

4-OXO-1,4-DIHYDRO-3-CINNOLINECARBOXAMIDES AS ANTIVIRAL AGENTS

5 Background of the Invention

1. Field of the Invention

The present invention provides novel cinnolines, which are useful as antiviral agents
10 (e.g. as agents against viruses of the herpes family).

2. Technology Description

The herpesviruses comprise a large family of double stranded DNA viruses. They are
15 also a source of the most common viral illnesses in man. Eight of the herpes viruses,
herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), varicella zoster virus (VZV),
human cytomegalovirus (HCMV), epstein-Barr virus (EBV), and human herpes
viruses 6, 7, and 8 (HHV-6, HHV-7, and HHV-8), have been shown to infect humans.

20 HSV-1 and HSV-2 cause herpetic lesions on the lips and genitals, respectively. They
also occasionally cause infections of the eye and encephalitis. HCMV causes birth
defects in infants and a variety of diseases in immunocompromised patients such as
retinitis, pneumonia, and gastrointestinal disease. VZV is the causative agent of
chicken pox and shingles. EBV causes infections mononucleosis. It can also cause
25 lymphomas in immunocompromised patients and has been associated with Burkitt's
lymphoma, nasopharyngeal carcinoma, and Hodgkins disease. HHV-6 is the
causative agent of roseola and may be associated with multiple sclerosis and chronic
fatigue syndrome. HHV-7 disease association is unclear, but it may be involved in
some cases of roseola. HHV-8 has been associated with Kaposi's sarcoma, body
30 cavity based lymphomas, and multiple myeloma.

U.S. Patent No. 4,826,837 discloses 4-hydroxycinnoline-3-carboxamides and their use for the treatment of neoplastic diseases and acute and chronic infections of both bacterial and viral origin in mammals.

- 5 U.S. Patent No. 4,886,800 discloses 4-substituted-cinnoline-3-carboxylic acids and 3-acyl-4-substituted-cinnoline derivatives and their use as central nervous system depressants.

- U.S. Patent Nos. 5,753,666 and 5,891,878 and WO 97/04775 disclose 1-alkyl-
10 substituted-quinolone-3-carboxamides that are alleged to have therapeutic utility via inhibition of Phosphodiesterase IV esterase and/or Tumor Necrosis factor activity.

- WO 99/38867 discloses 1-cycloalkyl-1,8-naphthyridin-4-one derivatives; pharmacologically acceptable salts or solvates thereof; and a phosphodiesterase IV
15 inhibitor containing any of the above as an active ingredient.

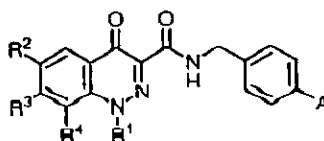
Commonly assigned PCT/US98/25192 discloses 4-hydroxyquinoline-3-carboxamides and hydrazides as antiviral agents.

- 20 Despite the above teachings, there still exists a need in the art for novel compounds that demonstrate desirable antiviral activity.

Brief Summary of the Invention

- 25 In accordance with the present invention, novel compounds which demonstrate antiviral activity are provided. More specifically, the compounds are 4-oxo-1,4-dihydro-3-cinnolinecarboxamides which are useful as antiviral agents, particularly against herpes viruses.

- 30 Even more specifically, the compounds are of formula (I)



or a pharmaceutically acceptable salt thereof wherein,

A is

- (a) Cl,
- 5 (b) Br,
- (c) CN,
- (d) NO₂, or
- (e) F;

R¹ is

- 10 (a) R⁵, or
- (b) SO₂R⁹

R², R³ and R⁴ may be the same or different and are selected from the group consisting of:

- (a) H,
- 15 (b) halo,
- (c) aryl,
- (d) S(O)_mR⁶,
- (e) (C=O)R⁶,
- (f) (C=O)OR⁹,
- 20 (g) cyano,
- (h) het, wherein said het is bound via a carbon atom,
- (i) OR¹⁰,
- (j) Ohet,
- (k) NR⁷R⁸
- 25 (l) SR¹⁰,
- (m) Shet,
- (n) NHCOR¹²,
- (o) NHSO₂R¹²,
- (p) C₁₋₇alkyl which may be partially unsaturated and optionally substituted
- 30 by one or more substituents of the group R¹¹, OR¹³, SR¹⁰, SR¹³, NR⁷R⁸,
halo, (C=O)C₁₋₇alkyl, or SO_mR⁹, and

- (q) R^3 together with R^2 or R^4 form a carbocyclic or het which may be optionally substituted by NR^7R^8 , or C_{1-7} alkyl which may be optionally substituted by OR^{14} ;

R^5 is

- 5 (a) $(CH_2CH_2O)_iR^{10}$,
 (b) C_{1-7} alkyl which may be partially unsaturated and is optionally substituted by one or more substituents selected from a group consisting of NR^7R^8 , R^{11} , SO_mR^9 , or OC_{2-4} alkyl which may be further substituted by het, OR^{10} , or NR^7R^8 , or
 10 (c) C_{3-8} cycloalkyl which may be partially unsaturated and optionally substituted by one or more substituents selected from a group consisting of R^{11} , NR^7R^8 , SO_mR^9 , or C_{1-7} alkyl optionally substituted by R^{11} , NR^7R^8 , or SO_mR^9 ;

R^6 is

- 15 (a) C_{1-7} alkyl,
 (b) NR^7R^8 ,
 (c) aryl, or
 (d) het, wherein said het is bound via a carbon atom;

R^7 and R^8 are independently

- 20 (a) H,
 (b) aryl,
 (c) C_{1-7} alkyl which may be partially unsaturated and is optionally substituted by one or more substituents selected from a group consisting of aryl, $NR^{10}R^{10}$, R^{11} , SO_mR^9 , $CONR^{10}R^{10}$, or halo, or;
 25 (d) C_{3-8} cycloalkyl which may be partially unsaturated and optionally substituted by one or more substituents selected from a group consisting of R^{11} , NR^7R^8 , SO_mR^9 , or C_{1-7} alkyl optionally substituted by R^{11} , NR^7R^8 , or SO_mR^9 , or
 30 (e) R^7 and R^8 together with the nitrogen to which they are attached form a het;

R^9 is

- (a) aryl,

- (b) het,
 - (c) C₃₋₈cycloalkyl,
 - (d) methyl, or
 - (e) C₂₋₇alkyl which may be partially unsaturated and is optionally substituted by one or more substituents selected from a group consisting of NR¹⁰R¹⁰, R¹¹, SH, CONR¹⁰R¹⁰, or halo;
- 5
- R¹⁰ is
- (a) H,
 - (b) methyl, or
 - (c) C₂₋₇alkyl optionally substituted by OH;
- 10
- R¹¹ is
- (a) OR¹⁰,
 - (b) Ohet,
 - (c) Oaryl,
 - (d) CO₂R¹⁰,
 - (e) het,
 - (f) aryl,
 - (g) CN, or
 - (h) C₃₋₈cycloalkyl which may be partially unsaturated and optionally substituted by one or more substituents selected from a group consisting of R¹¹, NR⁷R⁸, SO_mR⁹, or C₁₋₇alkyl optionally substituted by R¹¹, NR⁷R⁸, or SO_mR⁹;
- 15
- 20
- R¹² is
- (a) H,
 - (b) het,
 - (c) aryl,
 - (d) C₃₋₈cycloalkyl,
 - (e) methyl, or
 - (f) C₂₋₇alkyl optionally substituted by NR⁷R⁸ or R¹¹;
- 25
- 30 R¹³ is
- (a) (P=O)(OR¹⁴)₂,
 - (b) CO(CH₂)_nCON(CH₃)-(CH₂)_nSO₃M⁺,
 - (c) an amino acid,

- (d) $C(=O)aryl$, or
- (e) $C(=O)C_{1-7}alkyl$ optionally substituted by NR^7R^8 , aryl, het, CO_2H , or $O(CH_2)_nCO_2R^{14}$;

R^{14} is

- 5 (a) H, or
- (b) $C_{1-7}alkyl$;

each i is independently 2, 3, or 4;

each n is independently 1, 2, 3, 4 or 5;

- 10 each m is independently 0, 1, or 2;

M is sodium, potassium, or lithium;

aryl is a phenyl radical or an ortho-fused bicyclic carbocyclic radical wherein at least one ring is aromatic;

- 15 wherein any aryl is optionally substituted with one or more substituents selected from the group consisting of halo, OH, cyano, CO_2R^{14} , CF_3 , $C_{1-6}alkoxy$, and $C_{1-6}alkyl$ which maybe further substituted by one to three SR^{14} , $NR^{14}R^{14}$, OR^{14} , or CO_2R^{14} ;

het is a four- (4), five- (5), six- (6), or seven- (7) membered saturated or unsaturated heterocyclic ring having 1, 2, or 3 heteroatoms selected from the group consisting of oxygen, sulfur, and nitrogen, which is optionally fused to a benzene ring, or any

- 20 bicyclic heterocycle group;

wherein any het is optionally substituted with one or more substituents selected from the group consisting of halo, OH, cyano, phenyl, CO_2R^{14} , CF_3 , $C_{1-6}alkoxy$, oxo, oxime, and $C_{1-6}alkyl$ which maybe further substituted by one to three SR^{14} , $NR^{14}R^{14}$, OR^{14} , or CO_2R^{14} .

25

In particularly preferred embodiments, A is Cl and R^2 is either CH_2 -morpholine, alkynyl- CH_2OH , CH_2 -(tetrahydro-2H-pyran-4-yl) or $(CH_2)_3OH$.

- 30 Another embodiment of the present invention provides a pharmaceutical composition comprising a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In preferred embodiments, the composition preferably comprises a therapeutically effective amount of the compound or salt.

Still another embodiment of the present invention provides a method for treating a disease or condition in a mammal caused by a viral infection, particularly a herpes viral infection, comprising administering to the mammal a therapeutically effective
5 amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

A further embodiment of the present invention comprises the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof to prepare a medicament for treating or preventing diseases or disorders caused by a viral infection, and
10 particularly a herpes viral infection.

A final embodiment of the present invention comprises a method for inhibiting a viral DNA polymerase, comprising contacting (in vitro or in vivo) the polymerase with an effective inhibitory amount of a compound of formula (I) or a pharmaceutically
15 acceptable salt thereof.

An object of the present invention is to provide novel compounds having biological activity.

20 A further object of the present invention is to provide novel pharmaceutical compositions.

Still another object of the present invention is to provide a method for treating a disease or condition in a mammal caused by a viral infection, particularly a herpes
25 virus infection.

Another object of the present invention is to provide a method for inhibiting a viral DNA polymerase.

30 These, and other objects, will readily be apparent to those skilled in the art as reference is made to the detailed description of the preferred embodiment.

Detailed Description of the Preferred Embodiment

In describing the preferred embodiment, certain terminology will be utilized for the sake of clarity. Such terminology is intended to encompass the recited embodiment, as well as all technical equivalents which operate in a similar manner for a similar purpose to achieve a similar result.

1. Terminology Definitions

The following definitions are used, unless otherwise described: halo is fluoro, chloro, bromo, or iodo. Alkyl denotes both straight and branched groups; but reference to an individual radical such as "propyl" embraces only the straight chain radical, a branched chain isomer such as "isopropyl" being specifically referred to. When alkyl can be partially unsaturated, the alkyl chain may comprise one or more (e.g. 1, 2, 3, or 4) double or triple bonds in the chain.

Aryl denotes a phenyl radical or an ortho-fused bicyclic carbocyclic radical wherein at least one ring is aromatic. Het is a four- (4), five- (5), six- (6), or seven- (7) membered saturated or unsaturated ring containing 1, 2 or 3 heteroatoms selected from the group consisting of non-peroxide oxygen, sulfur, and nitrogen, which is optionally fused to a benzene ring, or any bicyclic heterocyclic group. Het includes "heteroaryl," which encompasses a radical attached via a ring carbon of a monocyclic aromatic ring containing five or six ring atoms consisting of carbon and 1, 2, 3, or 4 heteroatoms each selected from the group consisting of non-peroxide oxygen, sulfur, and N(X) wherein X is absent or is H, O, C₁₋₄alkyl, phenyl or benzyl.

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

starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase) and how to determine antiviral activity using the standard tests described herein, or using other similar tests which are well known in the art.

- 5 To the extent that any pharmaceutically active compound is disclosed or claimed, it is expressly intended to include all active metabolites produced in vivo.

The carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating a lower and upper number of carbon atoms in the moiety, i.e., the
10 prefix C_{i-j} indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus, for example, C₁₋₇alkyl refers to alkyl of one to seven carbon atoms, inclusive.

The compounds of the present invention are generally named according to the IUPAC
15 or CAS nomenclature system. Abbreviations which are well known to one of ordinary skill in the art may be used (e.g. "Ph" for phenyl, "Me" for methyl, "Et" for ethyl, "h" for hour or hours and "rt" for room temperature).

Specific and preferred values listed below for radicals, substituents, and ranges, are
20 for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents. The compounds of the invention include compounds of formula (I) or (II) having any combination of the values, specific values, more specific values, and preferred values described herein.

25 2. The Invention

The present invention provides compounds of formula (I):



or a pharmaceutically acceptable salt thereof wherein,

A is

- (a) Cl,
- (b) Br,
- (c) CN,
- (d) NO₂, or
- (e) F;

5

R¹ is

- (a) R⁵, or
- (b) SO₂R⁹

R², R³ and R⁴ may be the same or different and are selected from the group consisting

10 of:

- (a) H,
- (b) halo,
- (c) aryl,
- (d) S(O)_mR⁶,
- (e) (C=O)R⁶,
- (f) (C=O)OR⁹,
- (g) cyano,
- (h) het, wherein said het is bound via a carbon atom,
- (i) OR¹⁰,
- (j) Ohet,
- (k) NR⁷R⁸
- (l) SR¹⁰,
- (m) Shet,
- (n) NHCOR¹²,
- (o) NHSO₂R¹²,
- (p) C₁₋₇alkyl which may be partially unsaturated and optionally substituted by one or more substituents of the group R¹¹, OR¹³, SR¹⁰, SR¹³, NR⁷R⁸, halo, (C=O)C₁₋₇alkyl, or SO_mR⁹, and
- (q) R³ together with R² or R⁴ form a carbocyclic or het which may be optionally substituted by NR⁷R⁸, or C₁₋₇alkyl which may be optionally substituted by OR¹⁴;

15

20

25

30

R⁵ is

- (a) (CH₂CH₂O)_iR¹⁰,

- (b) C₁₋₇alkyl which may be partially unsaturated and is optionally substituted by one or more substituents selected from a group consisting of NR⁷R⁸, R¹¹, SO_mR⁹, or OC₂₋₄alkyl which may be further substituted by het, OR¹⁰, or NR⁷R⁸, or
- 5 (c) C₃₋₈cycloalkyl which may be partially unsaturated and optionally substituted by one or more substituents selected from a group consisting of R¹¹, NR⁷R⁸, SO_mR⁹, or C₁₋₇alkyl optionally substituted by R¹¹, NR⁷R⁸, or SO_mR⁹;

R⁶ is

- 10 (a) C₁₋₇alkyl,
 (b) NR⁷R⁸,
 (c) aryl, or
 (d) het, wherein said het is bound via a carbon atom;

R⁷ and R⁸ are independently

- 15 (a) H,
 (b) aryl,
 (c) C₁₋₇alkyl which may be partially unsaturated and is optionally substituted by one or more substituents selected from a group consisting of aryl, NR¹⁰R¹⁰, R¹¹, SO_mR⁹, CONR¹⁰R¹⁰, or halo, or;
 20 (d) C₃₋₈cycloalkyl which may be partially unsaturated and optionally substituted by one or more substituents selected from a group consisting of R¹¹, NR⁷R⁸, SO_mR⁹, or C₁₋₇alkyl optionally substituted by R¹¹, NR⁷R⁸, or SO_mR⁹, or
- 25 (e) R⁷ and R⁸ together with the nitrogen to which they are attached form a het;

