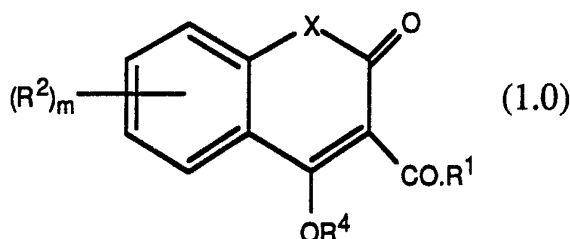




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C07D 215/56, A61K 31/47	A1	(11) International Publication Number: WO 92/04328 (43) International Publication Date: 19 March 1992 (19.03.92)
(21) International Application Number: PCT/US91/06250 (22) International Filing Date: 6 September 1991 (06.09.91) (30) Priority data: 579,749 7 September 1990 (07.09.90) US (60) Parent Application or Grant (63) Related by Continuation US 579,749 (CIP) Filed on 7 September 1990 (07.09.90) (71) Applicant (for all designated States except US): SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033 (US). (72) Inventors; and (75) Inventors/Applicants (for US only) : AFONSO, Adriano [IN/US]; 10 Woodmere Road, West Caldwell, NJ 07006 (US). WEINSTEIN, Jay [US/US]; 191 Bellevue Avenue, Upper Montclair, NJ 07043 (US). GENTLES, Margaret, Jevnik [US/US]; 68 Day Street, Bloomfield, NJ 07003 (US). ROSENBLUM, Stuart, Barry [US/US]; 16 Steven Terrance, West Orange, NJ 07052 (US).		(74) Agents: BLASDALE, John, H., C. et al.; Schering-Plough Corporation, One Giralda Farms, Madison, NJ 07940-1000 (US). (81) Designated States: AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH (European patent), CI (OAPI patent), CM (OAPI patent), CS, DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GA (OAPI patent), GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), MW, NL (European patent), NO, PL, RO, SD, SE (European patent), SN (OAPI patent), SU ⁺ , TD (OAPI patent), TG (OAPI patent), US. Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>

(54) Title: ANTIVIRAL COMPOUNDS AND ANTIHYPERTENSIVE COMPOUNDS**(57) Abstract**

Compounds useful as antiviral agents against DNA-containing viruses, such as herpes group viruses, are disclosed. The compounds are represented by compounds of formula (1.0) and their pharmaceutically acceptable salts and solvates. Pharmaceutical compositions containing compounds represented by formula (1.0) and methods of treating a viral infection using compounds represented by formula (1.0) are disclosed. Also disclosed are compounds useful as antihypertensive agents and methods of treating hypertension using such compounds. The antihypertensive agents are compounds represented by formula (1.0) wherein R⁴ is selected from the group consisting of alkyl and aminoalkyl. Preferably R¹ is H.

+ DESIGNATIONS OF "SU"

Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland	KR	Republic of Korea	SN	Senegal
CI	Côte d'Ivoire	LI	Liechtenstein	SU ⁺	Soviet Union
CM	Cameroon	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
DE	Germany	MC	Monaco	US	United States of America
DK	Denmark				

ANTIVIRAL COMPOUNDS AND
ANTIHYPERTENSIVE COMPOUNDS

BACKGROUND

5 This invention relates to compounds having antiviral activity and to
compounds having antihypertensive activity, pharmaceutical compositions
thereof, and methods of treatment utilizing the compositions. In particular,
this invention is related to compounds having antiviral activity against viruses
of the herpes group, pharmaceutical compositions containing the
10 compounds, and methods of treating viruses of the herpes group using the
pharmaceutical compositions.

There are four separate viruses of the herpes group which infect and
cause disease in humans. These are (1) herpes simplex virus 1 and 2
(HSV-1 and HSV-2, respectively); (2) cytomegalovirus (CMV); (3) varicella-
zoster virus (VZ); and (4) Epstein-Barr virus (EB). Examples of diseases
15 associated with herpes simplex virus infection include herpes labialis, genital
herpes (herpes progenitalis), neonatal herpes, herpetic keratitis, eczema
herpeticum, disseminated herpes, occupational herpes, herpetic
gingivostomatitis, meningitis (aseptic), and encephalitis.

CMV is widespread in humans and numerous other mammals. The
20 great majority of human CMV infections are subclinical; that is, the primary
infection occurs with no signs or symptoms. An exception to this is a
congenital infection which occasionally gives rise to cytomegalic inclusion
body disease in infants. There is also a mononucleosis-like syndrome
caused by the virus.

25 The great majority of serious cases due to CMV infection come from
recurring infections in immuno-compromised patients such as transplant

-2-

patients and cancer patients. It has been estimated that silent CMV infections have occurred in a majority of humans by the time adulthood is reached.

VZ virus is associated with chicken-pox (varicella) and shingles (zoster) in humans.

5 EB virus is quite common and causes glandular fever; it is also believed to be responsible for genetic damage that leads to Burkitt's lymphoma.

Examples of drugs used to treat herpes infections include: (1) IUDR (5'-iodo-2'-deoxyuridine); (2) Ara-C (1-[beta-D-arabinofuranosyl]-cytosine);
10 (3) Ara-A (9-[beta-D-arabinofuranosyl]adenine); and (4) Acyclovir (9-[(2-hydroxyethoxy)methyl]guanine). Also Haines et al. (U.S. 4,757,088 issued July 12, 1988) disclose that lidocaine (2-(diethylamino)-N-(2,6-dimethyl-phenyl)acetamide) is an antiviral agent in cell culture against HSV-1 and HSV-2, and is able to treat herpes virus infections of mammals. Haines et al.
15 also disclose that lidocaine is particularly effective in the treatment of HSV oral and genital lesions in humans. According to Haines et al., the addition of pantothenic acid or its alcohol and salt forms, dexpanthenol and pantothenate respectively, to lidocaine or lidocaine hydrochloride significantly enhances the antiviral activity of those drugs.

20 Human hypertension is a disease of multiple etiologies. Drugs that act to control one form may not be effective in controlling another. Therefore, further drugs that can be useful in treating hypertension are desirable.

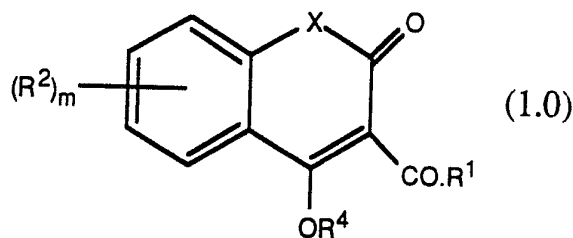
In view of current interest in the art for finding useful antihypertensive agents and useful antiviral agents, in particular, useful agents against viruses
25 of the herpes group, any new compounds exhibiting antihypertensive activity or antiviral activity would be a welcome contribution to the art. This invention provides such a contribution.

SUMMARY OF THE INVENTION

This invention provides compounds which are useful as antiviral
30 agents against DNA-containing viruses such as herpes group viruses. In particular, the compounds of this invention are useful against HSV-1 and HSV-2 and may also prove useful against CMV and EB.

The compounds of this invention are advantageous over known viral compounds because they inhibit early events in viral replication

-3-



and the pharmaceutically acceptable salts and solvates thereof;
wherein:

- (A) X is selected from the group consisting of N-R³, O, S, and C(R³)₂;
- 5 (B) R³ is selected from the group consisting of:
- | | |
|-------------------------|-----------------------|
| (1) alkyl; | (2) aralkyl; |
| (3) aryl; | (4) substituted aryl; |
| (5) alkaryl; | (6) alkyl heteroaryl; |
| (7) aryloxyalkoxyalkyl; | |
- 10 (8) -(CH₂)_a R¹¹ wherein a is an integer of 1 to 6 and R¹¹ is selected from the group consisting of -C(O)OR¹², -OR¹², -R¹², and -N(R¹²)₂, wherein each R¹² can be the same or different and is selected from the group consisting of alkyl, alkenyl and H; and
- 15 (9) -OR¹³ wherein R¹³ is selected from the group consisting of H, alkyl - which may be substituted with OH, SH, NH₂ and/or halogen - , alkaryl, alkenyl, and heteroaryl;
- and the two groups R³ on the same carbon atom can be the same or different;
- (C) R¹ is selected from the group consisting of:
- 20 (1) H; (2) alkyl;
- (3) aryl; (4) alkaryl;
- (5) alkenyl; (6) -N(R⁵)₂ wherein each R⁵ is independently selected from the group consisting of H, alkyl - which may be substituted with OH, SH, NH₂ and/or halogen - , aryl, alkaryl, alkenyl, heteroaryl, alkoxy, and hydroxy;
- 25 (7) heteroaryl; and (8) substituted alkyl;
- (D) Each R² for each m is independently selected from the group consisting of:
- 30 (1) alkyl; (2) alkoxy;
- (3) aryloxy; (4) aryl;

-4-

- (3) aryloxy; (4) aryl;
 (5) aralkoxy; (6) halogen atoms selected from the group consisting of F, Cl, Br and I;
 (7) -O-CO-R⁶ wherein R⁶ is alkyl - which may be substituted with OH, SH, NH₂ and/or halogen - ; aryl; alkaryl; alkenyl; and heteroaryl;
 (8) -N(R⁷)₂ wherein each R⁷ is independently selected from the group consisting of H, alkyl, aryl, and R⁶C(O)- wherein R⁶ is as above defined;
 (9) -OH; (10) -CH₂OH;
 (11) -COOH; (12) -COOR⁸, wherein R⁸ is selected from the group consisting of alkyl and aryl;
 (13) -SO₃H; (14) -SO₂NHR⁹, wherein R⁹ is selected from the group consisting of alkyl, aryl, and H;
 (15) (15) -PO₃H; (16) -PO(OR¹⁰)₂, wherein R¹⁰ is selected from the group consisting of alkyl and aryl;
 (17) -OPO₃H; (18) -OP(OR¹⁰)₂ wherein R¹⁰ is as above defined; and (19) -CF₃;
 (E) m is an integer from 0 to 4; and
 (F) R⁴ is selected from the group consisting of H, aminoalkyl and hydroxyalkyl.

Another embodiment of this invention provides compounds which have antihypertensive activity. The antihypertensive compounds are represented by Formula 1.0 wherein R¹, R², R³ m, and n are as described above, and R⁴ is an aminoalkyl group. In these compounds: R¹ is preferably hydrogen; R⁴ is preferably selected from the group consisting of H, -(CH₂)₃N(CH₃)₂ and (most preferably) -(CH₂)₂N(CH₃)₂; R² is preferably alkyl, more preferably methyl; and most preferably R² is at the C-6 position.

In still another embodiment this invention provides pharmaceutical compositions useful in treating viral infections or in treating hypertension comprising an effective amount of an antiviral or an antihypertensive compound of this invention together with a pharmaceutically acceptable carrier or excipient. Preferably the antiviral compounds are selected from the group of compounds represented by Formulas 1.3 to 1.25 below. Preferably the antihypertensive compounds are selected from the group consisting of compounds represented by Formulas 1.24 and 1.25 below.

-5-

In yet another embodiment this invention provides a method of treating a patient suffering from hypertension or having a viral infection by administering to such a patient an effective amount of an antihypertensive or an antiviral compound of this invention. Generally, in the method of treatment the compound is administered as one of the pharmaceutical compositions of this invention. Examples of viral infections treatable in accordance with the methods of this invention include the DNA-containing viruses such as the herpes viruses discussed above (e.g., HSV-1, HSV-2, CMV, VZ, EB, and the like).

DETAILED DESCRIPTION OF THE INVENTION

When used herein, the terms listed below have the scope indicated, unless indicated otherwise.

Acyl – represents alkyl-CO-, alkenyl-CO-, alkynyl-CO-, cycloalkyl-CO-, aryl-CO- or -cycloalkenyl-CO-. Preferably acyl represents a compound having the formula -C(O)R¹⁴ wherein R¹⁴ is selected from the group consisting of H, alkyl – which may be substituted with OH, SH, NH₂ and/or halogen – , aryl, alkaryl, alkenyl, -NH₂, -NHR¹⁵, -N(R¹⁵)₂, heteroaryl, and substituted alkyl, wherein R¹⁵ is selected from the group consisting of alkyl – which may be substituted with OH, SH, NH₂ and/or halogen – , alkaryl, alkenyl and heteroaryl. Representative examples of acyl groups include CH₃C(O)-, CH₃CH₂C(O)-, CH₃CH₂CH₂C(O)-, phenyl-C(O)-, pyridyl-C(O), and the like.

Alkaryl – represents an aryl group, as defined below, in which an alkyl group, as defined below, is substituted for one of the aryl H atoms. The aryl group may contain additional substituents selected from the group consisting of halogen atoms (i.e., Cl, Br, F, and/or I), alkoxy, and amino. Representative examples include CH₃phenyl-, CH₃CH₂phenyl- and the like.

Alkenyl – represents straight and branched carbon chains having at least one carbon-to-carbon double bond and preferably having from 2 to 6 carbon atoms. Preferably the alkenyl substituent has 1 or 2 double bonds. Representative examples include vinyl, allyl, butenyl and the like.

