (s, 3H), 1.29 (s, 3H), 1.76 – 1.67 (m, 4H), 1.24 - 1.20 (m, 4H).

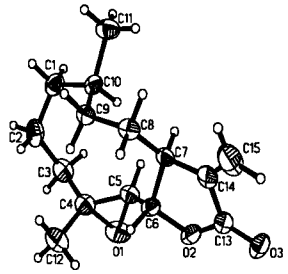
Example 11. Preparation of Compound **13.**

This molecule was synthesized from a mixture of **14** and **15** by addition of the dimethylamino group as described in the synthesis of **4**.

Example 12. Preparation of Compounds **14** and **15.**

To a solution of compound **2** in THF (5 mL) in a Parr bomb was added Pd/C (10% w/w, 60.0 mg). The bomb was charged with H_2 (50 psi) and the reaction was stirred at room temperature for 24 hours. The crude reaction products were then filtered through a pad of Celite and the pad was washed with CH_2Cl_2 (15 mL, 4x). Concentration of the eluant *in vacuo* afforded the hydrogenated products as a mixture of diasteromers. The crude reaction products were redissolved in THF (2 mL), treated with CH_3I (0.10 mL, 1.59 mmol), and allowed to stir overnight at room temperature. The material was then concentrated *in vacuo* to a yellow solid, resuspended in H_2O (5.0 mL), and stirred at 50 °C for 30 minutes. The heterogeneous solution solubilized within a few minutes. $NaHCO_3$ (saturated, aq., 20 mL) was added to the flask, and the crude material was extracted with CH_2Cl_2 (20 mL, 4x). The combined extracts were washed with $NaHCO_3$ (saturated, aq., 20 mL), brine (saturated, aq., 20 mL) and then dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude material was purified by preparative

HPLC (Zorbax SB-C18 column; 10-95% MeCN in H_2O over 47 min) to give compounds **14** and **15** (11.8 mg, 63%) as a mixture of diastereomers. The mixture was then subjected to further preparative HPLC purification (Zorbax SB-C18 column; isocratic 40:50:10 H_2O:MeCN:*i*-PrOH) to provide separated **14** (t_R = 55 min) and **15** (t_R = 59 min). Compound **14** (4.40 mg, 23%): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.25 (dd, J = 11.2, 4.2 Hz, 1H), 5.54 (d, J = 3.2 Hz, 1H), 3.96 (t, J = 8.9 Hz, 1H), 3.10 (d, J = 8.7 Hz, 1H), 2.98 - 2.78 (m, 1H), 2.25 - 2.10 (m, 2H), 1.73 (ddd, J = 13.0, 8.3, 4.2 Hz, 1H), 1.67 - 1.49 (m, 4H), 1.39 - 1.14 (m, 5H), 1.04 - 0.84 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.5, 139.4, 120.5, 81.5, 63.7, 61.9, 49.4, 39.5, 38.4, 36.5, 33.4, 28.8, 22.7, 21.7, 18.6; HRMS calcd for $(C_{15}H_{22}O_3 + Na)^+$ 273.1467, found 273.1470; HPLC retention time, 15.71 min. Compound **15** (7.40 mg, 39%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.16 (d, J = 3.5 Hz, 1H), 5.45 (d, J = 3.2 Hz, 1H), 3.76 (t, J = 9.6 Hz, 1H), 3.02 (d, J = 9.6 Hz, 1H), 2.89 (ddd, J = 10.0, 6.9, 3.6 Hz, 1H), 2.19 - 1.93 (m, 2H), 1.87 - 1.63 (m, 2H), 1.45 - 1.27 (m, 5H), 1.18 (s, 2H), 1.16 - 0.99 (m, 2H), 0.95 - 0.77 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.8, 139.6, 119.8, 81.1, 66.5, 61.4, 44.0, 36.8, 36.2, 30.2, 28.0, 24.8, 21.4, 20.7, 19.3; HRMS calcd for $(C_{15}H_{22}O_3 + Na)^+$ 273.1467, found 273.1463; HPLC retention time, 15.84 min. The structure of **15** (shown below) was confirmed by small molecule X-ray crystallography.



Example 13. Preparation of Compound **16.**

To a stirred solution of compound **8** (40 mg, 0.133 mmol) in dry THF was added Pd/C (100 mg). The reaction was then stirred under hydrogen gas for 2 days at room temperature. Pd/C was removed by filtration through celite. MeI (50 µL, 0.803 mmol) was added to the resulting filtrate and the reaction was allowed to stir overnight. The solvent was removed under reduced pressure and the residue was resuspended in H_2O (1 mL) and heated to 50 ℃ for 30 min. $NaHCO_3$ (saturated, aq., 20 mL) was added to the flask, and the crude material was extracted with CH_2Cl_2 (20 mL, 4x). The combined extracts were washed with $NaHCO_3$ (saturated, aq., 20 mL), brine (saturated, aq., 20 mL) and then dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude material was purified by preparative

HPLC (Zorbax SB-C18 column; 10-95% MeCN in H_2O over 47 min) to give compounds **16** (5 mg, 15%). HRMS calcd for $(C_{17}H_{29}NO_3 + H)^+$ 296.2226, found 296.2222

Example 14. Preparation of Compound **17.**

This molecule is a glutathione adduct of parthenolide and was prepared by reacting parthenolide (**1**) with glutathione.

Example 15. Preparation of Compound **18.**

This compound was isolated as a minor product (8% yield) from the reaction that yielded compound **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.19 (dd, J = 13.6, 3.8 Hz, 1H), 5.47 (t, J = 3.5 Hz, 1H), 5.10 (d, J = 3.1 Hz, 1H), 4.00 (dd, J = 9.8, 3.3 Hz, 1H), 3.03 - 2.94 (m, 1H), 2.65 - 2.35 (m, 2H), 2.27 - 1.94 (m, 2H) 1.82 - 1.76 (m, 3H), 1.68 - 1.53 (m, 2H), 1.32 - 1.24 (m, 2H), 1.07 (dd, J = 6.9, 2.8 Hz, 3H).

