



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification⁵ : C07D 487/22, A61K 31/475</p>	<p>A1</p>	<p>(11) International Publication Number: WO 94/25465</p> <p>(43) International Publication Date: 10 November 1994 (10.11.94)</p>													
<p>(21) International Application Number: PCT/US94/04866</p> <p>(22) International Filing Date: 3 May 1994 (03.05.94)</p> <p>(30) Priority Data:</p> <table border="0"> <tr> <td>08/057,133</td> <td>3 May 1993 (03.05.93)</td> <td>US</td> </tr> <tr> <td>08/213,657</td> <td>15 March 1994 (15.03.94)</td> <td>US</td> </tr> </table> <p>(60) Parent Applications or Grants</p> <p>(63) Related by Continuation</p> <table border="0"> <tr> <td>US</td> <td>08/057,133 (CON)</td> </tr> <tr> <td>Filed on</td> <td>3 May 1993 (03.05.93)</td> </tr> <tr> <td>US</td> <td>08/213,657 (CON)</td> </tr> <tr> <td>Filed on</td> <td>15 March 1994 (15.03.94)</td> </tr> </table> <p>(71) Applicant (for all designated States except US): SMITHKLINE BEECHAM CORPORATION [US/US]; Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): KINGSBURY, William, Dennis [US/US]; 865 Babb Circle, Wayne, PA 19087 (US). PENDRAK, Israil [US/US]; 2903 Bayton Road, Norristown, PA 19403 (US).</p>	08/057,133	3 May 1993 (03.05.93)	US	08/213,657	15 March 1994 (15.03.94)	US	US	08/057,133 (CON)	Filed on	3 May 1993 (03.05.93)	US	08/213,657 (CON)	Filed on	15 March 1994 (15.03.94)	<p>(74) Agents: STERCHO, Yuriy, P. et al.; SmithKline Beecham Corporation, Corporate Intellectual Property UW2220, P.O. Box 1539, 709 Swedeland Road, King of Prussia, PA 19406-0939 (US).</p> <p>(81) Designated States: AU, BB, BG, BR, BY, CA, CN, CZ, FI, HU, JP, KP, KR, KZ, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SI, SK, UA, US, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p>
08/057,133	3 May 1993 (03.05.93)	US													
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<p>(54) Title: SUBSTITUTED METHYLENEDIOXY[3',4':6,7]INDOLIZINO-[1,2-b]QUINOLINONES</p>															
<p>(57) Abstract</p>															
<p>Antiviral substituted methylenedioxyindolizino[1,2-<i>b</i>]quinolinones, compositions comprising such compounds, and a method of treating viral infection by using such compounds are disclosed herein.</p>															

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SUBSTITUTED METHYLENEDIOXY[3',4':6,7]INDOLIZINO-
[1,2-*b*]QUINOLINONES

This patent application is a continuation-in-part of U.S. Serial No.
5 08/057,133, filed on May 3, 1993 by Pendrak et al.

SCOPE OF THE INVENTION

This invention relates to antiviral compounds, pharmaceutical compositions
thereof, and a method of treating viral infections. More specifically, this invention
10 relates to certain indolizino[1,2-*b*]-quinolinyl derivatives which have antiviral activity.

BACKGROUND OF THE INVENTION

Certain 1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolinones are known to have
15 cytotoxic and antiviral activity. Camptothecin is an example of one such compound.
It is a water-insoluble, cytotoxic alkaloid produced by Camptotheca acuminata trees
indigenous to China and Nothapodytes foetida trees indigenous to India.
Camptothecin and its close congeners are known to inhibit eukaryotic topoisomerase
I. The cytotoxic and antitumor activity of camptothecin and its close congeners is
20 due to this inhibition of eukaryotic topoisomerase I (*Cancer Res.* 1988, 48, 1722;
Molec. Pharmacol. 1988, 34, 755). Compounds that are related in structure to
camptothecin but do not inhibit eukaryotic topoisomerase I are not cytotoxic to
mammalian cells and have no antitumor activity (*J. Med. Chem.* 1988, 32, 715;
Cancer Res. 1989, 49, 1465; *Cancer Res.* 1989, 49, 4358).

25 Camptothecin has been shown to have an effect on viruses by a number of
investigators in laboratory settings. Although camptothecin has demonstrated
antiviral activity in *in vitro* tissue culture systems, camptothecin and its close analogs
that have a hydroxylactone moiety cannot be considered as useful *in vivo* antiviral
agents because they inhibit mammalian topoisomerase I, inhibit host cell DNA
30 replication, and are cytotoxic to mammalian cells. Furthermore, camptothecin is not
expected to be attractive for drug development as an antiviral agent because of
unacceptable dose-limiting toxicity, unpredictable toxicity, poor aqueous solubility,
and/or unacceptable shelf life stability.

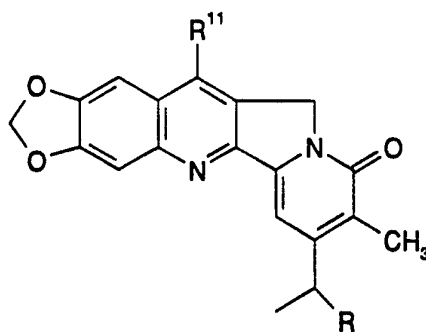
There is a need for new antiviral agents. Some substituted 1*H*-
35 pyrano[3',4':6,7]indolizino-[1,2-*b*]quinolinones that lack the E-ring α -hydroxy
lactone moiety of camptothecin have been shown to be non-cytotoxic to mammalian
cells and to lack antitumor activity (*Ann. Rev. Pharmacol. Toxicol.* 1977, 17, 117; *J.*
Med. Chem. 1989, 32, 715). This is because these compounds do not contain the

essential structural features required to inhibit eukaryotic topoisomerase I. But it has been found that certain 7-ethyl-7-hydroxy-7,8,11,13-tetrahydro-10H-dioxolo[4,5g]pyrano[3',4':6,7]indolizino[1,2-b]quinolinone-8,11-diones (hereinafter "methylenedioxyindolizino[1,2-b]quinolinones") lacking the hydroxylactone moiety do have antiviral activity without the undesirable features of camptothecin. As such

5 they are useful for treating viral infections.

SUMMARY OF THE INVENTION

10 In a first aspect, the present invention provides a method for treating viral infections, which method comprises administering to an infected host in need thereof an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, alone or in combination with a carrier, diluent or excipient.



(I)

15

wherein:

R is =O, -OH, and OR¹;

20

R¹ is -COR⁴, or -P(O)(OH)R⁵ wherein:

R³ is -H or lower alkyl;

25 R⁴ is -CR³R⁶R⁷;

-(CH₂)_nCH₂R⁷ (where n=0-3);

-(CH₂)_nCH₂COOH (where n=0-3);

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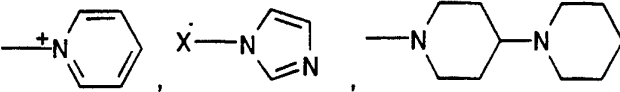
-NR⁹R¹⁰;

$-\text{NH}(\text{CH}_2)_n\text{CH}_2\text{R}^7$ (where $n = 1-3$); and

$-\text{NH}(\text{CH}_2)_n\text{CH}_2\text{COOH}$ (where $n = 0-3$);

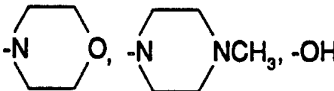
5 R^5 is OH or CH_2NH_2 ;

R^6 is H or the side chain of any naturally occurring α -amino acid;

10 R^7 is $-\text{NR}^9\text{R}^{10}$  where
 X is any pharmaceutically acceptable anion;

R^8 is lower alkyl;

15 R^9 and R^{10} are independently selected from the group consisting of -H, -C₁₋₆ alkyl, and R^9 and R^{10} taken together to form a 5-7 membered saturated heterocyclic ring containing the nitrogen on which R^9 and R^{10} are substituted; and
 R^{11} is $-\text{CH}_2\text{R}^{12}$, wherein:

20 R^{12} is $-\text{N}(\text{CH}_3)_2$ 

In another aspect, this invention relates to novel compounds of Formula I, and pharmaceutically acceptable salts thereof.

In yet another aspect, this invention relates to a composition comprising a novel compound of Formula I in combination with an acceptable carrier, excipient or diluent, particularly a pharmaceutically acceptable carrier, excipient or diluent.

