INSTRUCTIONS
(a) If Convention application insert "Convention"

AMENDED

AUSTRALIAN Reg 1983 PATENT OFFICE

620561

(a) Convention

AUSTRALIA

Patents Act

(b) Delete one

APPLICATION FOR A (b) STANDARD ~~/PETTY~~ PATENT

(c) Insert FULL name(s) of applicant(s)

~~I~~/We (c) Bristol-Myers Squibb Company

(d) Insert FULL address(es) of applicant(s)

of (d) 345 Park Avenue,
New York, New York, 10154,
United States of America,

(e) Delete one

hereby apply for the grant of a (e) Standard/~~Petty~~ Patent for an invention entitled

(f) Insert TITLE of invention

(f) -3'-DEMETHOXYEPIPODOPHYLLOTOXIN GLUCOSIDE DERIVATIVES

(g) Insert "complete" or "provisional" or "petty patent"

which is described in the accompanying (g) complete specification.

(Note: The following applies only to Convention applications)

Details of basic application(s)

(h) Insert number, country and filing date for the/or each basic application

	Application No.	Country	Filing Date
(h)	091570	United States of America	31 August 1987

Address for Service: PHILLIPS ORMONDE AND FITZPATRICK
Patent and Trade Mark Attorneys
367 Collins Street
Melbourne, Australia 3000

(i) Insert date of signing

Dated (i) 19 January, 1990.

(j) Signature of applicant(s) (For body corporate see headnote*)

(k) Corporate seal if any

(k)

(j) PHILLIPS ORMONDE & FITZPATRICK
ATTORNEYS FOR:
BRISTOL-MYERS SQUIBB COMPANY

Note: No legalization or other witness required

PHILLIPS ORMONDE AND FITZPATRICK 21666/88
Patent and Trade Mark Attorneys
367 Collins Street
Melbourne, Australia

P17/2/83

CT-1871

AUSTRALIA

Patents Act

DECLARATION FOR A PATENT APPLICATION

▼ INSTRUCTIONS
(a) Insert "Convention" if applicable
(b) Insert FULL name(s) of applicant(s)

In support of the (a) convention application made by (b)

BRISTOL-MYERS COMPANY

(c) Insert "of addition" if applicable
(d) Insert TITLE of invention

(hereinafter called "applicant(s)" for a patent (c) for an invention entitled (d)

3'DEMETHOXYEPIPODOPHYLLOTOXIN GLUCOSIDE DERIVATIVES

(e) Insert FULL name(s) AND address(es) of declarant(s) (See headnote*)

I/~~We~~ (e) Isaac Jarkovsky, Assistant General Counsel of Bristol-Myers Company: 345 Park Avenue, New York, New York, United States of America

do solemnly and sincerely declare as follows:

~~1. I am/We are the applicant(s).~~

(or, in the case of an application by a body corporate)

1. I am/~~We are~~ authorized to make this declaration on behalf of the applicant(~~s~~).

~~2. I am/We are the actual inventor(s) of the invention.~~

(or, where the applicant(s) is/are not the actual inventor(s))

(f) Insert FULL name(s) AND address(es) of actual inventor(s)

2. (f) Mr Mark G. Saulnier: 1225 Randolph Road, Middletown, Connecticut and Mr Dolatrai M. Myas: 19 Thames Way, Madison, Connecticut both respectively of the United States of America

(g) Recite how applicant(s) derive(s) title from actual inventor(s) (See headnote**)

is/are the actual inventor(s) of the invention and the facts upon which the applicant(s) is/~~are~~ entitled to make the application are as follows:

(g) The applicant is the assignee of the said inventors.

(h) Insert country, filing date, and basic applicant(s) for the/or EACH basic application

*(**Note:** Paragraphs 3 and 4 apply **only** to Convention applications)*

3. The basic application(s) for patent or similar protection on which the application is based is/~~are~~ identified by **country, filing date, and basic applicant(s)** as follows:

(h) United States of America
31 August, 1987
mark G. Saulnier and Dolatrai M. Myas

4. The basic application(s) referred to in paragraph 3 hereof was/~~were~~ the first application(s) made in a Convention country in respect of the invention the subject of the application.

(k) Insert PLACE of signing

(l) Insert DATE of signing

(m) Signature(s) of declarant(s)

Note: No legalization or other witness required

Declared at (k) New York, N.Y. 10154 USA

Dated (l) May 31, 1988

(m) Isaac Jarkovsky, Assistant General Counsel - ~~Patents and Assistant~~ Secretary

To: The Commissioner of Patents

P18/7/78

PHILLIPS ORMONDE & FITZPATRICK
Patent and Trade Mark Attorneys
367 Collins Street
Melbourne, Australia

(12) PATENT ABRIDGMENT (11) Document No. AU-B-21666/88
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 620561