Example 16. Preparation of Compound **19.**

To a stirred solution of compound **5** (20 mg, 0.081 mmol) in pyridine (1 mL) was added $POCl_3$ (75 µL, 0.81 mmol) dropwise at 0 °C. The reaction was warmed to room temperature and stirred for 2 hours. Pyridine was removed under reduced pressure and the residue was dissolved in DCM (2 mL). $NaHCO_3$ (saturated, aq., 20 mL) was added to the flask, and the crude material was extracted with CH_2Cl_2 (20 mL, 4x). The combined extracts were washed with $NaHCO_3$ (saturated, aq., 20 mL), brine (saturated, aq., 20 mL) and then dried over Na_2SO_4. The crude material was MPLC purified on SiO_2 (10-50% EtOAc in hexanes over 18 min) to yield compound **19** (12 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.11 (d, J = 3.2 Hz, 1H), 5.52 (m, 1H), 5.37 (d, J = 3.0 Hz, 1H), 3.63 (t, J = 9.8 Hz, 1H), 3.39 (d, J = 10.0 Hz, 1H), 2.96 (br s, 2H), 2.81 - 2.74 (m, 1H), 2.30 (t, J = 13.3 Hz, 1H), 2.16 (ddd, J = 14.8, 5.8, 2.0 Hz, 1H), 2.08 (dq, J = 13.1, 2.3 Hz, 1H), 1.93 (s, 3H), 1.71 (d, J = 0.8 Hz, 3H). HRMS calcd for $(C_{15}H_{22}O_4 + Na)^+$ 289.1416, found 289.1421.

Example 17. The following illustrate representative pharmaceutical dosage forms, containing a compound of the invention, or a pharmaceutically acceptable salt thereof ('Compound X'), for therapeutic or prophylactic use in humans.

(i) Tablet 1	mg/tablet
Compound X=	100.0
Lactose	77.5
Povidone	15.0
Croscarmellose sodium	12.0
Microcrystalline cellulose	92.5
Magnesium stearate	3.0
	300.0

(ii) Tablet 2	mg/tablet
Compound X=	20.0
Microcrystalline cellulose	410.0
Starch	50.0
Sodium starch glycolate	15.0
Magnesium stearate	5.0
	500.0

(iii) Capsule	mg/capsule
Compound X=	10.0
Colloidal silicon dioxide	1.5
Lactose	465.5
Pregelatinized starch	120.0
Magnesium stearate	3.0
	600.0

(iv) Injection 1 (1 mg/ml)	mg/ml
Compound X= (free acid form)	1.0
Dibasic sodium phosphate	12.0
Monobasic sodium phosphate	0.7
Sodium chloride	4.5
1.0 N Sodium hydroxide solution (pH adjustment to 7.0-7.5)	q.s.
Water for injection	q.s. ad 1 mL

(v) Injection 2 (10 mg/ml)	mg/ml
Compound X= (free acid form)	10.0
Monobasic sodium phosphate	0.3
Dibasic sodium phosphate	1.1
Polyethylene glycol 400	200.0
01 N Sodium hydroxide solution (pH adjustment to 7.0-7.5)	q.s.
Water for injection	q.s. ad 1 mL

(vi) Aerosol	mg/can
Compound X=	20.0
Oleic acid	10.0
Trichloromonofluoromethane	5,000.0
Dichlorodifluoromethane	10,000.0
Dichlorotetrafluoroethane	5,000.0

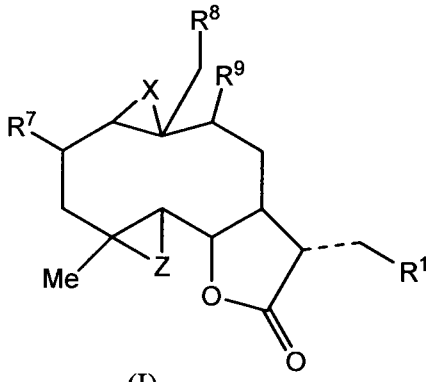
The above formulations may be obtained by conventional procedures well known in the pharmaceutical art.

All publications, patents, and patent documents are incorporated by reference herein, as though individually incorporated by reference. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

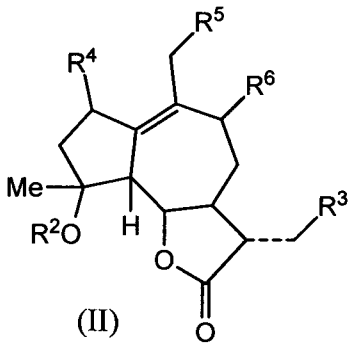
CLAIMS

What is claimed is:

1. A compound of formula I, formula II, formula III, formula IV, or formula V:



(I)



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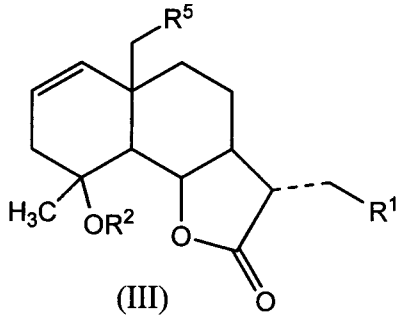
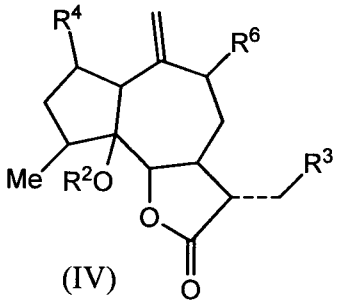
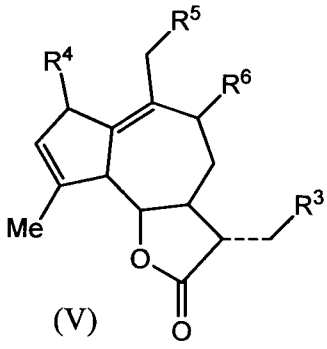