DETAILED DESCRIPTION OF THE INVENTIONDefinitions

The terms below, defined as follows, are used in describing the present
5 invention throughout this application.

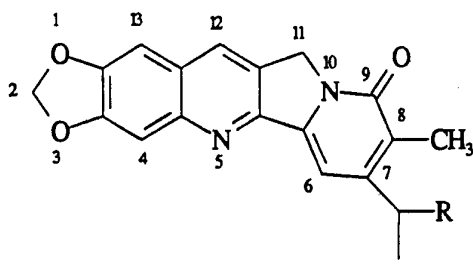
"Aliphatic" is intended to include saturated and unsaturated radicals. This
includes normal and branched chains, saturated or mono or poly unsaturated chains
where both double and triple bonds may be present in any combination. The phrases
"lower alkyl" and "C₁₋₆ alkyl" refer to and mean an alkyl group of 1 to 6 carbon
10 atoms in any isomeric form, but particularly the normal or linear form. "Lower
alkoxy" means the group lower alkyl-O-. "Halo" means fluoro, chloro, bromo or
iodo. "Acyl" means the radical having a terminal carbonyl carbon.

The phrase "5-7 membered saturated heterocyclic ring containing the
nitrogen" is intended to include saturated rings such as piperidine, pyrrolidine,
15 morpholine, piperazine, and N-alkyl piperazine.

Salts of any sort may be made from these compounds, provided there is an
acidic group present or a sufficiently basic nitrogen. Particularly preferred are the
pharmaceutically acceptable salts of the instant compounds. These latter salts are
those which are acceptable in their application to a pharmaceutical use. By that it is
20 meant that the salt will retain the biological activity of the parent compound and the
salt will not have untoward or deleterious effects in its application and use in treating
diseases.

Pharmaceutically acceptable salts are prepared in a standard manner. The
parent compound in a suitable solvent is reacted with an excess of an organic or
25 inorganic acid, in the case of acid addition salts of a base moiety, or an excess of
organic or inorganic base in the case where there is an acid group. Representative
acids are hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, acetic
acid, maleic acid, succinic acid or methanesulfonic acid. Cationic salts are readily
prepared from metal bases such as sodium, potassium, calcium, magnesium, zinc,
30 copper or the like and ammonia. Organic bases include the mono or disubstituted
amines, ethylenediamine, piperazine, amino acids, caffeine, and the like.

Here and throughout this application, the ring system of the compounds of the present invention are numbered according to Formula II.



5

II

If a chiral center or another form of an isomeric center is created by some combination of substituents, in a compound of the present invention, all forms of such isomer(s) are intended to be covered herein. Inventive compounds containing a chiral center may be used as a racemic mixture or the mixture may be separated and an individual enantiomer may be used alone.

The present invention provides a method for the treatment of viral infections caused by certain DNA viruses comprising administering to an infected animal, preferably a mammal, most preferably a human, in need thereof an effective amount of a compound of Formula I as described hereinabove, or a pharmaceutically acceptable salt thereof, alone or in combination with a carrier, excipient or diluent.

The present invention also provides compounds, and pharmaceutically acceptable salts thereof, which exhibit antiviral activity, said compounds having the structure represented by Formula I hereinabove.

More specifically, these compounds and the present method are especially useful in treating the following pathogens in humans:

Herpes Simplex virus types 1 and 2 (HSV-1 and HSV-2);

Cytomegalovirus (CMV);

Varicella Zoster Virus (VZV);

No unacceptable toxicological effects are expected when compounds of the present invention are administered in accordance with the present invention.

A preferred method for treating viral infections according to the present invention uses the following compounds of Formula I:

- 7-Acetyl-8-methyldioxolo[4,5-g]indolizino[1,2-b]quinolin-9(11*H*)-one;
- (±)-7-(1-Hydroxyethyl)-8-methyldioxolo[4,5-g]indolizino[1,2-b]quinolin-9(11*H*)-one;
- (±)-7-[1(Aminoacetyl)oxy]ethyl]-8-methyldioxolo[4,5-g]indolizino[1,2-b]quinolin-9(11*H*)-one hydrotrifluoroacetate;

7-Acetyl-12-dimethylaminomethyl-8-methyldioxolo [4,5-*g*] indolizino [1,2-*b*]quinolin-9(11H)-one; and

7-Acetyl-12-hydroxymethyl-8-methyldioxolo [4,5-*g*] indolizino [1,2-*b*]quinolin-9(11H)-one.

5 Preferred compounds of the present invention include:

7-Acetyl-8-methyldioxolo[4,5-*g*]indolizino[1,2-*b*]quinolin-9(11H)-one;

(±)-7-(1-Hydroxyethyl)-8-methyldioxolo[4,5-*g*]indolizino[1,2-*b*]quinolin-9(11H)-one;

10 (±)-7-[1(Aminoacetyl)oxy]ethyl]-8-methyldioxolo[4,5-*g*]indolizino[1,2-*b*]quinolin-9(11H)-one hydrotrifluoroacetate;

7-Acetyl-12-dimethylaminomethyl-8-methyldioxolo [4,5-*g*] indolizino [1,2-*b*]quinolin-9(11H)-one; and

7-Acetyl-12-hydroxymethyl-8-methyldioxolo [4,5-*g*] indolizino [1,2-*b*]quinolin-9(11H)-one.

15 The compounds of the present invention can be prepared by the following methods.

There are several methods for preparing these compounds. One generic process comprises preparing a 1-keto indolizine adduct and then condensing this fragment with the appropriate substituted aminobenzaldehyde or aminoacetophenone.

20 Starting materials are commercially available or can be made by published methods.

The reaction sequences are illustrated by Schemes I-III. Commercially available 2-pyrrolidone **1** can be alkylated with dimethyl sulfate to give ether **2** which can be condensed with acetonedicarboxylate to give indolizine **3**. Methylation of **3** with methyl iodide at ambient temperature in the inert solvent produced **4**, which can be

25 hydrolyzed with an aqueous base to give **5** followed by decarboxylation to produce **6**.

Triflation of **6** with *N*-phenyltriflimide in DMF in the presence of base, like triethylamine, can give **7**, which can be reacted via Heck reaction with *n*-

butylvinylether in the presence of palladium catalyst and base to give **8**. Hydrolysis

of **8** with acid, like 3N HCl, can give **9** which can be protected as a ketal using

30 ethyleneglycol and hydrochloride gas to give **10**. Compound **10** can be oxidized

using Davis reagent and base to give alcohol **11** which can be further oxidized with

pyridiniumchlorochromate in methylene chloride to give ketone-ketal **12**. Friedlander condensation of compound **12** with aminopiperinal **13** in the presence of

p-toluenesulfonic acid in toluene and subsequent hydrolysis with acid, like 3N HCl,