(54) Title
3'-DEMETHOXYEPIPODOPHYLLOTOXIN GLUCOSIDE DERIVATIVES

International Patent Classification(s)
(51)[4] C07H 017/04 A61K 031/70

(21) Application No. : 21666/88 (22) Application Date : 30.08.88

(30) Priority Data

(31) Number (32) Date (33) Country
091570 31.08.87 US UNITED STATES OF AMERICA

(43) Publication Date : 02.03.89

(44) Publication Date of Accepted Application : 20.02.92

(71) Applicant(s)
BRISTOL-MYERS SQUIBB COMPANY

(72) Inventor(s)
MARK G. SAULNIER; DOLATRAI M. MYAS

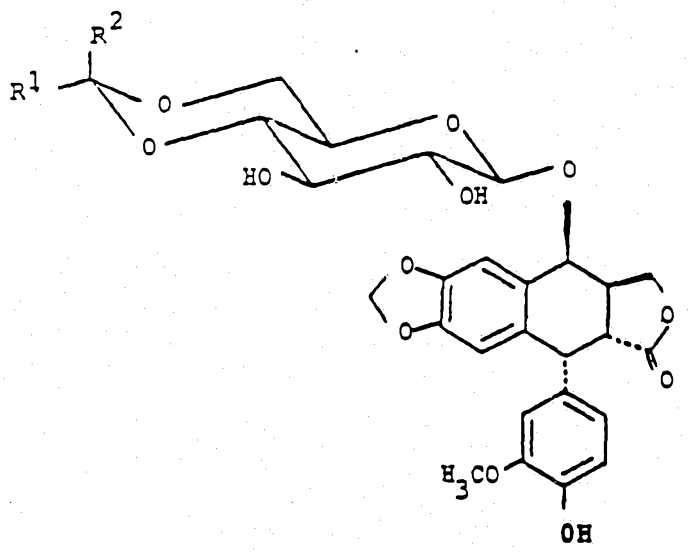
(74) Attorney or Agent
PHILLIPS ORMONDE & FITZPATRICK , 367 Collins Street, MELBOURNE VIC 3000

(56) Prior Art Documents
AU 15136/88 C07H 017/04
AU 18446/88 C07H 017/04

(57) The present invention relates to 3'-demethoxy epipodophyllotoxin glucoside derivatives, to their therapeutic anti-tumor use, and to pharmaceutical dosage forms containing these new agents.

CLAIM

1. A compound having the formula



. . ./2

wherein R^2 is hydrogen and R^1 is selected from the group consisting of C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_3-C_7 cycloalkyl furyl, thienyl, pyridyl, pyrrolyl, C_6-C_{10} aryl and C_7-C_{14} aralkyl, said aryl and aralkyl rings optionally bearing one or more substituents selected from halo, C_1-C_4 alkyl, nitro, hydroxy, C_1-C_4 alkoxy, C_1-C_4 alkanoyloxy, cyano, amino, C_1-C_4 alkylamino, di(c_1-C_4alkyl)amino, carboxy, C_1-C_4 alkylthio, mercapto, C_2-C_4 alkenoylamino, C_2-C_4 alkenyl and carbamoyl; or R^1 and R^2 are each C_1-C_{10} alkyl; or R^1 and R^2 and the carbon atom to which they are attached join to form a C_5-C_6 cycloalkyl group.

5. A pharmaceutical composition which comprises a compound of claim 1 and a pharmaceutically acceptable carrier.

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620561

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COMPLETE SPECIFICATION
(ORIGINAL)

Class Int. Class

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority

Related Art:

APPLICANT'S REFERENCE: CT-1871

Name(s) of Applicant(s):

~~Bristol-Myers Company~~ Bristol-Myers Squibb Company

Address(es) of Applicant(s):

345 Park Avenue,
New York,
New York,
UNITED STATES OF AMERICA.

Address for Service is:

PHILLIPS ORMONDE & FITZPATRICK
Patent and Trade Mark Attorneys
367 Collins Street
Melbourne 3000 AUSTRALIA

Complete Specification for the invention entitled:

3'-DEMETHOXYEPIPODOPHYLLOTOXIN GLUCOSIDE DERIVATIVES

Our Ref : 94533
POF Code: 1490/1490

The following statement is a full description of this invention, including the best method of performing it known to applicant(s):

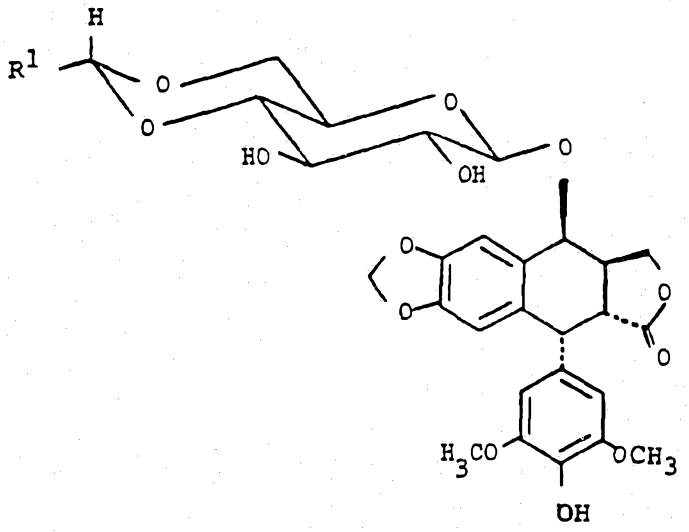
BACKGROUND OF THE INVENTION

1. Field of the Invention

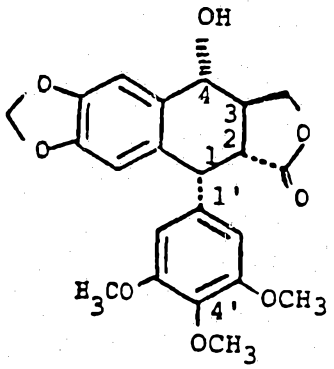
The present invention relates to 3'-demethoxy epipodophyllotoxin glucoside derivatives, to their therapeutic anti-tumor use, and to pharmaceutical dosage forms containing these new agents.