(III)



(IV)

or



(V)

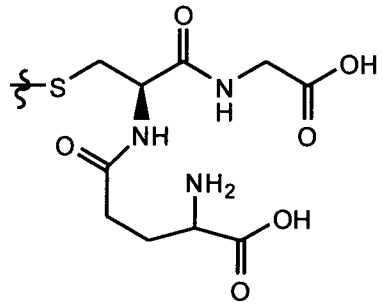
wherein:

X is O or CH_2, is absent, or taken together with the carbons to which it is attached forms a double bond;

Z is O or CH_2 or taken together with the carbons to which it is attached forms a double bond;

the bond represented by --- is a single or a double bond;

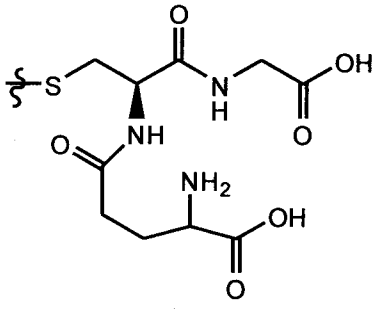
R^1 is H, halo, cyano, nitro, hydroxy, carboxy, trifluoromethyl, trifluoromethoxy, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkanoyloxy, aryl, heteroaryl, aryloxy, heteroaryloxy, a group of formula:



or –NR^cR^d; wherein any alkyl of R^1 is optionally substituted with one or more R^a ; and wherein any aryl, heteroaryl, or any aryl or heteroaryl portion of any aryloxy, or heteroaryloxy of R^1 is optionally substituted with one or more R^b;

R^2 is H, phosphate, trifluoromethyl, (C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl, or heteroaryl(C_1-C_6)alkyl; wherein any alkyl of R^2 is optionally substituted with one or more R^a ; and wherein any aryl, heteroaryl, or any aryl or heteroaryl portion of any aryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkyl of R^2 is optionally substituted with one or more R^b;

R^3 is H, halo, cyano, nitro, hydroxy, carboxy, trifluoromethyl, trifluoromethoxy, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkanoyloxy, aryl, heteroaryl, aryloxy, heteroaryloxy, a group of formula:



or –NR^cR^d; wherein any alkyl of R^3 is optionally substituted with one or more R^a ; and wherein any aryl, heteroaryl, or any aryl or heteroaryl portion of any aryloxy, or heteroaryloxy of R^3 is optionally substituted with one or more R^b;

R^4 is H or OR^v;

R^5 is H or OR^v;

R^6 is H or OR^v;

R^7 is H or OR^v;

R^8 is H or OR^v;

R^9 is H or OR^v;

each R^a is independently selected from halo, cyano, nitro, hydroxy, carboxy, oxo, $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkoxycarbonyl, $(C_1$-$C_6)$alkanoyloxy, aryl, heteroaryl, aryloxy, heteroaryloxy, $(C_1$-$C_6)$alkylthio, $-OP(=O)(OH)_2$, $-S(O)R^k$, $-S(O)_2R^k$, $-S(O)_3R^k$, $-S(O)_2NR^eR^f$, and $-NR^eR^f$; wherein each aryl, heteroaryl, aryloxy, and heteroaryloxy is optionally substituted with one or more groups independently selected from halo, cyano, nitro, hydroxy, carboxy, trifluoromethyl, trifluoromethoxy, $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkoxycarbonyl, $(C_1$-$C_6)$alkanoyloxy, $(C_1$-$C_6)$alkylthio, $-S(O)R^k$, $-S(O)_2R^k$, $-S(O)_3R^k$, $-S(O)_2NR^gR^h$, and $-NR^gR^h$;

each R^b is independently selected from halo, cyano, nitro, hydroxy, carboxy, trifluoromethyl, trifluoromethoxy, $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkoxycarbonyl, $(C_1$-$C_6)$alkanoyloxy, aryl, heteroaryl, aryloxy, heteroaryloxy, $(C_1$-$C_6)$alkylthio, $-OP(=O)(OH)_2$, $-S(O)R^k$, $-S(O)_2R^k$, $-S(O)_3R^k$, $-S(O)_2NR^mR^n$, and $-NR^mR^n$; wherein each aryl, heteroaryl, aryloxy, and heteroaryloxy is optionally substituted with one or more groups independently selected from halo, cyano, nitro, hydroxy, carboxy, trifluoromethyl, trifluoromethoxy, $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkoxycarbonyl, $(C_1$-$C_6)$alkanoyloxy, $(C_1$-$C_6)$alkylthio, $-S(O)R^k$, $-S(O)_2R^k$, $-S(O)_3R^k$, $-S(O)_2NR^mR^n$, and $-NR^mR^n$;

each R^c and R^d is independently selected from H, $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_3$-$C_6)$cycloalkyl$(C_1$-$C_6)$alkyl, hydroxy, aryl, heteroaryl, aryl$(C_1$-$C_6)$ alkyl and heteroaryl$(C_1$-$C_6)$ alkyl; or R^c and R^d together with the nitrogen to which they are attached form a aziridino, azetidino, morpholino, piperazino, pyrrolidino or piperidino; wherein any $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_3$-$C_6)$cycloalkyl$(C_1$-$C_6)$alkyl, aryl, heteroaryl, aryl$(C_1$-$C_6)$ alkyl or heteroaryl$(C_1$-$C_6)$alkyl of R^c and R^d is optionally substituted with one or more groups independently selected from hydroxy, carboxy, and NR^tR^u;

each R^e and R^f is independently selected from H, $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_3$-$C_6)$cycloalkyl$(C_1$-$C_6)$alkyl, aryl, heteroaryl, aryl$(C_1$-$C_6)$ alkyl and heteroaryl$(C_1$-$C_6)$ alkyl; or R^e and R^f together with the nitrogen to which they are attached form a aziridino, azetidino, morpholino, piperazino, pyrrolidino or piperidino; wherein any $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_3$-$C_6)$cycloalkyl$(C_1$-$C_6)$alkyl, aryl, heteroaryl, aryl$(C_1$-$C_6)$ alkyl or heteroaryl$(C_1$-$C_6)$alkyl of R^e and R^f is optionally substituted with one or more groups independently selected from hydroxy, carboxy, and NR^tR^u;

each R^g and R^h is independently selected from H, $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_3$-