Alkoxy – represents an alkyl radical attached through an oxygen atom (-O-alkyl). Representative examples include methoxy, ethoxy and the like.

-6-

Alkyl – represents straight or branched saturated hydrocarbon chains, which contain from 1 to 6 carbon atoms unless otherwise specified.

Representative examples include methyl, ethyl, propyl and the like.

5 Heteroarylalkyl – represents a heteroaryl group, as defined below, substituting an alkyl group, as defined above. Representative examples include pyridylmethyl, furylmethyl and the like.

10 Aryloxyalkoxyalkyl – represents a group wherein an aryloxy group substitutes an alkoxy group which in turn substitutes another alkyl group wherein the oxygen atom is attached to the aryl group at a ring carbon atom. Alkoxy is as defined above and aryl is as defined below. The aryl group may contain additional substituents selected from the group consisting of halogen atoms (i.e., Cl, Br, F, and/or I), alkoxy, alkyl, and amino. Representative examples include phenoxypropoxymethyl, phenoxyethoxymethyl and the like.

15 Aminoalkyl – represents NH_2 -alkyl-, alkyl-NH-alkyl-, or $(\text{alkyl})_2\text{N}$ -alkyl- wherein alkyl is as above defined and each alkyl may be the same or different. Representative examples include: aminoethyl, dimethylaminoethyl, dimethylaminopropyl, and the like.

20 Aralkyl – represents an alkyl group as defined above in which an aryl group as defined below is substituted for one of the alkyl hydrogen atoms. Representative examples include $-\text{CH}_2\text{phenyl}$, $-\text{CH}_2\text{CH}_2\text{phenyl}$, 4-[(1,1-dimethylethyl)dimethylsiloxy]-phenylmethyl, and the like.

25 Aralkoxy – represents an aralkyl group as defined above, which is attached through an oxygen atom (aralkyl-O-). Representative examples include phenylmethoxy, phenylethoxy, and the like. The aryl substituent of the aralkyloxy groups contains no other substituents.

30 Aryl – represents a mono- or bi-cyclic aromatic system. Examples of preferred aryl groups include those having from 6 to 14 carbon atoms. Representative examples include phenyl, 1-naphthyl, 2-naphthyl and indanyl. The aryl group may contain additional substituents selected from the group consisting of halogen atoms (i.e., Cl, Br, F, and/or I), alkoxy, alkyl, and amino.

35 Aryloxy – represents an aryl group as defined above, which is attached through an oxygen atom (aryl-O-). The aryl group may contain additional substituents selected from the group consisting of halogen atoms

-7-

(i.e., Cl, Br, F, and/or I), alkoxy, alkyl, and amino. Representative examples include phenoxy, naphthyloxy, and the like.

5 Cycloalkenyl – represents a carbocyclic ring having from 5 to 7 carbon atoms and at least one carbon-to-carbon double bond in the ring, such as cyclopentenyl, cyclohexenyl, cycloheptenyl, and the like.

Cycloalkyl – represents a saturated carbocyclic ring having from 3 to 8 carbon atoms. Representative examples include cyclopropyl, cyclohexyl, and the like.

10 Heteroaryl (including the heteroaryl portion of heteroarylmethyl) – represents aromatic systems having at least one O, S and/or N heteroatom in the ring structure. Examples of preferred heteroaryl groups include those containing from 3 to 14 carbon atoms. Representative examples of heteroaryl groups include but are not limited to: 2-, 3- or 4-pyridyl, 2- or 3-furyl, 2- or 3-thienyl, 2-, 4- or 5-thiazolyl, 2-, 4- or 5-imidazolyl, 2-, 4- or 5-pyrimidinyl, 2-pyrazinyl, 3- or 4-pyridazinyl, 3-, 5- or 6-[1,2,4-triazinyl], 3- or 5-[1,2,4-thiadiazolyl], 2-, 3-, 4-, 5-, 6- or 7-benzofuranyl, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 2- or 3-pyrrolyl, 2- or 3-N-methylpyrrolyl, and the like.

20 Hydroxyalkyl – represents an alkyl group, as defined above, wherein one or more hydroxy groups is substituted for one or more hydrogen atoms.

Substituted alkyl – represents an alkyl group, as defined above, wherein one or more of the alkyl H atoms is replaced with groups selected from the group consisting of alkyl, aryl, heteroaryl, -OH, -O-alkyl, -NH₂, -N(alkyl)₂ wherein each alkyl group may be the same or different, -SH, 25 -S-alkyl, -C(O)O-alkyl, -C(O)H, -NHC(:NH)NH₂, -C(O)NH₂, -OC(O)NH₂, NO₂ and -NHC(O)-alkyl, wherein alkyl, aryl, and heteroaryl are as above defined. Examples of substituted alkyl groups include hydroxyethyl, aminoethyl, mercaptoethyl, trifluoromethyl and the like.

30 Substituted aryl – represents an aryl group, as defined above, wherein one or more of the H atoms attached to the ring carbon atoms is replaced by groups independently selected from the group consisting of halo, alkyl, hydroxy, alkoxy, phenoxy, amino, alkylamino, and dialkylamino. Preferred substituted aryl groups are substituted phenyl groups.

Also as used herein, unless indicated otherwise, C(O) represents 35 C=O, and Ar represents aromatic.

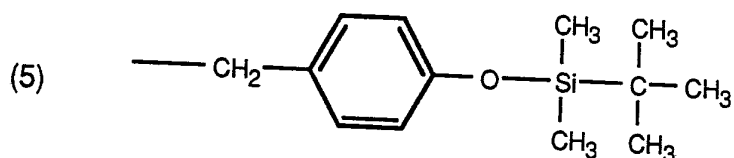
-8-

In the compounds of this invention R¹ is preferably selected from the group consisting of alkyl, and H. Most preferably R¹ is H. Preferably R² is selected from the group consisting of:

- 5
- | | |
|---------------------------|--------------------------------|
| (1) -CH ₃ ; | (2) -OCH ₃ ; |
| (3) -OCOCH ₃ ; | (4) -OCH ₂ -phenyl; |
| (5) Cl; | (6) F; |
| (7) I; | (8) -CF ₃ . |
- and

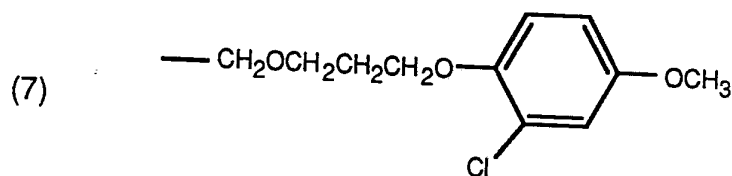
X is preferably NR³, where R³ is preferably selected from the group consisting of:

- 10
- | | |
|--------------------------------------|---------------------------------------|
| (1) -CH ₃ ; | (2) -C ₆ H ₁₃ ; |
| (3) -C ₇ H ₅ ; | (4) -CH ₂ -phenyl; |



([(1,1-dimethylethyl)dimethylsiloxy]-phenylmethyl);

- (6) -phenyl



(3-(2-chloro-4-methoxyphenoxy)propoxymethyl);

- (8) -CH₂CO₂CH₂CH=CH₂; and

- (9) -CH₂CO₂CH₃.

20 Preferably R⁴ is -(CH₂)₂N(CH₃)₂; when R⁴ is -(CH₂)₂N(CH₃)₂, the compounds are preferably used as the maleate or other salt.

A particularly preferred group of compounds of Formula 1.0 includes those wherein:

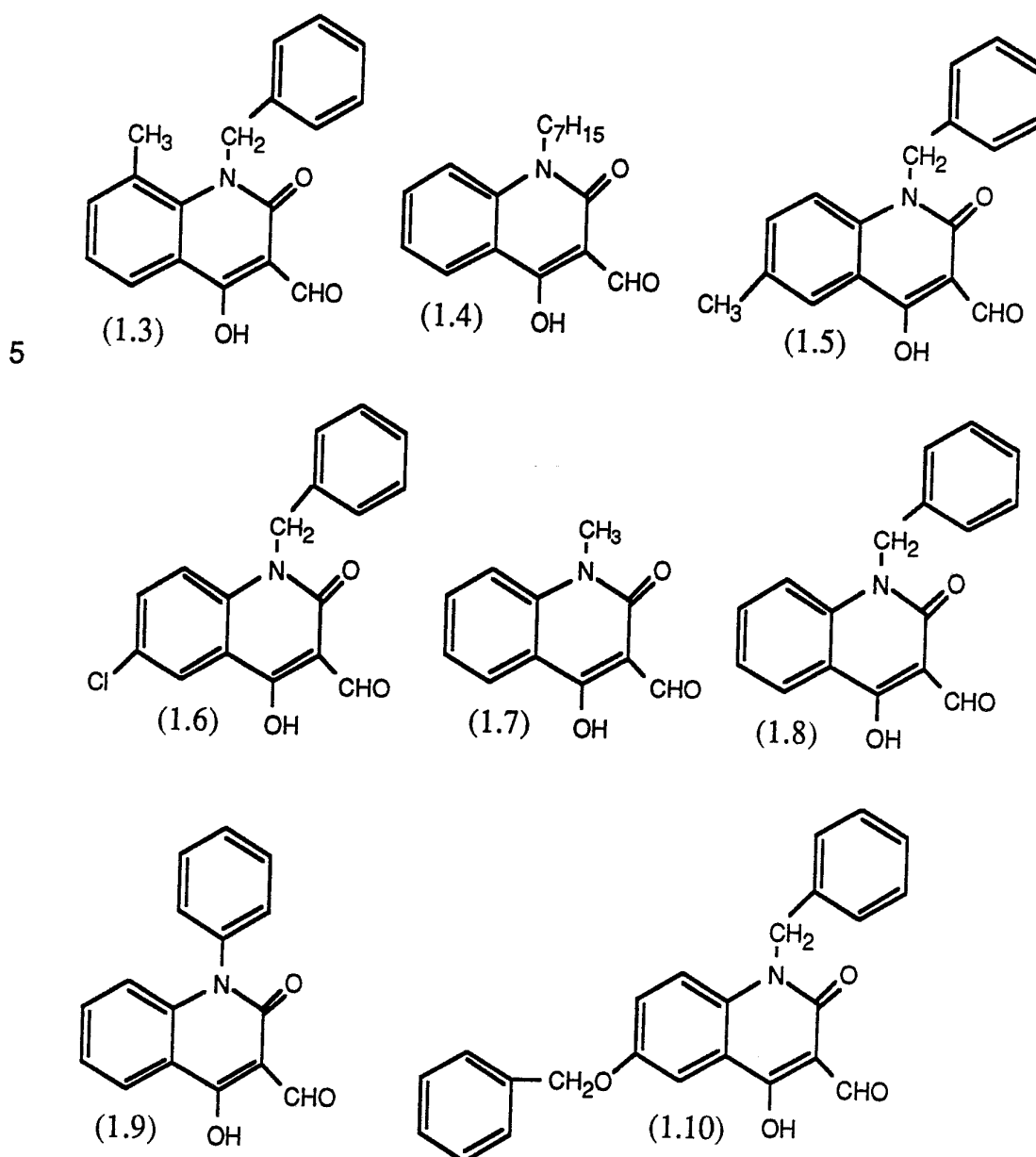
- 25
- (A) X is NR³;
 - (B) R¹ is selected from the group consisting of H and alkyl;
 - (C) R² is -CH₃ and m is 0 or 1;
 - (D) R³ is selected from the group consisting of:

(1) -C ₆ H ₁₃ ;	(2) -C ₇ H ₁₅ ;
and	(3) -CH ₂ -phenyl;