2. Description of the Related Art

Etoposide (VP-16, Ia) and teniposide (VM-26, Ib) are clinically useful anticancer agents derived from the naturally occurring lignan, podophyllotoxin (II). The numbering system used for nomenclature purposes is shown in Formula II. Etoposide and teniposide are 4'-demethyl epipodophyllotoxin derivatives; epipodophyllotoxin being



I



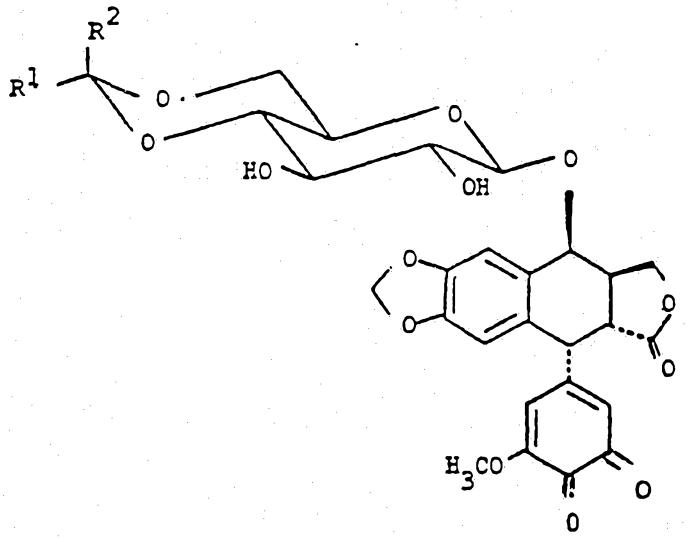
II

Ia $R^1 = CH_3$

Ib R^1 = 2-thienyl

the epimer of podophyllotoxin at the 4-position. Etoposide and teniposide are active in the treatment of a variety of cancers including small cell lung cancer, non-lymphocytic leukemia, and non-seminomatous testicular cancer (AMA Drug Evaluation, 5th Edition, American Medical Association, 1983, Chicago, Illinois, p. 1554-5).

Etoposide and teniposide, and methods for producing them, are disclosed in US Patent 3,524,844 to Keller-Juslen et al. Etoposide 3',4'-quinone (IIIa) has been generated from electrochemical oxidation of etoposide (Holthuis J. J. M., et al, J. Electroanal. Chem. Interfacial Electrochem., 1985, 184(2):317-29). The preparation of the quinone III by chemical oxidation is disclosed in US patent 4,609,644 to Josef Nemec. Epipodophyllotoxin 3',4'-quinone derivatives III wherein R^1 and R^2 have the definition given hereinbelow for Formula IV serve as the starting material for 3'-demethoxy epipodophyllotoxin derivatives of the present invention.

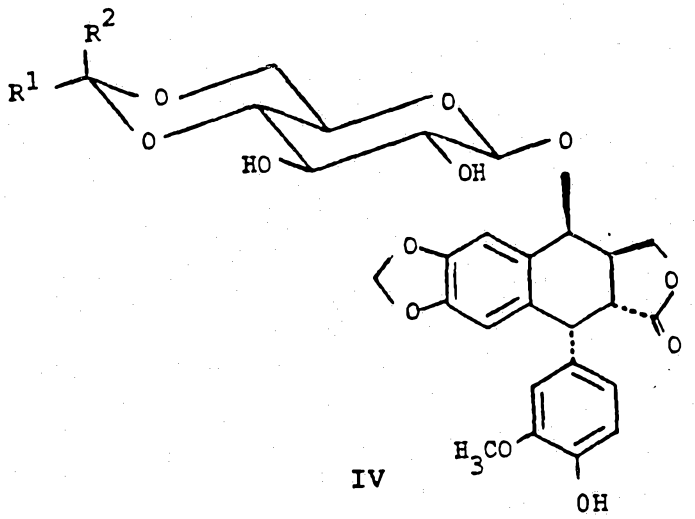


III

IIIa $R^1 = CH_3$; $R^2 = H$

SUMMARY OF THE INVENTION

The present invention provides 3'-demethoxy epipodophyllotoxin glucoside derivatives of Formula IV



IV

wherein R^2 is hydrogen and R^1 is selected from the group consisting of C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_3-C_7 cycloalkyl, furyl, thienyl, pyridyl, pyrrolyl, C_6-C_{10} aryl and C_7-C_{14} aralkyl, said aryl and aralkyl rings optionally bearing one or more substituents selected from halo, C_1-C_4 alkyl, nitro, hydroxy, C_1-C_4 alkoxy, C_1-C_4 alkanoyloxy, cyano, amino, C_1-C_4 alkylamino, di(C_1-C_4alkyl)amino, carboxy, C_1-C_4 alkylthio, mercapto, C_2-C_4 alkenoylamino, C_2-C_4 alkenyl and carbamoyl; or R^1 and R^2 are each C_1-C_{10} alkyl; or R^1 and R^2 and the carbon atom to which they are attached join to form a C_5-C_6 cycloalkyl group. A preferred embodiment provides compounds of Formula IV wherein R^2 is H, and R^1 is selected from C_1-C_{10} alkyl and thienyl, with methyl being the most preferred.