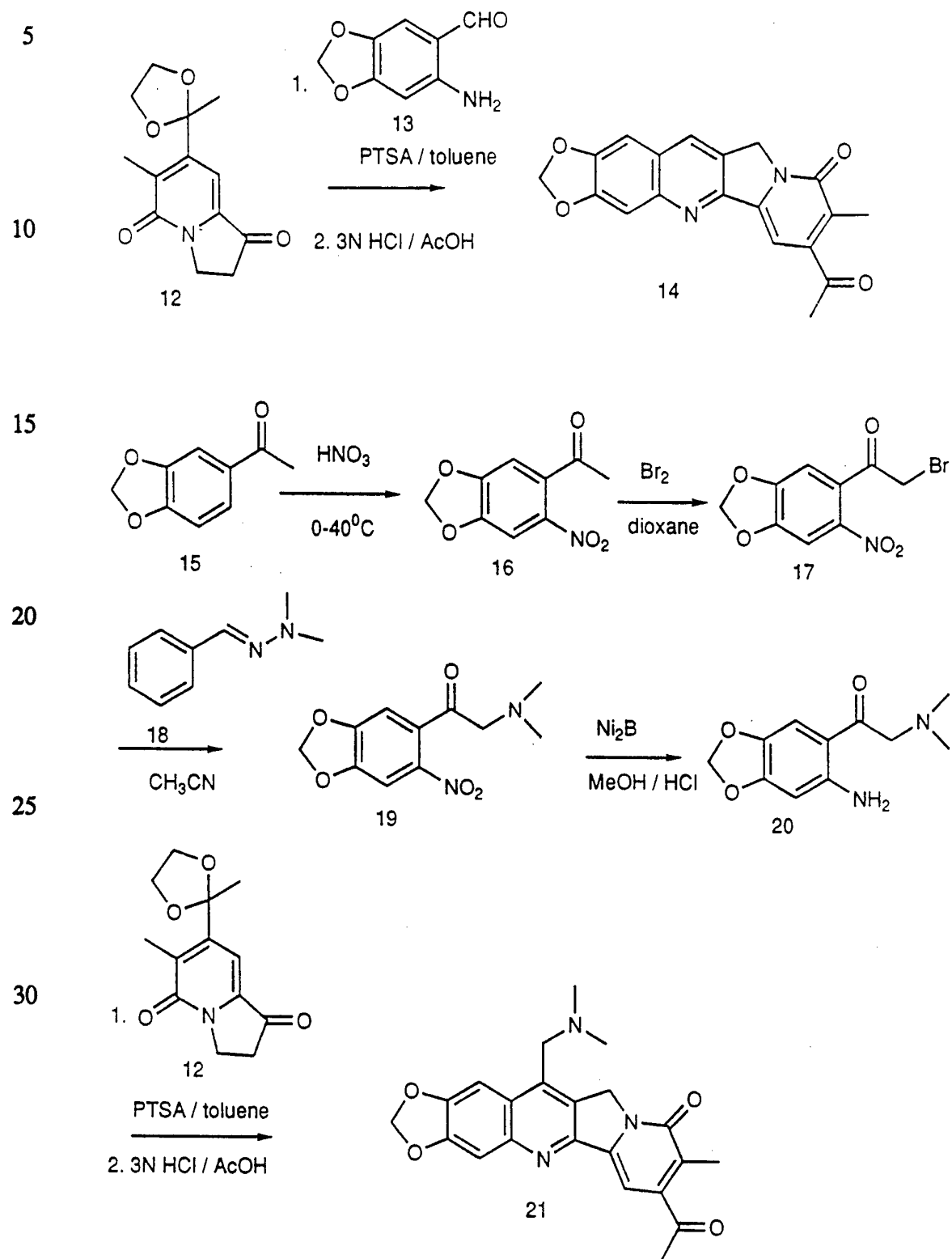
35 can give the title compound **14** (Scheme II). Aminoacetophenone **20** can be prepared

in four steps by first nitrating methylenedioxyacetophenone **15** with nitric acid to give compound **16** which can be brominated with bromine in dioxane to produce

compound **17**. Reaction of **17** with hydrazine **18** in acetonitrile can give compound

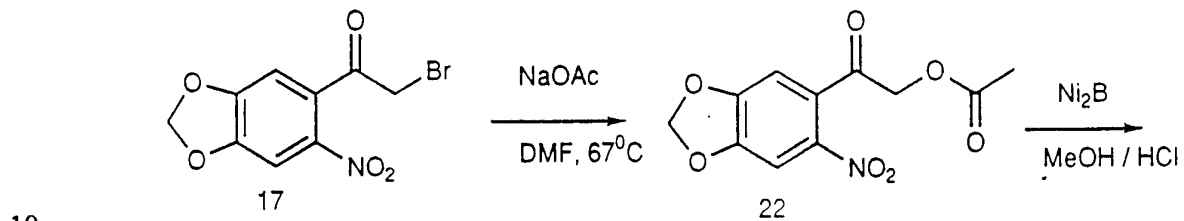
19 which can be reduced with nickel boride to give amine 20. Condensation of compound 12 and 20 as described previously can give the title compound 21 (Scheme II). Reaction of 17 with with sodium acetate in dimethylformamide produced compound 22 (Scheme III). Reduction of 22 with nickel boride can give
5 compound 23 which can be condensed with compound 12 and hydrolysed as described previously to produce the title compound 24.

SCHEME II



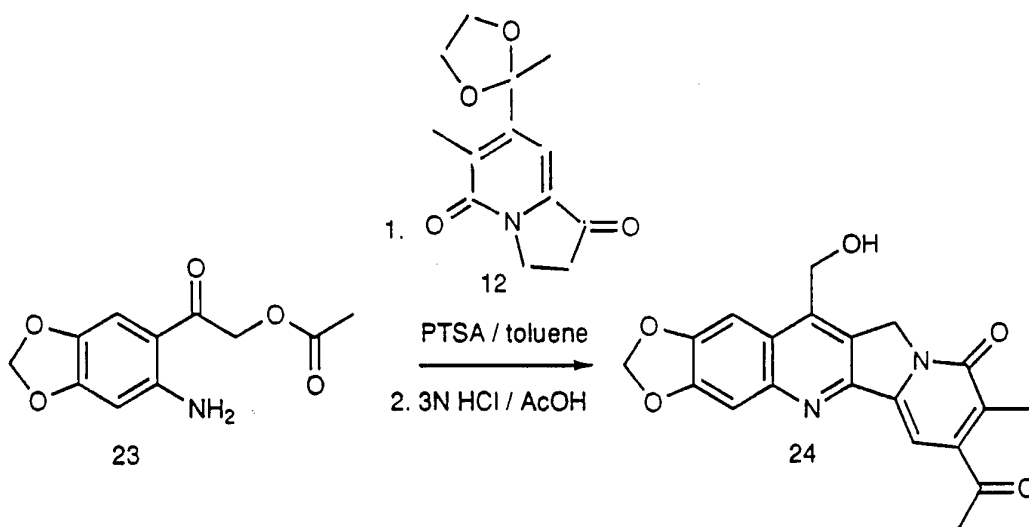
SCHEME III

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The assay used to test the compounds of the present invention for antiviral activity is well-known. A generalized description of the assay follows.

Well plates are seeded with the appropriate cells at a concentration of 1×10^5 cells per well suspended in 0.5 mL of Earle's Minimum Essential Medium (EMEM) containing 10% fetal bovine serum (FBS) and antibiotic and antimycotic solution. After the cells are 80-90% confluent (24 hours), old medium is removed and washed with Hank's buffered saline solution (HBSS). Cells are then infected for 1 hour at 37°C with 100-200 plaque forming units per well of a herpes simplex virus suspended in 250 mL HBSS. Following adsorption, the following are added:

- 10 A) 250 mL/well 2 x EMEM containing Human IgG (Sigma Chemical Co., St. Louis, Mo.) (ca. 0.1 mg/mL);
- B) 250 mL/well EMEM containing 10% FBS and antibiotic/antimycotic solution; and
- C) 250 mL/well HBSS containing appropriately diluted compound.

15 After 24-48 hours (best time determined by observation of plaques under a microscope), old medium is aspirated off. Each well is stained with a selected stain solution (0.5% crystal violet in MeOH:H₂O 7:3) and then rinsed with water, air dried, and the plaques are counted. Compound effectiveness is evaluated in terms of percent plaque reduction as compared to untreated, infected controls.

20 This assay can be used to test compound activity against many other viruses besides herpes simplex by simply modifying the cell type used in the first step to match the virus being tested, and otherwise following the procedure outlined above. Other cell types which can be used in this assay include mouse mammary tumor cells, human lung fibroblasts, sheep chorioplexus cells, and green monkey kidney cells.

25 Alternatively, other assays can be used to determine the antiviral activity of the present compounds. Such assays include the following types: cell count, clonogenic, cytopathic effect, dish-colony formation, microtiter-growth inhibition, thymidine incorporation and yield reduction. Each of these assays is well-known and is available either from the literature or from a commercial testing lab.

30 The present invention provides pharmaceutical compositions prepared from the compounds of Formula I. These compositions have both a human and veterinary utility, and comprise an excipient or carrier which is acceptable for the intended pharmaceutical end use and at least one inventive compound. For example, if a veterinary use is intended, the carrier may be a liquid, or spray, or may be formulated
35 in a solid, non-degradeable or degradeable form for insertion in the rumen. Selected excipients and carriers may be employed to prepare compositions acceptable or adaptable for humans use.

An effective amount of the pharmaceutical compositions of the present invention may be contained in one embodiment, such as in a single pill, capsule, or pre-measured intravenous dose or pre-filled syringe for injection. Alternatively, as is frequently the case, the composition will be prepared in individual dose forms where one unit, such as a pill, will contain a sub-optimal dose but the user will be instructed to take two or more unit doses per treatment. When the composition is presented as a cream, it will contain a discrete amount of drug and the user will apply some amount of the cream one or more times until the disease is in remission or has been effectively treated. Concentrates for later dilution by the end user may also be prepared, for instance for intravenous (IV) formulations and multi-dose injectable formulations.