C_6)cycloalkyl(C_1-C_6)alkyl, aryl, heteroaryl, aryl(C_1-C_6) alkyl and heteroaryl(C_1-C_6) alkyl; or R^g and R^h together with the nitrogen to which they are attached form a aziridino, azetidino, morpholino, piperazino, pyrrolidino or piperidino; wherein any (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, aryl, heteroaryl, aryl(C_1-C_6) alkyl or heteroaryl(C_1-C_6)alkyl of R^g and R^h is optionally substituted with one or more groups independently selected from hydroxy, carboxy, and NR^tR^u;

each R^k is independently selected from H, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, aryl, heteroaryl, aryl(C_1-C_6) alkyl and heteroaryl(C_1-C_6) alkyl;

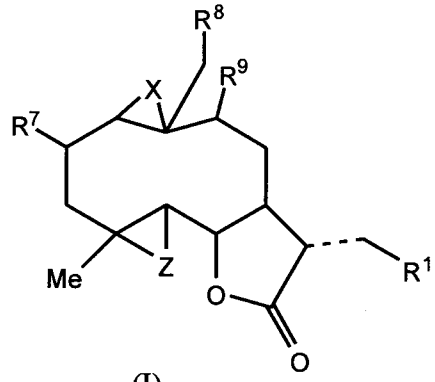
each R^m and R^n is independently selected from H, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, aryl, heteroaryl, aryl(C_1-C_6) alkyl and heteroaryl(C_1-C_6) alkyl; or R^m and R^n together with the nitrogen to which they are attached form a aziridino, azetidino, morpholino, piperazino, pyrrolidino or piperidino; wherein any (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, aryl, heteroaryl, aryl(C_1-C_6) alkyl or heteroaryl(C_1-C_6)alkyl of R^m and R^n is optionally substituted with one or more groups independently selected from hydroxy, carboxy, and NR^tR^u;

each R^t and R^u is independently selected from H, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, aryl, heteroaryl, aryl(C_1-C_6) alkyl and heteroaryl(C_1-C_6) alkyl; or R^t and R^u together with the nitrogen to which they are attached form a aziridino, azetidino, morpholino, piperazino, pyrrolidino or piperidino; and

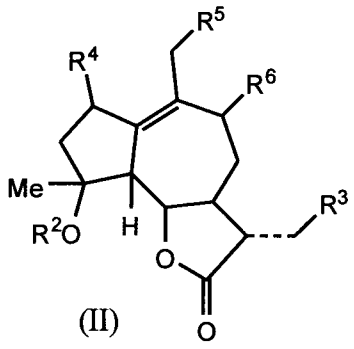
each R^v is H, (C_1-C_6)alkyl, phosphate, (C_1-C_6)alkoxycarbonyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl, or heteroaryl(C_1-C_6)alkyl; wherein any alkyl of R^v is optionally substituted with one or more R^a ; and wherein any aryl, heteroaryl, or any aryl or heteroaryl portion of any aryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkyl of R^v is optionally substituted with one or more R^b;

or a salt thereof.

2. The compound of claim 1 which is a compound of formula I, formula II, or formula III:

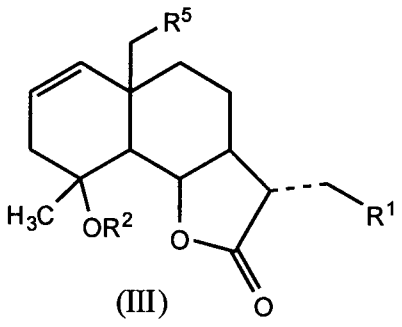


(I)



(II)

or



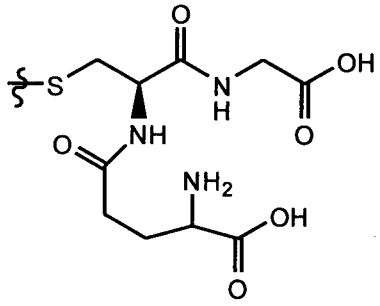
(III)

wherein:

X is O or CH_2, is absent, or taken together with the carbons to which it is attached forms a *cis*-double bond;

Z is O or CH_2 or taken together with the carbons to which it is attached forms a double bond; the bond represented by --- is a single or a double bond;

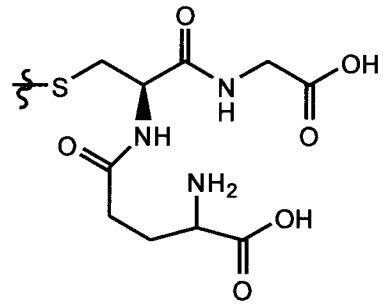
R^1 is H, halo, cyano, nitro, hydroxy, carboxy, trifluoromethyl, trifluoromethoxy, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxycarbonyl, $(C_1\text{-}C_6)$alkanoyloxy, aryl, heteroaryl, aryloxy, heteroaryloxy, a group of formula:



or $-NR^cR^d$; wherein any alkyl of R^1 is optionally substituted with one or more R^a; and wherein any aryl, heteroaryl, or any aryl or heteroaryl portion of any aryloxy, or heteroaryloxy of R^1 is optionally substituted with one or more R^b;

R^2 is H, trifluoromethyl, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxycarbonyl, aryl, heteroaryl, aryl$(C_1\text{-}C_6)$alkyl, or heteroaryl$(C_1\text{-}C_6)$alkyl; wherein any alkyl of R^2 is optionally substituted with one or more R^a; and wherein any aryl, heteroaryl, or any aryl or heteroaryl portion of any aryl$(C_1\text{-}C_6)$alkyl or heteroaryl$(C_1\text{-}C_6)$alkyl of R^2 is optionally substituted with one or more R^b;