Another aspect provides a method for inhibiting tumors in a mammalian host comprising administering to a

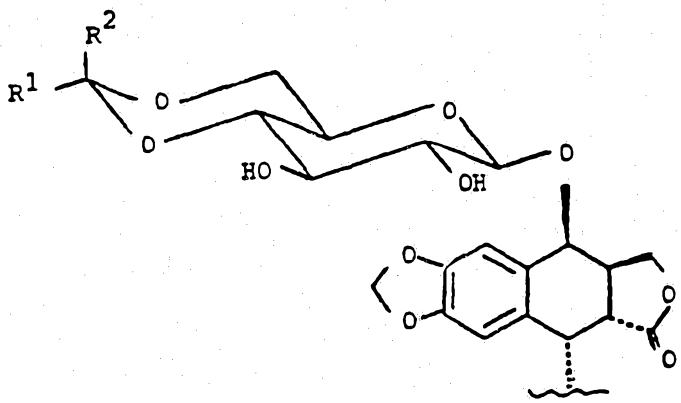
tumor-bearing host a tumor-inhibiting amount of a compound of Formula IV.

A further aspect provides a pharmaceutical composition comprising a compound of Formula IV in a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION OF THE INVENTION

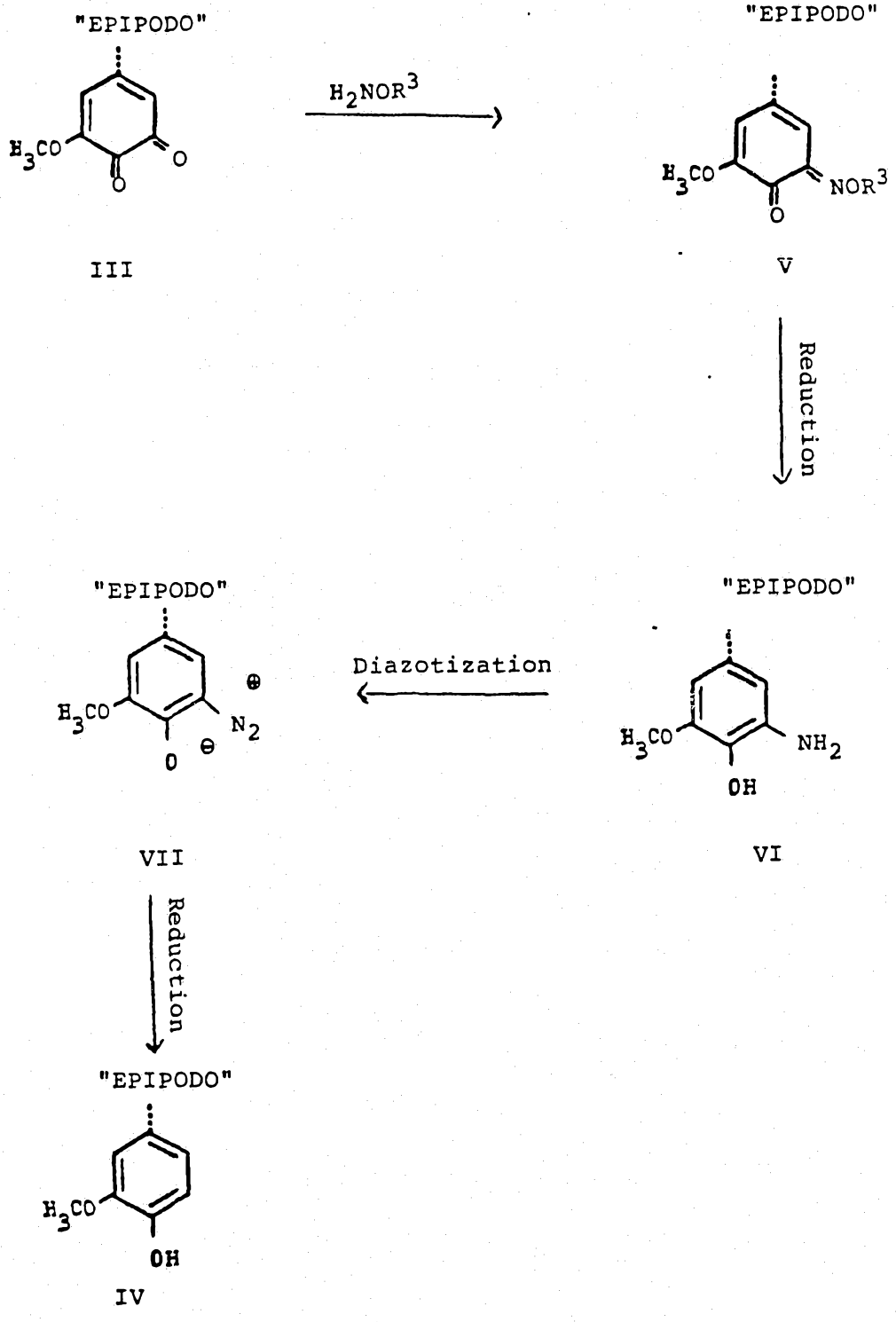
Compounds of the present invention may be prepared by the reaction sequence shown in Scheme I wherein R^3 is C_1-C_5 alkyl or aryl-C_1-C_5 alkyl, and the term "EPIPODO' is used to represent the fragment.

"EPIPODO"



wherein R^1 and R^2 are as defined on page 4.