Carriers or diluents contemplated for use in these compositions are generally known in the pharmaceutical formulary arts. Reference to useful materials can be found in well known compilations such as Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa.

The nature of the composition and the pharmaceutical carrier or diluent will, of course, depend upon the intended route of administration, for example whether by intravenous and intramuscular injection, parenterally, topically, orally, or by inhalation.

For parenteral administration the pharmaceutical composition will be in the form of a sterile injectable liquid such as an ampule or an aqueous or nonaqueous liquid suspension.

For topical administration the pharmaceutical composition will be in the form of a cream, ointment, liniment, lotion, paste, spray or drops suitable for administration to the skin, eye, ear, nose or genitalia.

For oral administration the pharmaceutical composition will be in the form of a tablet, capsule, powder, pellet, atroche, lozenge, syrup, liquid, or emulsion.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. When the pharmaceutical composition is employed in the form of a solution or suspension, examples of appropriate pharmaceutical carriers or diluents include: for aqueous systems, water; for non-aqueous systems: ethanol, glycerin, propylene glycol, olive oil, corn oil, cottonseed oil, peanut oil, sesame oil, liquid paraffins, and mixtures thereof with water; for solid systems: lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid, kaolin and mannitol; and for aerosol systems: dichlorodifluoromethane, chlorotrifluoroethane and compressed carbon dioxide. Also, in addition to the pharmaceutical carrier or diluent, the instant compositions may include other ingredients such as stabilizers, antioxidants, preservatives, lubricants, suspending agents, viscosity modifiers and the

like, provided that the additional ingredients do not have a detrimental effect on the therapeutic action of the instant compositions. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax, ethylcellulose, hydroxypropylmethylcellulose, methylmethacrylate and the like.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25 mg to about 1 gram. If a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable solution or suspension in an ampule or vial or nonaqueous liquid suspension. To obtain a stable water soluble dose form, a pharmaceutically acceptable salt of the compound of Formula I is dissolved in an aqueous solution of an organic or inorganic acid or base. If a soluble salt form is not available, the compound of Formula I may be dissolved in a suitable co-solvent or combinations thereof. Examples of such suitable cosolvents include, but are not limited to, alcohol, propylene glycol, polyethylene glycol 300, polysorbate 80, glycerin and the like in concentrations ranging from 0-60% of the total volume.

It will be appreciated that the actual preferred dosages of the compounds used in the compositions of this invention will vary according to the particular complex being used, the particular composition formulated, the mode of administration and the particular site, host and disease being treated. It is expected that these compounds will be active in the concentration ranges of two commercial antiviral drugs, Cytovene (ganciclovir) and Zovirax (acyclovir). The latter is manufactured in 200 mg capsules with instructions for treating herpes simplex viral infections by taking one capsule every 4 hours, but not to exceed 5 capsules per day.

EXAMPLES

In the following synthetic examples, temperature is in degrees Centigrade (°C). Unless otherwise indicated, all of the starting materials were obtained from commercial sources. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. These Examples are given to illustrate the invention, not to limit its scope. Reference is made to the claims for what is reserved to the inventors hereunder.

EXAMPLE 1Preparation of 7-Acetyl-8-methyldioxolo [4,5-g] indolizino [1,2-b] quinolin-9(1H)-one.5 1A) 2-Methoxy-pyrroline

2-Pyrrolidone (850 g, 760 mL, 10 mol; Aldrich) was added dropwise, over a period of two hours, to a stirred solution of dimethyl sulfate (1260 g, 945 mL, 10 mol; Aldrich) under an argon atmosphere, causing the temperature to rise to 45°C. When addition was complete the clear mixture was stirred for 16h at 60°C. It was then
10 poured onto ice and saturated K₂CO₃, and extracted with ether (2 X 1L). The combined organic phase was washed with brine, dried (Na₂SO₄), and solvent removed on the rotary evaporator, keeping the heating bath at 20°C. The residual liquid was distilled under vacuum into a chilled receiver to yield, after a small forerun 635 g (64%) of colorless liquid, b.p. 35°C / 15 Torr: ¹ NMR (400 MHz, CDCl₃)
15 δ 3.8 (s, 3H, OCH₃), 3.65 (t, 2H, CH₂-N), 2.45 (t, 2H, CH₂-N), 2.1 (m, 2H, -CH₂-).

1B) 7-Hydroxy-8-ethoxycarbonyl-2,3-dihydro-1H-indolizin-5-one

The mixture of compound of Example 1(A) (100 g, 100 mL, 1 mol) and 1,3-diethyl acetonedicarboxylate (202 g, 182 mL, 1.5 mol, Aldrich) alone with
20 triethylamine (10 mL) was kept at room temperature for 1.5 weeks. The crystals formed were separated by filtration and washed with petroleum ether and ethyl ether to give off white solid 94 g (41%), m.p. 131°C: ¹ NMR (400 MHz, CDCl₃) δ 5.8 (s, 1H, olefin), 4.4 (m, 3H, ethyl ester), 4.15 (t, 2H, CH₂-NCO), 3.5 (t, 2H, CH₂-olefin), 2.25 (m, 2H, -CH₂-), 1.4 (t, 3H, ethyl ester).

25

1C) 7-Hydroxy-8-ethoxycarbonyl-6-methyl-2,3-dihydro-1H-indolizin-5-one

To a solution of compound of Example 1(B) (10 g, 45 mmol) in dry THF (500 mL) under an argon atmosphere was added NaH (2 g, 49 mmol, 60% dispersion). The resulting mixture was stirred at room temperature for 10 min.
30 Methyl iodide (2.8 mL, 45 mmol) was added and mixture stirred at room temperature for 96h. Solvent was evaporated and residue purified by flash column chromatography (silica, 0-2% methanol: CH₂Cl₂) to give white solid 5.7 g (54%): ¹ NMR (400 MHz, CDCl₃) δ 11.4 (s, 1H, OH), 4.4 (m, 3H, ethyl ester), 4.15 (t, 2H, CH₂-NCO), 3.5 (t, 2H, CH₂-olefin), 2.25 (m, 2H, -CH₂-), 2.01 (s, 3H, CH₃), 1.4
35 (t, 3H, ethyl ester)

1D) 7-Hydroxy-8-carboxy-6-methyl-2,3-dihydro-1H-indolizin-5-one

To a solution of compound of Example 1(C) (1.2 g, 5 mmol) in methanol (30 mL), THF (20 mL) and H₂O (20 mL) was added LiOH (1g, 25 mmol) and mixture stirred at room temperature for 56h. Solvent was removed in vacuum. The resulting mixture was diluted with H₂O and acidified to (PH~5) with 3N HCl. The precipitated solid was filtered and washed with H₂O and dried in vacuum to give tan solid 0.8 g (76%): ¹ NMR (400 MHz, CD₃OD) δ 4.23 (m, 2H, CH₂-NCO), 3.5 (t, 2H, CH₂-olefin), 2.35 (m, 2H, -CH₂-), 1.95 (s, 3H, CH₃).

1E) 7-hydroxy-6-methyl-2,3-dihydro-indolizin-5-one

The compound of Example 1(D) (0.8 g, 3.75 mmol) and 2,4,6-trichlorophenol (6 g) were heated at 220°C until evolution of carbon dioxide stopped. The resulting mixture was cooled to room temperature and diluted with ethyl ether. The precipitated solid was filtered and dried to give solid 0.62 g (98%): ¹ NMR (400 MHz, CD₃OD) δ 6.1 (s, 1H, pyridyl), 4.23 (m, 2H, CH₂-NCO), 3.5 (t, 2H, CH₂-olefin), 2.35 (m, 2H, -CH₂-), 1.95 (s, 3H, CH₃).

1F) Trifluorometanesulfonic acid-6-methyl-5-oxo-1,2,3,5-tetrahydro-indolizin-7-yl-ester

To the solution of compound of Example 1(E) (5 g, 30 mmol) in DMF (100 mL) was added triethylamine (12.6 mL, 90 mmol) alone with N-phenyltrifluorometanesulfonimide (16 g, 45 mmol). The resulting mixture was stirred at room temperature for 1h. Solvent was removed in vacuum and residue purified by flash column chromatography (silica, 50-100% EtOAc: hexanes) to give tan solid 6.15 g (68%): ¹ NMR (400 MHz, CDCl₃) δ 6.15 (s, 1H, pyridyl), 4.16 (t, 2H, -CH₂), 3.13 (t, 2H, -CH₂-), 2.24 (m, 2H, -CH₂), 2.13 (s, 3H, CH₃).