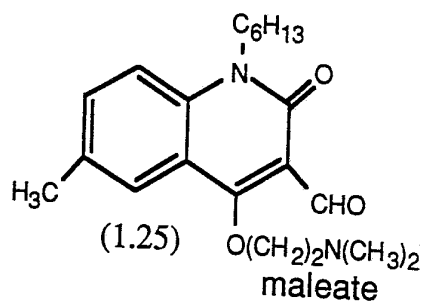
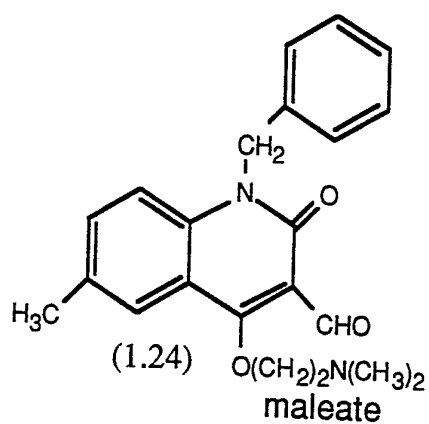
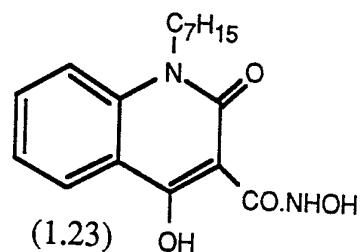
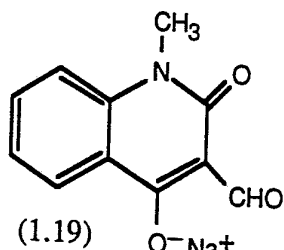
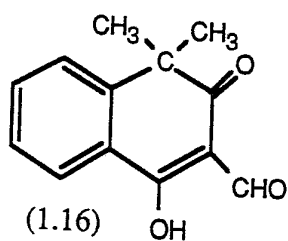
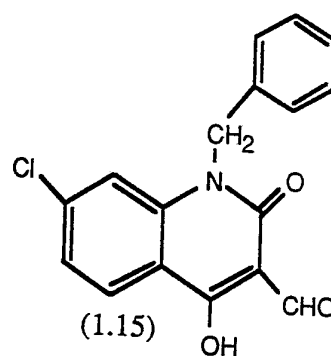
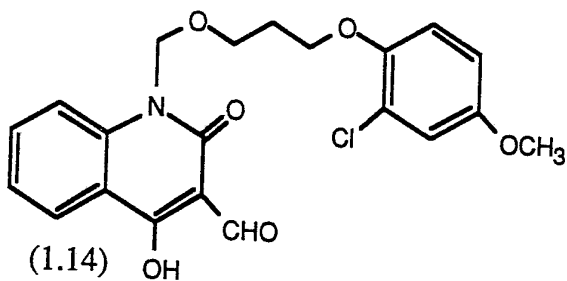
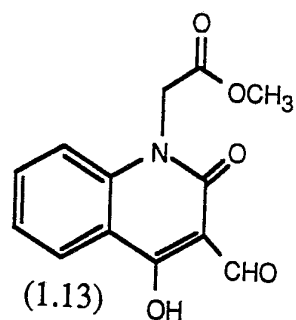
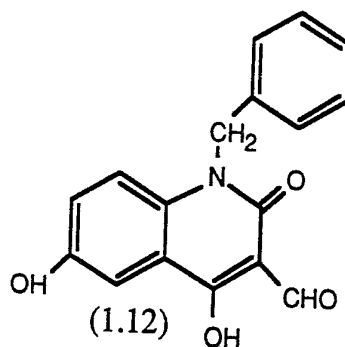
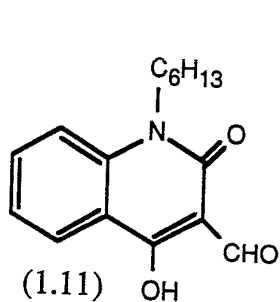
 and
 - (E) R⁴ is -O(CH₂)₂N(CH₃)₂.

Compounds of this invention include compounds selected from the group consisting of the following formulas 1.3 to 1.16, 1.19 and 1.23 to 1.25 (designated below each chemical formula) in the following Table:

TABLE OF CHEMICAL COMPOUNDS



-10-



-11-

Those skilled in the art will recognize that Formulas 1.24 and 1.25 represent the salts of maleic acid formed at the dimethylamino group of the $-(CH_2)_2N(CH_3)_2$ substituent.

Certain compounds of this invention may exist in isomeric forms. The invention contemplates all such isomers both in pure form and in admixture, including racemic mixtures.

Certain compounds of the invention can exist in unsolvated as well as solvated forms, including hydrated forms, e.g., hemihydrate. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol and the like, are equivalent to the unsolvated forms for purposes of the invention.

Certain compounds of the invention will be acidic in nature, e.g., those compounds which possess a carboxyl or phenolic hydroxyl group. These compounds may form pharmaceutically acceptable salts. Examples of such salts are the sodium, potassium, calcium, and aluminum salts. Also contemplated are salts formed with pharmaceutically acceptable amines such as ammonia, alkylamines, hydroxyalkylamines, N-methylglucamine and the like. Preferred salts are the sodium salts of the compounds of Formula 1.0 as exemplified by Formula 1.19. Thus, in the salts of the compounds of this invention, essentially R^4 is M^+ wherein M^+ is one equivalent of one of the metal cations disclosed above.

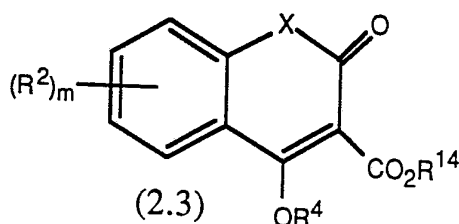
Certain compounds of the invention, e.g., those with a basic amino group, also form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those skilled in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium hydroxide, potassium carbonate, ammonia or sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the salts are otherwise equivalent to their respective free base forms for purposes of this invention.

-12-

The compounds of Formula 1.0 can be prepared by the processes described below. In these processes the substituents are as described above, unless indicated otherwise. Those skilled in the art will appreciate that, in the processes described below, the reactions are carried out at a temperature high enough to allow the reaction to proceed at a reasonable rate, but not so high as to cause undue degradation of reactants and/or products. Those skilled in the art will also appreciate that in the following reactions the desired products may be isolated by techniques well known in the art such as distillation, column chromatography, recrystallization, and the like.

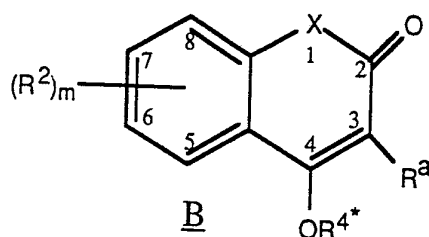
The invention provides a process for the preparation of compounds of Formula 1.0, which comprises one of the following processes (a) to (c):

(a) for the preparation of a compound of Formula 1.0 wherein R^1 is a hydrogen atom, the reduction of a corresponding 3-esterified carboxy compound of the formula 2.3:



wherein X, R^2 , R^4 and m are as defined for formula 1.0, and R^{14} is an alkyl group, with an appropriate hydride reducing agent;

(b) for the preparation of a compound of Formula 1.0 wherein R^4 is hydroxyalkyl or aminoalkyl and R^1 has any value defined above for Formula 1.0, the reaction of a compound of Formula B



-13-

wherein R^{4*} of Formula B is lower alkyl and R^a is CHO, by nucleophilic substitution with R^4O^- in solution in an excess of the alcohol R^4OH , wherein R^4 is aminoalkyl or hydroxyalkyl;

- 5 (c) for the preparation of a compound of Formula 1.0 wherein R^1 is an alkyl group, the reaction of a compound of the Formula 2.3 defined in process (a) above, in solution in a suitable solvent, with a metal-alkyl reagent.

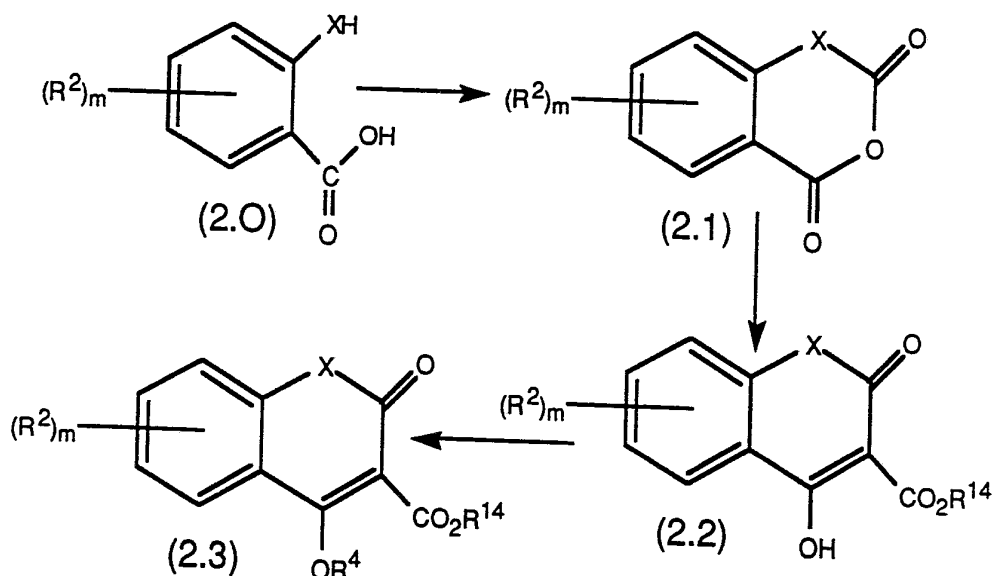
- 10 In process (a), the compound of the formula 2.3 can be reduced with (for example) one molar equivalent of a reducing agent such as diisobutylaluminum hydride in solution in an inert organic solvent such as an aromatic hydrocarbon solvent (e.g. toluene), preferably at low temperature.

- 15 In process (b), the displacement of the radical OR^{4*} (i.e., lower alkoxy, preferably methoxy) at position 4 is preferably effected by means of an excess of the alcohol R^4OH , to which a catalytic amount of a strong base such as sodium hydride has been added to generate the anion R^4O^- . The general reaction can be carried out by following procedures known in the art (see, for example, J. March, Advanced Organic Chemistry, cited above, at page 295, the disclosure of which is incorporated herein by reference thereto).

- 20 In process (c), the reaction is carried out in a suitable anhydrous solvent such as tetrahydrofuran, preferably with a molar equivalent of an alkylating agent such as a metal alkyl, e.g. a dialkyl-lithiocuprate $(R^1)_2LiCu$.

- 25 The starting materials for these processes can be prepared by methods known in the art. For example, a starting material of Formula 2.3 can be prepared by the following sequence of reactions:

-14-

SCHEME I

In this Scheme, the radicals X, R¹, R² and R¹⁴ and m are as defined for Formula 1.0.

5 The conversion of a compound of Formula 2.0 into a compound of the Formula 2.1, and the conversion of a compound of the Formula 2.1 into a compound of the Formula 2.2, represent reactions well known to those skilled in the art; see for example G.M. Coppola et al., *Synthesis*, 505 (1980), the disclosure of which is incorporated herein by reference thereto.

10 In the first step, a suitable 2-substituted benzoic acid 2.0 in aqueous 2N HCl is reacted with trichloromethyl chloroformate to form a compound 2.1, which is an isatoic anhydride when X is NH or NR³. The 2-substituted benzoic acid 2.0 will have the appropriate R² substituent group(s) to give the desired end product.

15 When X in the compound of Formula 1.0 is to be NR³, but is NH in the isatoic anhydride of the formula 2.1, then this compound of the Formula 2.1 can be reacted with a suitable R³-halide (wherein R³ is as above defined) to produce the desired R³-substituted isatoic anhydride of the formula 2.1. This is also disclosed by G.M. Coppola et al., *Synthesis*, 505 (1980).

20 In the second step, the compound of formula 2.1 is reacted with the anion derived from a malonate ester to produce the compound of the formula

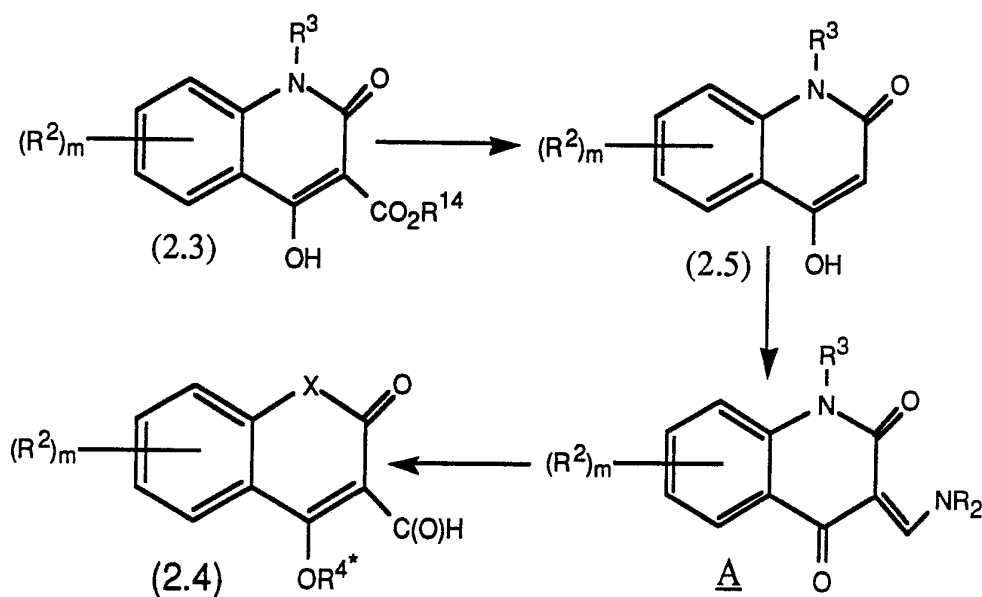
-15-

2.2 (which is a quinolinone when X is NR³). R¹⁴ is ethyl when diethyl malonate is used in the reaction.

In the third step, the compound of the formula 2.2 can be reacted with suitable reagents to produce the compound of the formula 2.3 having an ether group at C-4. This reaction can be carried out by standard methods for the preparation of ethers, for example by reaction of an alkali metal salt of the compound of the Formula 2.2 with a halide R⁴.Hal (where R⁴ is preferably alkyl, e.g., CH₃), or by reaction of the compound of the Formula 2.2 with a diazoalkane such as diazomethane, in a suitable organic solvent.