Scheme I


"EPIPODO"
H_2NOR^3
"EPIPODO"
H_3CO
O
O
H_3CO
NOR^3
O
III
V
Reduction
"EPIPODO"
"EPIPODO"
H_3CO
$\oplus$
N_2
$\ominus$
O
Diazotization
H_3CO
NH_2
OH
VII
VI
Reduction
"EPIPODO"
H_3CO
OH
IV

The ortho-quinones III are, as previously mentioned, know compounds and may be prepared by oxidizing 4'-dimethylepipodophyllotoxin glucosides according to the procedure described in US 4,609,644 (J. Nemec, 1986). Reaction of the ortho-quinones III with an O-substituted hydroxylamine, or an acid addition salt thereof, in an inert organic solvent provides the corresponding 3'-oxime ether V. The reaction is preferably carried out at room temperature for a period sufficient to obtain the mono oxime ether, for example from about 30 minutes to about one hour. The products thus formed may be isolated and purified e.g. by flash chromatography; or alternatively, they may be reduced directly, without first being isolated, to the corresponding amine compound of Formula VI. Reduction of the oxime ether to the corresponding 3'-amino compound may be effected by conventional methodologies, e.g. a mild chemical reducing agent, or hydrogenation in the presence of a suitable catalyst such as Pt, Pd, Ni, Ru or Rh. Catalytic hydrogenation is preferably employed. Amine compounds of Formula VI may also be prepared directly from the ortho-quinone III by treatment with ammonia or an alkylamine at room temperature; reaction with the latter yields both the amine VI and the corresponding alkyl substituted amine. The preferred preparative method is the reduction of the oxime ether of Formula V. Diazotization of VI in an inert solvent at reduced temperature followed by aqueous work-up provides the diazonium salt VII. Reduction of the diazonium salt using reagents known in the art for this purpose, such as hypophosphorous acid, sodium borohydride, or an excess of thiophenol provides 3'-demethoxy-4'demethylepipodophyllotoxin of Formula IV.

BIOLOGICAL ACTIVITY

3'-Demethoxy etoposide was evaluated for its antitumor activity against transplantable murine P388 leukemia.

Female CDF_1 mice were implanted intraperitoneally with a tumor inoculum of 10^6 ascites cells of P388 murine leukemia and treated with various doses of a test compound; four mice were used for each dose level and ten were used as saline-treated control. The compounds were administered by intraperitoneal injection on days 5 and 8 (day 1 being the day of tumor implantation). Antitumor activity was expressed as % T/C which is the ratio of the median survial time (MST) of drug-treated group to the MST o saline-treated control group. A compound showing a % T/C value of 125 or greater is generally considred to have significant antitumor activity in the P388 test. The experiment lasted 31 days at the end of which time the number of survivors was noted. Table I presents the results of the above-described evaluation; only the maximum % T/C and the dose showing the maximum effect are reported.

Table 1. Antitumor activity against P388 Leukemia

Compound	Dose (mg/kg/inj.)	Max. % T/C
3'-Demethoxy etoposide	40	245
Etoposide	60	260

It is apparent from the animal test results provided above that compounds of formula IV possess effective

inhibitory action against mammalian tumors. Accordingly, this invention provides a method for inhibiting mammalian tumors which comprises administering an effective tumor-inhibiting dose of an antitumor compound of formula IV to a tumor bearing host.

Another aspect of this invention provides a pharmaceutical composition which comprises an effective tumor-inhibiting amount of an antitumor compound of formula IV and a pharmaceutically acceptable carrier. These compositions may be made up of any pharmaceutical form appropriate for the desired route of administration. Examples of such compositions include solid compositions for oral administration such as tablets, capsules, pills, powders and granules, liquid compositions for oral administration such as solutions, suspensions, syrups or elixirs and preprations for parenteral administration such as sterile solutions, suspensions or emulsions. They may also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, physiological saline or some other sterile injectable medium immediately before use.

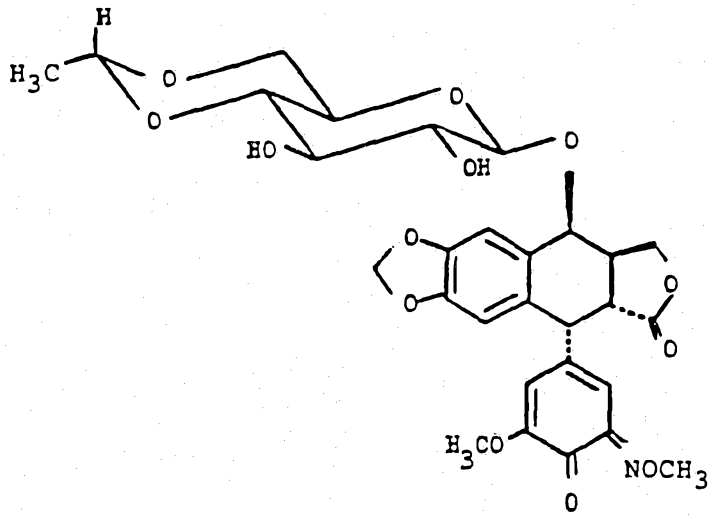
Optimal dosages and regimens for a given mammalian host can be readily ascertained by those skilled in the art. It will, of course, be appreciated that the actual dose used will vary according to the particular composition formulated, the particular compound used, the mode of application and the particular situs, host and disease being treated. Many factors that modify the action of the drug will be taken into account including age, weight, sex, diet, time of administration, route of administration, rate of excretion, condition of the patient, drug combinations, reaction sensitivities and severity of the disease.

The following examples are for illustrative purposes only and should not be construed as limiting the scope of the invention.