R^3 is H, halo, cyano, nitro, hydroxy, carboxy, trifluoromethyl, trifluoromethoxy, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxycarbonyl, $(C_1\text{-}C_6)$alkanoyloxy, aryl, heteroaryl, aryloxy, heteroaryloxy, a group of formula:



or $-NR^cR^d$; wherein any alkyl of R^3 is optionally substituted with one or more R^a ; and wherein any aryl, heteroaryl, or any aryl or heteroaryl portion of any aryloxy, or heteroaryloxy of R^3 is optionally substituted with one or more R^b;

R^4 is H or OR^v;

R^5 is H or OR^v;

R^6 is H or OR^v;

R^7 is H or OR^v;

R^8 is H or OR^v;

R^9 is H or OR^v;

each R^a is independently selected from halo, cyano, nitro, hydroxy, carboxy, oxo, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxycarbonyl, $(C_1\text{-}C_6)$alkanoyloxy, aryl, heteroaryl, aryloxy, heteroaryloxy, $(C_1\text{-}C_6)$alkylthio, $-S(O)R^k$, $-S(O)_2R^k$, $-S(O)_3R^k$, $-S(O)_2NR^eR^f$, and $-NR^eR^f$; wherein each aryl, heteroaryl, aryloxy, and heteroaryloxy is optionally substituted with one or more groups independently selected from halo, cyano, nitro, hydroxy, carboxy, trifluoromethyl, trifluoromethoxy, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxycarbonyl, $(C_1\text{-}C_6)$alkanoyloxy, $(C_1\text{-}C_6)$alkylthio, $-S(O)R^k$, $-S(O)_2R^k$, $-S(O)_3R^k$, $-S(O)_2NR^gR^h$, and $-NR^gR^h$;

each R^b is independently selected from halo, cyano, nitro, hydroxy, carboxy, trifluoromethyl, trifluoromethoxy, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxycarbonyl, $(C_1\text{-}C_6)$alkanoyloxy, aryl, heteroaryl, aryloxy, heteroaryloxy, $(C_1\text{-}C_6)$alkylthio, $-S(O)R^k$, $-S(O)_2R^k$, $-S(O)_3R^k$, $-S(O)_2NR^mR^n$, and $-NR^mR^n$; wherein each aryl, heteroaryl, aryloxy, and heteroaryloxy is optionally substituted with one or more groups independently selected from halo, cyano, nitro, hydroxy,

carboxy, trifluoromethyl, trifluoromethoxy, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkanoyloxy, (C_1-C_6)alkylthio, -S(O)R^k, -S(O)$_2R^k$, -S(O)$_3R^k$, -S(O)$_2NR^mR^n$, and –NR^mR^n;

each R^c and R^d is independently selected from H, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, hydroxy, aryl, heteroaryl, aryl(C_1-C_6) alkyl and heteroaryl(C_1-C_6) alkyl; or R^c and R^d together with the nitrogen to which they are attached form a aziridino, azetidino, morpholino, piperazino, pyrrolidino or piperidino; wherein any (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, aryl, heteroaryl, aryl(C_1-C_6) alkyl or heteroaryl(C_1-C_6)alkyl of R^c and R^d is optionally substituted with one or more groups independently selected from hydroxy, carboxy, and NR^tR^u;

each R^e and R^f is independently selected from H, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, aryl, heteroaryl, aryl(C_1-C_6) alkyl and heteroaryl(C_1-C_6) alkyl; or R^e and R^f together with the nitrogen to which they are attached form a aziridino, azetidino, morpholino, piperazino, pyrrolidino or piperidino; wherein any (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, aryl, heteroaryl, aryl(C_1-C_6) alkyl or heteroaryl(C_1-C_6)alkyl of R^e and R^f is optionally substituted with one or more groups independently selected from hydroxy, carboxy, and NR^tR^u;

each R^g and R^h is independently selected from H, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, aryl, heteroaryl, aryl(C_1-C_6) alkyl and heteroaryl(C_1-C_6) alkyl; or R^g and R^h together with the nitrogen to which they are attached form a aziridino, azetidino, morpholino, piperazino, pyrrolidino or piperidino; wherein any (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, aryl, heteroaryl, aryl(C_1-C_6) alkyl or heteroaryl(C_1-C_6)alkyl of R^g and R^h is optionally substituted with one or more groups independently selected from hydroxy, carboxy, and NR^tR^u;

each R^k is independently selected from H, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, aryl, heteroaryl, aryl(C_1-C_6) alkyl and heteroaryl(C_1-C_6) alkyl;

each R^m and R^n is independently selected from H, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, aryl, heteroaryl, aryl(C_1-C_6) alkyl and heteroaryl(C_1-C_6) alkyl; or R^m and R^n together with the nitrogen to which they are attached form a aziridino, azetidino, morpholino, piperazino, pyrrolidino or piperidino; wherein any (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, aryl, heteroaryl, aryl(C_1-C_6) alkyl or heteroaryl(C_1-C_6)alkyl of R^m and R^n is optionally substituted with one or more groups independently selected from hydroxy, carboxy, and

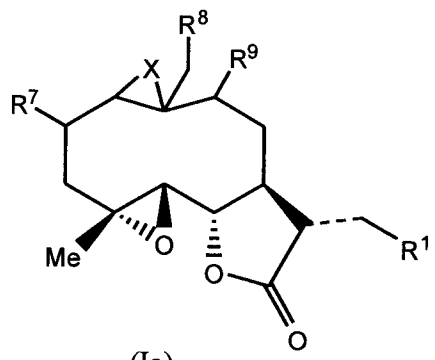
NR^tR^u;

each R^t and R^u is independently selected from H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_6)$alkyl, aryl, heteroaryl, aryl$(C_1\text{-}C_6)$ alkyl and heteroaryl$(C_1\text{-}C_6)$ alkyl; or R^t and R^u together with the nitrogen to which they are attached form a aziridino, azetidino, morpholino, piperazino, pyrrolidino or piperidino; and