1G) 7-(1-Butoxy-vinyl)-6-methyl-2,3-dihydro-1H-indolizin-5-one

To the solution of compound of Example 1(F) (6.15 g, 20 mmol) in DMF (100 mL) was added triethylamine (5.5 mL, 40 mmol) alone with n-butyl vinyl ether (10.3 mL, 80 mmol). To the resulting mixture was added Pd(OAc)₂ (0.27 g, 1.2 mmol) alone with 1,3-bis(diphenylphosphino)propane (0.49 g, 1.2 mmol). The resulting mixture was stirred at 60°C for 5h. Solvent was removed in vacuum and residue purified by flash column chromatography (silica, 30-60% EtOAc: hexane) to give oil 5 g (89%): ¹ NMR (400 MHz, CDCl₃) δ 6.15 (s, 1H, pyridyl), 4.35 (d, 1H, olefin), 4.16 (m, 3H, -CH₂; olefine), 3.79 (t, 2H, CH₂-O), 3.1 (T, 2H, -CH₂-), 2.2 (m, 5H, -CH₃; -CH₂-), 1.72 (m, 2H, alkyl), 1.48 (m, 2H, alkyl), 0.95 (t, 3H, alkyl).

1H) 7-Acetyl-6-methyl-2,3-dihydro-1H-indolizin-5-one

To the solution of compound of Example 1(G) (5 g, 20 mmol) in glacial acetic acid (10 mL) was added 3N HCl (3 mL) and the reaction mixture was stirred

at room temperature for 1h. Solvent was removed in vacuum and residue resuspended in EtOAc, washed with 5% NaHCO₃, NaCl, dried (Na₂SO₄). Solvent was removed in vacuum and residue purified by flash column chromatography (silica, 40-100% EtOAc: hexane and 0-5% methanol: CH₂Cl₂) to give solid 2.3 g (52%).

5 m.p. 101-102°C.

1I) 6-Methyl-7-(2-methyl-[1,3]-dioxolan-2yl)-2,3-dihydro-1H-indolizin-5-one

HCl gas was bubbled in to the solution of compound of Example 1(H) (2 g, 10.4 mmol) in ethylene glycol (50 mL) at 0°C. The resulting solution was allowed to
10 warm-up to room temperature and stirred at room temperature for 14h. The resulting mixture was poured in to the solution NH₄OH and ice. The mixture was extracted with CH₂Cl₂, washed with H₂O, NaCl and dried (Na₂SO₄). Solvent was removed in vacuum and residue purified by flash column chromatography (silica, 0-5% methanol: CH₂Cl₂) to give solid 2.13 g (86%). ¹ NMR (400 MHz, CDCl₃) δ 6.37
15 (s, 1H, pyridyl), 4.14 (t, 2H, -CH₂-), 4.02 (m, 2H, ketal), 3.73 (m, 2H, ketal), 3.04 (t, 2H, -CH₂-), 2.27 (s, 3H, -CH₃), 2.16 (m, 2H, -CH₂-), 1.61 (s, 3H, -CH₃).

1J) 1-Hydroxy-6-methyl-7-(2-methyl-[1,3]-dioxolan-2yl)-2,3-dihydro-1H-indolizin-5-one

To the solution of diisopropylamine (1.89 mL, 13.6 mmol) in THF (20 mL) at
20 -78°C was added n-butyllithium (5.4 mL, 13.6 mmol) and the resulting mixture was stirred at -78°C for 10 min. The solution of compound of Example 1(I) (2.13g, 9 mmol) in THF (100 mL) was added via addition funnel and the resulting mixture was stirred at -78°C for 10 min. Davis reagent (3.54 g, 18 mmol) in THF (20 mL) was
25 added at once and the resulting mixture was stirred at -78°C for 1h. Saturated solution of NH₄Cl (20 mL) was added at -78°C and the resulting mixture was extracted with CH₂Cl₂. Aqueous layer was acidified with 3N HCl and extracted with with CH₂Cl₂. The combined organic fractions were washed with H₂O, brine and dried (Na₂SO₄). Solvent was removed in vacuum and residue purified by flash
30 column chromatography (silica, 0-7% methanol: CH₂Cl₂) to give foam 1.16 g (51%). ¹ NMR (400 MHz, CDCl₃) δ 6.66 (s, 1H, pyridyl), 5.21 (br s, 1H, -CH-OH), 4.14 (m, 1H, -CH₂-), 4.04 (br s, 1H, -OH), 3.99 (m, 3H, ketal, -CH₂-), 3.73 (m, 2H, ketal), 2.46 (m, 1H, -CH₂-), 2.27 (s, 3H, -CH₃), 2.16 (m, 1H, -CH₂-), 1.61 (s, 3H, -CH₃).

35

1K) 6-Methyl-7-(2-methyl-[1,3]-dioxolan-2yl)-2,3-dihydro-1H-indolizin-1,5-dione

To the solution of compound of Example 1(J) (1.1g, 4.3 mmol) in CH₂Cl₂ (100 mL) was added pyridiniumchlorochromate (1.89 g, 8.7 mmol) and the resulting

mixture was stirred at room temperature for 12h. The mixture was diluted with CH₂Cl₂ and the resulting residue was filtered through the bed of celite. Solvent was removed in vacuum and residue purified by flash column chromatography (silica, 0-3% methanol: CH₂Cl₂) to give foam 0.8 g (74%). ¹H NMR (400 MHz, CDCl₃):
5 δ 7.20 (s, 1H, pyridyl), 4.28 (br s, 2H, -CH₂-), 4.07 (br s, 2H, ketal), 3.73 (br s, 2H, ketal), 2.89 (br s, 2H, -CH₂-), 2.42 (s, 3H, -CH₃), 1.61 (s, 3H, -CH₃).

1L) 7-Acetyl-8-methyldioxolo [4,5-*g*] indolizino [1,2-*b*] quinolin-9(11H)-one

To the solution of compound of Example 1(K) (0.1g, 0.4 mmol) in toluene (10
10 mL) was added aminopiperinal (73 mg, 0.44mmol) alone with p-toluenesulfonicacid (2mg, catalyst). The resulting mixture was refluxed uner Dean-Stark trap for 12h. The mixture was cooled and diluted with hexane and Et₂O. The precipitated tan solid was filtered and dried in vacuo to give ketal 65mg (43%). ¹H NMR (400 MHz, CDCl₃): δ 8.1 (s, 1H, 12-quinolyl), 7.57 (s, 1H, 13-quinolyl), 7.48 (s, 1H, 4-quinolyl), 7.14 (s, 1H, 6-pyridyl), 6.18
15 (s, 2H, O-CH₂-O), 5.19 (s, 2H, 11-CH₂-), 4.09 (m, 2H, ketal), 3.84 (m, 2H, ketal), 2.45 (s, 3H, -CH₃), 1.72 (s, 3H, -CH₃).

To the ketal above (65 mg, 0.17 mmol) in glacial acetic acid (5 mL) was added 3N HCl (1 mL). The resulting mixture was heated at 70°C for 1h. The mixture was diluted with H₂O and extracted with CH₂Cl₂. The organic layer was
20 washed with brine and dried (Na₂SO₄). Solvent was removed in vacuo to give yellow solid 28 mg (50%). ¹H NMR (400 MHz, CDCl₃+ CD₃OD): δ 8.23 (s, 1H, 12-quinolyl), 7.49 (s, 1H, 13-quinolyl), 7.35 (s, 1H, 4-quinolyl), 7.19 (s, 1H, 6-pyridyl), 6.20 (s, 2H, O-CH₂-O), 5.23 (s, 2H, 11-CH₂-), 2.64 (s, 3H, -CH₃), 2.32 (s, 3H, -CH₃); Anal. (C₁₉H₁₄N₂O₄ · 0.5 H₂O) calcd.: C, 66.47; H, 4.40; N, 8.16
25 found: C, 66.41; H 4.20; N, 8.14. m.p >300°C.