In the following examples, all temperatures are given in degrees Centigrade. Melting points were recorded on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H NMR spectra were recorded either on a Bruker WM 360 or a Varian VX2 200 spectrophotometer (using $CDCl_3$ as an internal reference). Chemical shifts are reported in δ units and compling constants in Hertz. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bp, broad peak; and dd, doublet of doublet. Infrared spectra were determined either on a Beckman Model 4240 or a Perkin-Elmer 1800 Fourier Transform Infrared Spectrophotometer and are reported in reciprocal centimeters (cm^{-1}). Thin-layer chromatography (TLC) was carried out on precoated silica gel plates (60F-254) using UV light and/or iodine vapors as visualizing agents. High and low resolution mass spectra were recorded on KRATOS MS 50 and KRATOS MS 25RFA Spectrophotometer, respectively. "Flash Chromatography" refers to the method described by Still (Still, W.C. et al, J. Org. Chem., 1978, 43:2923) and was carried out using either E. Merck silica gel (200-400 mesh) or Woelm silica gel (32-63 μm). All evaporations of solvents were performed under reduced pressure.

Example 1

Etoposide-ortho-quinone-3'-O-methyloxime Va



A solution of etoposide ortho-quinone IIIa (350 mg, 0.611 mmol) in pyridine (20 ml) was treated with a solution of methoxylamine hydrochloride (350 mg, 4.19 mmol) in pyridine (10 ml). The resultant orange solution was stirred for 30 minutes at room temperature and the pyridine was then removed in vacuo. The residue was dissolved in CH_2Cl_2 (50 ml) and partitioned with H_2O (20 ml) and 1N HCl (10 ml). The aqueous layer was further extracted with CH_2Cl_2 (25 ml) and the combined organic extracts were dried over $MgSO_4$. The solvent was evaporated in vacuo to give a dark orange oil. Flash chromatography on silica gel (14 g) with 5% CH_3OH in CH_2Cl_2 gave 243 mg (66%) of the title compound as an orange solid. Trituration with Et_2O provided the analytical sample. On a larger scale, this oxime is generally not purified but is directly hydrogenated to the amine VIa in an overall yield of ca 70%.

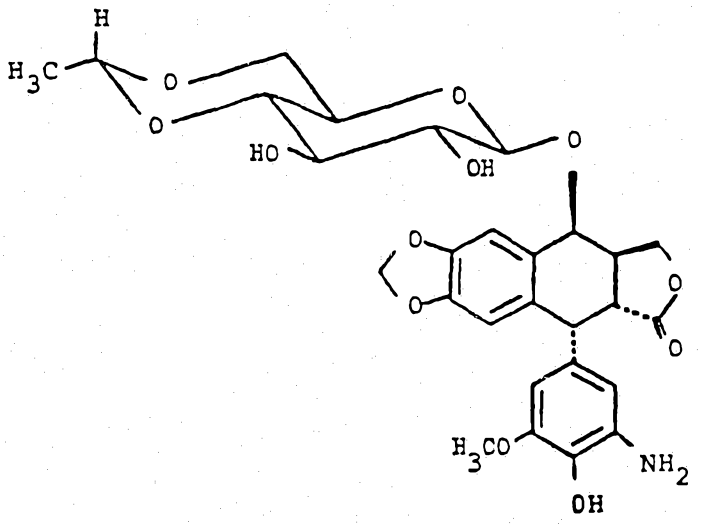
IR (KBr) 3480, 1775, 1670, 1625, 1488, 1237, 1040 cm^{-1}.

^1H NMR ($CDCl_3$) δ 6.82 (s,1H), 6.56 (s,1H), 6.48 (d,1H), 6.07 (d,1H), 6.01 (d,1H) 5.75 (d,1H), 4.92 (d,1H), 4.76 (q,1H), 4.66 (d,1H), 4.50 (dd,1H), 4.38 (dd,1H), 4.27 (d,1H), 4.22-4.17 (m,1H), 4.15 (s,3H), 3.79 (s,3H), 3.78-3.74 (m,1H), 3.63-3.58 (m,1H), 3.44 (dd,1H), 3.38-3.30 (m,3H), 2.95-2.87 (m,1H), 1.40 (d,3H).

Anal. Calcd for $C_{29}H_{31}NO_{13}$: C,57.90; H,5.19; N,2.33. Found: C,56.01; H,5.04; N,2.41.

Example 2

3-Amino-3'-demethoxy etoposide VIa



The crude oxime Va obtained from etoposide ortho-quinone IIIa (4.1 g, 7.2 mmol) and methoxylamine hydrochloride (4.1 g, 49 mmol) by the procedure described in Example 1 was dissolved in reagent alcohol (275 ml) and treated with 20% palladium hydroxide on carbon (290 mg) and 10% palladium on carbon (1.6 g). The mixture was hydrogenated at 40-50 psi H_2. After 16 h, the mixture was filtered through Celite, washed with ethyl acetate, and the solvent was evaporated. The crude product was purified by flash chromatography on 300 g. E. Merck 230-400 mesh silica

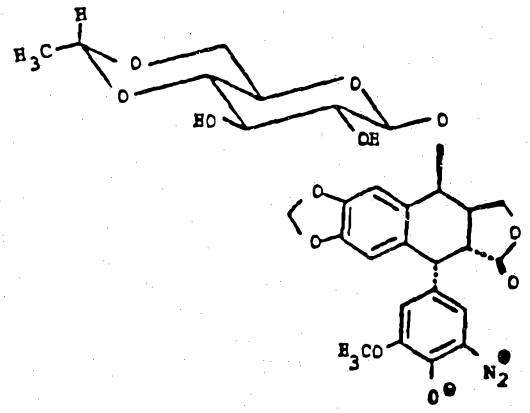
gel using 8:2 EtOAc/hexane as eluent to provide 2.89 g (70% overall) of the title compound as a white solid. Recrystallization from ethanol gave the analytical sample.