A more detailed illustration of the preparation of compounds of the Formula A follows in Scheme II, which shows how the starting materials wherein X is NR³ may be prepared:

SCHEME II



In this Scheme, the radicals R², R³, R⁴, and R¹⁴ and m are as defined for Formula 1.0, and each R is an inert organic group, or the two groups R together with the adjacent nitrogen atom can form a heterocyclic ring containing from 5 to 7 atoms and, if desired, a further heteroatom selected from O, N and S. R is preferably alkyl, especially methyl. The quinolinone 2.3, whose preparation is given in Scheme I above, can be decarboxylated to produce the quinolinone 2.5 by procedures well known in the art, for

-16-

example by means of alkali; see (for example) G. M. Coppola et al., J. Org. Chem., 41, 825 (1976), the disclosure of which is incorporated herein by reference thereto.

5 The quinolinone 2.5 can then be converted into the disubstituted aminomethylene quinolinone dione (or enamine) A by reaction with an excess of a dimethylformamide dialkylacetal in an appropriate solvent for a few hours, e.g., with dimethylformamide dimethylacetal in a low-boiling solvent such as dichloromethane.

10 The enamine of the Formula A can then be hydrolyzed in aqueous solution at acidic pH, e.g. with mineral acid, especially at pH ~3. It usually proceeds to completion in a few minutes at room temperature. R^{4*} in the resulting compound of the Formula 2.4 is hydrogen, and the corresponding compound of the Formula 2.4 wherein R^{4*} is lower alkyl, e.g., methyl, can be prepared by standard methods for the preparation of ethers, for example by
15 reaction of an alkali metal salt of the compound of the Formula 2.4 wherein R^{4*} is a hydrogen atom with a halide R²⁵.Hal (where R²⁵ is preferably alkyl, e.g., CH₃), or by reaction of the compound of the Formula 2.4 with a diazoalkane such as diazomethane, in a suitable organic solvent.

20 The compounds of this invention can be administered in any number of conventional dosage forms, e.g., topical, oral, parenteral, rectal, transdermal, inhalation and the like. Oral or rectal dosage forms include capsules, tablets, pills, powders, cachets and suppositories. Liquid oral dosage forms include solutions and suspensions. Parenteral preparations include sterile solutions and suspensions. Inhalation administration can be
25 in the form of a nasal or oral spray, or by insufflation. Topical dosage forms can be creams, ointments, lotions, transdermal devices (e.g., of the conventional patch or matrix type) and the like.

30 The formulations and pharmaceutical compositions contemplated by the above dosage forms can be prepared with conventional pharmaceutically acceptable excipients and additives, using conventional techniques. Such pharmaceutically acceptable excipients and additives are intended to include carriers, binders, flavorings, buffers, thickeners, coloring agents, stabilizing agents, emulsifying agents, dispersing agents, suspending agents, perfumes, preservatives lubricants, etc.

-17-

Suitable pharmaceutical acceptable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, low melting waxes, cocoa butter and the like. Capsules can be made wherein
5 the active compound is inserted into pharmaceutically acceptable capsules as a carrier. The active compounds of this invention can be mixed with pharmaceutically acceptable excipients or be used in finely divided powder form without excipients for inclusion into the capsules. Similarly, cachets are included.

10 Liquid form preparations include solutions, suspensions and emulsions such as water or water-propylene glycol solutions for parenteral injection. Liquid preparations can also be formulated in solution in polyethylene glycol and/or propylene glycol, which may contain water. Aqueous solutions suitable for oral use can be prepared by adding the
15 active component in water and adding suitable colorants, flavors, stabilizing, sweetening, solubilizing and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the active component in finely divided form in water with viscous material, i.e., pharmaceutically acceptable natural or synthetic gums, resins,
20 methylcellulose, sodium carboxymethylcellulose and other well-known suspending agents.

Formulations for topical application may include the above liquid forms, as well as creams, aerosols, sprays, dusts, powders, lotions and ointments which are prepared by combining an active ingredient according
25 to this invention with conventional pharmaceutical acceptable diluents and carriers commonly used in topical dry, liquid, cream and aerosol formulations. Ointment and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Such bases may, thus, for example, include water and/or an
30 oil such as liquid paraffin or a vegetable oil such as peanut oil or castor oil. Thickening agents which may be used according to the nature of the base include soft paraffin, aluminum stearate, cetostearyl alcohol, propylene glycol, polyethylene glycols, woolfat, hydrogenated lanolin, beeswax, etc.

35 Lotions may be formulations with an aqueous or oil base and will, in general, also include one or more of pharmaceutically acceptable

-18-

stabilizing agents, emulsifying agents, dispersing agents, suspending agents, thickening agents, coloring agents, perfumes and the like.

Powders may be formed with the aid of any suitable pharmaceutically acceptable powder base, e.g., talc, lactose, starch, etc. Drops may be formulated with an aqueous base or non-aqueous base also comprising one or more pharmaceutically acceptable dispersing agents, suspending agents, solubilizing agents, etc.

The topical pharmaceutical compositions may also include one or more preservatives or bacteriostatic agents, e.g., chlorocresol, methyl hydroxybenzoate, propyl hydroxybenzoate, benzalkonium chlorides, etc.

The topical pharmaceutical compositions may also contain an active compound of this invention in combination with other active ingredients such as antimicrobial agents, particularly antibiotics, anesthetics, analgesics and antipruritic agents.

Also included are solid form preparations which are intended for conversion, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions. These particular solid form preparations are most conveniently provided in unit dose form and as such are used to provide a single liquid dosage unit. Alternatively, sufficient solid may be provided so that after conversion to liquid form, multiple individual liquid doses may be obtained by measuring predetermined volumes of the liquid form preparation as with a syringe, teaspoon or other volumetric container. When multiple liquid doses are so prepared, it is preferred to maintain the unused portion of said liquid doses under conditions which retard possible decomposition. The solid form preparations intended to be converted to liquid form may contain, in addition to the active material, pharmaceutically acceptable flavorants, colorants, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents and the like. The solvent utilized for preparing the liquid form preparation may be water, isotonic water, ethanol, glycerine, propylene glycol and the like as well as mixtures thereof. Naturally, the solvent utilized will be chosen with regard to the route of administration, for example, liquid preparations containing large amounts of ethanol are not suitable for parenteral use.

The compounds of this invention may also be deliverable transdermally for systemic distribution. The transdermal compositions can

-19-

take the form of creams, lotions and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

5 The compounds of this invention may be administered by any conventional mode of administration by employing an effective antiviral amount of the appropriate compound of this invention for such mode. The dosages may be varied depending upon the requirements of the patient in the judgment of the attending clinician, the severity of the condition being treated and the particular compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Treatment can be initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage should be increased by small amounts until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

10 Thus, depending on the mode, dosages of from about 0.1 to about 100 mg/kg of body weight per day may be administered to provide antiviral activity. For example, when administered orally doses of from about 20 to about 60 mg/kg of body weight may be used; and when administered parenterally, e.g., intravenously, dosages of from about 5 to about 20 mg/kg body weight may be used.

20 When administered topically, the amount of compound administered varies widely with the amount of skin being treated, as well as with the concentration of active ingredient applied to the affected area. Preferably, topical compositions contain from about 0.10 to about 10 percent by weight of the active ingredient and are applied as needed according to the judgment of the attending clinician. When administered rectally, the compounds of this invention may be administered in daily doses ranging from about 0.1 mg/kg to about 100 mg/kg.

30 The dosage to be administered and the route of administration depends upon the particular compound used, the age and general health of the patient and the severity of the viral condition. Thus, the dose ultimately decided upon must be left to the judgment of a trained health-care practitioner.

-20-

EXAMPLES

The following Examples are illustrative only and should not be construed as limiting the invention in any way. Those skilled in the art will appreciate that variations are possible which are within the spirit and scope of the appended claims.

PREPARATION A

Preparation of 1-Benzyl-4-Hydroxy-6-Methyl-2(1H)-Quinolinone

Step (1): Preparation of 6-Methyl-Isatoic Anhydride.

A solution of 2-amino-5-methyl-benzoic acid (4.5 gm) in 2N HCl (15 ml) and water (35 ml) was stirred vigorously while trichloromethyl chloroformate (5.6 gm) was added dropwise. The reaction was stirred for an additional 10 mins and then filtered; the solid cake was washed with water and dried under reduced pressure to give 6-Methyl-Isatoic Anhydride as a light yellow powder (4.7 gm).

Step (2): Preparation of 1-Benzyl-6-Methyl-Isatoic Anhydride.

A solution of 6-methyl-isatoic anhydride (4.5 gm) in DMF (30 ml) was added dropwise to a stirred suspension of 60% sodium hydride (1.0 gm) in DMF (20 ml) under nitrogen atmosphere. The reaction was then warmed to 45°C and stirred until hydrogen evolution ceased. It was then cooled and a solution of benzyl bromide (4.4 gm) in DMF (10 ml) was added slowly. Stirring was continued for one hour at room temperature and the solution was then evaporated under reduced pressure at 45°C. The resulting solid was suspended in methylene chloride, the insoluble inorganic solid was removed by filtration and the filtrate was evaporated to give 1-benzyl-6-methyl-isatoic anhydride as a crystalline solid.

Step (3): Preparation of 1-Benzyl-3-Ethoxycarbonyl-4-Hydroxy-6-Methyl-2(1H)-Quinolinone.

A solution of diethyl malonate (4.07 gm) in dimethyl acetamide (10 ml) was added dropwise to a stirred suspension of 60% sodium hydride (1.01 gm) in the same solvent (10 ml), under a nitrogen atmosphere, in an oil bath at 25°C. After hydrogen evolution ceased, the temperature was raised to 80°C while adding a solution of 1-benzyl-6-methyl-isatoic anhydride (4.5 gm) in DMA (50 ml). After carbon dioxide evolution ceased, the reaction mixture was heated at 120°C for 17 hours and then was

-21-

concentrated under reduced pressure to a volume of 25 ml. and then was diluted with water (50 ml). The milky solution was washed with ether, the aqueous layer was acidified with mineral acid to pH3 and the resulting crystalline product 1-benzyl-3-ethoxycarbonyl-6-methyl-2(1H)-quinolinone was isolated by filtration.

Step (4): Preparation of 1-Benzyl-4-Hydroxy-6-Methyl-2(1H)-Quinolinone.

The product from Step (3) was dissolved in 2N sodium hydroxide (150 ml) and the solution was refluxed for 4 hours. Then the solution was cooled and acidified with mineral acid to pH3. The solid was filtered off, dried and crystallized from ethyl acetate/hexane to give 1-benzyl-4-hydroxy-6-methyl-2(1H)-quinolinone (4.0 gm). That the expected product was obtained was confirmed by the spectral data: MS: m/e 265 (M^+); NMR (DMSO): δ 2.32 (s, 3H, CH_3 -Ar), 5.43 (s, 2H, CH_2 -Ar), 5.96 (s, 1H, =CH-), 11.48 (s, 1H, OH) ppm.

PREPARATION B

Preparation of 1-Methyl-3-Formyl-4-Hydroxy-2(1H)-Quinolinone (Formula 1.7)

Step (1): Preparation of 1-methyl-3-dimethylaminomethylene-(1H)-quinolin-2,4-dione

A suspension of 1-methyl-4-hydroxy-2(1H)-quinolinone (1.0 gm) in dimethyl formamide dimethyl acetal (5 ml) and methylene chloride (2.0) was refluxed for 1 hr. The resulting dark orange solution was evaporated under reduced pressure to give 1-methyl-3-dimethylamino-methylene-(1H)-quinolin-2,4-dione.

Step (2): Preparation of 1-methyl-3-formyl-4-hydroxy-2(1H)-quinolinone.

The product from Step (1) was dissolved in distilled water (50 ml) by gentle warming and then the resulting solution was filtered. The clear filtrate was cooled in an ice bath and acidified to pH3 with mineral acid. The resulting crystalline precipitate was washed with water and dried to give 1-methyl-3-formyl-4-hydroxy-2(1H)-quinolinone. That the expected product was obtained was confirmed by the spectral data: MS: m/e 203 (M^+); NMR ($CDCl_3$): δ 3.6 (s, 3H, NCH_3), 10.28 (s, 1H, CHO) ppm.

-22-

EXAMPLES 1 TO 16EXAMPLE 1Preparation of 1-Benzyl-3-Formyl-4-Hydroxy-8-Methyl-2(1H)-Quinolinone
(Formula 1.3)

5 Step (1): Preparation of 1-Benzyl-4-Hydroxy-8-Methyl-2(1H)-Quinolinone.

Starting with 2-amino-3-methylbenzoic acid and following the procedure set forth in Preparation A, 1-benzyl-4-hydroxy-8-methyl-2(1H)-quinolinone was produced. That the expected product was obtained was
10 confirmed by the spectral data: m/e 266 (M^+ +1); NMR (DMSO): δ 2.46 (s, 3H, CH_3 -Ar), 5.58 (s, 2H, CH_2 -Ar), 5.96 (s, 1H, =CH-), 11.5 (br, 1H, OH) ppm.

Step (2): Preparation of 1-Benzyl-3-Formyl-4-Hydroxy-8-Methyl-2(1H)-Quinolinone.