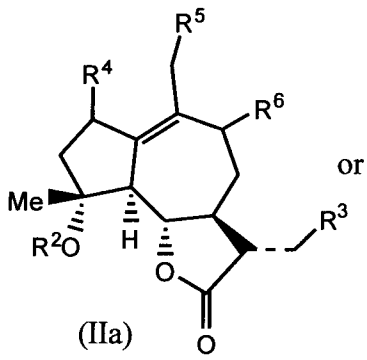
each R^v is H, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxycarbonyl, aryl, heteroaryl, aryl$(C_1\text{-}C_6)$alkyl, or heteroaryl$(C_1\text{-}C_6)$alkyl; wherein any alkyl of R^v is optionally substituted with one or more R^a ; and wherein any aryl, heteroaryl, or any aryl or heteroaryl portion of any aryl$(C_1\text{-}C_6)$alkyl or heteroaryl$(C_1\text{-}C_6)$alkyl of R^v is optionally substituted with one or more R^b;

or a salt thereof.

3. The compound of claim 1 which is a compound of formula Ia, IIa, or IIIa:

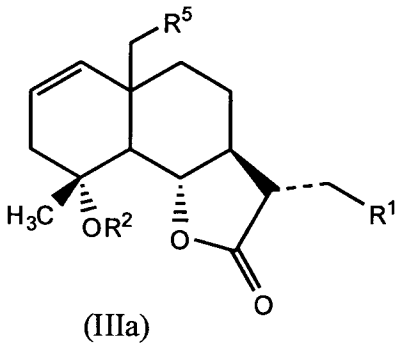


(Ia)



(IIa)

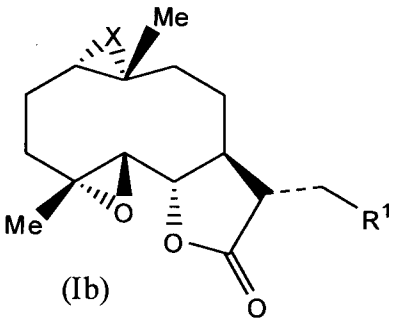
or



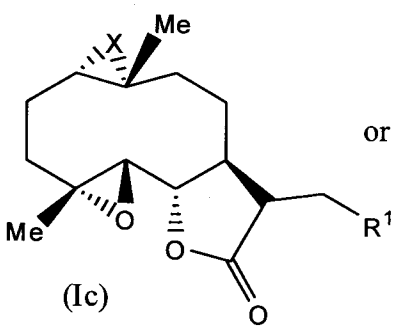
(IIIa)

or a salt thereof.

4. The compound of claim 1 which is a compound of formula Ib, Ic, or Id:

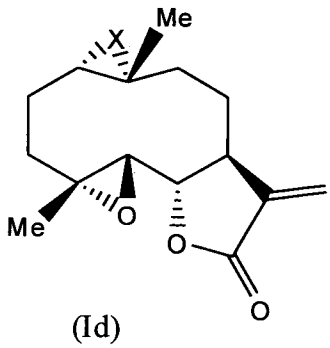


(Ib)



(Ic)

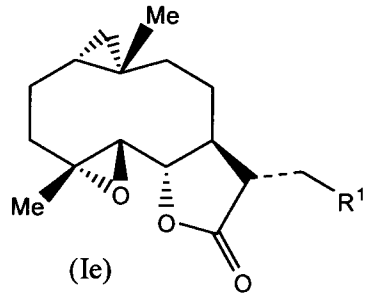
or



(Id)

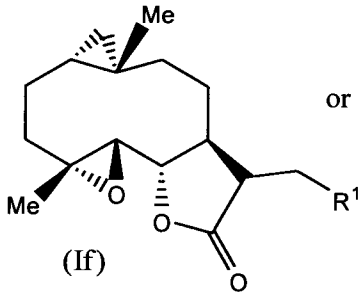
or a salt thereof.

5. The compound of claim 1 which is a compound of formula Ie, If, or Ig:



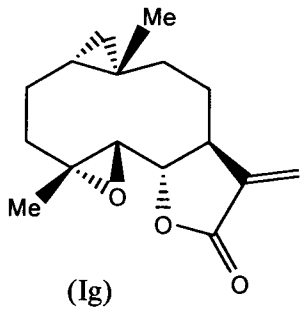
(Ie)

or



(If)

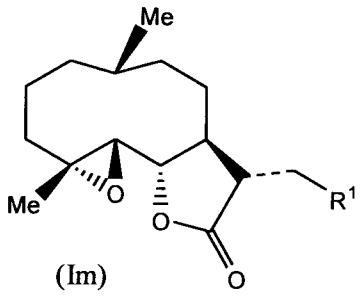
or



(Ig)

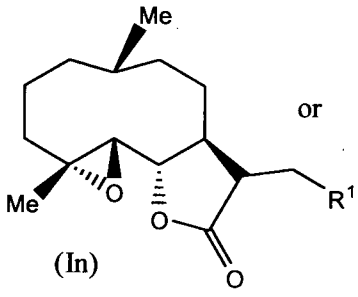
or a salt thereof.

6. The compound of claim 1 which is a compound of formula Im, In, or Io:



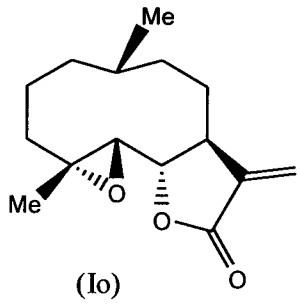
(Im)

or



(In)

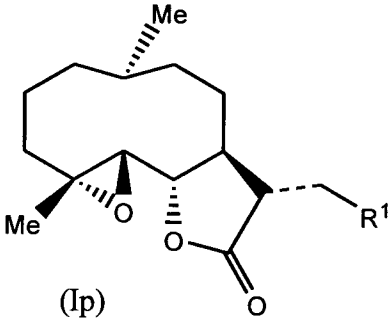
or



(Io)

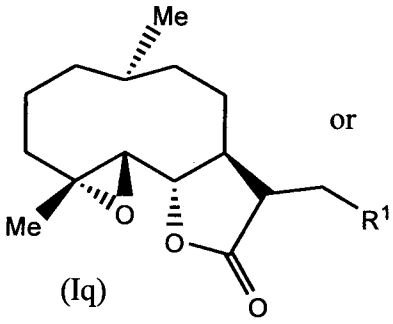
or a salt thereof.