R⁹ is

- (a) aryl,
 (b) het,
 30 (c) C₃₋₈cycloalkyl,
 (d) methyl, or

- (e) C₂₋₇alkyl which may be partially unsaturated and is optionally substituted by one or more substituents selected from a group consisting of NR¹⁰R¹⁰, R¹¹, SH, CONR¹⁰R¹⁰, or halo;

R¹⁰ is

- 5 (a) H,
(b) methyl, or
(c) C₂₋₇alkyl optionally substituted by OH;

R¹¹ is

- 10 (a) OR¹⁰,
(b) Ohet,
(c) Oaryl,
(d) CO₂R¹⁰,
(e) het,
(f) aryl,
15 (g) CN, or
(h) C₃₋₈cycloalkyl which may be partially unsaturated and optionally substituted by one or more substituents selected from a group consisting of R¹¹, NR⁷R⁸, SO_mR⁹, or C₁₋₇alkyl optionally substituted by R¹¹, NR⁷R⁸, or SO_mR⁹;

20

R¹² is

- (a) H,
(b) het,
(c) aryl,
25 (d) C₃₋₈cycloalkyl,
(e) methyl, or
(f) C₂₋₇alkyl optionally substituted by NR⁷R⁸ or R¹¹;

R¹³ is

- (a) (P=O)(OR¹⁴)₂,
30 (b) CO(CH₂)_nCON(CH₃)-(CH₂)_nSO₃⁻M⁺,
(c) an amino acid,
(d) C(=O)aryl, or

- (e) $C(=O)C_{1-7}\text{alkyl}$ optionally substituted by NR^7R^8 , aryl, het, CO_2H , or $O(CH_2)_nCO_2R^{14}$;

R^{14} is

- (a) H, or
5 (b) $C_{1-7}\text{alkyl}$;

each i is independently 2, 3, or 4;

each n is independently 1, 2, 3, 4 or 5;

each m is independently 0, 1, or 2;

- 10 M is sodium, potassium, or lithium;

aryl is a phenyl radical or an ortho-fused bicyclic carbocyclic radical wherein at least one ring is aromatic;

wherein any aryl is optionally substituted with one or more substituents selected from the group consisting of halo, OH, cyano, CO_2R^{14} , CF_3 , $C_{1-6}\text{alkoxy}$, and $C_{1-6}\text{alkyl}$

- 15 which maybe further substituted by one to three SR^{14} , $NR^{14}R^{14}$, OR^{14} , or CO_2R^{14} ;

het is a four- (4), five- (5), six- (6), or seven- (7) membered saturated or unsaturated heterocyclic ring having 1, 2, or 3 heteroatoms selected from the group consisting of oxygen, sulfur, and nitrogen, which is optionally fused to a benzene ring, or any bicyclic heterocycle group;

- 20 wherein any het is optionally substituted with one or more substituents selected from the group consisting of halo, OH, cyano, phenyl, CO_2R^{14} , CF_3 , $C_{1-6}\text{alkoxy}$, oxo, oxime, and $C_{1-6}\text{alkyl}$ which maybe further substituted by one to three SR^{14} , $NR^{14}R^{14}$, OR^{14} , or CO_2R^{14} .

- 25 Specifically, $C_{1-7}\text{alkyl}$ can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-butyl, pentyl, 3-pentyl, hexyl, or heptyl; $C_{3-7}\text{cycloalkyl}$ can be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl.

When $C_{1-7}\text{alkyl}$ is partially unsaturated, it can specifically be vinyl, allyl, 1-propenyl,

- 30 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1,3-butadienyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, ethynyl, 1-propynyl, 2-propynyl, 1-butylnyl, 2-butylnyl, 3-butylnyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 5-hexenyl-1-ynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, or 5-hexynyl.

Particularly preferred compounds are those where A is Cl and R² is either CH₂-morpholine, alkynyl-CH₂OH, CH₂-(tetrahydro-2H-pyran-4-yl), or (CH₂)₃OH.

5 Specifically preferred compounds include, but are not limited to the following:

N-(4-chlorobenzyl)-6-iodo-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

10 N-(4-chlorobenzyl)-6-(3-hydroxy-1-propynyl)-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-6-(hydroxymethyl)-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

15 N-(4-chlorobenzyl)-6-(4-hydroxy-1-butynyl)-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

20 N-(4-chlorobenzyl)-8-([(1R,2R)-1-hydroxy-2-methylcyclohexyl]ethynyl)-1-methyl-4-oxo-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-(cyclopropylethynyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

25 N-(4-chlorobenzyl)-8-[3-(dimethylamino)-1-propynyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

30 N-(4-chlorobenzyl)-1-methyl-4-oxo-8-{4-[(4R)-2-oxo-1,3-oxazolidin-4-yl]-1-butynyl}-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-(4-hydroxy-1-butynyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-[(1-hydroxycyclohexyl)ethynyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

5 N-(4-chlorobenzyl)-8-(3,3-dicyclopropyl-3-hydroxy-1-propynyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-[(3S)-3-hydroxy-1-butynyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

10

8-{3-[(aminocarbonyl)amino]-3-methyl-1-butynyl}-N-(4-chlorobenzyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

15 N-(4-chlorobenzyl)-1-methyl-8-[3-methyl-3-(4-thioxo-1,3,5-triazinan-1-yl)-1-butynyl]-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-[(3R)-3-hydroxy-1-butynyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

20

N-(4-chlorobenzyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-8-{4-[(4R)-2-oxo-1,3-oxazolidin-4-yl]-1-butynyl}-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-[3-(1,1-dioxido-4-thiomorpholinyl)-1-propynyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

25

N-(4-chlorobenzyl)-8-(5-hydroxy-1-pentynyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

30

N-(4-chlorobenzyl)-8-[[(1R,2S)-2-hydroxycyclopentyl]ethynyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-(3-hydroxy-3-methyl-1-butynyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-[3-(4,5-dichloro-1H-imidazol-1-yl)-1-propynyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

5 N-(4-chlorobenzyl)-8-(3-hydroxy-1-propynyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-1-methyl-4-oxo-8-(phenylethynyl)-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

10 N-(4-chlorobenzyl)-8-(3-hydroxy-3-phenyl-1-propynyl)-1-methyl-4-oxo-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

15 N-(4-chlorobenzyl)-8-(3-hydroxy-1-propynyl)-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-(4-hydroxy-1-butyryl)-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

20 N-(4-chlorobenzyl)-8-(3-hydroxy-1-propynyl)-1-methyl-4-oxo-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-(4-hydroxy-1-butyryl)-1-methyl-4-oxo-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

25 N-(4-chlorobenzyl)-8-[3-(dimethylamino)-1-propynyl]-1-methyl-4-oxo-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

30 N-(4-chlorobenzyl)-1-[3-(methylsulfonyl)propyl]-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-1-[3-(methylsulfonyl)propyl]-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

5 N-(4-chlorobenzyl)-1-[(2-hydroxyethoxy)methyl]-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-6-(4-morpholinylmethyl)-4-oxo-1-tetrahydro-3-furanyl-1,4-dihydro-3-cinnolinecarboxamide;

10

N-(4-chlorobenzyl)-1-(1,2-diethyl-4-pyrazolidinyl)-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

15

N-(4-chlorobenzyl)-6-(4-morpholinylmethyl)-1-(3-oxetanyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-1-{3-[(3-hydroxypropyl)sulfonyl]propyl}-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

20

N-(4-chlorobenzyl)-1-[2-(2-ethoxyethoxy)ethyl]-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-6-(4-morpholinylmethyl)-4-oxo-1-[(phenylsulfinyl)methyl]-1,4-dihydro-3-cinnolinecarboxamide;

25

N-(4-chlorobenzyl)-6-(4-morpholinylmethyl)-4-oxo-1-[(phenylsulfonyl)methyl]-1,4-dihydro-3-cinnolinecarboxamide;

30

N-(4-chlorobenzyl)-6-(4-morpholinylmethyl)-4-oxo-1-[(phenylsulfonyl)methyl]-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-6-(4-morpholinylmethyl)-4-oxo-1-tetrahydro-2H-pyran-3-yl-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-1-[(methylsulfanyl)methyl]-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

5 N-(4-chlorobenzyl)-1-[[[(4-chlorophenyl)sulfinyl]methyl]-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-6-(4-morpholinylmethyl)-4-oxo-1-tetrahydro-2H-pyran-4-yl-1,4-dihydro-3-cinnolinecarboxamide;

10

N-(4-chlorobenzyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-8-(4-thiomorpholinylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

15

N-(4-chlorobenzyl)-8-[(4-hydroxy-1-piperidiny)methyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

20 N-(4-chlorobenzyl)-8-[[[(3R)-3-hydroxypyrrolidinyl]methyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-[(3-hydroxy-1-piperidiny)methyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

25 [3-[[[(4-chlorobenzyl)amino]carbonyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-8-cinnolinyl]methyl 4-morpholinecarboxylate

N-(4-chlorobenzyl)-8-(hydroxymethyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

30

N-(4-chlorobenzyl)-8-[(3-cyanobenzyl)amino]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-1-methyl-6,8-bis(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

5 8-[(1-acetyl-4-piperidinyl)amino]-N-(4-chlorobenzyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-1-methyl-8-{[1-methyl-2-(phenylsulfonyl)ethyl]amino}-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

10 N-(4-chlorobenzyl)-8-{[3-(4-methoxyphenyl)-1-methylpropyl]amino}-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

8-amino-N-(4-chlorobenzyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

15 N-(4-chlorobenzyl)-1-methyl-6-(4-morpholinylmethyl)-8-[(3-nitrobenzyl)amino]-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

20 N-(4-chlorobenzyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-8-(tetrahydro-2H-pyran-4-ylamino)-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-6-(3-hydroxy-1-propyl)-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

25 N-(4-chlorobenzyl)-6-(4-hydroxy-1-butyl)-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

30 N-(4-chlorobenzyl)-8-{[(1R,2R)-1-hydroxy-2-methylcyclohexyl]ethyl}-1-methyl-4-oxo-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-(cyclopropylethyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-[3-(dimethylamino)-1-propyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

5 N-(4-chlorobenzyl)-1-methyl-4-oxo-8-{4-[(4R)-2-oxo-1,3-oxazolidin-4-yl]-1-butyl}-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-(4-hydroxy-1-butyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

10

N-(4-chlorobenzyl)-8-[(1-hydroxycyclohexyl)ethyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

15

N-(4-chlorobenzyl)-8-(3,3-dicyclopropyl-3-hydroxy-1-propyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-[(3S)-3-hydroxy-1-butyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

20

8-[3-[(aminocarbonyl)amino]-3-methyl-1-butyl]-N-(4-chlorobenzyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-1-methyl-8-[3-methyl-3-(4-thioxo-1,3,5-triazinan-1-yl)-1-butyl]-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

25

N-(4-chlorobenzyl)-8-[(3R)-3-hydroxy-1-butyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

30

N-(4-chlorobenzyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-8-{4-[(4R)-2-oxo-1,3-oxazolidin-4-yl]-1-butyl}-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-[3-(1,1-dioxido-4-thiomorpholinyl)-1-propyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-(5-hydroxy-1-pentyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

5 N-(4-chlorobenzyl)-8-([(1R,2S)-2-hydroxycyclopentyl]ethyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-(3-hydroxy-3-methyl-1-butyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

10

N-(4-chlorobenzyl)-8-[3-(4,5-dichloro-1H-imidazol-1-yl)-1-propyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

15

N-(4-chlorobenzyl)-8-[3-(1H-imidazol-1-yl)-1-propyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-[3-(1H-imidazol-1-yl)-1-propynyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

20

N-(4-chlorobenzyl)-8-(3-hydroxy-1-propyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-1-methyl-4-oxo-8-(phenylethyl)-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

25

N-(4-chlorobenzyl)-8-(3-hydroxy-3-phenyl-1-propyl)-1-methyl-4-oxo-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

30

N-(4-chlorobenzyl)-8-(3-hydroxy-1-propyl)-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-(4-hydroxy-1-butyl)-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-(3-hydroxy-1-propyl)-1-methyl-4-oxo-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

5 N-(4-chlorobenzyl)-8-(4-hydroxy-1-butyl)-1-methyl-4-oxo-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-[3-(dimethylamino)-1-propyl]-1-methyl-4-oxo-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

10

N-(4-chlorobenzyl)-1-methyl-8-{{methyl(tetrahydro-2-furanylmethyl)amino}methyl}-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide.

15

The following Charts A-O describe the preparation of the compounds of the present invention. All of the starting materials and final compounds are prepared by procedures described in these charts or by procedures analogous thereto, which would be well known to one of ordinary skill in organic chemistry. All of the variables used

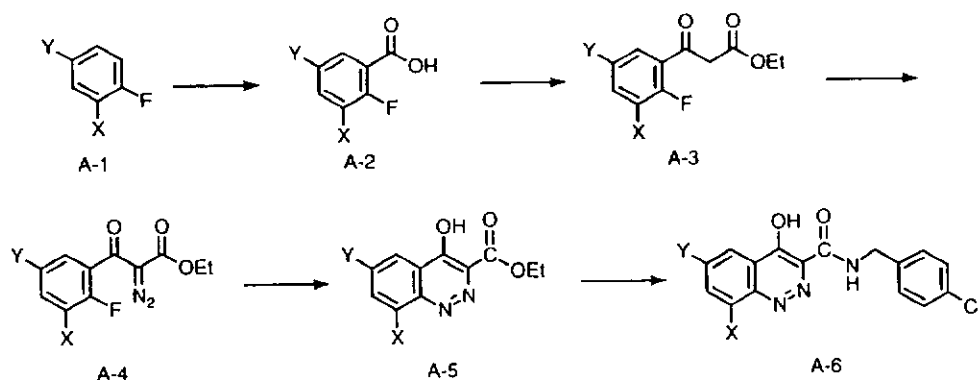
20 in the charts are as defined below or as in the claims.

The general ring system can be prepared in several ways. An example of the first route is shown in Chart A. Carboxylation of 4-fluoro-1-iodobenzene (X=H, Y=I) by treatment with a base such as lithium diisopropylamide followed by quenching with

25 CO₂ provides the alpha-fluorocarboxylic acid A-2. This can be elaborated to the beta-ketoester by activation of the acid with a condensing agent such as 1,1'-carbonyldiimidazole, and displacement with the TMS ester of ethyl malonate. Diazotization, reduction and cyclization provides the 4-hydroxycinnoline-3-carboxylic ester (*Chem Pharm Bull*, 1988, 38, 1321). Treatment with an amine such as 4-

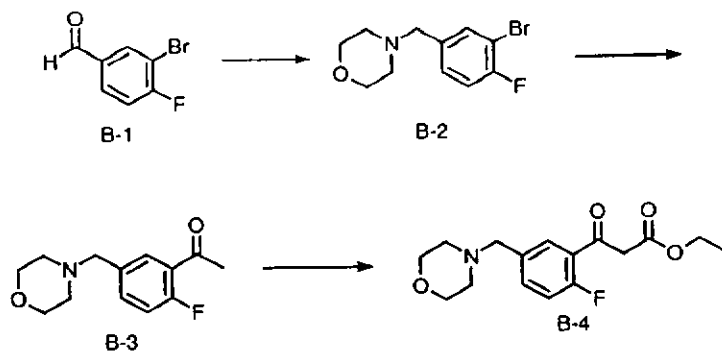
30 chlorobenzylamine at elevated temperature provides the 4-hydroxycinnoline-3-carboxamide.

Chart A.