EXAMPLE 2Preparation of 7-Acetyl-12-dimethylaminomethyl-8-methyldioxolo [4,5-g] indolizino [1,2-b]quinolin-9(1H)-one.5 2A) 1-(2-nitro-phenyl)ethanone

To the cooled 65% HNO₃ (200 mL) was added 3,4-Methylenedioxyacetophenone (41 g, 0.25 mol; Aldrich) and the resulting mixture was stirred at 40°C for 1h with the evolution of heat. When the evolution of the heat ceased the mixture was poured into the ice. The water was decanted and the resulting gum was triturated with methanol. The product solidified and filtered to give solid 40g (76%). ¹H NMR (400 MHz, CDCl₃): δ 7.55 (s, 1H, aromatic), 6.76 (s, 1H, aromatic), 6.19 (s, 2H, O-CH₂-O), 2.56 (s, 3H, -CH₃); m.p 112°C.

15 2B) 2-Bromo-1-(2-nitro-phenyl)ethanone

To the solution of compound of Example 2(A) (10 g, 47.8 mmol) in dioxane (30 mL) was added dropwise the solution of bromine (2.5 mL, 48.3 mmol) in dioxane (100 mL) via the addition funnel. The resulting mixture was stirred at room temperature for 4h. Solvent was removed in vacuum and mixture was diluted with Et₂O, washed with 5% NaHCO₃, H₂O, brine and dried (Na₂SO₄). Solvent was removed in vacuum and residue purified by flash column chromatography (silica, 0-60% Et₂O: hexane) to give lacrymatory solid 8g (58%). ¹H NMR (400 MHz, CDCl₃): δ 7.62 (s, 1H, aromatic), 6.84 (s, 1H, aromatic), 6.22 (s, 2H, O-CH₂-O), 4.23 (s, 2H, CH₂Br).

25 2C) N'-benzylidene-N,N-dimethyl-hydrazine

To the solution of benzaldehyde (5 g, 47 mmol; Aldrich) in ethanol (250 mL) at 10°C was added dropwise N,N-dimethylhydrazine (5.37 mL, 70.6 mmol; Aldrich) in ethanol (50 mL). The resulting mixture was allowed to warm up to room temperature and was stirred at room temperature for 30 min, and then refluxed for 20h. Solvent was removed in vacuum and resulting mixture was diluted with H₂O, extracted with Et₂O. Organic layer was washed with brine and dried (Na₂SO₄). Solvent was removed in vacuum to give light yellow oil 5.2 g (74%). ¹H NMR (400 MHz, CDCl₃): δ 7.6 (m, 2H, aromatic), 7.3 (m, 2H, aromatic), 7.2 (m, 3H, aromatic; CH=N), 2.95 (s, 6H, dimethylamino).

35

2D) 2-Dimethylamino-1-(2-nitro-phenyl)-ethanone

To the solution of compound of Example 2(B) (0.5 g, 1.73 mmol) in CH₃CN (5 mL) was added compound of Example 2(C) (0.26 g, 1.73 mmol) and the resulting mixture was allowed to stand at room temperature for 24h. The product precipitated and filtered to give solid 126 mg (25%). ¹H NMR (400 MHz, CDCl₃+CD₃OD): δ 7.65 (s, 1H, aromatic), 7.19 (s, 1H, aromatic), 6.27 (s, 2H, O-CH₂-O), 4.67 (s, 2H, CH₂N⁺(CH₃)₂), 3.09 (s, 6H, dimethylamino⁺).

2E) 1-(2-Amino-phenyl)-2-dimethylamino-ethanone

To the solution of compound of Example 2(D) (0.126 g, 0.38 mmol) in methanol (5 mL) was added 1N HCl (3 mL) alone with Ni₂B (200 mg) and the resulting mixture was heated at 60°C for 1h. The mixture was diluted with H₂O and extracted with EtOAc. The organic layer was washed with brine and dried (Na₂SO₄). Solvent was removed in vacuum to give solid 76 mg (90%). ¹H NMR (400 MHz, CDCl₃): δ 7.28 (s, 1H, aromatic), 6.45 (br s, 2H, -NH₂), 6.13 (s, 1H, aromatic), 5.9 (s, 2H, O-CH₂-O), 3.52 (s, 2H, CH₂N(CH₃)₂), 2.34 (s, 6H, dimethylamino).

2F) 7-Acetyl-12-dimethylaminomethyl-8-methyldioxolo [4.5-g] indolizino [1.2-b] quinolin-9(11H)-one

Compound of Example 1(K) (71 mg, 0.28 mmol) and compound of Example 2(E) (71 mg; 0.31 mmol) were reacted following the procedure of Example 1(L). Solvent was evaporated and residue purified by flash column chromatography (silica, 0-10% methanol: CH₂Cl₂) to give ketal as yellow solid 25 mg (25%). ¹H NMR (400 MHz, CDCl₃): δ 7.61 (s, 1H, quinolylyl), 7.49 (s, 1H, quinolylyl), 7.45 (s, 1H pyridyl), 6.15 (s, 2H, O-CH₂-O), 5.23 (s, 2H, 11-CH₂), 4.07 (m, 2H, ketal), 3.82 (m, 2H, ketal), 3.80 (s, 2H, CH₂N(CH₃)₂), 2.45 (s, 3H, -CH₃), 2.29 (s, 6H, dimethylamino), 1.71 (s, 3H, -CH₃).

The ketal above was hydrolyzed following the procedure of Example 1(L). The resulting residue was lyophilized to give solid 12 mg (65%). ¹H NMR (400 MHz, D₂O): δ 7.4 (s, 1H, quinolylyl), 7.2 (s, 1H, quinolylyl), 7.01 (s, 1H pyridyl), 6.3 (s, 2H, O-CH₂-O), 5.18 (s, 2H, 11-CH₂), 3.65 (s, 2H, CH₂N(CH₃)₂), 2.98 (s, 6H, dimethylamino⁺), 2.66 (s, 3H, -CH₃), , 2.17 (s, 3H, -CH₃).

EXAMPLE 3**Preparation of 7-Acetyl-12-hydroxymethyl-8-methyldioxolo [4.5-g] indolizino [1.2-b] quinolin-9(11H)-one.****3A) Acetic acid-2-(2-nitro-phenyl)-2-oxo-ethyl ester**

5 To the solution of compound of Example 2(B) (0.5 g, 1.73 mmol) in DMF (10 mL) was added sodium acetate (0.43 g, 5.19 mmol) and the resulting mixture was heated at 67°C for 1h. The resulting mixture was diluted with H₂O and extracted with EtOAc, washed with brine and dried (Na₂SO₄). The solution was triturated with hexane and precipitated solid was filtered to give 0.32 g (74%). ¹H NMR (400 MHz, CDCl₃): δ 7.58 (s, 1H, aromatic), 7.84 (s, 1H, aromatic), 6.2 (s, 10 2H, O-CH₂-O), 4.92 (s, 2H, CH₂-OAc), 2.06 (s, 3H, -CH₃).

3B) Acetic acid-2-(2-amino-phenyl)-2-oxo-ethyl ester

Compound of Example 3(A) (0.3 g, 1.2 mmol) was reduced following the procedure of Example 2(E) to give foam 0.24 g (92%). ¹H NMR (400 MHz, 15 CDCl₃): δ 6.89 (s, 1H, aromatic), 6.43 (br s, 2H, -NH₂), 6.17 (s, 1H, aromatic), 5.91 (s, 2H, O-CH₂-O), 5.17 (s, 2H, CH₂-OAc), 2.23 (s, 3H, -CH₃).

3C) 7-Acetyl-12-hydroxymethyl-8-methyldioxolo [4.5-g] indolizino [1.2-b] quinolin-9(11H)-one

Compound of Example 1(K) (50 mg, 0.2 mmol) and compound of Example 20 3(B) (50 mg; 0.22 mmol) were reacted following the procedure of Example 1(L). The precipitated solid was filtered to give ketal 45 mg (50%). ¹H NMR (400 MHz, CDCl₃): δ 7.50 (s, 1H, quinolylyl), 7.30 (s, 1H, quinolylyl), 7.15 (s, 1H pyridyl), 6.20 (s, 2H, O-CH₂-O), 5.5 (s, 2H, -CH₂Ac), 5.30 (s, 2H, 11-CH₂), 4.07 (m, 2H, ketal), 3.82 (m, 2H, ketal), 2.50 (s, 3H, -CH₃), 2.20 (s, 3H, -CH₃), 1.71 (s, 3H, -CH₃).