15 Following the procedure set forth in Preparation B, 1-benzyl-4-hydroxy-8-methyl-2(1H)-quinolinone was converted to 1-benzyl-3-formyl-4-hydroxy-8-methyl-2(1H)-quinolinone. That the expected product was obtained was confirmed by the spectral data: MS: m/e 293 (M^+); NMR (DMSO): δ 2.46 (s, 3H, CH_3 -Ar), 5.68 (s, 2H, CH_2 -Ar), 10.12 (s, 1H, CHO)
20 ppm.

EXAMPLE 2Preparation of 1-Heptyl-3-Formyl-4-Hydroxy-2(1H)-Quinolinone
(Formula 1.4)

25 Step (1): Following the procedure set forth in Preparation A, steps (2-4), isatoic anhydride was converted to 1-heptyl-4-hydroxy-2(1H)-quinolinone.

Step (2): Following the procedure set forth in Preparation B, 1-heptyl-4-hydroxy-2(1H)-quinolinone was converted to 1-heptyl-3-formyl-4-hydroxy-2(1H)-quinolinone. That the expected product was obtained was
30 confirmed by the spectral data: m/e 287 (M^+); NMR (DMSO): δ 0.88 (t, 3H, CH_3 - CH_2), 4.20 (m, 2H, N- CH_2), 10.10 (s, 1H, CHO) ppm.

-23-

EXAMPLE 3**Preparation of 1-Benzyl-3-Formyl-4-Hydroxy-6-Methyl-2(1H)-Quinolinone**
(Formula 1.5)

Following the procedure set forth in Preparation B, 1-benzyl-4-hydroxy-6-methyl-2(1H)-quinolinone (obtained by Preparation A) was converted to 1-benzyl-3-formyl-4-hydroxy-6-methyl-2(1H)-quinolinone. That the expected product was obtained was confirmed by the spectral data: MS: m/e 293 (M^+); NMR (DMSO): δ 2.35 (s, 3H, CH₃), 5.45 (s, 2H, CH₂-Ar), 10.14 (s, 1H, CHO) ppm.

EXAMPLE 4**Preparation of 1-Benzyl-3-Formyl-4-Hydroxy-6-Chloro-2(1H)-Quinolinone**
(Formula 1.6)

Step (1): Preparation of 1-Benzyl-4-Hydroxy-6-Chloro-2(1H)-Quinolinone.

Starting with 2-amino-5-chlorobenzoic acid and following the procedure set forth in Preparation A, 1-benzyl-4-hydroxy-6-chloro-2(1H)-quinolinone was obtained. That the expected product was obtained was confirmed by the spectral data: FAB MS: m/e 286 ($M^+ + 1$); NMR (DMSO): δ 5.45 (s, 2H, CH₂-Ar), 6.0 (s, 1H, =CH-) ppm.

Step (2): Preparation of 1-Benzyl-3-Formyl-4-Hydroxy-6-Chloro-2(1H)-Quinolinone.

Following the procedure set forth in Preparation B, 1-benzyl-4-hydroxy-6-chloro-2(1H)-quinolinone was converted to 1-benzyl-3-formyl-4-hydroxy-6-chloro-2(1H)-quinolinone. That the expected product was obtained was confirmed by the spectral data: MS: m/e 313 ($M^+ + 1$); NMR (DMSO): δ 5.48 (s, 2H, CH₂-Ar), 10.14 (s, 1H, CHO) ppm.

EXAMPLE 5**Preparation of 1-Benzyl-3-Formyl-4-Hydroxy-2(1H)-Quinolinone**
(Formula 1.8)

Step (1): Preparation of 1-Benzyl-4-Hydroxy-2(1H)-Quinolinone.

Using isatoic anhydride and following the procedure set forth in Steps (2) to (4) of Preparation A, 1-benzyl-4-hydroxy-2(1H)-quinolinone was obtained. That the expected product was obtained was confirmed by the

-24-

spectral data: MS: m/e 251 (M^+); NMR (DMSO): δ 5.47 (s, 2H, CH_2 -Ar), 6.03 (s, 1H, =CH), 11.6 (s, H, OH) ppm.

Step (2): Preparation of 1-Benzyl-3-Formyl-4-Hydroxy-2(1H)-Quinolinone.

5 Following the Procedure set forth in Preparation B, 1-benzyl-4-hydroxy-2(1H)-quinolinone was converted to 1-benzyl-3-formyl-4-hydroxy-2(1H)-quinolinone. That the expected product was obtained was confirmed by the spectral data: MS (FAB): m/e 370 (M^++1); NMR (DMSO): δ 5.50 (s, 2H, CH_2 -Ar), 10.18 (s, 1H, CHO) ppm.

10

EXAMPLE 6

Preparation of 1-Phenyl-3-Formyl-4-Hydroxy-2(1H)-Quinolinone (Formula 1.9)

Step (1): Preparation of 1-Phenyl-4-Hydroxy-2(1H)-Quinolinone.

15 Starting with N-phenylaminobenzoic acid and following the procedure set forth in Preparation A, 1-phenyl-4-hydroxy-2(1H)-quinolinone was obtained. That the expected product was obtained was confirmed by the spectral data: MS: m/e 237 (M^+); NMR (DMSO): δ 5.92 (s, 1H, =CH), 11.60 (s, 1H, OH) ppm.

20

Step (2): Preparation of 1-Phenyl-3-Formyl-4-Hydroxy-2(1H)-Quinolinone.

Following the procedure set forth in Preparation B, 1-phenyl-4-hydroxy-2(1H)-quinolinone was converted to 1-phenyl-3-formyl-4-hydroxy-2(1H)-quinolinone. That the expected product was obtained was confirmed
25 by the spectral data: MS: m/e 265 (M^+); NMR (DMSO): δ 10.08 (s, 1H, CHO) ppm.

EXAMPLE 7

Preparation of 1-Benzyl-3-Formyl-4-Hydroxy-6-Benzyloxy-2(1H)-Quinolinone (Formula 1.10)

30

Step (1): Preparation of 1-Benzyl-4-Hydroxy-6-Benzyloxy-2(1H)-Quinolinone.

Starting with 2-amino-5-benzyloxybenzoic acid and following the procedure set forth in Preparation A, 1-benzyl-4-hydroxy-6-benzyloxy-2(1H)-quinolinone was obtained.

Step (2): Preparation of 1-Benzyl-3-Formyl-4-Hydroxy-6-Benzyloxy-2(1H)-Quinolinone.

Following the procedure of set forth in Preparation B, 1-benzyl-4-hydroxy-6-benzyloxy-2(1H)-quinolinone was converted to 1-benzyl-3-formyl-4-hydroxy-6-benzyloxy-2(1H)-quinolinone. That the expected product was obtained was confirmed by the spectral data: MS: m/e 385 (M^+); NMR ($CDCl_3$): δ 5.10 (s, 2H, OCH_2 -Ar), 5.49 (s, 2H, NCH_2 -Ar), 10.34 (s, 1H, CHO), 14.78 (s, 1H, OH) ppm.

EXAMPLE 8

10 Preparation of 1-Hexyl-3-Formyl-4-Hydroxy-2(1H)-Quinolinone
(Formula 1.11)

Step (1): Preparation of 1-Hexyl-4-Hydroxy-2(1H)-Quinolinone.

Following the procedure set forth in Steps (2) to (4) of Preparation A, isatoic anhydride was reacted with hexyl bromide to give 1-hexyl-4-hydroxy-2(1H)-quinolinone. That the expected product was obtained was confirmed by the spectral data: MS: m/e 245 (M^+); NMR (DMSO): δ 0.9 (t, 3H, CH_3-CH_2-), 4.06 (t, 2H, $N-CH_2$), 6.18 (s, 1H, $=CH$), 11.87 (br, 1H, OH) ppm.

Step (2): Preparation of 1-Hexyl-3-Formyl-4-Hydroxy-2(1H)-Quinolinone.

20 Following the procedure set forth in Preparation B, 1-hexyl-4-hydroxy-2(1H)-quinolinone was converted to 1-hexyl-3-formyl-4-hydroxy-2(1H)-quinolinone. That the expected product was obtained was confirmed by the spectral data: MS (FAB): m/e 274 ($M^+ + 1$); NMR (DMSO): δ 0.90 (t, 3H, CH_3-CH_2), 4.20 (t, 2H, N- CH_2), 10.11 (s, 1H, CHO) ppm.

EXAMPLE 9

25 EXAMPLE 9
Preparation of 1-Benzyl-3-Formyl-4,6-Dihydroxy-2(1H)-Quinolinone
(Formula 1.12)

Step (1): Preparation of 1-Benzyl-4,6-Dihydroxy-2(1H)-Quinolinone.

30 1-Benzyl-4-hydroxy-6-benzoyloxy-2(1H)-quinolinone (Step (1) of Example 7) was subjected to hydrogenolysis using a palladium catalyst and acetic acid as a solvent to produce 1-benzyl-4,6-dihydroxy-2(1H)-quinolinone.

-26-

Step (2): Preparation of 1-Benzyl-3-Formyl-4,6-Dihydroxy-2(1H)-Quinolinone.

Following the procedure set forth in Preparation B, 1-benzyl-4,6-dihydroxy-2(1H)-quinolinone was converted to 1-benzyl-3-formyl-4,6-dihydroxy-2(1H)-quinolinone. That the expected product was obtained was confirmed by the spectral data: MS: m/e 295 (M^+); NMR (DMSO): δ 5.45 (s, 2H, NCH₂-Ar), 9.92 (s, 1H, OH), 10.15 (s, 1H, CHO) ppm.

EXAMPLE 10

Preparation of 1-[3-(2-Chloro-4-Methoxyphenoxy)Propyloxymethyl]-3-Formyl-4-Hydroxy-2(1H)-Quinolinone (Formula 1.14)

Step (1): Preparation of 1-[3-(2-Chloro-4-Methoxyphenoxy)Propyloxymethyl]-4-Hydroxy-2(1H)-Quinolinone.

A solution of 2-chloro-4-methoxyphenol (15.5 gm) in DMF (20 ml) was added to a suspension of 60% sodium hydride (4 gm) in DMF (10 ml). To the resulting solution there was added a solution of 3-chloropropyl benzoate (15.5 gm) in DMF (20 ml). The solution was heated at 80°C for 20 hrs, then diluted with ethyl acetate, then washed with water then dried and then evaporated. The crude product was dissolved in a 1:1 mixture of methanol/THF (40 ml) to which 10% sodium hydroxide (50 ml) was added. The mixture was refluxed for 3hrs, then diluted with ethyl acetate, then washed with water and then evaporated. The crude product was purified by chromatography on silica gel using 40% ethyl acetate in hexane as the eluting solvent. The product was then dissolved in dichloroethane (40 ml) containing paraformaldehyde (2.25 gm). The solution was cooled in an ice bath and a stream of HCl gas was bubbled through the solution for 3.5 hrs. The solution was then dried over magnesium sulfate and the solvent was then removed under reduced pressure. Following the procedure set forth in Steps (2) to (4) of Preparation A, the resulting 3-(2-chloro-4-methoxyphenoxy) propyloxymethyl chloride was reacted with isatoic anhydride to give 1-[3-(2-chloro-4-methoxyphenoxy)-propyloxymethyl]-4-hydroxy-2(1H)-quinolinone. That the expected product was obtained was confirmed by the spectral data: MS: m/e 389 (M^+); NMR (DMSO): δ 1.9 (t, 2H, CH₂), 3.65 (t, 2H, CH₂O), 3.70 (s, 3H, OCH₃), 3.90 (t, 2H, CH₂O), 5.65 (s, 2H, NCH₂O), 5.84 (s, 1H, =CH).

-27-

Step (2): Preparation of 1-[3-(2-Chloro-4-Methoxyphenoxy)-Propoxymethyl]-3-Formyl-4-Hydroxy-2(1H)-Quinolinone.

Following the procedure set forth in Preparation B, 1-[3-(2-chloro-4-methoxyphenoxy)propyloxymethyl]-4-hydroxy-2(1H)-quinolinone was
 5 converted to 1-[3-(2-chloro-4-methoxyphenoxy)propyloxymethyl]-3-formyl-4-hydroxy-2(1H)-quinolinone. That the expected product was obtained was confirmed by the spectral data: MS: m/e 417 (M^+); NMR ($CDCl_3$): δ 2.01 (q, 2H, CH_2), 3.75 (s, 3H, OCH_3), 3.85 (q, 4H, CH_2-O), 10.21 (s, 1H, CHO).

EXAMPLE 11

10 Preparation of 1-Benzyl-3-Formyl-4-Hydroxy-7-Chloro-2(1H)-Quinolinone (Formula 1.15)

Step (1): Preparation of 1-Benzyl-4-Hydroxy-7-Chloro-2(1H)-Quinolinone.

Following the procedure set forth in Preparation A, 2-amino-4-
 15 chlorobenzoic acid and isatoic anhydride were converted to 1-benzyl-4-hydroxy-7-chloro-2(1H)-quinolinone. That the expected product was obtained was confirmed by the spectral data: MS: m/e 285 (M^+); NMR (DMSO): δ 5.36 (s, 2H, CH_2-Ar), 5.98 (s, 1H, $=CH-$), 11.75 (br, 1H, OH) ppm.