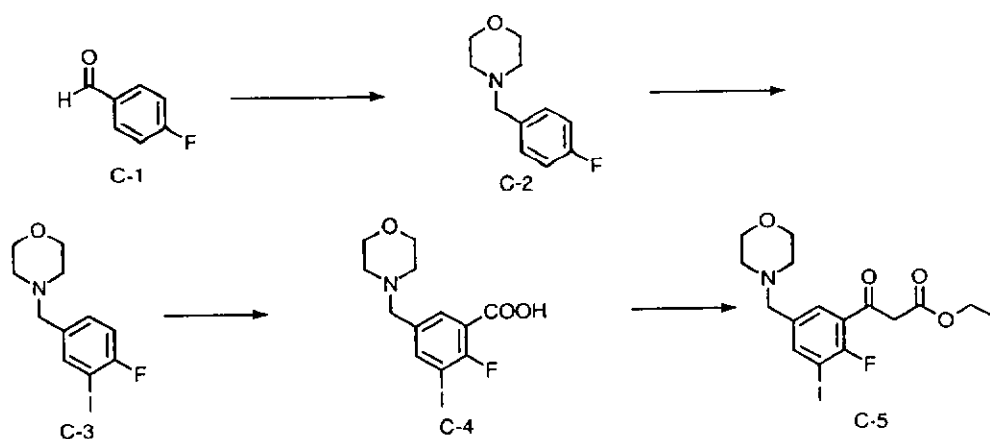
The requisite beta-ketoesters A-3 can be prepared by several different methods, one of which is shown in Chart B. Reductive amination of 3-bromo-4-fluorobenzaldehyde with an amine such as morpholine provides the substituted benzene B-2. Metallation with n-BuLi and trapping N-methoxy-N-methylacetamide will give the ketone B-3 which can be elaborated to the beta-ketoester by treatment with sodium hydride and diethyl carbonate.

10 CHART B



Alternatively, the fluorobenzene C-2 can be directly lithiated with lithium diisopropylamide. Trapping of the resulting anion with an electrophile such as iodine followed by a subsequent deprotonation and trapping with CO₂ will provide the disubstituted acid C-4. This again can be elaborated to the beta-ketoester by activation of the acid with a condensing agent such as 1,1'-carbonyldiimidazole and displacement with the TMS ester of ethyl malonate.

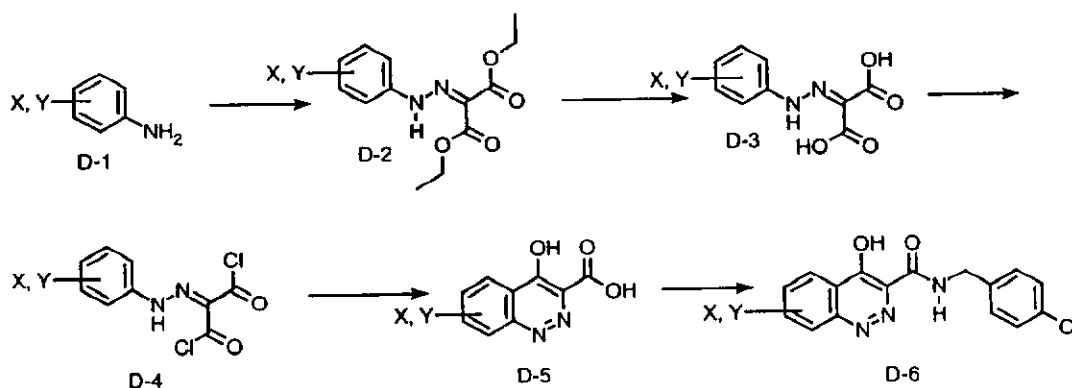
CHART C



The cinnoline ring system can be prepared as shown in Chart D. Diazotization of an aniline followed by treatment with diethyl malonate provides the cyclization precursor. Cyclization is then effected by hydrolysis to the diacid, treatment with thionyl chloride to form the diacid chloride and cyclization promoted by TiCl_4 (*J. Chem. Soc.* **1961**, 2828-2843). The resulting cinnoline 3-carboxylic acid can then be condensed with an amine such as 4-chlorobenzylamine by activation of the acid with a condensing agent such as 1,1'-carbonyldiimidazole and subsequent coupling of the activated acid with the desired amine.

10

CHART D.



The requisite anilines for the above synthesis can be obtained from commercial sources, prepared according to literature procedures or further functionalized, an example of which is shown in Chart E. Iodination of the aniline can be accomplished by treatment with an appropriate iodinating agent, such as ICl .

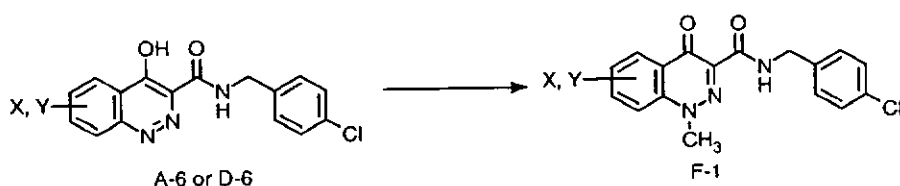
15

CHART E



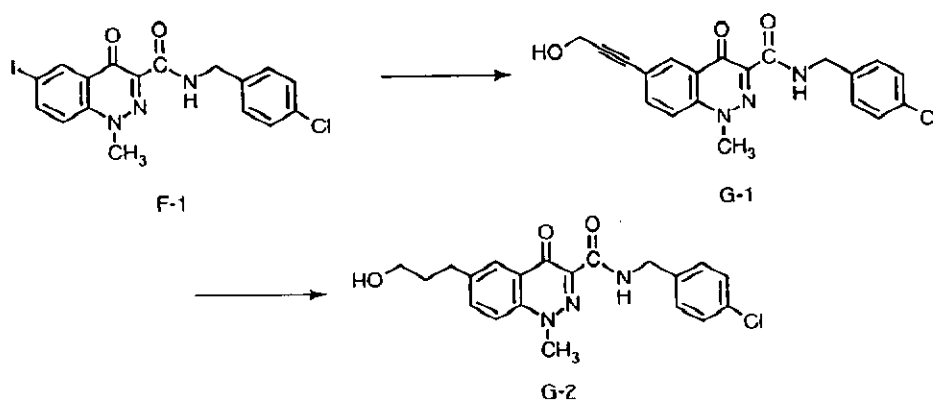
The cinnolines (A-6 or D-6 or O-6) can be alkylated by treatment with an alkylating agent such as methyl iodide and potassium carbonate in a DMF solution or by treatment with a base such as sodium hydride or lithium bis(trimethylsilyl)amide followed by treatment with an alkylating agent. Alternatively, the compounds may be alkylated on nitrogen under Mitsunobu conditions using reagents such as triphenylphosphine, diethyl azodicarboxylate and an appropriate alcohol such as methanol (Chart F).

CHART F.



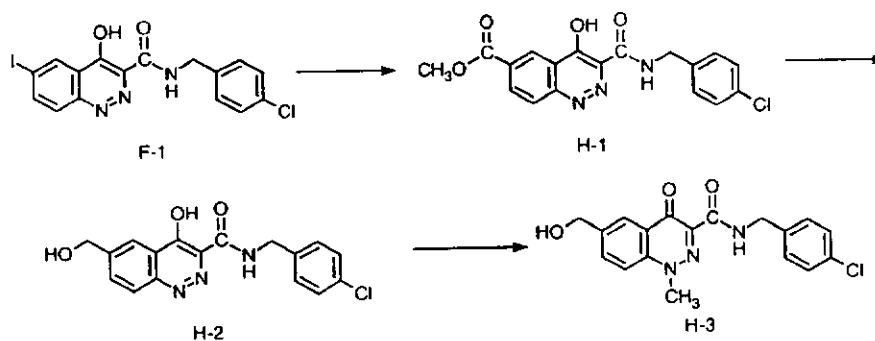
The substituted cinnolines can be further elaborated. One such elaboration is a palladium-catalyzed coupling of compounds such as F-1 where Y = I with acetylenes such as propargyl alcohol shown in Chart G. Reduction of the alkyne by hydrogenation in the presence of an appropriate catalyst such as palladium or platinum gives the corresponding alkane G-2.

CHART G.



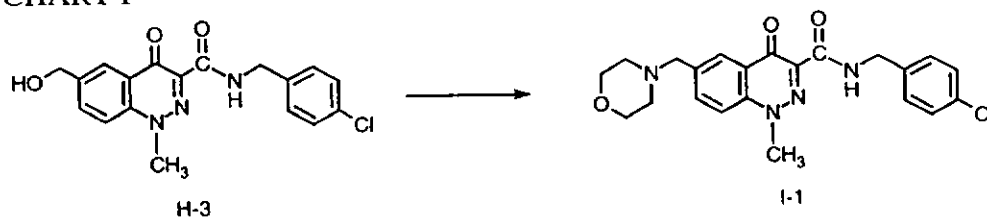
A second example of elaboration of the cinnoline substitution is the preparation of the hydroxymethyl substituted cinnoline shown in Chart H. Palladium catalyzed carbomethylation of the cinnoline ring system (F-1 where X = I) provides the methyl ester H-1. Reduction of the ester provides the 6-hydroxymethyl substituted cinnoline. This can be alkylated on nitrogen by treatment with an alkylating agent such as methyl iodide and potassium carbonate in a DMF solution.

CHART H.



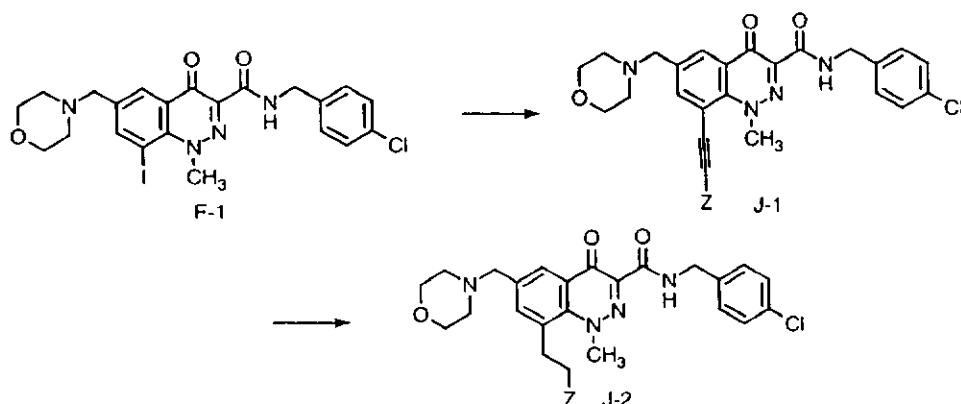
Alcohols such as the one depicted in Chart H can be further elaborated as shown in Chart I by activation with reagents such as methanesulfonyl chloride and displacement with nucleophiles such as thiols or amines (e.g. morpholine).

15 CHART I



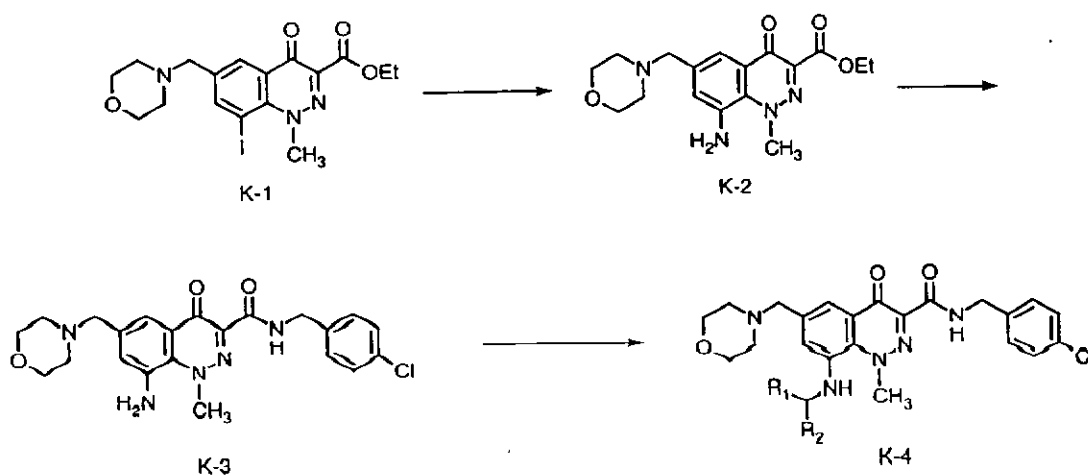
The compounds prepared as in Chart F can be further elaborated. One example of such an elaboration is shown in Chart J. Compound F-1 (where Y = morpholinylmethyl and X = I) can undergo palladium-catalyzed coupling with acetylenes to produce compounds such as J-1. Hydrogenation with an appropriate catalyst such as palladium on carbon would provide compounds such as J-2.

CHART J



- 5 Another example of a further manipulation of the cinnolines is shown in Chart K. Treatment of the ester K-1 with lithium bis(trimethylsilyl)amide and copper iodide followed by treatment with methanol will give the corresponding aminocinnoline K-2 (*JCS Chem Comm*, 1974, 256). Amide formation by treatment with an amine such as 4-chlorobenzylamine followed by reductive amination with an aldehyde or ketone will
- 10 give the amino-substituted compounds K-3.

CHART K



- 15 The requisite ester K-1 can be prepared by alkylation of the ester A-5 with an appropriate alkylating agent such as methyl iodide with an appropriate base such as K₂CO₃ or by treatment with a base such as sodium hydride followed by treatment with an alkylating agent such as methyl iodide as shown in Chart L.

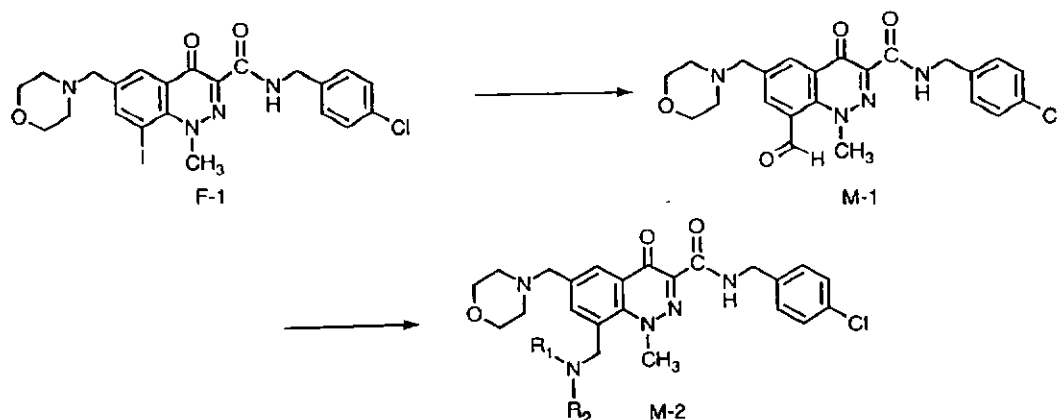
CHART L



- 5 Further functionalization of the cinnoline nucleus can also be accomplished as shown in Chart M. Palladium-catalyzed carbonylation of the cinnoline F-1 (where X = I) in the presence of a silane such as trioctylsilane or tributyltin hydride will give the aldehyde M-1. Reductive aminations with primary or secondary amines in the presence of sodium triacetoxyborohydride will give the aminomethyl derivatives M-2.