7. The compound of claim 1 which is a compound of formula Ip, Iq, or Ir:



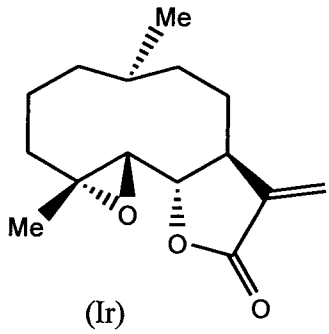
(Ip)

or



(Iq)

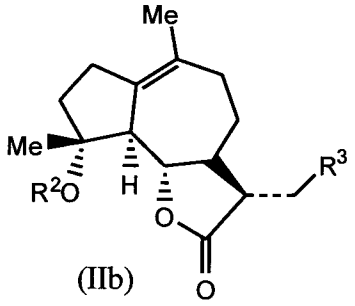
or



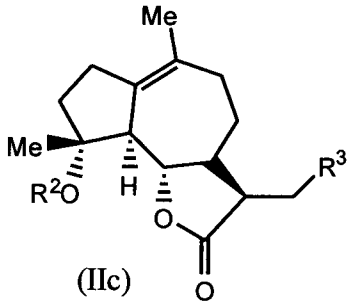
(Ir)

or a salt thereof.

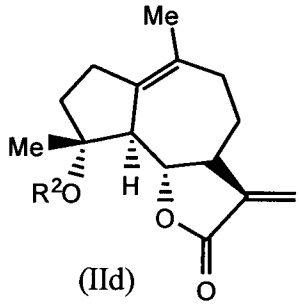
8. The compound of claim 1 which is a compound of formula IIb, IIc, or IId:



(IIb)



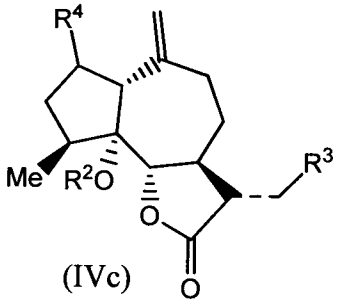
(IIc)



(IId)

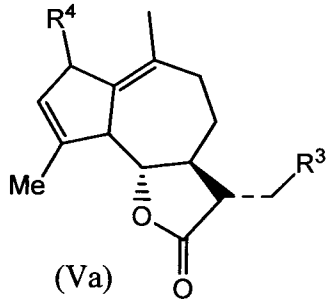
or a salt thereof.

9. The compound of claim 1 which is a compound of formula IVc, or Va:



(IVc)

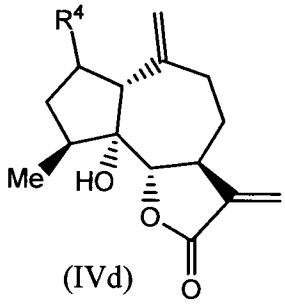
or



(Va)

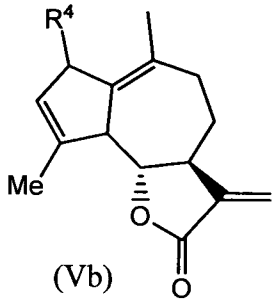
or a salt thereof.

10. The compound of claim 1 which is a compound of formula IVd, or Vb:



(IVd)

or



(Vb)

or a salt thereof.

11. The compound of claim 1 which is compound **3**, **4**, **6**, **8**, **13**, **14**, **15**, or **16**, or a salt thereof.

12. The compound of claim 1 which is not compound **1**, **2**, **5**, **7**, **9**, **10**, **11**, **12**, **17**, **18**, or **19**, or a salt thereof.

13. The compound of any one of claims 1-7 wherein R^1 is H.

14. The compound of any one of claims 1-7 wherein R^1 is $-NR^cR^d$.

15. The compound of claim 1, 2, 3, 8, or 9 wherein R^2 is H.

16. The compound of claim 1, 2, 3, 8, or 9 wherein R^2 is $(C_1\text{-}C_6)$alkyl, that is optionally substituted with one or more R^a.

17. The compound of claim 1, 2, 3, 8, or 9 wherein R^3 is H.

18. The compound of claim 1, 2, 3, 8, or 9 wherein R^3 is $-NR^cR^d$.

19. A pharmaceutical composition comprising a compound as described in any one of claims 1-18, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable diluent or carrier.

20. A method for treating cancer in a mammal, comprising administering a compound as described in any one of claims 1-18, or a pharmaceutically acceptable salt thereof, to the mammal.

21. A method for treating a cardiovascular disease in a mammal, comprising administering a compound as described in any one of claims 1-18, or a pharmaceutically acceptable salt thereof, to the mammal.

22. A method for inhibiting the NF-κB signaling pathway in a cell, comprising contacting the cell *in vitro* or *in vivo* with an effective amount of a compound as described in any one of claims 1-18, or a pharmaceutically acceptable salt thereof.

23. A method for preventing or treating a pathological condition or symptom in a mammal, such as a human, wherein the activity of the NF-κB signaling pathway is implicated and antagonism of its action is desired comprising administering to a mammal in need of such therapy, an effective amount of a compound as described in any one of claims 1-14, or a pharmaceutically acceptable salt thereof.