25 The ketal above (40 mg, 0.1 mmol) was hydrolyzed following the procedure of Example 1(L) to give solid 30 mg (65%). ¹H NMR (400 MHz, DMSO-d₆): δ 7.50 (s, 1H, quinolylyl), 7.40 (s, 1H, quinolylyl), 7.20 (s, 1H pyridyl), 6.25 (s, 2H, O-CH₂-O), 5.4 (s, 2H, -CH₂Ac), 5.17 (s, 2H, 11-CH₂), 2.55 (s, 3H, -CH₃), 2.20 (s, 3H, -CH₃).

EXAMPLE 4

30 **(±)-7-(1-Hydroxyethyl)-8-methyldioxolo [4.5-g] indolizino [1.2-b] quinolin-9(11H)-one.**

4A) (±)-7-(1-Hydroxyethyl)-8-methyldioxolo [4.5-g] indolizino [1.2-b] quinolin-9(11H)-one.

35 To the solution of 7-Acetyl-8-methyldioxolo [4,5-g] indolizino [1,2-b]

quinolin-9(1H)-one (2 mg, 5 μmol) in a mixture of MeOH (0.2 mL), CH₂Cl₂ (0.6 mL) and THF (0.2 mL) was added a single portion of sodium borohydride (2 mg, 55 μmol). After stirring at room temperature for 1.5h, the solvent was removed in vacuum. The resulting residue was treated with 10% aqueous NH₄Cl (150 μL) and allowed to stand at 4⁰C overnight. The solid which was formed was collected by filtration, washed sparingly with H₂O and dried to give yellow solid 1.7 mg, (89%): ¹H NMR (400 MHz, CDCl₃): δ 8.2 (s, 1H, 12-quinoly), 7.4 (s, 1H, 13-quinoly), 7.12 (s, 1H, 4-quinoly), 7.1 (s, 1H, 6-pyridyl), 6.15 (s, 2H, O-CH₂-O), 5.2 (s, 2H, 11-CH₂-), 4.89 (m, 1H, CHOH), 2.3 (s, 3H, Methyl) 1.5 (d, 3H, aliphatic).

10

EXAMPLE 5

(±)-7-[1-(Aminoacetyl)oxyethyl]-8-methyldioxolo [4,5-g] indolizino [1,2-b] quinolin-9(1H)-one Hydrotrifluoroacetate.

15 5A) (±)-7-[1-[[[(1,1-Dimethylethoxy)carbonyl]aminolacetyl]oxyethyl]-8-methyldioxolo [4,5-g] indolizino [1,2-b] quinolin-9(1H)-one.

To a suspension of (t-butoxycarbonyl)glycine (2 mg, 10 μmol) in CH₂Cl₂ (2 mL) under an argon atmosphere was added 1,3-dicyclohexylcarbodiimide (2 mg, 10 μmol). After stirring at room temperature for 0.5 h, (±)-7-(1-Hydroxyethyl)-8-methyldioxolo [4,5-g] indolizino [1,2-b] quinolin-9(1H)-one (2 mg, 5 μmol) was added, followed by 1 mg of 4-dimethylaminopyridine. The resulting mixture was stirred at room temperature overnight, then was filtered. The filtrate was washed successively with 2.5% aqueous NaHCO₃ (2 mL), 0.1 N HCl (2 mL) and H₂O (2 mL), dried (Na₂SO₄). The solid residue was purified by flash column chromatography (silica, 0-3% methanol: CH₂Cl₂) to give the title compound 2.5 mg, (75%): ¹H NMR (400 MHz, CDCl₃): δ 8.2 (s, 1H, 12-quinoly), 7.4 (s, 1H, 13-quinoly), 7.12 (s, 1H, 4-quinoly), 7.1 (s, 1H, 6-pyridyl), 6.15 (s, 2H, O-CH₂-O), 5.89 (m, 1H, CHOH), 5.2 (s, 2H, 11-CH₂-), 5.03 (br s, 1H, NH), 4.14-3.94 (m, 2H, CH₂-NCO), 2.3 (s, 3H, Methyl), 1.44 (s, 9H, t-Bu), 1.5 (d, 3H, aliphatic).

30

5B) (±)-7-[1-(Aminoacetyl)oxyethyl]-8-methyldioxolo [4,5-g] indolizino [1,2-b] quinolin-9(1H)-one Hydrotrifluoroacetate.

To a stirring suspension of (±)-7-[1-[[[(1,1-Dimethylethoxy)carbonyl]amino]acetyl]oxyethyl]-8-methyldioxolo [4,5-g] indolizino [1,2-b] quinolin-9(1H)-one (2.5mg, 4 μmol) in 1,3-dimethoxybenzene (2 mL) under an argon atmosphere was added trifluoroacetic acid (2 mL). After stirring for 1.5 h at room temperature, the mixture was concentrated under reduced pressure. The residue was dissolved in H₂O, extracted with Et₂O, filtered and lyophilized to afford the title compound as a

35

pale yellow solid 1.8 mg, (79%): ¹H NMR (400MHz, CD₃OD) δ 8.12 (s, 1H, 12-quinolyl), 7.45 (s, 1H, 13-quinolyl), 7.13 (s, 1H, 4-quinolyl), 7.16 (s, 1H, 6-pyridyl), 6.15 (s, 2H, O-CH₂-O), 5.89 (m, 1H, CHOH), 5.1 (s, 2H, 11-CH₂-), 4.02 (br s, 2H, CH₂N), 2.25 (s, 3H, Methyl), 1.4 (d, 3H, aliphatic).

5

EXAMPLE 6

Parenteral Composition

To prepare a parenteral pharmaceutical composition of this invention suitable for administration by injection, 100 mg of a water soluble salt of a compound of
10 Formula I is mixed with 10 ml of 0.9% sterile saline, and the mixture is incorporated into a dosage unit form suitable for administration by injection.

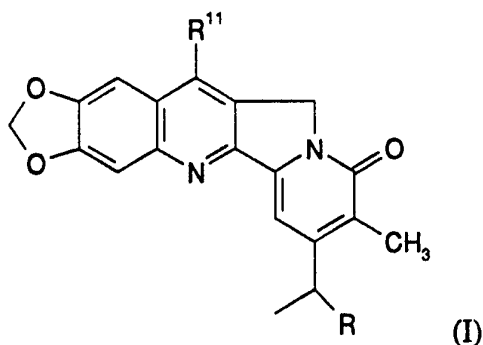
EXAMPLE 7

Oral Composition

15 To prepare an oral pharmaceutical composition of this invention, 100 mg of a compound of Formula I is mixed with 750 mg of lactose, and the mixture is incorporated into an oral dosage unit form, such as a hard gelatin capsule, which is suitable for oral administration.

We claim:

1. A method for treating viral infections comprising administering to an infected host in need thereof an effective amount of a compound of Formula I, or a
 5 pharmaceutically acceptable salt thereof, alone or in combination with a carrier, diluent or excipient



10 wherein:

R is =O, -OH, and OR¹;

R¹ is OCOR⁴, or OP(O)(OH)R⁵ wherein:

15

R³ is -H or lower alkyl;

R⁴ is -CR³R⁶R⁷;

20

-(CH₂)_nCH₂R⁷ (where n=0-3);

-(CH₂)_nCH₂COOH (where n=0-3);

-NR⁹R¹⁰;

25

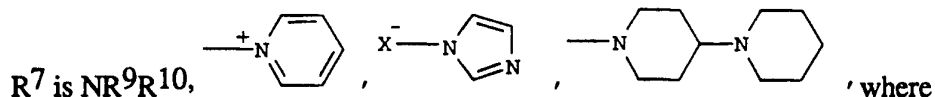
-NH(CH₂)_nCH₂R⁷ (where n = 1-3); and

-NH(CH₂)_nCH₂COOH (where n = 0-3);

30

R⁵ is OH or CH₂NH₂;

R⁶ is H or the side chain of any naturally occurring α-amino acid;

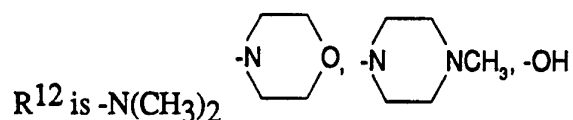


X is any pharmaceutically acceptable anion;

5 R⁸ is lower alkyl;

R⁹ and R¹⁰ are independently selected from the group consisting of -H, -C₁₋₆ alkyl, and R⁹ and R¹⁰ taken together to form a 5-7 membered saturated heterocyclic ring containing the nitrogen on which R⁹ and R¹⁰ are substituted; and

10 R¹¹ is -CH₂R¹², wherein:



2. The method of claim 1 wherein said compound is selected from the group consisting of:

15 7-Acetyl-8-methyldioxolo[4,5-g]indolizino[1,2-*b*]quinolin-9(11*H*)-one;
(±)-7-(1-Hydroxyethyl)-8-methyldioxolo[4,5-g]indolizino[1,2-*b*]quinolin-9(11*H*)-one;

20 (±)-7-[1(Aminoacetyl)oxy]ethyl]-8-methyldioxolo[4,5-g]indolizino[1,2-*b*]quinolin-9(11*H*)-one hydrotrifluoracetate;

7-Acetyl-12-dimethylaminomethyl-8-methyldioxolo [4,5-*g*] indolizino [1,2-*b*]quinolin-9(11*H*)-one; and

7-Acetyl-12-hydroxymethyl-8-methyldioxolo [4,5-*g*] indolizino [1,2-*b*]quinolin-9(11*H*)-one.