10

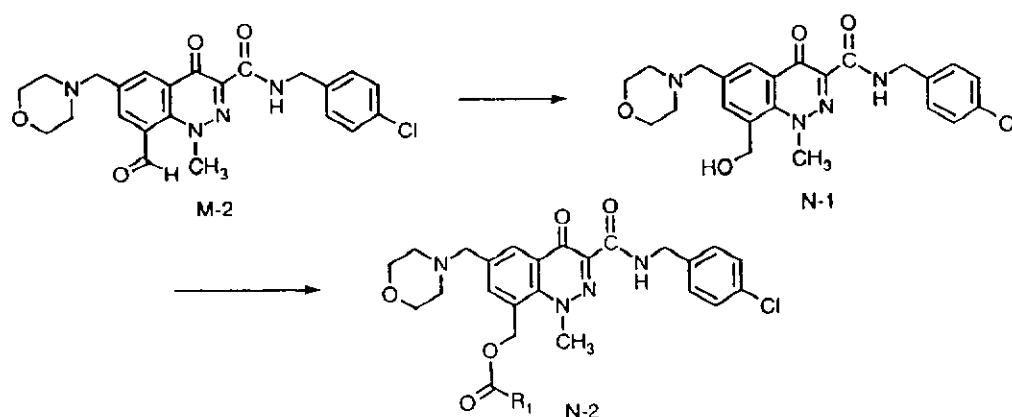
CHART M



- 15 An additional example of further functionalization of the substituted cinnolines is shown in Chart N. Reduction of the aldehyde M-1 with a reagent such as sodium borohydride followed by acylation of the resulting alcohol will provide esters and carbamates N-2.

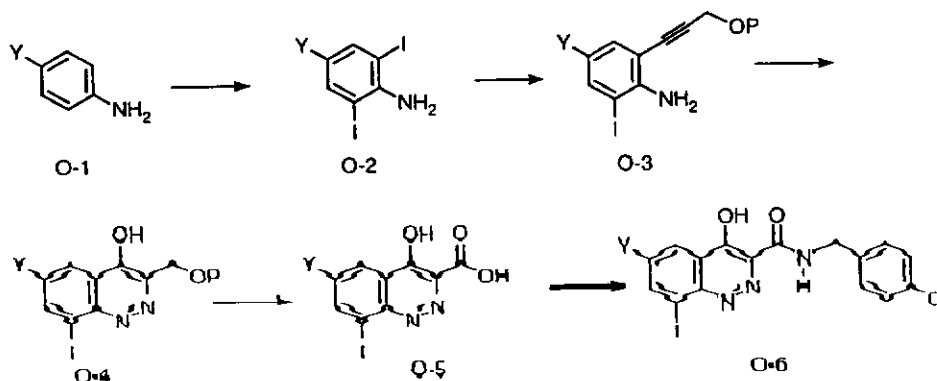
CHART N

20



Another alternative route to the cinnoline ring system is outlined in Chart O. The key step in this sequence involves the diazotization and cyclization of an *ortho*-alkynyl aniline O-3 to generate the 4-hydroxy-3-substituted cinnoline O-4 (*Leibigs Ann.* 1995, 775-779). The *ortho*-alkynyl aniline O-3 can be obtained from a 4-substituted aniline via bis-iodination and cross-coupling with an alkyne. Deprotection of O-4 followed by oxidation utilizing an oxidizing agent such as pyridinium dichromate or a two step procedure employing reagents such as IBX followed by NaClO₂ would provide the acid O-5. The resulting cinnoline 3-carboxylic acid can then be condensed with an amine such as 4-chlorobenzylamine by activation of the acid with a condensing agent such as 1,1'-carbonyldiimidazole and subsequent coupling of the activated acid with the desired amine.

CHART O



15

The inventive compounds may be used in their native form or as salts. In cases where compounds are sufficiently basic or acidic to form stable nontoxic acid or base salts, administration of the compounds as salts may be appropriate. Examples of

pharmaceutically acceptable salts are organic acid addition salts formed with acids that form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, α -ketoglutarate, and α -glycerophosphate. Suitable inorganic salts may also be formed, including
5 hydrochloride, sulfate, nitrate, bicarbonate, and carbonate salts.

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

Compounds of the present invention can conveniently be administered in a pharmaceutical composition containing the compound in combination with a suitable
15 excipient, the composition being useful in combating viral infections. Pharmaceutical compositions containing a compound appropriate for antiviral use are prepared by methods and contain excipients which are well known in the art. A generally recognized compendium of such methods and ingredients is Remington's Pharmaceutical Sciences by E.W. Martin (Mark Publ. Co., 15th Ed., 1975). To the extent
20 necessary for completion, this publication is expressly incorporated by reference. The compounds and compositions of the present invention can be administered parenterally (for example, by intravenous, intraperitoneal or intramuscular injection), topically, intranasally, intravaginally, orally, or rectally, depending on whether the preparation is used to treat internal or external viral infections.

25 For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the
30 compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices such as those which rely on osmotic delivery sold by Alza Corporation under the OROS trademark.

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

Pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid

dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the
5 required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged
10 absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

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

For topical administration, the present compounds may be applied in pure form, i.e., when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically
25 acceptable carrier, which may be a solid or a liquid.

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

or sprayed onto the affected area using pump-type or aerosol sprayers. Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application
5 directly to the skin of the user.

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

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

The compound is conveniently administered in unit dosage form; for example, containing 5 to 1000 mg, conveniently 10 to 750 mg, most conveniently, 50 to 500 mg of active ingredient per unit dosage form. The desired dose may conveniently be
20 presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator or by application of a plurality of drops into the eye.

25

For internal infections, the compositions can be administered orally or parenterally at dose levels, calculated as the free base, of about 0.1 to 300 mg/kg, preferably 1.0 to 30 mg/kg of mammal body weight, and can be used in man in a unit dosage form, administered one to four times daily in the amount of 1 to 1000 mg per unit dose.

30

For parenteral administration or for administration as drops, as for eye infections, the compounds are presented in aqueous solution in a concentration of from about 0.1 to

about 10%, more preferably about 0.1 to about 7%. The solution may contain other ingredients, such as emulsifiers, antioxidants or buffers.

Generally, the concentration of the compound(s) of formula I in a liquid composition, such as a lotion, will be from about 0.1-25 wt-%, preferably from about 0.5-10 wt-%. The concentration in a semi-solid or solid composition such as a gel or a powder will be about 0.1-5 wt-%, preferably about 0.5-2.5 wt-%.

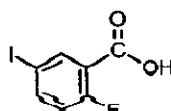
The exact regimen for administration of the compounds and compositions disclosed herein will necessarily be dependent upon the needs of the individual subject being treated, the type of treatment and, of course, the judgment of the attending practitioner. The compounds of the present invention can be administered to an animal in need of treatment. In most instances, this will be a human being, but the treatment of livestock (e.g.: cows, pigs, goats, sheep, deer, etc.) and companion animals (e.g. dogs, cats, fish, horses and birds) is also specifically contemplated as falling within the scope of the instant invention.

The invention will be further described by the following non-limiting examples.

20

Preparation 1

2-fluoro-5-iodobenzoic acid



25

To a -78°C solution of $i\text{Pr}_2\text{NH}$ (16.80 mL) in 200 mL freshly distilled THF is added n -butyllithium (68 mL) dropwise, maintaining the temperature of the reaction below -65°C . The reaction is stirred for 10 minutes, then 1-fluoro-4-iodobenzene (11.50 mL) as a solution in 10 mL THF is added over 20 minutes. The reaction is stirred at -78°C for 90 minutes, then cannulated rapidly into diethyl ether (180 mL) and dry ice (approximately 75 g). The reaction is stirred at room temperature overnight. To the ether solution is added 1N NaOH (100 mL) and water (200 mL) and the solution

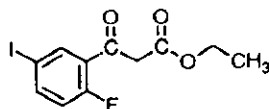
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placed in a separatory funnel. The aqueous layer is removed. The organic layer is washed with H₂O (2X 100 mL). All the aqueous portions are combined, chilled in ice/H₂O, and acidified to pH 2 with 6N HCl. This solution is then extracted with diethyl ether (2X 200 mL). The ether portions are combined, dried over Na₂SO₄,
 5 filtered, and concentrated to give a pale yellow solid. The solid is dissolved in a minimal amount of EtOAc on the steam bath, and hexanes are added to affect recrystallization. After standing in the freezer overnight, the product is obtained as a crystalline white solid (15.44 g, 58%). Physical characteristics are as follows: m.p. 157-159 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.34, 7.88, 6.97; IR (drift) 3098, 3079, 3051, 3017, 3007, 2998, 2981, 2971, 2881, 2817, 1708, 1681, 1300, 1236, 824 cm⁻¹;
 10 Anal. Calcd for C₇H₄FIO₂: C, 31.61; H, 1.52; Found: C, 31.70; H, 1.59.

Preparation 2

Ethyl 3-(2-fluoro-5-iodophenyl)-3-oxopropanoate

15



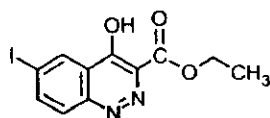
To a solution of 2-fluoro-5-iodobenzoic acid (Prep. 1, 4.03 g) in 11 mL freshly distilled THF is added 1,1-carbonyldiimidazole (CDI) (2.96 g) in small portions.
 20 Vigorous gas evolution is observed. The reaction is stirred overnight. In a separate flask, ethyl malonate potassium salt (2.84 g) is suspended in 10 mL CH₃CN. To this solution is added chlorotrimethylsilane (2.15 mL) and the reaction is stirred at room temperature overnight. The latter reaction is cooled to 0 °C and DBU (5.00 mL) is added dropwise. This reaction is stirred at 0 °C for 3 h. The solution of the CDI
 25 adduct is then cannulated over and the mixture is stirred at 0 °C for 2 h. Upon complete conversion to product as evidenced by TLC, the solution is quenched with water and 6N HCl (8 mL). The reaction is partitioned with diethyl ether. The organic layer is washed with 1N HCl and then brine, dried over Na₂SO₄, filtered, and concentrated to give a light orange oil. The oil is dissolved in EtOAc and adsorbed
 30 onto silica. Purification by chromatography (eluent 3% EtOAc/hexanes) affords the desired product as a colorless oil which crystallized upon standing (2.51 g, 49%). Physical characteristics are as follows: m.p. 54-56 °C; ¹H NMR (300 MHz, CDCl₃) δ

12.67, 8.18, 7.70, 6.89, 5.54, 4.28, 1.35; IR (drift) 2984, 1627, 1558, 1476, 1422, 1390, 1358, 1292, 1262, 1221, 1201, 1071, 1028, 823, 807 cm^{-1} ; MS (EI) m/z 336 (M^+), 336, 249, 122, 107, 94, 86, 84, 69, 68, 51; Anal. Calcd for $C_{11}H_{10}FIO_3$: C, 39.31; H, 3.00; Found: C, 39.35; H, 2.92.

5

Preparation 3

Ethyl 4-hydroxy-6-iodo-3-cinnolinecarboxylate



10

A solution of tosyl azide (0.69 g, prepared according to *Org. Prep. Proc. Intl.*, 1981, 13, 112.) in CH_3CN (2 mL) is added in one portion to a solution of ethyl 3-(2-fluoro-5-iodophenyl)-3-oxopropanoate (Prep. 2, 1.01 g) and NEt_3 (0.47 mL) in CH_3CN (10 mL) cooled below 10 $^\circ\text{C}$ in an ice/water bath. The reaction is stirred for 15 minutes at this temperature, then at room temperature for 2 h. The reaction is concentrated in vacuo keeping the temperature of the rotary evaporator bath below 50 $^\circ\text{C}$. The residue is cooled in an ice bath and 2N NaOH was added. The aqueous solution is extracted with CHCl_3 (2X 200 mL). The organic portions are combined, washed with water, then dried over Na_2SO_4 , filtered, and concentrated in vacuo to give a yellow oil. The oil is purified by chromatography (eluent CH_2Cl_2 (1L)) to give the intermediate diazo compound as a pale yellow oil (1.20 g, quant.). Physical characteristics are as follows: ^1H NMR (300 MHz, CDCl_3) δ 7.75, 6.87, 4.24, 1.24.

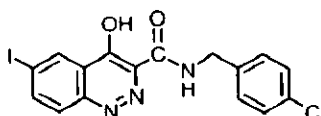
To a solution of the diazo compound (1.11 g) in 12 mL isopropyl ether is added tributylphosphine (0.86 mL) as a solution in 4 mL isopropyl ether. The reaction is stirred at room temperature for 30 minutes, then refluxed for 5 h. The reaction is cooled to room temperature and the resulting yellow solid is filtered and dried. The solid is dissolved in $\text{CH}_2\text{Cl}_2/\text{MeOH}$ and adsorbed onto silica. Purification by chromatography (eluent 1% MeOH/ CH_2Cl_2 (1L), 2% MeOH/ CH_2Cl_2 (1L), 4% MeOH/ CH_2Cl_2 (1L), 5% MeOH/ CH_2Cl_2 (1L)) affords the desired product as a yellow solid (0.22 g, 21%). Physical characteristics are as follows: m.p. 242-244 $^\circ\text{C}$; ^1H

NMR (300 MHz, DMSO- d_6) δ 14.00, 8.38, 8.13, 7.49, 4.30, 1.30; IR (drift) 3164, 3128, 3093, 1700, 1621, 1518, 1455, 1373, 1348, 1297, 1224, 1198, 1121, 824, 802 cm^{-1} ; MS (EI) m/z 344 (M^+), 272, 120, 92, 91, 89, 86, 84, 73, 63, 58; HRMS (FAB) calcd for $C_{11}H_9IN_2O_3+H_1$ 344.9738, found 344.9739.

5

Preparation 4

N-(4-chlorobenzyl)-4-hydroxy-6-iodo-3-cinnolinecarboxamide



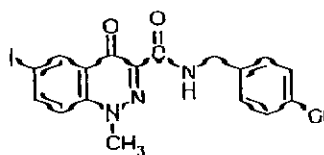
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A solution of ethyl 4-hydroxy-6-iodo-3-cinnolinecarboxylate (Prep. 3, 0.27 g) and 4-chlorobenzylamine (3.50 mL) is heated at 90 °C for 30 minutes. The reaction is cooled slightly and poured into 25 mL EtOAc. Hexanes are added to precipitate the product and the resulting solid is filtered and dried. The product is further purified by trituration with CH_2Cl_2 /hexanes (0.29 g, 85%). Physical characteristics are as follows: m.p. 307-308 °C; ^1H NMR (300 MHz, DMSO- d_6) δ 9.99, 8.47, 8.15, 7.57, 7.40, 4.55; IR (drift) 2972, 2958, 2901, 2846, 1645, 1601, 1557, 1488, 1458, 1356, 933, 922, 822, 806, 722 cm^{-1} ; MS (ESI) m/z 439.8 ($M+H$) $^+$, 437.8 ($M-H$) $^-$; Anal. Calcd for $C_{16}H_{11}ClIN_3O_2$: C, 43.71; H, 2.52; N, 9.56; Found: C, 43.94; H, 2.50; N, 9.43.

20

Example 1

N-(4-chlorobenzyl)-6-iodo-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide



25

Iodomethane (0.028 mL) is added to a suspension of N-(4-chlorobenzyl)-4-hydroxy-6-iodo-3-cinnolinecarboxamide (Prep. 4, 0.16 g) and K_2CO_3 (0.20 g.) in 6 mL anhydrous DMF. The reaction is heated at 90 °C for 1 h. The reaction is cooled to room temperature and poured into 75 mL H_2O . The resulting yellow solid is filtered

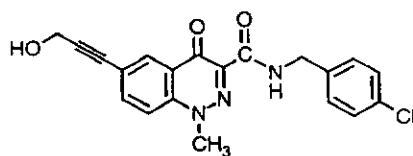
and dried. The solid is dissolved in CH_2Cl_2 and adsorbed onto silica. Purification by chromatography (CH_2Cl_2 (2L), 0.5% MeOH/ CH_2Cl_2 (2L), 0.75% MeOH/ CH_2Cl_2 (1L), 1% MeOH/ CH_2Cl_2 (1L), 1.5% MeOH/ CH_2Cl_2 (1L), 3.5% MeOH/ CH_2Cl_2 (1L), 10% MeOH/ CH_2Cl_2 (1L)) affords the product as an off-white solid (0.062 g, 39%).