IR (KBr) 3455, 1775, 1615, 1490, 1235, 1070, 1030, 1000, 930 cm^{-1}.

^1H NMR ($CDCl_3$) δ 6.76 (s,1H), 6.48 (s,1H), 6.37 (d,1H), 5.96 (ABq,2H), 5.65 (d,1H), 4.87 (d,1H), 4.73 (q,1H), 4.61 (d,1H), 4.47 (d,1H), 4.38 (dd,1H), 4.23-4.16 (m,2H), 3.78 (s,3H), 3.76-3.72 (m,1H), 3.60-3.55 (m,1H), 3.42 (dd,1H), 3.37-3.30 (m,2H), 3.21 (dd,1H), 2.97-2.88 (m,1H), 1.37 (d,3H).

Anal. Calcd for $C_{28}H_{31}NO_{12}$: C,58.63; H,5.45; N,2.44. Found: C,57.85; H,5.76; N,2.35

Example 3. Etoposide 3'-diazonium hydroxide inner salt VIIa.



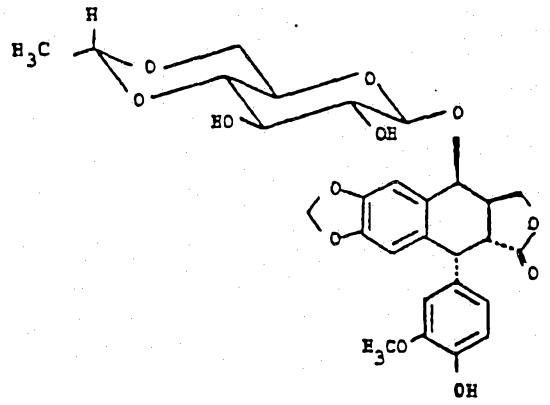
Glacial acetic acid (3.0 ml, 26.2 mmol) followed by $NaNO_2$ (0.15 g, 2.17 mmol) were added to a solution of 3'-aminoetoposide (product of Example 2, 0.22 g, 0.384 mmol) in dry THF (17 ml) stirring at 0°C under N_2. The reaction mixture was stirred for ~~3.4 hours~~ 3 hours, 24 minutes at 0°C and poured into 150 ml of CH_2Cl_2. The dark red organic layer was washed with 100 ml of aqueous $NaHCO_3$. The combined organic extracts

were washed with 100 ml of saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated <u>in vacuo</u> to provide 0.177 g (79%) of a reddish orange solid: mp. slow decomposition 150°C.

IR (KBr) 3440 (b), 2930, 2160, 2120, 1779 cm^{-1}.

^1H NMR ($CDCl_3$) δ 6.78 (s,1H), 6.73 (s,1H), 6.52 (s,1H), 5.97 (d,J=8.3Hz,2H), 5.82 (s,1H), 4.86 (d,J=2.2Hz,1H), 4.72 (m,1H), 4.54 (d,J=7.6Hz,1H), 4.43 (t,J=9.0Hz,1H), 4.35 (d,J=5.1Hz,1H), 4.26 (t,J=8.3Hz,1H), 4.14 (m,1H), 3.71 (s,3H), 3.55 (t,J=9.7Hz,1H), 3.40 (t,J=8.1Hz,1H), 3.3 (bm,4H), 3.02 (m,1H), 1.35 (d,J=4.9Hz,3H).

<u>Example 4</u>. <u>3'-Demethoxy etoposide IV.</u>



The crude etoposide diazonium salt of Example 3 (1.03 g, 1.76 mmol) was dissolved in absolute methanol (100 ml) and treated with sodium borohydride powder (400 mg) followed after 5 minutes by the addition of glacial acetic acid (5 ml). The mixture was stirred at room temperature for 2 hours, the solvent was evaporated <u>in vacuo</u>, and the residue was treated with H_2O (100 ml) and extracted with CH_2Cl_2 (100 ml then 2x50 ml). The combined extracts were washed with saturated aqueous sodium bicarbonate (25 ml) and brine (75 ml) and dried over $MgSO_4$. Rotary evaporation followed by flash chromatography on silica gel (32 g) using 3-4% CH_3OH in CH_2Cl_2 as eluant provided 400 mg (41%) of the title compound as a colorless solid, mp 190-195°C.

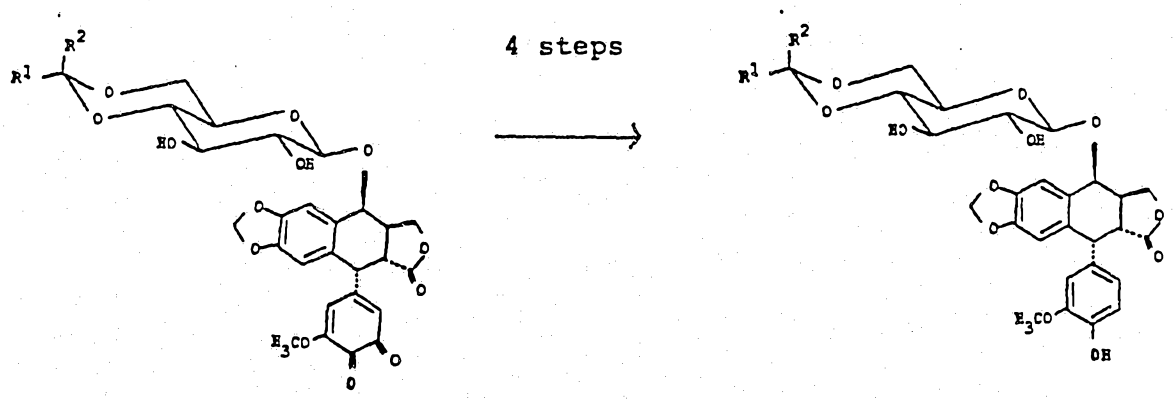
IR (KBr) 3455, 1775, 1515, 1485, 1388, 1170, 1090, 1075, 1035, 1005, 933, 700 cm^{-1}.