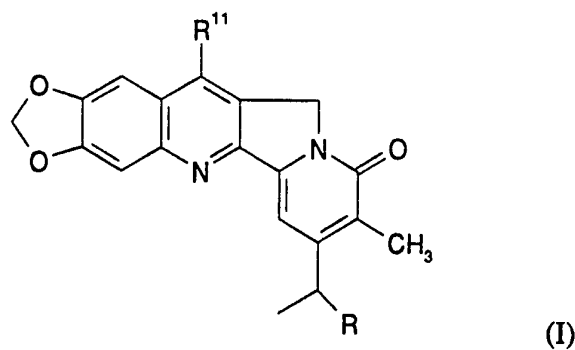
25

3. The method of claim 2 wherein said compound is 7-acetyl-8-methyldioxolo[4,5-*g*]indolizino[1,2-*b*]quinolin-9(11*H*)-one.

4. The method of claim 2 wherein said compound is 7-acetyl-12-dimethylaminomethyl-8-methyldioxolo [4,5-*g*] indolizino [1,2-*b*]quinolin-9(11*H*)-one.

5. A compound of formula I, or a pharmaceutically acceptable salt thereof,

35



wherein:

5 R is =O, -OH, and OR¹

R¹ is OCOR⁴, or OP(O)(OH)R⁵ wherein:

R³ is -H or lower alkyl;

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R⁴ is -CR³R⁶R⁷;

-(CH₂)_nCH₂R⁷ (where n=0-3);

15

-(CH₂)_nCH₂COOH (where n=0-3);

-O(CH₂)_nCH₂COOH (where n = 0-3);

-NR⁹R¹⁰;

20

-NH(CH₂)_nCH₂R⁷ (where n = 1-3); and

-NH(CH₂)_nCH₂COOH (where n = 0-3);

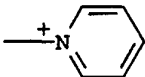
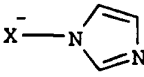
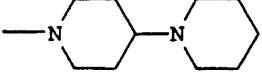
25

R⁵ is OH or CH₂NH₂;

R⁶ is H or the side chain of any naturally occurring α-amino acid;

where X is any pharmaceutically acceptable anion;

30

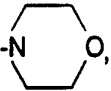
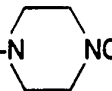
R⁷ is NR⁹R¹⁰, , , , where X is any pharmaceutically acceptable anion;

R⁸ is lower alkyl;

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R⁹ and R¹⁰ are independently selected from the group consisting of -H, -C₁₋₆ alkyl, and R⁹ and R¹⁰ taken together to form a 5-7 membered saturated heterocyclic ring containing the nitrogen on which R⁹ and R¹⁰ are substituted; and R¹¹ is -CH₂R¹², wherein:

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R¹² is -N(CH₃)₂ , , -NCH₃, -OH

6. The compound of claim 5 wherein said compound is selected from the group consisting of:

15 7-Acetyl-8-methyldioxolo[4,5-g]indolizino[1,2-b]quinolin-9(11*H*)-one; (±)-7-(1-Hydroxyethyl)-8-methyldioxolo[4,5-g]indolizino[1,2-b]quinolin-9(11*H*)-one;

(±)-7-[1(Aminoacetyl)oxy]ethyl]-8-methyldioxolo[4,5-g]indolizino[1,2-*b*]quinolin-9(11*H*)-one hydrotrifluoracetate;

20 7-Acetyl-12-dimethylaminomethyl-8-methyldioxolo [4,5-*g*] indolizino [1,2-*b*]quinolin-9(11*H*)-one; and

7-Acetyl-12-hydroxymethyl-8-methyldioxolo [4,5-*g*] indolizino [1,2-*b*] quinolin-9(11*H*)-one.

25 7. The compound of claim 6 wherein said compound is 7-acetyl-8-methyldioxolo[4,5-*g*]indolizino[1,2-*b*]quinolin-9(11*H*)-one.

8. The compound of claim 6 wherein said compound is 7-acetyl-12-dimethylaminomethyl-8-methyldioxolo [4,5-*g*] indolizino [1,2-*b*]quinolin-9(11*H*)-one.

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9. A formulation comprising a compound of claim 5 in admixture with a carrier or excipient.

10. The formulation of claim 9 wherein said carrier or excipient is a pharmaceutically acceptable carrier or excipient.

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11. The method of claim 1 wherein the viral infection is caused by a herpesvirus.
12. The method of claim 11 wherein said virus is herpes simplex type 1 and said
5 infected host is a mammal.
13. The method of claim 11 wherein said virus is herpes simplex type 2 and said
infected host is a mammal.
- 10 14. The method of claim 1 wherein said viral infection is caused by
cytomegalovirus and said infected host is a mammal.
15. The method of claim 1 wherein said viral infection is caused by varicella
zoster virus and said infected host is a mammal.

15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/04866

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :C07D 487/22; A61K 31/475

US CL :546/48; 514/80, 283; A61K 31/475

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)

U.S. : 546/48; 514/80, 283; A61K 31/475

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)

CAS online structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO, A, 92/07856 (ALLAUDEEN et al.) 14 May 1992. See claims 1, 2, 7-9, 40-42, 47-52, 73-6 where Y is CH , X is -C-6 and R is lower alkyl.	1-15
Y	US, A, 5,225,404 (GIOVANNELLA et al.) 06 July 1992. See claim 1.	1-8
Y	US, A, 4,981,968 (WALL et al.) 01 January 1991. See column 3, lines 48-50.	1-15
A	US, A, 4,914,205 (SAWADA et al.) 03 April 1990.	1-15

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

* Special categories of cited documents:	"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
"A" document defining the general state of the art which is not considered to be of particular relevance	"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
"E" earlier document published on or after the international filing date	"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
"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)	"&"	document member of the same patent family
"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		

Date of the actual completion of the international search

08 JUNE 1994

Date of mailing of the international search report

AUG 05 1994

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/04866

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Chemical Abstracts, Vol. 84, issued 1976, Atherton et al., "Interferon Induction by Viruses and Polynucleotides" See page 428, abstract No. 103727f. J. Gen. Virol. 1975, Pt 3. 297-3054.	1-15
Y	Chemical Abstracts, Vol. 77 issued 1972, Horwitz et al. "Camptothecin, Mechanism of Inhibition of Adenovirus Formation". See page 7079, col. 1, Abstract No. 70781u, Virology Vol. 48, No. 3 pages 690-8 (1972).	1-15
Y	JP, A, 51-91297 (Nippon Chemifar) 08 October 1976. See abstract.	5-8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/04866

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international 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 II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

Please See Extra 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 fee, this Authority did not invite payment of any additional fee.
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.:
1-15(part of 1,5,9-15)

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/04866

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

- I. Claims 1, 5, 9-15 (part of each) and 2-4, 6-8, drawn to non-morpholino, non-piperazino compounds and antiviral use.
- II. Claims 1, 5, 9-15 (part of each) drawn to Morpholine compounds, use.
- III. Claims 1, 5, 9-15 (part of each) drawn to Piperazine compounds, use.

PCT Rule 13.3 permits a lack of unity holding where joined in a single claim. Applicants did not disclose Groups II and III in their first priority application, as having the "special technical feature" in common with I. The technical feature is shared with the art, i.e. not "special".