- 5 Physical characteristics are as follows: m.p. 194-195 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 9.86, 8.52, 8.24, 7.76, 7.40, 7.38, 4.55, 4.22; IR (drift) 1671, 1601, 1589, 1549, 1544, 1490, 1463, 1412, 1320, 1278, 1180, 819, 808, 723, 666 cm^{-1} ; MS (ESI) m/z 453.7 ($\text{M}+\text{H}$) $^+$, 452.8 ($\text{M}-\text{H}$) $^-$; Anal. Calcd for $\text{C}_{17}\text{H}_{13}\text{ClIN}_3\text{O}_2$: C, 45.01; H, 2.89; N, 9.26; Found: C, 44.63; H, 2.98; N, 8.91.

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Example 2

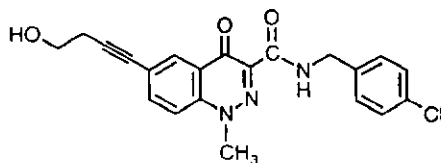
- N-(4-chlorobenzyl)-6-(3-hydroxy-1-propynyl)-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide
- 15



- A suspension of N-(4-chlorobenzyl)-6-iodo-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide (Ex. 1, 0.13 g), propargyl alcohol (0.035 mL), CuI (0.028 g), and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (0.013 g) in 11 mL diethylamine is stirred at room temperature for 18 h. The solid in the reaction is filtered, washed with water, and dried. The solid is dissolved in CH_2Cl_2 and adsorbed onto silica. Purification by chromatography (eluent CH_2Cl_2 (1L), 1% MeOH/ CH_2Cl_2 (1L), 2% MeOH/ CH_2Cl_2 (1L), 3% MeOH/ CH_2Cl_2 (1L), 5% MeOH/ CH_2Cl_2 (1L)) affords the desired product as a tan solid (0.094 g, 85%). Physical characteristics are as follows: m.p. 229-231 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 9.92, 8.19, 7.96, 7.40, 5.45, 4.55, 4.36, 4.24; IR (drift) 3365, 3273, 1656, 1598, 1551, 1479, 1410, 1351, 1284, 1034, 1028, 821, 812, 671, 646 cm^{-1} ; MS (ESI) m/z 382.1 ($\text{M}+\text{H}$) $^+$; HRMS (FAB) calcd for $\text{C}_{20}\text{H}_{16}\text{ClIN}_3\text{O}_3+\text{H}_1$ 382.0958, found
- 20
- 25
- 30 382.0963.

Example 3

N-(4-chlorobenzyl)-6-(4-hydroxy-1-butynyl)-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide



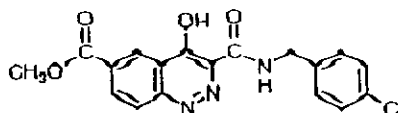
5

A solution of N-(4-chlorobenzyl)-6-iodo-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide [Example 1] (0.12 g), copper iodide (0.020 g), Pd(PPh₃)₂Cl₂ (0.0067 g) and 3-butyn-1-ol (0.030 mL) in 10 mL diethylamine is stirred at room temperature for 18 h. The reaction is partitioned between ethyl acetate and H₂O. The aqueous layer is extracted 3X with ethyl acetate. The organics are combined, dried over Na₂SO₄, filtered and concentrated. The residue is dissolved in CH₂Cl₂/MeOH and adsorbed onto silica. Purification by Biotage Flash 40S (eluent CH₂Cl₂ (1L), 1% MeOH/CH₂Cl₂ (1L), 2% MeOH/CH₂Cl₂ (1L), 3% MeOH/CH₂Cl₂ (1L)) affords the desired product which is recrystallized with CH₂Cl₂/hexanes (0.059 g, 56%). Physical characteristics are as follows: m.p. 227-229 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.90, 8.18, 7.93, 7.40, 4.97, 4.55, 4.24, 3.62, 2.62; IR (drift) 3238, 3176, 1671, 1614, 1594, 1551, 1493, 1470, 1411, 1321, 1281, 1045, 825, 808, 733 cm⁻¹; MS (ESI) *m/z* 396.0 (M+H)⁺; HRMS (FAB) calcd for C₂₁H₁₈ClN₃O₃+H₁ 396.1115, found 396.1114.

20

Preparation 5

Methyl 3-{[(4-chlorobenzyl)amino]carbonyl}-4-hydroxy-6-cinnolinecarboxylate



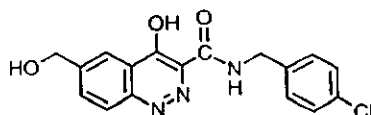
25

A flame-dried flask is charged with N-(4-chlorobenzyl)-4-hydroxy-6-iodo-3-cinnolinecarboxamide (Prep. 4, 0.23 g), NEt₃ (0.15 mL), Pd(PPh₃)₂Cl₂ (0.071 g), methanol (0.85 mL), and anhydrous DMF (5 mL). The reaction is placed under a CO

balloon atmosphere and heated at 70 °C for 5 h at which point TLC shows disappearance of starting material. The reaction is cooled to room temperature and poured into 40 mL 1N HCl. The resulting solid is filtered and dried. The crude solid is dissolved in CH₂Cl₂/MeOH and adsorbed onto silica. Purification by chromatography (eluent 1% MeOH/CH₂Cl₂ (1L), 1.5% MeOH/CH₂Cl₂ (1L), 2% MeOH/CH₂Cl₂ (3L), 3% MeOH/CH₂Cl₂ (1L)) affords the desired product as an off-white solid (0.12 g, 64%). Physical characteristics are as follows: m.p. 308-310 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 14.37, 9.80, 8.72, 8.34, 7.83, 7.41, 4.55, 3.92; IR (drift) 1725, 1661, 1625, 1600, 1581, 1535, 1486, 1296, 1276, 1245, 1237, 1129, 823, 806, 761 cm⁻¹; MS (EI) *m/z* 371 (M⁺), 142, 141, 140, 139, 125, 89, 88, 74, 73, 51; HRMS (FAB) calcd for C₁₈H₁₄ClN₃O₄+H₁ 372.0751, found 372.0757.

Preparation 6

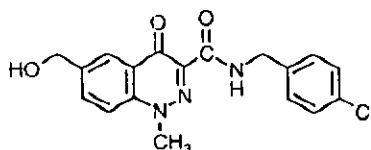
N-(4-chlorobenzyl)-4-hydroxy-6-(hydroxymethyl)-3-cinnolinecarboxamide



To a suspension of methyl 3-([(4-chlorobenzyl)amino]carbonyl)-4-hydroxy-6-cinnolinecarboxylate (Prep 5, 0.48 g) in 40 mL THF is added lithium aluminum hydride (2.60 μL) dropwise. The reaction turns a dark green color. After 1 h, the reaction is quenched carefully with water, 15% NaOH, and water again. The reaction is filtered to remove aluminum salts. The filtrate is concentrated and the resulting residue is dissolved in CH₂Cl₂/MeOH and adsorbed onto silica. Purification by chromatography (eluent CH₂Cl₂ (1L), 0.5% MeOH/CH₂Cl₂ (1L), 1% MeOH/CH₂Cl₂ (1L), 2% MeOH/CH₂Cl₂ (1L), 3% MeOH/CH₂Cl₂ (1L), 4% MeOH/CH₂Cl₂ (1L), 5% MeOH/CH₂Cl₂ (2L), 5.5% MeOH/CH₂Cl₂ (2L)) affords the desired product (0.23 g, 52%). Physical characteristics are as follows: m.p. 296-298 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.12, 8.14, 7.84, 7.74, 7.41, 5.50, 4.66, 4.56; IR (drift) 2922, 2873, 1647, 1602, 1555, 1490, 1358, 1183, 1022, 930, 919, 836, 808, 722, 684 cm⁻¹; MS (FAB) *m/z* 344 (MH⁺), 346, 344, 287, 229, 153, 133, 125, 121, 107, 103; HRMS (FAB) calcd for C₁₇H₁₄ClN₃O₃+H₁ 344.0802, found 344.0805.

Example 4

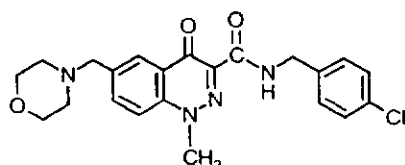
- 5 N-(4-chlorobenzyl)-6-(hydroxymethyl)-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide



- 10 A solution of N-(4-chlorobenzyl)-4-hydroxy-6-(hydroxymethyl)-3-cinnolinecarboxamide (Prep. 6, 0.12 g), K₂CO₃ (0.21 g) and iodomethane (26 μ L) in 5 mL anhydrous DMF is heated at 90 °C for 1.5 h. The reaction is cooled to room temperature and poured into 50 mL water. The resulting solid is filtered and dried, then dissolved in CH₂Cl₂/MeOH and adsorbed onto silica. Purification by
- 15 chromatography (eluent CH₂Cl₂ (1L), 0.5% MeOH/CH₂Cl₂ (2L), 1% MeOH/CH₂Cl₂ (1L), 1.5% MeOH/CH₂Cl₂ (1L), 2% MeOH/CH₂Cl₂ (1L), 2.5% MeOH/CH₂Cl₂ (3L), 3% MeOH/CH₂Cl₂ (1L), 4% MeOH/CH₂Cl₂ (1L), 6% MeOH/CH₂Cl₂ (1L), 8% MeOH/CH₂Cl₂ (1L)) affords the desired product as a white solid (0.044 g, 36%). Physical characteristics are as follows: m.p. 203-205 °C; ¹H NMR (300 MHz, DMSO-
- 20 *d*₆) δ 10.11, 8.23, 7.95, 7.92, 7.40, 5.54, 4.68, 4.56, 4.26; IR (drift) 3380, 1653, 1600, 1551, 1482, 1406, 1351, 1107, 1090, 1015, 813, 801, 727, 709, 659 cm⁻¹; MS (FAB) *m/z* 358 (MH⁺), 511, 361, 360, 359, 358, 217, 127, 125, 123, 39; HRMS (FAB) calcd for C₁₈H₁₆ClN₃O₃+H₁ 358.0958, found 358.0961.

Example 5

- 5 N-(4-chlorobenzyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide

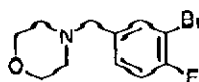


- To a solution of N-(4-chlorobenzyl)-6-(hydroxymethyl)-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide [Example 4] (0.062 g), DMAP (0.015 g) and collidine (0.030 mL) in 5 mL anhydrous DMF in a flame-dried flask is added methanesulfonyl chloride (0.015 mL) in one portion. The reaction is stirred at room temperature for 18 h. Morpholine (0.16 mL) is then added in one portion and the reaction is stirred at room temperature for 5 h. The reaction is poured into 50 mL water. The aqueous solution is extracted 3X with CH₂Cl₂, then 2X with EtOAc. The organics are combined, dried over Na₂SO₄, filtered and concentrated. The residue is dissolved in CH₂Cl₂ and adsorbed onto silica. Purification by Biotage Flash 40S (eluent CH₂Cl₂ (1L), 1% MeOH/CH₂Cl₂ (1L), 2% MeOH/CH₂Cl₂ (1L), 3.5% MeOH/CH₂Cl₂ (1L), 5% MeOH/CH₂Cl₂ (1L)) affords the desired product as a pale yellow solid (0.034 g, 46%). Physical characteristics are as follows: m.p. 190-192 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.17, 7.94, 7.40, 4.56, 4.26, 3.66, 3.58, 2.39; MS (ESI) *m/z* 427.0 (M+H)⁺; HRMS (FAB) calcd for C₂₂H₂₃ClN₄O₃+H₁ 427.1537, found 427.1544.

An alternate synthesis route for Example 5 is as follows:

Preparation 7

- 25 4-(3-Bromo-4-fluorobenzyl)morpholine



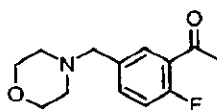
- A solution of 3-bromo-4-fluorobenzaldehyde (50.0 g) in 1,2-dichloroethane (500 mL) is cooled to 0 °C. Acetic acid (14.1 mL) and morpholine (23.6 mL) are added slowly, maintaining the temperature below 4 °C. Sodium triacetoxyborohydride (78.3 g) is added all at once, maintaining the temperature below 5 °C. The mixture is allowed to

warm to rt and stirred for 18 hrs. The reaction is quenched with 1 N NaOH (200 mL) and extracted with CH₂Cl₂ (500 mL). The organic layer is washed with 1 N NaOH (2 x 200 mL). The aqueous layers are combined and back-extracted with CH₂Cl₂ (100 mL). The organic layers are combined and extracted with 0.5 N HCl (5 x 250 mL).
 5 The acidic aqueous layers are combined, and 2 N NaOH is added until the solution is basic (pH = 12). The aqueous layer is then extracted with CH₂Cl₂ (6 x 100 mL). The organic layers are combined, dried (MgSO₄) and concentrated in vacuo to a clear, colorless oil. The crude product is distilled (126°C, 0.3 Torr) to afford 48.9 g (72%) of the title compound as a clear, colorless oil. Physical characteristics: Bp 126 °C
 10 (0.3 Torr); ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.62, 7.35-7.29, 3.56, 3.45, 2.34; ¹³C NMR (75 MHz, DMSO-*d*₆) δ 157.3, 136.1, 133.3, 129.8, 116.2, 107.7, 66.1, 60.9, 53.0; IR (liq.) 2855, 2807, 1495, 1455, 1348, 1257, 1244, 1118, 1009, 862 cm⁻¹; MS (ESI+) *m/z* 274 (M+H)⁺. Anal. Calcd for C₁₁H₁₃BrFNO: C, 48.20; H, 4.78; N, 5.11; Br, 29.15. Found: C, 48.04; H, 4.79; N, 5.11; Br, 28.18.

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Preparation 8

1-(2-Fluoro-5-(4-morpholinylmethyl)phenyl)ethanone



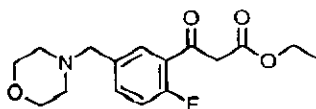
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4-(3-Bromo-4-fluorobenzyl)morpholine (Preparation 7, 35.5 g) is dissolved in THF (400 mL) and cooled to -75°C. A solution of *n*-butyllithium in hexane (2.5 M, 57.0 mL) is added via addition funnel, maintaining the temperature below -68°C. A solution of *N*-methoxy-*N*-methylacetamide (16.0 g) in THF (50 mL) is added via
 25 addition funnel, maintaining the temperature below -65°C. The reaction is stirred at -75°C for 1 h and allowed to warm to rt overnight. The reaction is quenched with 1 N HCl (150 mL) and poured into ethyl acetate (400 mL). The aqueous layer is separated, basified with sat. aq. NaHCO₃, and extracted with ethyl acetate (2 x 100 mL). The combined organic layers are washed with sat. NaHCO₃ (2 x 100 mL) and
 30 brine (50 mL). The combined aqueous washes are back-extracted with ethyl acetate (100 mL). The organic layers are combined, dried (Na₂SO₄), and concentrated in vacuo to a yellow oil. The crude product is distilled (135°C, 0.3 Torr) to afford 19.7 g

(64%) of the title compound as a clear, colorless oil. Physical characteristics: Bp 135 °C (0.3 Torr); ^1H NMR (300 MHz, DMSO- d_6) δ 7.72, 7.61-7.56, 7.31, 3.56, 3.48, 2.58, 2.34; IR (liq.) 1996, 1979, 1919, 1688, 1612, 1492, 1417, 1361, 1291, 1281, 1212, 1118, 865 cm^{-1} ; MS (ESI+) m/z 238 ($\text{M}+\text{H}$) $^+$. Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{FNO}_2$: C, 65.81; H, 6.80; N, 5.90. Found: C, 65.43; H, 6.75; N, 5.84.