Step (2): Preparation of 1-Benzyl-3-Formyl-4-Hydroxy-7-
 20 Chloro-2(1H)-Quinolinone.

Following the procedure set forth in Preparation B, 1-benzyl-4-hydroxy-7-chloro-2(1H)-quinolinone was converted to 1-benzyl-3-formyl-4-hydroxy-7-chloro-2(1H)-quinolinone. That the expected product was obtained was confirmed by the spectral data: MS (FAB): m/e 314 (M^++1);
 25 NMR (DMSO): δ 5.5 (s, 2H, CH_2-Ar), 10.15 (s, 1H, CHO) ppm.

EXAMPLE 12

Preparation of 1,1-Dimethyl-2,4-Diketo-3-Formyl-1,2,3,4-Tetrahydronaphthalene (Formula 1.16)

Step (1): Preparation of α,α -Dimethyl-Homophthalic
 30 Anhydride.

A solution of dimethyl ester of homophthalic acid (7.2 g) in dimethylformamide (40 ml) was stirred at room temperature with 60% sodium hydride (1.38 g) for 10 minutes and then methyl iodide (5 ml) in dimethylformamide (10 ml) was added. The reaction was stirred for 1 hour

-28-

and worked up by diluting with ice, extracting with ethyl acetate and evaporating to constant weight. The residual oil was remethylated under the same conditions as described and the crude product on distillation gave the α,α -dimethylphthalic acid dimethyl ester (5.9 g) which was stirred in
5 tetrahydrofuran (50 ml) and in sodium hydroxide (50 ml) at 90°C for 24 hours. The reaction was concentrated and then acidified with mineral acid followed by extraction with ethyl acetate. The extracts were evaporated under reduced pressure and the product was dissolved in acetic anhydride and refluxed for 2 hours. The reaction was then evaporated to dryness and
10 azeotroped with benzene to give the title compounds (3.9 g). That the expected product was obtained was confirmed by the spectral data MS: m/e 190 (M^+); NMR ($CDCl_3$): δ 1.62 (s, 6H, CH_3), 3.62 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3).

Step (2): Preparation of α,α -Dimethyl-2,4-Diketo-1,2,3,4-Tetrahydronaphthalene.
15

A solution of the product from Step (1) (3.9 g) in tetrahydrofuran (40 ml) was reacted with 3M methyl magnesium bromide (10 ml) at -78°C for 0.5 hr followed by work up by acidification and extraction with ethyl acetate. The extract was concentrated to a low volume (25 ml) and treated with an excess
20 of a solution of diazomethane in ether for 15 minutes followed by evaporation to give 2-(α -methoxycarbonyl-iso-propyl)-acetophenone as an oil (4.1 g). That the expected product was obtained was confirmed by the spectral data: MS: m/e 220 (M^+); NMR ($CDCl_3$): δ 1.50 (s, 6H, CH_3), 2.08, 3.80 (s, 6H, OCH_3). The latter product was dissolved in dimethylformamide (20 ml) and
25 stirred with 60% sodium hydride (0.5 g) at room temperature for 10 mins and then at 40°C for 20 mins. Work up by diluting the reaction with ice, and acidification with mineral acid, gave the title compound (2.7 g) as a crystalline solid. That the expected product was obtained was confirmed by the spectral data: MS: m/e 188 (M^+); NMR ($DMSO$): δ 1.42 (s, 6H, CH_3),
30 5.62 (s, 1H, $CH=$), 11.70 (s, 1H, OH).

Step (3): Preparation of 1,1-Dimethyl-2,4-Diketo-3-Formyl-1,2,3,4-Tetrahydronaphthalene:

The product from step (2) was converted to the title compound by following the procedure described in Preparation B. That the expected
35 product was obtained was confirmed by the spectral data: MS: m/e 216 (M^+); NMR ($CDCl_3$): δ 1.55, 1.68 (s, 6H, CH_3), 9.92, 10.5 (s, 1H, CHO).

-29-

EXAMPLE 13**Preparation of 1-Methyl-3-Formyl-4-Hydroxy-2(1H)-Quinolinone. Sodium Salt (Formula 1.19)**

Sodium hydroxide (1N, 27 ml) was added to a stirred suspension of
5 1-methyl-3-formyl-4-hydroxy-2(1H)-quinolinone (6.2 gm, obtained in
accordance with Preparation B) in distilled water (200 ml). The resulting
neutral solution was filtered through a Millipore filter (0.45 μ) and lyophilized
to give 1-methyl-3-formyl-4-hydroxy-2(1H)-quinolinone, sodium salt as an
amorphous powder. That the expected product was obtained was confirmed
10 by the spectral data: MS (FAB): m/e 248 (M^+ +23); NMR (D_2O): δ 9.70
(s, 1H, CHO).

EXAMPLE 14**Preparation of 1-Heptyl-3-Hydroxyaminocarbonyl-4-Hydroxy-2(1H)-Quinolinone (Formula 1.23)**

15 Step (1): Preparation of 1-Heptyl-3-Ethoxycarbonyl-4-Hydroxy-
2(1H)-Quinolinone.

Following the procedure set forth in Preparation A, steps (2-3) isatoic
anhydride was converted to the title compound.

20 Step (2): Preparation of 1-Heptyl-3-Hydroxyaminocarbonyl-4-
Hydroxy-2(1H)Quinolinone.

A round-bottomed flask was charged with the product from step (1)
(493 mg, 1.49 mmole), sodium methoxide (208 mg, 3.85 mmole),
hydroxylamine (278 mg, 4.0 mmole) and methanol (10 mL). The reaction
was stirred for 24 hrs and the precipitated product was collected by filtration,
25 washed with water and dried in vacuo to give the title compound (40% yield).
That the expected product was obtained was confirmed by the spectral data:
M.S. (FAB): m/e 319 (M^+ +H); NMR (DMSO- d_6): δ 8.25 (1H, d), 7.85 (1H,
dd), 7.7 (1H, d), 7.45 (dd), 4.4 (2H, m, CH_2N), 2.95 (br s, exchangeable
protons), 1.8 (2H, m), 1.55 (8H, m), 0.95 (3H, t, CH_3).

-30-

EXAMPLE 15**Preparation of 1-Benzyl-3-Formyl-4-((2-Dimethylamino)ethoxy)-6-Methyl-2(1H)-Quinolinone, Maleate (Formula 1.24)**

Step (1): Preparation of 1-Benzyl-3-Formyl-4-Methoxy-6-

5 **Methyl-2(1H)-Quinolinone**

A solution of 1-benzyl-3-ethoxycarbonyl-4-hydroxy-6-methyl-2(1H)-quinolinone (12.4g, obtained in step 3 of Preparation A) in dichloromethane (50 ml) and methanol (10 ml) was treated with excess diazomethane in ether for 10 mins and was then evaporated. The crude methylation product upon
10 chromatography on silica gel yielded 1-benzyl-3-ethoxycarbonyl-4-methoxy-6-methyl-2(1H)-quinolinone (11.5 g). The latter product (7.13 g) in dry toluene (80 ml) was cooled to -78°C and a 1M solution of di-isobutyl aluminum hydride (30 ml) was added dropwise in 10min. After 2.5 hrs of stirring at -78°C, the reaction mixture was worked up by stirring with aqueous
15 ammonium chloride/1N hydrochloric acid followed by extraction with methylene chloride. The crude reduction product was chromatographed on silica gel and crystallized from ethyl acetate/hexane to give 1-benzyl-3-formyl-4-methoxy-6-methyl-2(1H)-quinolinone as a yellow solid (7.8 g). That the expected product was obtained was confirmed by the spectral data: NMR
20 (CDCl₃): δ 2.40 (s, 3H, CH₃), 4.18 (s, 3H, OCH₃), 10.58 (s, 1H, CHO); MS (FAB): m/e 308 (M⁺ + 1).

Step (2): Preparation of 1-Benzyl-3-Formyl-4-((2-Dimethylamino)ethoxy)-6-Methyl 2(1H)-Quinolinone, Maleate

2-Dimethylaminoethanol (2 ml) was stirred with 60% sodium hydride
25 (20 mg) until a clear solution was obtained. Then the product of Step (1) was added. After stirring for 1 hour, the reaction was diluted with ethylacetate and washed several times with brine. The organic phase was dried and then evaporated to dryness under reduced pressure. The crude product was purified by chromatography on silica gel and dissolved in a solution of maleic
30 acid (200 mg) in ether (30 ml). The resulting suspension was stirred for 1 hour and filtered to give the title compound as yellow crystals. That the expected product was obtained was confirmed by the spectral data: MS (FAB): m/e 365 (M⁺ + 1); NMR (CDCl₃): δ 3.12 (s, 3H, CH₃-Ar), 3.81 (t, 2H, CH₂-N), 4.65 (t, 2H, CH₂O), 5.55 (s, 2H, CH₂Ar), 6.30 (s, 2H, CH=), 10.50
35 (s, 1H, CHO).

-31-

EXAMPLE 16**Preparation of 1-Hexyl-3-Formyl-4-(2-Dimethylaminoethoxy)-6-Methyl-2(1H)-Quinolinone, Maleate salt (Formula 1.25)**

Step (1): Preparation of 1-Hexyl-3-Formyl-4-Methoxy-6-Methyl-2(1H)-Quinolinone

Using hexyl bromide instead of benzyl bromide and following steps (1-3) in Preparation A, 1-hexyl-3-ethoxycarbonyl-4-hydroxy-2(1H)-quinolinone was obtained. Then, following the procedure set forth in Example 15, Step (1), the 1-hexyl-3-ethoxycarbonyl-4-hydroxy-2(1H)-quinolinone was converted to the title compound. That the expected product was obtained was confirmed by the spectral data: MS: m/e 301 (M^+); NMR ($CDCl_3$): δ 4.15 (s, 3H, OCH_3), 10.56 (s, 1H, CHO).

Step (2): Preparation of 1-Hexyl-3-Formyl-4-(2-Dimethylaminoethoxy)-6-Methyl-2(1H)-Quinolinone, Maleate salt

The title compound was obtained by starting with the product from Step (1) and following the procedure described in Example 15, Step (2). That the expected product was obtained was confirmed by the spectral data: MS (FAB): m/e 359 ($M^+ + 1$); NMR ($CDCl_3$): δ 3.10 (s, 6H, $(CH_3)_2N$), 3.78 (t, 2H, CH_2N), 4.60 (t, 2H, CH_2O), 6.30 (s, 2H, $CH=$), 10.45 (s, 1H, CHO).

Those skilled in the art will appreciate that the compound of Formula 1.13 can be prepared by the procedures described in Preparations A and B.

BIOLOGICAL DATA**Cell and Virus Culture**

HeLa and Vero cell cultures were maintained in Eagles Minimal Essential Medium (EMEM) which was supplemented with glutamine, penicillin, streptomycin and 10% fetal calf serum (10% EMEM). Stock cultures of HSV-2 (strain MS available from ATCC VR-540) were grown in and harvested from Vero cells. Viral stocks were titered in Vero cells according to established procedures.

Plasmid Constructions

Plasmid pON^{ori}-245 contains the promoter of the HSV-1 thymidine kinase (tk) gene located immediately 5' of the *E. coli lacZ* gene. In this arrangement, the tk promoter controls transcription from the bacterial gene in

-32-

transient expression assays. Additionally, an SV40 polyadenylation signal is present at the 3' end of the lac Z gene to allow for the efficient translation of the mRNA in eucaryotic cells. The expression of beta galactosidase in a transient assay using pON 245^{ori}- is dependent upon superinfection of the transfected cells with HSV. Therefore, a compound which interferes with early steps of HSV replication will also inhibit beta-galactosidase production in transfected cells. For example, see European Patent Application No. 88302149.5 filed March 11, 1988 and published September 14th 1988 as 282,330, the disclosure of which is incorporated herein by reference thereto.

10 Transient Expression of Beta Galactosidase in Transfected Cells

HeLa cells were seeded into 96 well microtiter plates and allowed to grow to 80% confluency (approximately 35000 cells/well). One half microgram of plasmid pON 245^{ori}- DNA was introduced into the cells of each well by the DEAE Dextran precipitation technique (Graham and Van der Eb, 1973). Four to six hours later, the cells were rinsed with Hank's Balanced Salt Solution (HBSS), overlaid with 10% EMEM and incubated at 37°C. At 24 hours post-transfection, cells were rinsed, overlaid with 10% EMEM again and re-incubated at 37°C. At 48 hours post-transfection, cells were rinsed and overlaid with either EMEM containing 2% fetal calf serum (2% EMEM), 2% EMEM containing HSV-2 (strain MS, Multiplicity of Infection [moi] = 5 pfu/cell) or 2% EMEM containing HSV-2 and the appropriate concentration of the compound to be tested. Twenty-four hours later, the cells were harvested and assayed for beta-galactosidase activity as described below.