24. The method of claim 20 wherein the cancer is a blood cancer, or a cancerous solid tumor.

25. The method of claim 20 wherein the cancer is leukemia, breast, pancreatic, or prostate cancer.

26. The method of claim 20 wherein the cancer is a cancer that has an established cancer stem cell population.

27. A compound as described in any one of claims 1-18, or a pharmaceutically acceptable salt thereof, for use in medical therapy.

28. A compound as described in any one of claims 1-18, or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment of cancer.

29. A compound as described in any one of claims 1-18, or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment of a cardiovascular disease.

30. The use of a compound as described in any one of claims 1-18, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament useful for the treatment of cancer in a mammal.

31. The invention provides the use of compound as described in any one of claims 1-18, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament useful for the treatment of a cardiovascular disease in a mammal.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/034527

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

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

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

4, 5(completely); 1-3, 11-14, 19-31(partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/034527

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D307/93 C07D493/04 A61K31/343 A61P9/00 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WAGNER S ET AL: "Development of a Structural Model for NF-.kappa.B Inhibition of Sesquiterpene Lactones Using Self-Organizing Neural Networks", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 49, no. 7, 1 January 2006 (2006-01-01), pages 2241-2252, XP002536718, ISSN: 0022-2623, DOI: 10.1021/JM051125N page 2248; figure 7; compounds 25, 36, 43 page 2246; table 6; compounds 25, 36, 43 ----- -/--	1-31

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 June 2012	07/08/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Beligny, Samuel

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STEFFEN WAGNER ET AL: "Neural Networks as Valuable Tools To Differentiate between Sesquiterpene Lactones' Inhibitory Activity on Serotonin Release and on NF-[kappa]B", JOURNAL OF MEDICINAL CHEMISTRY, vol. 51, no. 5, 1 March 2008 (2008-03-01), pages 1324-1332, XP055028926, ISSN: 0022-2623, DOI: 10.1021/jm701318x page 1329; compounds 1-4, 6	1-4,12, 13,19-31
X	WEDGE D E ET AL: "Fungicidal activity of natural and synthetic sesquiterpene lactone analogs", PHYTOCHEMISTRY, PERGAMON PRESS, GB, vol. 53, no. 7, 1 April 2000 (2000-04-01), pages 747-757, XP004291370, ISSN: 0031-9422, DOI: 10.1016/S0031-9422(00)00008-X page 750; figure 1; compounds 21, 22	1-4,12, 13
X	JOSÉ CASTAÑEDA-ACOSTA ET AL: "The molecular structures of three germacrolides related to parthenolide", JOURNAL OF CHEMICAL CRYSTALLOGRAPHY, vol. 27, no. 11, 1 November 1997 (1997-11-01), pages 635-639, XP055029099, ISSN: 1074-1542, DOI: 10.1007/BF02576404 page 635; compounds 1, 2	1-4,12, 13
X	J. ALBERTO MARCO ET AL: "New Germacranolides and Eudesmanolides from North African Artemisia herba-alba", JOURNAL OF NATURAL PRODUCTS, vol. 57, no. 7, 1 July 1994 (1994-07-01), pages 939-946, XP055029105, ISSN: 0163-3864, DOI: 10.1021/np50109a010 page 943; compound 19	1-3,12, 13
X	ESSAM ABDEL SATTAR ET AL: "Antitumor Germacranolides from Anvillea garcinii", JOURNAL OF NATURAL PRODUCTS, vol. 59, no. 4, 1 January 1996 (1996-01-01), pages 403-405, XP055029130, ISSN: 0163-3864, DOI: 10.1021/np960064g page 403; compounds 3, 4	1-3,12, 13,19, 20, 24-28,30

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	MOHAMED MOUMOU ET AL: "10[alpha]-Hydroxy-4,9-dimethyl-13-[(4-phenylpiperazin-1-yl)methyl]-3,8,15-trioxatetracyclo[10.3.0.0 2,4 .0 7,9]tetradecan-14-one", ACTA CRYSTALLOGRAPHICA SECTION E STRUCTURE REPORTS ONLINE, vol. 67, no. 11, 22 October 2011 (2011-10-22), pages O2981-O2982, XP055029145, DOI: 10.1107/S1600536811042012 the whole document	1-3,12, 13
X,P	MOHAMED MOUMOU ET AL: "10[alpha]-Hydroxy-4,9-dimethyl-13-(pipyridin-1-ylmethyl)-3,8,15-trioxatetracyclo[10.3.0.0 2,4 .0 7,9]tetradecan-14-one", ACTA CRYSTALLOGRAPHICA SECTION E STRUCTURE REPORTS ONLINE, vol. 67, no. 11, 22 October 2011 (2011-10-22), pages O3003-O3004, XP055029148, DOI: 10.1107/S1600536811042644 the whole document	1-3,12, 13
X,P	MOHAMED MOUMOU ET AL: "10[alpha]-Hydroxy-4,9-dimethyl-13-[(pyrrolidin-1-yl)methyl]-3,8,15-trioxatetracyclo[10.3.0.0 2,4 .0 7,9]pentadecan-14-one", ACTA CRYSTALLOGRAPHICA SECTION E STRUCTURE REPORTS ONLINE, vol. 67, no. 7, 30 June 2011 (2011-06-30), pages O1842-O1843, XP055029149, DOI: 10.1107/S1600536811024688 the whole document	1-3,12, 13

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 4, 5(completely); 1-3, 11-14, 19-31(partially)

   Compounds of Formula (I) with two 3-membered rings fused to the 10-membered ring

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2. claims: 6, 7(completely); 1-3, 11-14, 19-31(partially)

   Compounds of Formula (I) with one 3-membered ring fused to the 10-membered ring

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3. claims: 1-3, 12-14, 19-31(all partially)

   Compounds of Formula (I) with no further rings fused to the 10-membered ring

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4. claims: 8-10(completely); 1-3, 11, 12, 15-31(partially)

   Compounds of Formula (II), (IV), and (V)

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5. claims: 1-3, 12-16, 19-31(all partially)

   Compounds of Formula (III)