Preparation 9

Ethyl 3-(2-fluoro-5-(4-morpholinylmethyl)phenyl)-3-oxopropanoate



10

Sodium hydride (60% dispersion in mineral oil, 6.6 g) is slowly added to a solution of 1-(2-fluoro-5-(4-morpholinylmethyl)phenyl)ethanone (Preparation 8, 19.6 g) in diethyl carbonate at 0 °C. The mixture is stirred at 0 °C for 1 h and allowed to warm to rt overnight. The reaction is quenched with acetic acid (10 mL), diluted with water (200 mL) and made basic with sat. aq. Na_2CO_3 . The mixture is extracted with diethyl ether (3 x 200 mL). The combined organic layers are washed with sat. NaHCO_3 (100 mL) and brine (50 mL). The combined aqueous layers are back-extracted with diethyl ether (50 mL). The organic layers are combined, dried (Na_2SO_4) and concentrated in vacuo to an orange oil. The crude product is purified by column chromatography (heptane/IPA, 8/1; 4/1; $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 98/2) to afford 20.2 g (79%) of the compound as a yellow oil. Physical characteristics: ^1H NMR (300 MHz, DMSO- d_6) δ 7.78, 7.65-7.60, 7.32, 4.10, 4.05, 3.57, 3.50, 2.34, 1.16; IR (liq.) 1996, 1979, 1744, 1689, 1626, 1611, 1493, 1331, 1260, 1215, 1147, 1117, 865 cm^{-1} ; MS (ESI+) m/z 310 ($\text{M}+\text{H}$) $^+$. Anal. Calcd for $\text{C}_{16}\text{H}_{20}\text{FNO}_4$: C, 62.12; H, 6.52; N, 4.53. Found: C, 61.96; H, 6.67; N, 4.44.

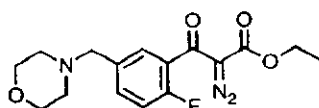
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Preparation 10

Ethyl 2-diazo-3-[2-fluoro-5-(4-morpholinylmethyl)phenyl]-3-oxopropanoate

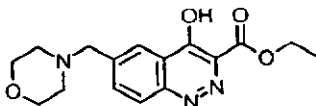
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To a solution of ethyl 3-(2-fluoro-5-(4-morpholinylmethyl)phenyl)-3-oxopropanoate (Preparation 9, 5.00g) and triethylamine (2.48 mL) in 50 mL CH₃CN cooled to 0 °C is added toluenesulfonyl azide (3.51g, prepared according to *Org. Prep. Proc. Intl.*, 1981, 13, 112) in 10 mL CH₃CN. The reaction is stirred at 0 °C for 15 min then at room temperature for 2 h. The reaction is concentrated (below 50 °C). 2N NaOH (25 mL) is added. The aqueous layer is extracted with CHCl₃ (3X). The combined organic layers are washed, dried and concentrated to yield 4.68 g (86%) of the desired product as a yellow oil. Physical characteristics are as follows: ¹H NMR (CDCl₃) δ 7.52, 7.44, 7.06, 4.24, 3.75, 3.55, 2.50, 1.24; MS (ESI+) for C₁₆H₁₈FN₃O₄ *m/z* 336.1 (M+H)⁺.

Preparation 11

Ethyl 4-hydroxy-6-(4-morpholinylmethyl)-3-cinnolinecarboxylate

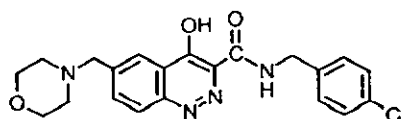


A solution of Bu₃P (3.90 mL) in dioxane (20 mL) is added to a stirred solution of ethyl 2-diazo-3-[2-fluoro-5-(4-morpholinylmethyl)phenyl]-3-oxopropanoate (Preparation 10, 3.16 g) in dry dioxane (56 mL). The mixture is stirred at room temperature for 30 min then gently refluxed for 1.5 h. The reaction is cooled and concentrated. The crude product is purified by column chromatography (CH₂Cl₂/MeOH, 99/1; CH₂Cl₂/MeOH, 98/2; CH₂Cl₂/MeOH, 95/5) to yield 0.200 g of the desired product as an off-white solid. Additional material can be obtained by heating the acyclic intermediate which is isolated in the chromatography at 130 °C in diglyme (32 mL) for 3.5 h. The resulting mixture is concentrated. The crude product is purified by column chromatography (CH₂Cl₂/MeOH, 99/1; CH₂Cl₂/MeOH, 98/2; CH₂Cl₂/MeOH, 95/5) to yield 0.531 g of the desired product. Retreatment the unreacted starting material from the first step to Bu₃P (dioxane, reflux, 5 h).

chromatography, and cyclization of the uncyclized product as above (diglyme, 3.5 h) provides an additional 1.06 g of the desired product to give an overall yield of 1.79 g (40%). Physical characteristics are as follows: m.p. 195-197 °C (dec); ¹H NMR (DMSO-d₆) δ 14.0, 8.01, 7.83, 7.67, 4.30, 3.60, 2.38, 1.30; MS (ESI-) for C₁₆H₁₉N₃O₄ *m/z* 316.1 (M-H)⁻.

Preparation 12

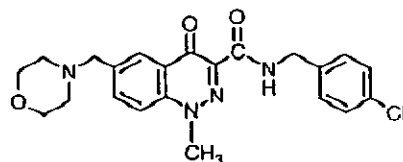
10 N-(4-chlorobenzyl)-4-hydroxy-6-(4-morpholinylmethyl)-3-cinnolinecarboxamide



A solution of ethyl 4-hydroxy-6-(4-morpholinylmethyl)-3-cinnolinecarboxylate (Preparation 11, 0.382 g) and 4-chlorobenzylamine (1.46 mL) is heated to 80 °C for 30 min over which time a solid forms. The reaction is diluted with Et₂O and the resulting solid is collected and dried to yield 0.443 g (89%) of the desired compound as an off-white solid. Physical characteristics are as follows: m.p. 277-280 °C (dec); ¹H NMR (DMSO-d₆) δ 10.12, 8.09, 7.86, 7.74, 7.40, 4.56, 3.63, 3.58, 2.38; MS (ESI+) for C₂₁H₂₁ClN₄O₃ *m/z* 413.0 (M+H)⁺; MS (ESI-), 410.9 (M-H)⁻.

Example 5

25 N-(4-chlorobenzyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide



To a suspension of N-(4-chlorobenzyl)-4-hydroxy-6-(4-morpholinylmethyl)-3-cinnolinecarboxamide [Preparation 12] (200 mg) in dry DMSO (15 mL) is added lithium bis(trimethylsilyl)amide (0.51 mL of a 1 M solution in hexanes). The mixture is stirred for 15 min over which time everything dissolves. Methyl iodide (0.032 mL)

is then added and the reaction is stirred for an additional 2 h. The mixture is partitioned between EtOAc and water. The aqueous layer is extracted with EtOAc (3X). The combined organic layers are washed with brine, dried and condensed. The crude product is chromatographed on silica (gradient CH_2Cl_2 , 1% MeOH/ CH_2Cl_2 , 2% MeOH/ CH_2Cl_2 , 3% MeOH/ CH_2Cl_2). Fractions homogeneous by TLC are combined and concentrated. The residue from the column is dissolved in CH_2Cl_2 . Hexanes are added to precipitate the product. The resulting solid is collected and dried to yield 0.079 g (39%) of the title compound as a white solid. Physical characteristics are the same as reported above.

10

Testing of Inventive Compounds

The antiviral activity of a compound of the invention can be determined using pharmacological models which are well known to the art, or using Test A described below.

15

The compounds of formula (I) and pharmaceutically acceptable salts thereof are useful as antiviral agents. Thus, they are useful to combat viral infections in animals, including man. The compounds are generally active against herpes viruses, and are particularly useful against the varicella zoster virus (VZV), the Epstein-Barr virus, the herpes simplex virus, the human herpes virus type 8 (HHV-8) and the cytomegalovirus (CMV).

20

While many of the compounds of the present invention have shown activity against the CMV polymerase, these compounds may be active against the cytomegalovirus by this or other mechanisms of action. Thus, the description below of these compounds' activity against the CMV polymerase is not meant to limit the present invention to a specific mechanism of action.

25

30

Test A

The HCMV polymerase assay is performed using a scintillation proximity assay (SPA) as described in several references, such as N.D. Cook, et al., Pharmaceutical

Manufacturing International, pages 49-53 (1992); K. Takeuchi, Laboratory Practice, September issue (1992); US Patent No. 4,568,649 (1986); which are incorporated by reference herein. Reactions are performed in 96-well plates. The assay is conducted in 100 μ l volume with 5.4 mM HEPES (pH 7.5), 11.7 mM KCl, 4.5 mM $MgCl_2$, 0.36 mg/ml BSA, and 90 nM 3H -dTTP. Assays are run with and without CHAPS, (3-[(3-cholamidopropyl)-dimethylammonio]-1-propane-sulfonate) at a final concentration of 2 mM. HCMV polymerase is diluted in enzyme dilution buffer containing 50% glycerol, 250 mM NaCl, 10 mM HEPES (pH 7.5), 100 μ g/ml BSA, and 0.01% sodium azide. The HCMV polymerase, which is expressed in recombinant baculovirus-infected SF-9 cells and purified according to literature procedures, is added at 10% (or 10 μ l) of the final reaction volume, i.e., 100 μ l. Compounds are diluted in 50% DMSO and 10 μ l are added to each well. Control wells contain an equivalent concentration of DMSO. Unless noted otherwise, reactions are initiated via the addition of 6 nM biotinylated poly(dA)-oligo(dT) template/primer to reaction mixtures containing the enzyme, substrate, and compounds of interest. Plates are incubated in a 25°C or 37°C H_2O bath and terminated via the addition of 40 μ l/reaction of 0.5 M EDTA (pH 8) per well. Reactions are terminated within the time-frame during which substrate incorporation is linear and varied depending upon the enzyme and conditions used, i.e., 30 min. for HCMV polymerase. Ten μ l of streptavidin-SPA beads (20 mg/ml in PBS/10% glycerol) are added following termination of the reaction. Plates are incubated 10 min. at 37 °C, then equilibrated to room temperature, and counted on a Packard Topcount. Linear regressions are performed and IC_{50} 's are calculated using computer software.

A modified version of the above HCMV polymerase assay is performed as described above, but with the following changes: Compounds are diluted in 100% DMSO until final dilution into assay buffer. In the previous assay, compounds are diluted in 50% DMSO. 4.5 mM dithiothreitol (DTT) is added to the polymerase buffer. Also, a different lot of CMV polymerase is used, which appears to be more active resulting in a more rapid polymerase reaction. Results of the testing of representative compounds of formula I in this assay are shown in Table 1. All results are listed as Polymerase IC_{50} (μ M) values. In Table 1, the term "nd" refers to activity data not determined.

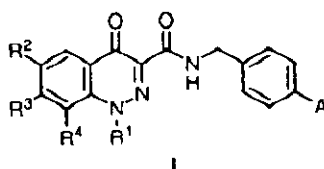
Example	HCMV	HSV	VZV
1	5.5	nd	nd
2	2.7	1.7	1.1
3	9.8	nd	nd
4	16.7	nd	nd
5	1.2	nd	nd

Having described the invention in detail and by reference to the preferred embodiments thereof, it will be apparent that modifications and variations are possible
5 without departing from the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A compound of formula I:

5



or a pharmaceutically acceptable salt thereof wherein,

A is

10

- (a) Cl,
- (b) Br,
- (c) CN,
- (d) NO₂, or
- (e) F;

15 R¹ is

- (a) R⁵, or
- (b) SO₂R⁹

R², R³ and R⁴ may be the same or different and are selected from the group consisting of:

20

- (a) H,
- (b) halo,
- (c) aryl,
- (d) S(O)_mR⁶,
- (e) (C=O)R⁶,
- (f) (C=O)OR⁹,
- (g) cyano,
- (h) het, wherein said het is bound via a carbon atom,
- (i) OR¹⁰,
- (j) Ohet,
- (k) NR⁷R⁸
- (l) SR¹⁰,
- (m) Shet,
- (n) NHCOR¹²,

30

- (o) $\text{NHSO}_2\text{R}^{12}$,
- (p) $\text{C}_{1-7}\text{alkyl}$ which may be partially unsaturated and optionally substituted by one or more substituents of the group R^{11} , OR^{13} , SR^{10} , SR^{13} , NR^7R^8 , halo, $(\text{C}=\text{O})\text{C}_{1-7}\text{alkyl}$, or SO_mR^9 , and
- 5 (q) R^3 together with R^2 or R^4 form a carbocyclic or het which may be optionally substituted by NR^7R^8 , or $\text{C}_{1-7}\text{alkyl}$ which may be optionally substituted by OR^{14} ;

R^5 is

- (a) $(\text{CH}_2\text{CH}_2\text{O})_i\text{R}^{10}$,
- 10 (b) $\text{C}_{1-7}\text{alkyl}$ which may be partially unsaturated and is optionally substituted by one or more substituents selected from a group consisting of NR^7R^8 , R^{11} , SO_mR^9 , or $\text{OC}_{2-4}\text{alkyl}$ which may be further substituted by het, OR^{10} , or NR^7R^8 , or
- (c) $\text{C}_{3-8}\text{cycloalkyl}$ which may be partially unsaturated and optionally
- 15 substituted by one or more substituents selected from a group consisting of R^{11} , NR^7R^8 , SO_mR^9 , or $\text{C}_{1-7}\text{alkyl}$ optionally substituted by R^{11} , NR^7R^8 , or SO_mR^9 ;

R^6 is

- (a) $\text{C}_{1-7}\text{alkyl}$,
- 20 (b) NR^7R^8 ,
- (c) aryl, or
- (d) het, wherein said het is bound via a carbon atom;

R^7 and R^8 are independently

- (a) H,
- 25 (b) aryl,
- (c) $\text{C}_{1-7}\text{alkyl}$ which may be partially unsaturated and is optionally substituted by one or more substituents selected from a group consisting of aryl, $\text{NR}^{10}\text{R}^{10}$, R^{11} , SO_mR^9 , $\text{CONR}^{10}\text{R}^{10}$, or halo, or;
- (d) $\text{C}_{3-8}\text{cycloalkyl}$ which may be partially unsaturated and optionally
- 30 substituted by one or more substituents selected from a group consisting of R^{11} , NR^7R^8 , SO_mR^9 , or $\text{C}_{1-7}\text{alkyl}$ optionally substituted by R^{11} , NR^7R^8 , or SO_mR^9 , or

- (e) R^7 and R^8 together with the nitrogen to which they are attached form a het;

R^9 is

- 5 (a) aryl,
(b) het,
(c) C_{3-8} cycloalkyl,
(d) methyl, or
(e) C_{2-7} alkyl which may be partially unsaturated and is optionally substituted by one or more substituents selected from a group
10 consisting of $NR^{10}R^{10}$, R^{11} , SH, $CONR^{10}R^{10}$, or halo;

R^{10} is

- (a) H,
(b) methyl, or
(c) C_{2-7} alkyl optionally substituted by OH;

15 R^{11} is

- (a) OR^{10} ,
(b) Ohet,
(c) Oaryl,
(d) CO_2R^{10} ,
20 (e) het,
(f) aryl,
(g) CN, or
(h) C_{3-8} cycloalkyl which may be partially unsaturated and optionally substituted by one or more substituents selected from a group
25 consisting of R^{11} , NR^7R^8 , SO_mR^9 , or C_{1-7} alkyl optionally substituted by R^{11} , NR^7R^8 , or SO_mR^9 ;