^1H NMR ($CDCl_3$) δ 6.99 (d, 1H,J=1.7Hz), 6.79 (s, 1H), 6.65 (d,1H,J=8.2Hz), 6.51 (s, 1H), 6.01 (dd,1H,J=1.7 and 8.2Hz), 5.96 (d,2H), 5.50 (s, 1H), 4.87 (d,1H,J=3.4Hz), 4.73 (q,1H,J=5Hz), 4.64 (d,1H,J=7.6Hz), 4.57 (d,1H,J=5.2Hz), 4.39 (dd,1H), 4.21-4.13 (m,2H), 3.85 (s,3H), 3.71 (dd,1H), 3.56 (dd,1H), 3.43 (m,1H), 3.33-3.30 (m,2H), 3.23 (dd,1H,J=5.2 and 14.1Hz), 2.91-2.82 (m,1H), 2.66 (br s, 1H), 2.39 (br s, 1H), 1.37 (d,3H,J=5Hz).

Anal. calcd for $C_{28}H_{30}O_{12}$:C, 60.21; H, 5.41.
Found: C, 59.45; H, 5.57.

Example 5

The procedures described in Examples 1 to 4 are repeated with the exception that etoposide ortho-quinone is replaced with epipodophyllotoxin glucoside ortho-quinones having R^1 and R^2 as shown below to provide the corresponding 3'-demethoxy derivatives.



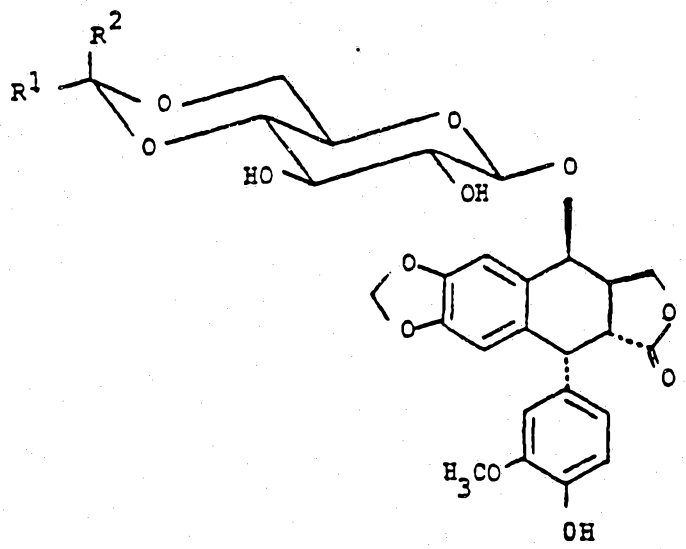
R^1	R^2
2-thienyl	H
2-furyl	H
cyclohexyl	H
phenyl	H
benzyl	H
4-methylphenyl	H
3-methoxyphenyl	H
4-hydroxyphenyl	H
4-(N,N-dimethylphenyl)	H
2-chlorophenyl	H
methyl	methyl
ethyl	methyl

$R^1+R^2 = (CH_2)_4$

$= (CH_2)_5$

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound having the formula



wherein R^2 is hydrogen and R^1 is selected from the group consisting of C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_3-C_7 cycloalkyl furyl, thienyl, pyridyl, pyrrolyl, C_6-C_{10} aryl and C_7-C_{14} aralkyl, said aryl and aralkyl rings optionally bearing one or more substituents selected from halo, C_1-C_4 alkyl, nitro, hydroxy, C_1-C_4 alkoxy, C_1-C_4 alkanoyloxy, cyano, amino, C_1-C_4 alkylamino, di(c_1-C_4alkyl)amino, carboxy, C_1-C_4 alkylthio, mercapto, C_2-C_4 alkenoylamino, C_2-C_4 alkenyl and carbamoyl; or R^1 and R^2 are each C_1-C_{10} alkyl; or R^1 and R^2 and the carbon atom to which they are attached join to form a C_5-C_6 cycloalkyl group.

2. A compound of claim 1 wherein R^2 is H and R^1 is methyl or 2-thienyl.

3. A compound of either one of claims 1 or 2 wherein R^1 is methyl.

4. A method of inhibiting tumors in a mammalian host which comprises administering to a tumor-bearing host an effective tumor-inhibiting amount of a compound of claim 1.

5. A pharmaceutical composition which comprises a compound of claim 1 and a pharmaceutically acceptable carrier.

6. A compound according to claim 1 substantially as hereinbefore described with reference to any one of the examples.

7. A method according to claim 4 substantially as hereinbefore described with reference to any one of the examples.

8. A pharmaceutical composition according to claim 5 substantially as hereinbefore described with reference to any one of the examples.

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