25 Beta Galactosidase Assay

All determinations of beta galactosidase activity were performed in 96-well microtiter plates. The intracellular level of beta-galactosidase activity in each well was determined from cell lysates of the monolayer cultures. Aliquots were assayed by incubation in the presence of beta-galactosidase substrate, 4-methylumbelliferyl- β -D-galactoside (MUG, 125 ug/ ml, Sigma), for 2 hours. The generation of fluorescent product was quantified on a Microfluor microfluorimeter (Dynatech) after addition of 0.1 M glycine, pH 10.3 (Spaete and Mocarski, 1985). The inhibitory activity of a compound was plotted versus the concentration and an IC₅₀ value (the concentration in mcg/ml of compound required to reduce beta-galactosidase expression by 50%) was obtained for each compound tested.

-33-

Compound Toxicity Assay

Compounds which demonstrated a significant inhibitory activity in the HeLa cell beta-galactosidase assay were assayed for their inhibitory effect on HeLa cell translation. HeLa cells were treated with inhibitory compound for 24 hours, after which levels of translational activity were assayed.

For assay of translational activity, HeLa cultures were grown to 80% confluency in 96 well microtiter plates, treated with appropriate concentrations of compound in 2% EMEM during an overnight incubation at 37°C, then rinsed with HBSS and overlaid with 0.8 ml of 2% EMEM containing 8 µCi of tritiated leucine (³H-LEU, 141 Ci/mMol, Amersham Corp., Arlington Heights IL). After a 1 hour incubation at 36.5°C, the cells were rinsed twice with phosphate-buffered saline (PBS) and lysed in 400 µl/well of 1x PBS, 0.5% sodium dodecyl sulphate (SDS). After a 10 min incubation at 36.5°C, the contents of the well were transferred to a well in a Millititer HA microfiltration plate (Millipore Corp., Bedford, MA). The TCA-insoluble proteins were precipitated onto the filter disc by a 10 min fixation with 5% TCA, followed by filtration under vacuum and three 10 minute rinses with 95% ethanol. The filters were dried at room temperature, cut from the millititer plate and transferred to scintillation vials. TCA-precipitable counts were assayed in 5 ml of Scintisol (Isolab, Akron, OH). The inhibitory activity of a compound was plotted versus the concentration and an IC₅₀ value (that concentration of the compound required to decrease cellular translational activity by 50%) was derived for each compound.

Analysis of In Vivo Efficacy

The in vivo assessment of anti-HSV efficacy was determined in the prophylactic guinea pig model of HSV infection described by Stansberry et al. (1982). Dosing of guinea pigs comprised an initial treatment with test compound given 24 hours prior to virus infection and subsequent administration of the compound every eight hours (T.I.D.) for a total of 10 days. Test compounds were administered subcutaneously in 0.5% buffered methyl cellulose at a dose of 60 mg per kg body weight of the animal. Animals were monitored daily for the development of genital lesions and neurological symptomology, both of which were recorded and compared to the results obtained with parallel groups which received placebo or acyclovir. Efficacy was evaluated for each compound by scoring the ability of the

-34-

compound to ameliorate genital lesions produced by infection with HSV-2, strain MS, expressed as Maximum Lesion Scores (MLS) on a scale of 1 (least lesions) to 4 (severe lesions).

The in vitro anti-HSV activity

5

The in vitro anti-HSV activity is set forth in Table I.

Table I

EX	FORMULA	ANTI-HSV ACTIVITY HSV- β -Gal ASSAY IC ₅₀ (mcg/ml)	CYTOTOXICITY ³ H-LEU ASSAY IC ₅₀ (mcg/ml)
1	1.3	3	29
2	1.4	4, 4*	32, 22
3	1.5	4	16
4	1.6	4	15
PREP B	1.7	7, 7*	56, 40
5	1.8	7	29
6	1.9	8	12
7	1.10	10	32
8	1.11	8	20
9	1.12	13	--
10	1.14	18	--
11	1.15	5	23
12	1.16	7	34
*Repeat			

-35-

In Vivo Anti-HSV Activity

In vivo anti-HSV activity is set forth in Table II.

Table II

Formula	MLS ⁽¹⁾	Neurological Dysfunction (%) ²
Placebo	2.22	66
Acyclovir	1.61	44
1.9	0.67	0

(1) Maximum Lesion Scores on a scale of 1 to 4.

(2) Percentage of animals developing loss of bladder/hindlimb control.

Antihypertensive Activity5 I. SHR Assay

The ability of the compounds to lower blood pressure can be assessed in vivo in conscious spontaneously hypertensive rats (SHRs). SHR males are purchased from Taconic Farms, Germantown, New York and are approximately 16-18 weeks old when anesthetized with ether. The caudal (ventral tail) artery is
10 cannulated with polyethylene tubing (PE50), and blood pressure and heart rate are recorded as described by Baum, T. et. al., J. Cardiovasc. Pharmacol., Vol 5, pp. 655-667 (1983). Rats are placed into plastic cylindrical cages where they rapidly recover consciousness. Blood pressure and heart rate are allowed to
15 stabilize for approximately 90 minutes prior to administration of the test compound. Compounds are administered orally as solutions or suspensions in 0.4% aqueous methylcellulose vehicle via a feeding needle. The compound or 0.4% aqueous methylcellulose vehicle is given in a volume of 4 ml/kg to SHRs that been fasted overnight. Activity is expressed as the fall in mean blood
20 pressure (MBP) in millimeters of mercury (mm Hg). Compound-induced changes are compared with the changes in an appropriate placebo group.

-36-

The SHR results are given in Table III.

Table III

Formula	Dose, P.O. (mpk)	Fall in MBP (mm Hg)
1.3	25	7
1.6	25	48
1.5	50	40

II. Phosphodiesterase inhibition in vitro

Phosphodiesterase enzymes are known to hydrolyze cGMP in smooth muscle. High levels of cGMP are associated with the relaxation of vascular smooth muscle and with a consequent subsequent reduction in blood pressure. Thus, it is believed that by inhibiting these phosphodiesterase enzymes, cGMP levels in muscle will be either maintained or increased with a subsequent reduction in blood pressure.

Compounds are evaluated for inhibition of a phosphodiesterase enzyme which hydrolyzes cyclic guanosine monophosphate (cGMP). The enzyme, cGMP phosphodiesterase (cGMP-PDE), is a homogeneous enzyme obtained from bovine lung and purified by ion-exchange chromatography, gel filtration, and sucrose gradient centrifugation. cGMP-PDE is highly selective for cGMP. Bovine aorta homogenates and primary cultures of bovine aortic endothelial and vascular smooth muscle cells contain an enzyme with properties very similar to the lung isozyme.

The enzyme assay is performed using a Biomek Automated Pipetting Station. Compounds are dissolved in distilled water or DMSO and diluted with 10% DMSO. Compounds are tested at several concentrations at log intervals, typically 0.1, 1.0, 10, and 100 μ M final concentration.

Assays contain the following components:

- 1 μ M substrate 3 H-cGMP
- 50 mM Tris-HCl, pH 7.5, 5 mM magnesium chloride (MgCl_2)
- 0.5 mg/ ml snake venom alkaline phosphatase.

Assays are initiated by addition of enzyme and stopped by addition of 10 mM isobutylmethylxanthine, a general phosphodiesterase inhibitor. Assays are performed for 25 minutes at room temperature to achieve 5-10%

hydrolysis of substrate. The negatively charged substrates are then separated from guanosine by binding to an anion-exchange resin (AGI-X8) and centrifugation or filtration, and the product is quantitated by scintillation counting in counts.

5 % Inhibition = 100-[(cpm compound-blank)/(cpm control-blank)X100]
Activity is expressed as a percentage of control.

Activity is expressed as the IC₅₀ value, i.e., the concentration required to inhibit activity of the enzyme by 50 per cent. The cGMP-PDE IC₅₀ results are set forth in Table IV.

TABLE IV
IN-VITRO cGMP-PDE RESULTS

FORMULA	cGMP-PDE IC ₅₀ (μM)
1.3	10
1.6	17
1.5	90
1.9	18

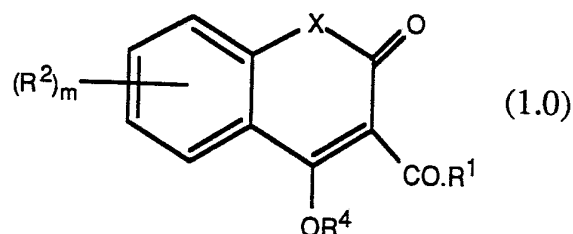
A compound within the scope of the antihypertensive compounds of this invention did not show optimum antihypertensive activity when tested using the assays described above. This compound is a compound of Formula 1.0 wherein X is N, R¹ is H, R³ is -C₇H₁₅, n is 1, and R⁴ is -(CH₂)₂N(CH₃)₂. The SHR result for this compound was +7 at 25 mpk (p.o.).

The invention having been thus described, it will be obvious that it may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the invention and all such modifications are included within the scope of the claims.

-38-

CLAIMS:

1. A compound of Formula 1.0:



and the pharmaceutically acceptable salts and solvates thereof;

5 wherein:

(A) X is selected from the group consisting of N-R³, O, S, and C(R³)₂;

(B) R³ is selected from the group consisting of:

- | | |
|-------------------------|-----------------------|
| (1) alkyl; | (2) aralkyl; |
| (3) aryl; | (4) substituted aryl; |
| (5) alkaryl; | (6) alkyl heteroaryl; |
| (7) aryloxyalkoxyalkyl; | |

(8) -(CH₂)_a R¹¹ wherein a is an integer of 1 to 6 and R¹¹ is selected from the group consisting of -C(O)OR¹², -OR¹², -R¹², and -N(R¹²)₂, wherein each R¹² can be the same or different and is selected from the group consisting of alkyl, alkenyl and H; and

(9) -OR¹³ wherein R¹³ is selected from the group consisting of H, alkyl - which may be substituted with OH, SH, NH₂ and/or halogen - , alkaryl, alkenyl, and heteroaryl;

and the two groups R³ on the same carbon atom can be the same or different;

(C) R¹ is selected from the group consisting of:

- | | |
|--------------|---|
| (1) H; | (2) alkyl; |
| (3) aryl; | (4) alkaryl; |
| (5) alkenyl; | (6) -N(R ⁵) ₂ wherein each R ⁵ is |

independently selected from the group consisting of H, alkyl - which may be substituted with OH, SH, NH₂ and/or halogen - , aryl, alkaryl, alkenyl, heteroaryl, alkoxy, and hydroxy;

(7) heteroaryl; and (8) substituted alkyl;

(D) Each R² for each m is independently selected from the group consisting of:

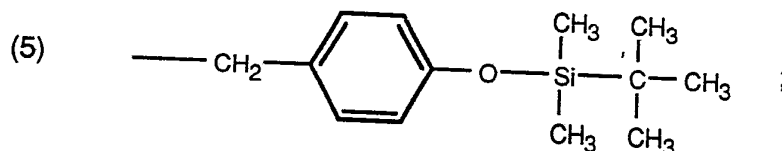
- | | |
|------------|-------------|
| (1) alkyl; | (2) alkoxy; |
|------------|-------------|

-39-

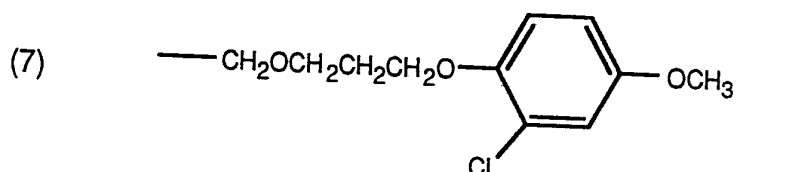
- (3) aryloxy; (4) aryl;
 (5) aralkyloxy; (6) halogen atoms selected from the group consisting of F, Cl, Br and I;
 (7) -O-CO-R⁶ wherein R⁶ is alkyl - which may be substituted with OH, SH, NH₂ and/or halogen - ; aryl; alkaryl; alkenyl; and heteroaryl;
 (8) -N(R⁷)₂ wherein each R⁷ is independently selected from the group consisting of H, alkyl, aryl, and R⁶C(O)- wherein R⁶ is as above defined;
 (9) -OH; (10) -CH₂OH;
 (11) -COOH; (12) -COOR⁸, wherein R⁸ is selected from the group consisting of alkyl and aryl;
 (13) -SO₃H; (14) -SO₂NHR⁹, wherein R⁹ is selected from the group consisting of alkyl, aryl, and H;
 (15) (15) -PO₃H; (16) -PO(OR¹⁰)₂, wherein R¹⁰ is selected from the group consisting of alkyl and aryl;
 (17) -OPO₃H; (18) -OP(OR¹⁰)₂ wherein R¹⁰ is as above defined; and (19) -CF₃;
 (E) m is an integer from 0 to 4; and
 (F) R⁴ is selected from the group consisting of H, aminoalkyl and hydroxyalkyl.

2. The compound of Claim 1 wherein R¹ is H.
3. The compound of Claim 1 wherein X is NR³, wherein R³ is as defined in Claim 1.
4. The compound of Claim 1 wherein R² is selected from the group consisting of:
- (1) -CH₃; (2) -OCH₃;
 (3) -OCOCH₃; (4) -OCH₂-phenyl;
 (5) Cl; (6) F;
 (7) I; and (8) -CF₃.
5. The compound of Claim 1 wherein R³ is selected from the group consisting of:
- (1) -CH₃; (2) -C₆H₁₃;

-40-

(3) $-C_7H_{15}$;(4) $-CH_2$ -phenyl;

(6) phenyl;



5

(8) $-CH_2CO_2CH_2CH=CH_2$; and(9) $-CH_2CO_2CH_3$.