R^{12} is

- 30 (a) H,
(b) het,
(c) aryl,
(d) C_{3-8} cycloalkyl,
(e) methyl, or

(f) C_{2-7} alkyl optionally substituted by NR^7R^8 or R^{11} ;

R^{13} is

(a) $(P=O)(OR^{14})_2$,

(b) $CO(CH_2)_nCON(CH_3)-(CH_2)_nSO_3^-M^+$,

5 (c) an amino acid,

(d) $C(=O)$ aryl,

(e) $C(=O)C_{1-7}$ alkyl optionally substituted by NR^7R^8 , aryl, het, CO_2H , or $O(CH_2)_nCO_2R^{14}$, or

(f) $C(=O)NR^7R^8$

10 R^{14} is

(a) H, or

(b) C_{1-7} alkyl;

each i is independently 2, 3, or 4;

15 each n is independently 1, 2, 3, 4 or 5;

each m is independently 0, 1, or 2;

M is sodium, potassium, or lithium;

aryl is a phenyl radical or an ortho-fused bicyclic carbocyclic radical wherein at least one ring is aromatic;

20 wherein any aryl is optionally substituted with one or more substituents selected from the group consisting of halo, OH, cyano, CO_2R^{14} , CF_3 , C_{1-6} alkoxy, and C_{1-6} alkyl which maybe further substituted by one to three SR^{14} , $NR^{14}R^{14}$, OR^{14} , or CO_2R^{14} ;

het is a four- (4), five- (5), six- (6), or seven- (7) membered saturated or unsaturated heterocyclic ring having 1, 2, or 3 heteroatoms selected from the group consisting of

25 oxygen, sulfur, and nitrogen, which is optionally fused to a benzene ring, or any bicyclic heterocycle group;

wherein any het is optionally substituted with one or more substituents selected from the group consisting of halo, OH, cyano, phenyl, CO_2R^{14} , CF_3 , C_{1-6} alkoxy, oxo,

oxime, and C_{1-6} alkyl which maybe further substituted by one to three SR^{14} , $NR^{14}R^{14}$,

30 OR^{14} , or CO_2R^{14} .

2. The compound of claim 1 wherein A is Cl.

3. The compound of claim 1 wherein R¹ is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, carboxymethyl, (C1-7 alkoxy)carbonylmethyl, 2-hydroxyethyl, 2-(2-methoxyethoxy)ethyl, 3-(2-tetrahydropyranyloxy)propyl, 2-morpholinoethyl, 2-(diethylamino)ethyl, 2-(dimethyl-
5 amino)ethyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-(1-methylpyrrolidin-2-yl)ethyl, 2-(diisopropylamino)ethyl, 2-pyrrolidin-1-ylethyl, 3-(dimethylamino)propyl, and vinyl.
4. The compound of claim 1 wherein R² is selected from the group consisting of
10 CH₂-morpholine, alkynyl-CH₂OH, CH₂-(tetrahydro-2H-pyran-4-yl), and (CH₂)₃OH.
5. The compound of claim 1 which is selected from the group consisting of
15 N-(4-chlorobenzyl)-6-iodo-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-6-(3-hydroxy-1-propynyl)-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

20 N-(4-chlorobenzyl)-6-(hydroxymethyl)-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-6-(4-hydroxy-1-butyryl)-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;
25 N-(4-chlorobenzyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide; N-(4-chlorobenzyl)-8-([(1R,2R)-1-hydroxy-2-methylcyclohexyl]ethynyl)-1-methyl-4-oxo-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

30 N-(4-chlorobenzyl)-8-(cyclopropylethynyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-[3-(dimethylamino)-1-propynyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-1-methyl-4-oxo-8-{4-[(4R)-2-oxo-1,3-oxazolidin-4-yl]-1-butynyl}-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

5

N-(4-chlorobenzyl)-8-(4-hydroxy-1-butynyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

10

N-(4-chlorobenzyl)-8-[(1-hydroxycyclohexyl)ethynyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-(3,3-dicyclopropyl-3-hydroxy-1-propynyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

15

N-(4-chlorobenzyl)-8-[(3S)-3-hydroxy-1-butynyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

8-{3-[(aminocarbonyl)amino]-3-methyl-1-butynyl}-N-(4-chlorobenzyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

20

N-(4-chlorobenzyl)-1-methyl-8-[3-methyl-3-(4-thioxo-1,3,5-triazinan-1-yl)-1-butynyl]-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

25

N-(4-chlorobenzyl)-8-[(3R)-3-hydroxy-1-butynyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-8-{4-[(4R)-2-oxo-1,3-oxazolidin-4-yl]-1-butynyl}-1,4-dihydro-3-cinnolinecarboxamide;

30

N-(4-chlorobenzyl)-8-[3-(1,1-dioxido-4-thiomorpholinyl)-1-propynyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

- N-(4-chlorobenzyl)-8-(5-hydroxy-1-pentynyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;
- 5 N-(4-chlorobenzyl)-8-([(1R,2S)-2-hydroxycyclopentyl]ethynyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;
- N-(4-chlorobenzyl)-8-(3-hydroxy-3-methyl-1-butynyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;
- 10 N-(4-chlorobenzyl)-8-[3-(4,5-dichloro-1H-imidazol-1-yl)-1-propynyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;
- N-(4-chlorobenzyl)-8-(3-hydroxy-1-propynyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;
- 15 N-(4-chlorobenzyl)-1-methyl-4-oxo-8-(phenylethynyl)-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;
- N-(4-chlorobenzyl)-8-(3-hydroxy-3-phenyl-1-propynyl)-1-methyl-4-oxo-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;
- 20 (tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;
- N-(4-chlorobenzyl)-8-(3-hydroxy-1-propynyl)-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;
- 25 N-(4-chlorobenzyl)-8-(4-hydroxy-1-butynyl)-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;
- N-(4-chlorobenzyl)-8-(3-hydroxy-1-propynyl)-1-methyl-4-oxo-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;
- 30 N-(4-chlorobenzyl)-8-(4-hydroxy-1-butynyl)-1-methyl-4-oxo-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-[3-(dimethylamino)-1-propynyl]-1-methyl-4-oxo-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

5 N-(4-chlorobenzyl)-1-[3-(methylsulfonyl)propyl]-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-1-[3-(methylsulfonyl)propyl]-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

10 N-(4-chlorobenzyl)-1-[(2-hydroxyethoxy)methyl]-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-6-(4-morpholinylmethyl)-4-oxo-1-tetrahydro-3-furanyl-1,4-dihydro-3-cinnolinecarboxamide;

15 N-(4-chlorobenzyl)-1-(1,2-diethyl-4-pyrazolidinyl)-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

20 N-(4-chlorobenzyl)-6-(4-morpholinylmethyl)-1-(3-oxetanyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-1-{3-[(3-hydroxypropyl)sulfonyl]propyl}-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

25 N-(4-chlorobenzyl)-1-[2-(2-ethoxyethoxy)ethyl]-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-6-(4-morpholinylmethyl)-4-oxo-1-[(phenylsulfinyl)methyl]-1,4-dihydro-3-cinnolinecarboxamide;

30 N-(4-chlorobenzyl)-6-(4-morpholinylmethyl)-4-oxo-1-[(phenylsulfonyl)methyl]-1,4-dihydro-3-cinnolinecarboxamide;

- N-(4-chlorobenzyl)-6-(4-morpholinylmethyl)-4-oxo-1-[(phenylsulfanyl)methyl]-
1,4-dihydro-3-cinnolinecarboxamide;
- 5 N-(4-chlorobenzyl)-6-(4-morpholinylmethyl)-4-oxo-1-tetrahydro-2H-pyran-3-yl-
1,4-dihydro-3-cinnolinecarboxamide;
- N-(4-chlorobenzyl)-1-[(methylsulfanyl)methyl]-6-(4-morpholinylmethyl)-4-oxo-
1,4-dihydro-3-cinnolinecarboxamide;
- 10 N-(4-chlorobenzyl)-1-1-[(4-chlorophenyl)sulfinyl]methyl-6-(4-
morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;
- N-(4-chlorobenzyl)-6-(4-morpholinylmethyl)-4-oxo-1-tetrahydro-2H-pyran-4-yl-
1,4-dihydro-3-cinnolinecarboxamide;
- 15 N-(4-chlorobenzyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-8-(4-
thiomorpholinylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;
- N-(4-chlorobenzyl)-8-[(4-hydroxy-1-piperidiny]methyl)-1-methyl-6-(4-
20 morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;
- N-(4-chlorobenzyl)-8-1-[(3R)-3-hydroxypyrrolidinyl]methyl-1-methyl-6-(4-
morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;
- 25 N-(4-chlorobenzyl)-8-[(3-hydroxy-1-piperidiny]methyl)-1-methyl-6-(4-
morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;
- [3-1-[(4-chlorobenzyl)amino]carbonyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-
1,4-dihydro-8-cinnolinyl]methyl 4-morpholinecarboxylate
- 30 N-(4-chlorobenzyl)-8-(hydroxymethyl)-1-methyl-6-(4-morpholinylmethyl)-4-
oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-[(3-cyanobenzyl)amino]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

5 N-(4-chlorobenzyl)-1-methyl-6,8-bis(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

8-[(1-acetyl-4-piperidiny)amino]-N-(4-chlorobenzyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

10 N-(4-chlorobenzyl)-1-methyl-8-[[1-methyl-2-(phenylsulfonyl)ethyl]amino]-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-[[3-(4-methoxyphenyl)-1-methylpropyl]amino]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

15 8-amino-N-(4-chlorobenzyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

20 N-(4-chlorobenzyl)-1-methyl-6-(4-morpholinylmethyl)-8-[(3-nitrobenzyl)amino]-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-8-(tetrahydro-2H-pyran-4-ylamino)-1,4-dihydro-3-cinnolinecarboxamide;

25 N-(4-chlorobenzyl)-6-(3-hydroxy-1-propyl)-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-6-(4-hydroxy-1-butyl)-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

30

N-(4-chlorobenzyl)-8-[[[(1R,2R)-1-hydroxy-2-methylcyclohexyl]ethyl]-1-methyl-4-oxo-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-(cyclopropylethyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

5 N-(4-chlorobenzyl)-8-[3-(dimethylamino)-1-propyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-1-methyl-4-oxo-8-{4-[(4R)-2-oxo-1,3-oxazolidin-4-yl]-1-butyl}-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

10

N-(4-chlorobenzyl)-8-(4-hydroxy-1-butyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

15 N-(4-chlorobenzyl)-8-[(1-hydroxycyclohexyl)ethyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-(3,3-dicyclopropyl-3-hydroxy-1-propyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

20 N-(4-chlorobenzyl)-8-[(3S)-3-hydroxy-1-butyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

8-{3-[(aminocarbonyl)amino]-3-methyl-1-butyl}-N-(4-chlorobenzyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

25

N-(4-chlorobenzyl)-1-methyl-8-[3-methyl-3-(4-thioxo-1,3,5-triazinan-1-yl)-1-butyl]-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

30 N-(4-chlorobenzyl)-8-[(3R)-3-hydroxy-1-butyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-8-{4-[(4R)-2-oxo-1,3-oxazolidin-4-yl]-1-butyl}-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-[3-(1,1-dioxido-4-thiomorpholinyl)-1-propyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

5 N-(4-chlorobenzyl)-8-(5-hydroxy-1-pentyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-[(1R,2S)-2-hydroxycyclopentyl]ethyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

10

N-(4-chlorobenzyl)-8-(3-hydroxy-3-methyl-1-butyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

15 N-(4-chlorobenzyl)-8-[3-(4,5-dichloro-1H-imidazol-1-yl)-1-propyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-[3-(1H-imidazol-1-yl)-1-propyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

20

N-(4-chlorobenzyl)-8-[3-(1H-imidazol-1-yl)-1-propynyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-(3-hydroxy-1-propyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

25

N-(4-chlorobenzyl)-1-methyl-4-oxo-8-(phenylethyl)-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

30

N-(4-chlorobenzyl)-8-(3-hydroxy-3-phenyl-1-propyl)-1-methyl-4-oxo-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-(3-hydroxy-1-propyl)-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-(4-hydroxy-1-butyl)-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

5 N-(4-chlorobenzyl)-8-(3-hydroxy-1-propyl)-1-methyl-4-oxo-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

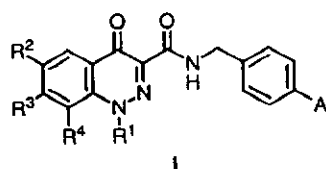
N-(4-chlorobenzyl)-8-(4-hydroxy-1-butyl)-1-methyl-4-oxo-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

10

N-(4-chlorobenzyl)-8-[3-(dimethylamino)-1-propyl]-1-methyl-4-oxo-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

15 N-(4-chlorobenzyl)-1-methyl-8-{[methyl(tetrahydro-2-furanylmethyl)amino]methyl}-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide.

6. A composition of matter comprising a pharmaceutically effective amount of a
20 compound of formula (I):



25 or a pharmaceutically acceptable salt thereof wherein,

A is

- (a) Cl,
- (b) Br,
- (c) CN,
- (d) NO₂, or
- (e) F;

30

R¹ is

- (a) R⁵, or
- (b) SO₂R⁹

R^2 , R^3 and R^4 may be the same or different and are selected from the group consisting of:

- (a) H,
- (b) halo,
- 5 (c) aryl,
- (d) $S(O)_mR^6$,
- (e) $(C=O)R^6$,
- (f) $(C=O)OR^9$,
- (g) cyano,
- 10 (h) het, wherein said het is bound via a carbon atom,
- (i) OR^{10} ,
- (j) Ohet,
- (k) NR^7R^8
- (l) SR^{10} ,
- 15 (m) Shet,
- (n) $NHCOR^{12}$,
- (o) $NHSO_2R^{12}$,
- (p) C_{1-7} alkyl which may be partially unsaturated and optionally substituted by one or more substituents of the group R^{11} , OR^{13} , SR^{10} , SR^{13} , NR^7R^8 , halo, $(C=O)C_{1-7}$ alkyl, or SO_mR^9 , and
- 20 (q) R^3 together with R^2 or R^4 form a carbocyclic or het which may be optionally substituted by NR^7R^8 , or C_{1-7} alkyl which may be optionally substituted by OR^{14} ;

R^5 is

- 25 (a) $(CH_2CH_2O)_iR^{10}$,
- (b) C_{1-7} alkyl which may be partially unsaturated and is optionally substituted by one or more substituents selected from a group consisting of NR^7R^8 , R^{11} , SO_mR^9 , or OC_{2-4} alkyl which may be further substituted by het, OR^{10} , or NR^7R^8 , or
- 30 (c) C_{3-8} cycloalkyl which may be partially unsaturated and optionally substituted by one or more substituents selected from a group consisting of R^{11} , NR^7R^8 , SO_mR^9 , or C_{1-7} alkyl optionally substituted by R^{11} , NR^7R^8 , or SO_mR^9 ;

R⁶ is

- (a) C₁₋₇alkyl,
- (b) NR⁷R⁸,
- (c) aryl, or
- 5 (d) het, wherein said het is bound via a carbon atom;

R⁷ and R⁸ are independently

- (a) H,
- (b) aryl,
- 10 (c) C₁₋₇alkyl which may be partially unsaturated and is optionally substituted by one or more substituents selected from a group consisting of aryl, NR¹⁰R¹⁰, R¹¹, SO_mR⁹, CONR¹⁰R¹⁰, or halo, or;
- (d) C₃₋₈cycloalkyl which may be partially unsaturated and optionally substituted by one or more substituents selected from a group consisting of R¹¹, NR⁷R⁸, SO_mR⁹, or C₁₋₇alkyl optionally substituted by
- 15 R¹¹, NR⁷R⁸, or SO_mR⁹, or
- (e) R⁷ and R⁸ together with the nitrogen to which they are attached form a het;

R⁹ is

- 20 (a) aryl,
- (b) het,
- (c) C₃₋₈cycloalkyl,
- (d) methyl, or
- (e) C₂₋₇alkyl which may be partially unsaturated and is optionally
- 25 substituted by one or more substituents selected from a group consisting of NR¹⁰R¹⁰, R¹¹, SH, CONR¹⁰R¹⁰, or halo;

R¹⁰ is

- (a) H,
- (b) methyl, or
- 30 (c) C₂₋₇alkyl optionally substituted by OH;

R¹¹ is

- (a) OR¹⁰,
- (b) Ohet,

- (c) Oaryl,
 (d) CO_2R^{10} ,
 (e) het,
 (f) aryl,
 5 (g) CN, or
 (h) C_{3-8} cycloalkyl which may be partially unsaturated and optionally substituted by one or more substituents selected from a group consisting of R^{11} , NR^7R^8 , SO_mR^9 , or C_{1-7} alkyl optionally substituted by R^{11} , NR^7R^8 , or SO_mR^9 ;

10

R^{12} is

- (a) H,
 (b) het,
 (c) aryl,
 15 (d) C_{3-8} cycloalkyl,
 (e) methyl, or
 (f) C_{2-7} alkyl optionally substituted by NR^7R^8 or R^{11} ;

R^{13} is

- (a) $(\text{P}=\text{O})(\text{OR}^{14})_2$,
 20 (b) $\text{CO}(\text{CH}_2)_n\text{CON}(\text{CH}_3)-(\text{CH}_2)_n\text{SO}_3^-\text{M}^+$,
 (c) an amino acid,
 (d) $\text{C}(=\text{O})\text{aryl}$, or
 (e) $\text{C}(=\text{O})\text{C}_{1-7}\text{alkyl}$ optionally substituted by NR^7R^8 , aryl, het, CO_2H , or $\text{O}(\text{CH}_2)_n\text{CO}_2\text{R}^{14}$;

25 R^{14} is

- (a) H, or
 (b) $\text{C}_{1-7}\text{alkyl}$;

each i is independently 2, 3, or 4;
 30 each n is independently 1, 2, 3, 4 or 5;
 each m is independently 0, 1, or 2;
 M is sodium, potassium, or lithium;

- aryl is a phenyl radical or an ortho-fused bicyclic carbocyclic radical wherein at least one ring is aromatic;
- wherein any aryl is optionally substituted with one or more substituents selected from the group consisting of halo, OH, cyano, CO_2R^{14} , CF_3 , C_{1-6} alkoxy, and C_{1-6} alkyl
- 5 which maybe further substituted by one to three SR^{14} , $\text{NR}^{14}\text{R}^{14}$, OR^{14} , or CO_2R^{14} ;
- het is a four- (4), five- (5), six- (6), or seven- (7) membered saturated or unsaturated heterocyclic ring having 1, 2, or 3 heteroatoms selected from the group consisting of oxygen, sulfur, and nitrogen, which is optionally fused to a benzene ring, or any bicyclic heterocycle group;
- 10 wherein any het is optionally substituted with one or more substituents selected from the group consisting of halo, OH, cyano, phenyl, CO_2R^{14} , CF_3 , C_{1-6} alkoxy, oxo, oxime, and C_{1-6} alkyl which maybe further substituted by one to three SR^{14} , $\text{NR}^{14}\text{R}^{14}$, OR^{14} , or CO_2R^{14} ;
- 15 and a pharmaceutically effective carrier.
7. The composition of claim 6 wherein A is Cl.
8. The composition of claim 6 wherein R^1 is selected from the group consisting of
- 20 methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, carboxymethyl, (C_{1-7} alkoxy)carbonylmethyl, 2-hydroxyethyl, 2-(2-methoxyethoxy)ethyl, 3-(2-tetrahydropyranyloxy)propyl, 2-morpholinoethyl, 2-(diethylamino)ethyl, 2-(dimethylamino)ethyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-(1-methylpyrrolidin-2-yl)ethyl, 2-(diisopropylamino)ethyl, 2-pyrrolidin-1-ylethyl, 3-
- 25 (dimethylamino)propyl, and vinyl.
9. The composition of claim 6 wherein R^2 is selected from the group consisting of CH_2 -morpholine, CH_2 -(tetrahydro-2H-pyran-4-yl), alkynyl- CH_2OH and $(\text{CH}_2)_3\text{OH}$.
- 30 10. The composition of claim 6 wherein said compound is selected from the group consisting of

N-(4-chlorobenzyl)-6-iodo-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-6-(3-hydroxy-1-propynyl)-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

5

N-(4-chlorobenzyl)-6-(hydroxymethyl)-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-6-(4-hydroxy-1-butynyl)-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

10

N-(4-chlorobenzyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide; N-(4-chlorobenzyl)-8-([(1R,2R)-1-hydroxy-2-methylcyclohexyl]ethynyl)-1-methyl-4-oxo-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

15

N-(4-chlorobenzyl)-8-(cyclopropylethynyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-[3-(dimethylamino)-1-propynyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

20

N-(4-chlorobenzyl)-1-methyl-4-oxo-8-{4-[(4R)-2-oxo-1,3-oxazolidin-4-yl]-1-butynyl}-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

25

N-(4-chlorobenzyl)-8-(4-hydroxy-1-butynyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-[(1-hydroxycyclohexyl)ethynyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

30

N-(4-chlorobenzyl)-8-(3,3-dicyclopropyl-3-hydroxy-1-propynyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-[(3S)-3-hydroxy-1-butynyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

5 8-{3-[(aminocarbonyl)amino]-3-methyl-1-butynyl}-N-(4-chlorobenzyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-1-methyl-8-[3-methyl-3-(4-thioxo-1,3,5-triazinan-1-yl)-1-butynyl]-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

10 N-(4-chlorobenzyl)-8-[(3R)-3-hydroxy-1-butynyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-8-{4-[(4R)-2-oxo-1,3-oxazolidin-4-yl]-1-butynyl}-1,4-dihydro-3-cinnolinecarboxamide;

15 N-(4-chlorobenzyl)-8-[3-(1,1-dioxido-4-thiomorpholinyl)-1-propynyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

20 N-(4-chlorobenzyl)-8-(5-hydroxy-1-pentynyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-[[1R,2S)-2-hydroxycyclopentyl]ethynyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

25 N-(4-chlorobenzyl)-8-(3-hydroxy-3-methyl-1-butynyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-[3-(4,5-dichloro-1H-imidazol-1-yl)-1-propynyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

30 N-(4-chlorobenzyl)-8-(3-hydroxy-1-propynyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-1-methyl-4-oxo-8-(phenylethynyl)-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

5 N-(4-chlorobenzyl)-8-(3-hydroxy-3-phenyl-1-propynyl)-1-methyl-4-oxo-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-(3-hydroxy-1-propynyl)-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

10 N-(4-chlorobenzyl)-8-(4-hydroxy-1-butynyl)-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-(3-hydroxy-1-propynyl)-1-methyl-4-oxo-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

15 N-(4-chlorobenzyl)-8-(4-hydroxy-1-butynyl)-1-methyl-4-oxo-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

20 N-(4-chlorobenzyl)-8-[3-(dimethylamino)-1-propynyl]-1-methyl-4-oxo-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-1-[3-(methylsulfonyl)propyl]-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

25 N-(4-chlorobenzyl)-1-[3-(methylsulfonyl)propyl]-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-1-[(2-hydroxyethoxy)methyl]-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

30 N-(4-chlorobenzyl)-6-(4-morpholinylmethyl)-4-oxo-1-tetrahydro-3-furanyl-1,4-dihydro-3-cinnolinecarboxamide; ...

N-(4-chlorobenzyl)-1-(1,2-diethyl-4-pyrazolidinyl)-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

5 N-(4-chlorobenzyl)-6-(4-morpholinylmethyl)-1-(3-oxetanyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-1-{3-[(3-hydroxypropyl)sulfonyl]propyl}-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

10 N-(4-chlorobenzyl)-1-[2-(2-ethoxyethoxy)ethyl]-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-6-(4-morpholinylmethyl)-4-oxo-1-[(phenylsulfinyl)methyl]-1,4-dihydro-3-cinnolinecarboxamide;

15 N-(4-chlorobenzyl)-6-(4-morpholinylmethyl)-4-oxo-1-[(phenylsulfonyl)methyl]-1,4-dihydro-3-cinnolinecarboxamide;

20 N-(4-chlorobenzyl)-6-(4-morpholinylmethyl)-4-oxo-1-[(phenylsulfanyl)methyl]-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-6-(4-morpholinylmethyl)-4-oxo-1-tetrahydro-2H-pyran-3-yl-1,4-dihydro-3-cinnolinecarboxamide;

25 N-(4-chlorobenzyl)-1-[(methylsulfanyl)methyl]-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-1-[(4-chlorophenyl)sulfinyl]methyl}-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

30 N-(4-chlorobenzyl)-6-(4-morpholinylmethyl)-4-oxo-1-tetrahydro-2H-pyran-4-yl-1,4-dihydro-3-cinnolinecarboxamide;

- N-(4-chlorobenzyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-8-(4-thiomorpholinylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;
- 5 N-(4-chlorobenzyl)-8-[(4-hydroxy-1-piperidiny)methyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;
- N-(4-chlorobenzyl)-8-[[3-(3R)-3-hydroxypyrrolidinyl]methyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;
- 10 N-(4-chlorobenzyl)-8-[(3-hydroxy-1-piperidiny)methyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;
- [3-[[4-(4-chlorobenzyl)amino]carbonyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-8-cinnolinyl]methyl 4-morpholinecarboxylate
- 15 N-(4-chlorobenzyl)-8-(hydroxymethyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;
- N-(4-chlorobenzyl)-8-[(3-cyanobenzyl)amino]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;
- 20 N-(4-chlorobenzyl)-1-methyl-6,8-bis(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;
- 8-[(1-acetyl-4-piperidiny)amino]-N-(4-chlorobenzyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;
- 25 N-(4-chlorobenzyl)-1-methyl-8-[[1-methyl-2-(phenylsulfonyl)ethyl]amino]-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;
- 30 N-(4-chlorobenzyl)-8-[[3-(4-methoxyphenyl)-1-methylpropyl]amino]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

8-amino-N-(4-chlorobenzyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

5 N-(4-chlorobenzyl)-1-methyl-6-(4-morpholinylmethyl)-8-[(3-nitrobenzyl)amino]-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-8-(tetrahydro-2H-pyran-4-ylamino)-1,4-dihydro-3-cinnolinecarboxamide;

10 N-(4-chlorobenzyl)-6-(3-hydroxy-1-propyl)-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

15 N-(4-chlorobenzyl)-6-(4-hydroxy-1-butyl)-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

20 N-(4-chlorobenzyl)-8-[(1R,2R)-1-hydroxy-2-methylcyclohexyl]ethyl-1-methyl-4-oxo-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-(cyclopropylethyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

25 N-(4-chlorobenzyl)-8-[3-(dimethylamino)-1-propyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-1-methyl-4-oxo-8-{4-[(4R)-2-oxo-1,3-oxazolidin-4-yl]-1-butyl}-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

30 N-(4-chlorobenzyl)-8-(4-hydroxy-1-butyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-[(1-hydroxycyclohexyl)ethyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

5 N-(4-chlorobenzyl)-8-(3,3-dicyclopropyl-3-hydroxy-1-propyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-[(3S)-3-hydroxy-1-butyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

10 8-{3-[(aminocarbonyl)amino]-3-methyl-1-butyl}-N-(4-chlorobenzyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-1-methyl-8-[3-methyl-3-(4-thioxo-1,3,5-triazinan-1-yl)-1-butyl]-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

15 N-(4-chlorobenzyl)-8-[(3R)-3-hydroxy-1-butyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

20 N-(4-chlorobenzyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-8-{4-[(4R)-2-oxo-1,3-oxazolidin-4-yl]-1-butyl}-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-[3-(1,1-dioxido-4-thiomorpholinyl)-1-propyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

25 N-(4-chlorobenzyl)-8-(5-hydroxy-1-pentyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

30 N-(4-chlorobenzyl)-8-[(1R,2S)-2-hydroxycyclopentyl]ethyl-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-(3-hydroxy-3-methyl-1-butyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-[3-(4,5-dichloro-1H-imidazol-1-yl)-1-propyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

5 N-(4-chlorobenzyl)-8-[3-(1H-imidazol-1-yl)-1-propyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-[3-(1H-imidazol-1-yl)-1-propynyl]-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

10 N-(4-chlorobenzyl)-8-(3-hydroxy-1-propyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-1-methyl-4-oxo-8-(phenylethyl)-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

15 N-(4-chlorobenzyl)-8-(3-hydroxy-3-phenyl-1-propyl)-1-methyl-4-oxo-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

20 N-(4-chlorobenzyl)-8-(3-hydroxy-1-propyl)-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-(4-hydroxy-1-butyl)-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

25 N-(4-chlorobenzyl)-8-(3-hydroxy-1-propyl)-1-methyl-4-oxo-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-8-(4-hydroxy-1-butyl)-1-methyl-4-oxo-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

30 N-(4-chlorobenzyl)-8-[3-(dimethylamino)-1-propyl]-1-methyl-4-oxo-6-(tetrahydro-2H-pyran-4-ylmethyl)-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-1-methyl-8-{{methyl(tetrahydro-2-furanylmethyl)amino]methyl}-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-cinnolinecarboxamide.

11. Use of a compound of claim 1 for the preparation of a medicament for treating or preventing a viral infection in a mammal.
12. The use according to claim 11 wherein said viral infection is a herpes virus infection.
13. The use according to claim 11 wherein the mammal is a human.
14. The use according to claim 11 wherein said mammal is a livestock or companion animal.
15. The use according to claim 12 wherein the infection is herpes simplex virus type 1, 2, 6, 7 or 8, varicella zoster virus, human cytomegalovirus, or epstein-Barr virus.
16. The use according to claim 11 wherein the amount administered is from about 0.1 to about 300 mg/kg of body weight.
17. The use according to claim 16 wherein the amount administered is from about 1 to about 30 mg/kg of body weight.
18. The use according to claim 11 wherein the compound is administered parenterally, intranasally, topically, intravaginally, orally, or rectally.
19. A method for inhibiting a viral DNA polymerase, comprising contacting the polymerase with an effective inhibitory amount of a compound of claim 1.
20. The method of claim 19 wherein the polymerase and the compound are contacted in vitro.

21. The method of claim 20 wherein the polymerase and the compound are contacted
in vivo.

5 22. A compound selected from the group consisting of:

N-(4-chlorobenzyl)-6-iodo-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxamide;

N-(4-chlorobenzyl)-6-(3-hydroxy-1-propynyl)-1-methyl-4-oxo-1,4-dihydro-3-
cinnolinecarboxamide;

10

N-(4-chlorobenzyl)-6-(hydroxymethyl)-1-methyl-4-oxo-1,4-dihydro-3-
cinnolinecarboxamide;

15

N-(4-chlorobenzyl)-6-(4-hydroxy-1-butynyl)-1-methyl-4-oxo-1,4-dihydro-3-
cinnolinecarboxamide; and

N-(4-chlorobenzyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-
cinnolinecarboxamide.

23. The compound of any one of claims 1 to 10 for use in medical treatment.

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24. The compound of claim 23 wherein the treatment is the treatment or prevention of a
herpesviral infection.

25. The use of a compound of any one of claims 1 to 10 to prepare a medicament for
treating or preventing a herpesviral infection in a mammal.