6. The compound of Claim 5 wherein:

(A) X is NR^3 ;

10

(B) R^1 is selected from the group consisting of H, alkyl – which may be substituted with OH, SH, NH_2 and/or halogen –, alkaryl, alkylene, and heteroaryl;(C) R^2 is selected from the group consisting of:(1) $-CH_3$;(2) $-OCH_3$;(3) $-OCOCH_3$;(4) $-OCH_2$ -phenyl;

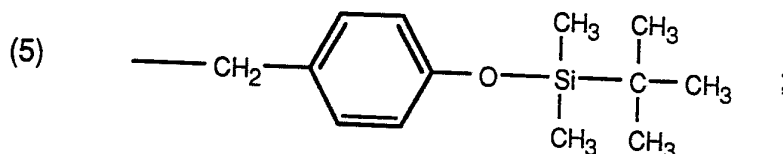
15

(5) Cl;

(6) F;

(7) I;

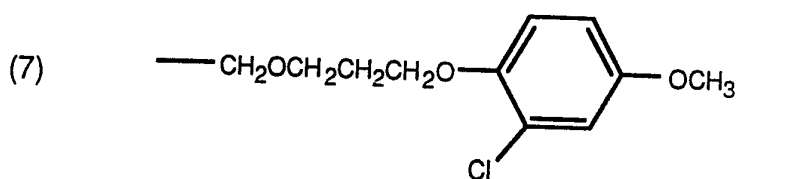
and

(8) $-CF_3$; and m is 0, 1 or 2;(D) R^3 is selected from the group consisting of:(1) $-CH_3$;(2) $-C_6H_{13}$;(3) $-C_7H_{15}$;(4) $-CH_2$ -phenyl;

20

(6) phenyl;

-41-



(8) $-\text{CH}_2\text{CO}_2\text{CH}_2\text{CH}=\text{CH}_2$; and

(9) $-\text{CH}_2\text{CO}_2\text{CH}_3$;

and R^4 is $-\text{O}(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$.

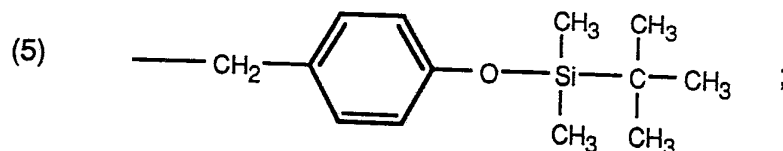
- 5 7. The compound of Claim 6 wherein R^1 is H.
8. The compound of Claim 1 wherein R^4 is an aminoalkyl group .
9. The compound of Claim 8 wherein R^4 is $-(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$.
10. The compound of Claim 9 wherein R^1 is H and R^2 is alkyl.
11. The compound of Claim 10 wherein R^2 is $-\text{CH}_3$.
- 10 12. The compound of Claim 1 wherein said compound is selected from the group consisting of the formulas 1.3 to 1.16, 1.19, and 1.23 to 1.25 in the TABLE OF CHEMICAL COMPOUNDS herein.
13. The compound of Claim 1 wherein said compound is selected from the group consisting of the formulas 1.24 and 1.25 in the TABLE OF
- 15 CHEMICAL COMPOUNDS herein.
14. The compound of Claim 1 wherein:
 - (A) X is $\text{C}(\text{R}^3)_2$;
 - (B) R^1 is selected from the group consisting of H, alkyl – which may be substituted with OH, SH, NH_2 and/or halogen – , alkaryl, alkylene, and heteroaryl;
 - (C) R^2 is selected from the group consisting of:

(1) $-\text{CH}_3$;	(2) $-\text{OCH}_3$;
(3) $-\text{OCOCH}_3$;	(4) $-\text{OCH}_2\text{-phenyl}$;
(5) Cl;	(6) F;
	(7) I;

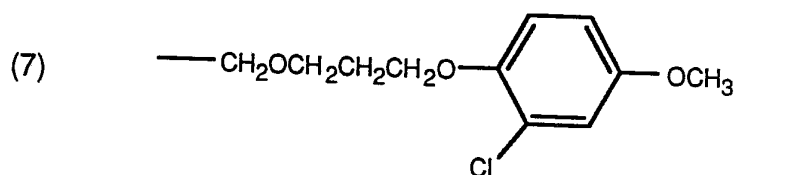
 and (8) $-\text{CF}_3$; and m is 0, 1 or 2;
 - (D) R^3 is selected from the group consisting of:

(1) $-\text{CH}_3$;	(2) $-\text{C}_6\text{H}_{13}$;
----------------------	----------------------------------

-42-

(3) $-C_7H_{15}$;(4) $-CH_2$ -phenyl;

(6) phenyl;



5

(8) $-CH_2CO_2CH_2CH=CH_2$; and(9) $-CH_2CO_2CH_3$.15. The compound of Claim 14 wherein R^1 is H.

16. The compound of Claim 1 wherein:

(A) X is O or S;

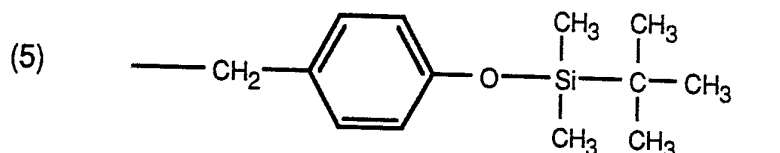
10 (B) R^1 is selected from the group consisting of H, alkyl – which may be substituted with OH, SH, NH_2 and/or halogen –, alkaryl, alkylene, and heteroaryl;

(C) R^2 is selected from the group consisting of:

15 (1) $-CH_3$; (2) $-OCH_3$;
 (3) $-OCOCH_3$; (4) $-OCH_2$ -phenyl;
 (5) Cl; (6) F; (7) I;
 and (8) $-CF_3$; and m is 0, 1 or 2;

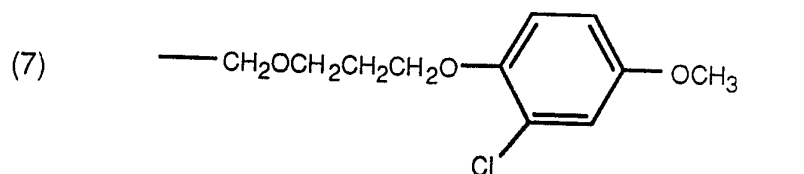
(D) R^3 is selected from the group consisting of:

20 (1) $-CH_3$; (2) $-C_6H_{13}$;
 (3) $-C_7H_{15}$; (4) $-CH_2$ -phenyl;



(6) phenyl;

-43-

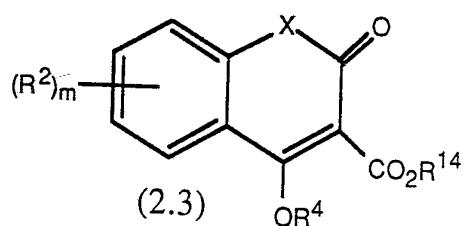


(8) $-\text{CH}_2\text{CO}_2\text{CH}_2\text{CH}=\text{CH}_2$; and

(9) $-\text{CH}_2\text{CO}_2\text{CH}_3$.

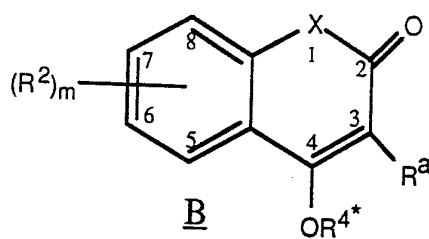
17. The compound of Claim 16 wherein R^1 is H.
- 5 18. The compound of Claim 1 wherein:
 - (A) X is NR^3 ;
 - (B) R^1 is selected from the group consisting of H and alkyl;
 - (C) R^2 is $-\text{CH}_3$ and m is 0 or 1;
 - (D) R^3 is selected from the group consisting of:
 - 10 (1) $-\text{C}_6\text{H}_{13}$; (2) $-\text{C}_7\text{H}_{15}$;
 - and (3) $-\text{CH}_2$ -phenyl; and
 - (E) R^4 is $-\text{O}(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$.
19. The maleate salt of a compound of Claim 1 wherein R^4 is $-\text{O}(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$.
- 15 20. A pharmaceutical composition comprising an effective amount of a compound of Claim 1 and a pharmaceutically acceptable carrier.
21. A method of treating a viral infection in a patient in need of such treatment comprising administering an effective amount of a compound of Claim 1 to said patient.
- 20 22. A method of treating hypertension in a patient in need of such treatment comprising administering to such patient an effective antihypertensive amount of a compound of Claim 8.
23. A process for the preparation of compounds of Formula 1.0 defined in claim 1, which comprises one of the following processes (a) to (c):
 - 25 (a) for the preparation of a compound of Formula 1.0 wherein R^1 is a hydrogen atom, the reduction of a corresponding 3-esterified carboxy compound of the formula 2.3:

-44-



wherein X, R², R⁴ and m are as defined in claim 1, and R¹⁴ is an alkyl group, with an appropriate hydride reducing agent;

- (b) for the preparation of a compound of Formula 1.0 wherein R⁴ is hydroxyalkyl or aminoalkyl and R¹ is as defined in claim 1, the reaction of a compound of Formula B



- wherein R^{4*} of Formula B is lower alkyl and R^a is CHO, by nucleophilic substitution with R⁴O⁻ in solution in an excess of the alcohol R⁴OH, wherein R⁴ is aminoalkyl or hydroxyalkyl; and

- (c) for the preparation of a compound of Formula 1.0 defined in claim 1 wherein R¹ is an alkyl group, the reaction of a compound of the Formula 2.3 defined in process (b) above, in solution in a suitable solvent, with a metal-alkyl reagent.
24. The use of a compound claimed in claim 1 for treating viral diseases.
25. The use of a compound claimed in claim 1 for the manufacture of a medicament for the treatment of viral diseases.
26. A method of manufacturing a pharmaceutical composition comprising the admixing of a compound claimed in claim 1 with a pharmaceutically acceptable carrier or excipient.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/06250

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)⁶

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: C 07 D 215/56, A 61 K 31/47

II. FIELDS SEARCHED

Minimum Documentation Searched⁷

Classification System

Classification Symbols

IPC5

C 07 D

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in Fields Searched⁸

III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹

Category *

Citation of Document,¹¹ with indication, where appropriate, of the relevant passages¹²

Relevant to Claim No.¹³

X	EP, A1, 0059698 (AB LEO) 8 September 1982, see the whole document	1-20, 23, 25-26
	--	
A	EP, A2, 0172004 (THE BOOTS COMPANY PLC) 19 February 1986, see the whole document	1-20, 23, 26
	--	
A	GB, A, 1207771 (WARNER-LAMBERT PHARMACEUTICAL COMPANY) 7 October 1970, see the whole document	1-20, 23, 25-26
	--	
X	US, A, 3960868 (P.G. FERRINI ET AL.) 1 June 1976, see the whole document	1-20, 23, 25-26
	--	

* Special categories of cited documents: ¹⁰

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

"E" earlier document 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

"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

IV. CERTIFICATION

Date of the Actual Completion of the International Search

2nd December 1991

Date of Mailing of this International Search Report

21. 01. 92

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

Natalie Weinberg

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

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

1. ☒ Claim numbers 21, 22 and 24 because they relate to subject matter not required to be searched by this Authority, namely:

Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods (see PCT Rule 39(iv)).

2. ☐ Claim numbers..... 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. ☐ Claim numbers..... because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ 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 claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

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

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. PCT/US 91/06250**

SA 50942

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 31/10/91.
The European Patent office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A1- 0059698	08/09/82	AU-B- 547849	07/11/85
		AU-D- 8107682	09/09/82
		CA-A- 1182455	12/02/85
		JP-A- 57171975	22/10/82
		US-A- 4547511	15/10/85
		US-A- 4738971	19/04/88
EP-A2- 0172004	19/02/86	JP-A- 61063657	01/04/86
		US-A- 4855291	08/08/89
GB-A- 1207771	07/10/70	DE-A- 1913466	06/11/69
		FR-A- 2004175	21/11/69
US-A- 3960868	01/06/76	AT-B- 332406	27/09/76
		AT-A-B- 332407	27/09/76
		AT-A-B- 332408	27/09/76
		AT-A-B- 338267	10/08/77
		AT-A-B- 338268	10/08/77
		AT-A-B- 338269	10/08/77
		AU-D- 6877174	13/11/75
		CA-A- 1034124	04/07/78
		DE-A- 2421121	16/01/75
		FR-A-B- 2228488	06/12/74
		GB-A- 1467061	16/03/77
		JP-A- 50018480	26/02/75
		NL-A- 7405910	13/11/74
		BE-A- 814843	12/11/74
		CH-A- 578534	13/08/76

For more details about this annex : see Official Journal of the European patent Office, No. 12/82