

PYRIDINONE HYDROXYCYCLOPENTYL CARBOXAMIDES: HIV INTEGRASE INHIBITORS WITH THERAPEUTIC APPLICATIONS

FIELD OF THE INVENTION

5 The present invention relates to the field of antiviral therapy, in particular the treatment of HIV infections in humans, preferably in combination therapy.

RELATED APPLICATIONS AND GRANT SUPPORT

10 The present application claims the benefit of priority from provisional applications serial number US61/283,675, filed December 7, 2009 and US61/320,429, filed April 2, 2010, of identical title, the entirety of which applications are incorporated by reference herein.

15 The present invention was made with government support under Grant Number RO1 AI 43181 of the National Institutes of Health. Consequently, the government retains rights in the invention.

BACKGROUND OF THE INVENTION

20 The human immunodeficiency virus, HIV, encodes three key viral enzymes through its *pol* gene and these enzymes are critical for the replication of this virus [Katz & Skalka, *Annu. Rev. Biochem.*, 63, 133-173 (1994); Frankel, *Annu. Rev. Biochem.*, 67, 1-25 (1998)]. Drug discovery involving two of these enzymes, HIV reverse transcriptase (RT) and HIV protease (PR), have led to clinically approved therapeutic agents for the treatment of acquired immunodeficiency syndrome (AIDS) and AIDS related complex (ARC) in HAART (highly-active antiretroviral therapy)[Johnson & Gerber, in "Advances in Internal Medicine," vol. 44. Mosby: St. Louis, 1-40 (2000); De Clercq, *Nature Reviews: Drug Discovery*, 11, 13-25 (2002); Asante-Appiah & Skalka, *Adv. Virus Res.*, 52, 351-369 (1999); Nair, in "Recent Advances in Nucleosides: Chemistry and Chemotherapy," Elsevier Science: Netherlands, 149-166 (2002)]. However, the third enzyme of the *pol* gene, HIV integrase, has received less consideration [Miller & Hazuda, *Current Opinion in Microbiology*, 4, 535-539 (2001); Nair, *Rev. Med. Virol.*, 12, 179-193 (2002); Nair, *Rev. Med. Virol.*, 17, 277-295 (2007); Nair, *Current Pharmaceutical Design*, 9, 2553-2565 (2003); Pommier, *et al.*, *Nature Rev. Drug Discovery* 4, 236-248 (2005)]. At present there is only one integrase inhibitor (Raltegravir,

Isentress) that is approved for clinical use for HIV/AIDS [*J. Med. Chem.* 51, 5843-5855 (2008); US Patent Publ. No. 2006/0122205 A1, NDA Report 22-145, September 5, 2007]. HIV-1 integrase is involved in the integration of HIV DNA into human chromosomal DNA. Because integrase has no human counterpart and because it is required for HIV replication, it is an attractive target for the discovery of anti-HIV agents.

A variety of compounds are inhibitors of HIV integrase including oligonucleotides, dinucleotides, heterocycles, natural products, diketone acids, functionalized naphthyridines and pyrimidines and others [Nair, *Rev. Med. Virol.*, 17, 277-295 (2007); Egbertson, *Curr. Top. Med. Chem.* 7, 1251-1272 (2007)]. Some diketone acids with aryl or heteroaryl substitutions are inhibitors of HIV integrase, but most commonly of only the strand transfer step [Wai, *et al.*, "4-Aryl-2,4-dioxobutanoic acid inhibitors of HIV-1 integrase and viral replication in cells," *J. Med. Chem.* 43, 4923-4926 (2000); Pais, G. C. G., *et al.*, "Structure activity of 3-aryl-1,3-diketone-containing compounds as HIV-1 integrase inhibitors," *J. Med. Chem.* 45, 3184-3194 (2002); Sechi, M., *et al.*, "Design and synthesis of novel indole beta-diketone acid derivatives as HIV-1 integrase inhibitors," *J. Med. Chem.* 47, 5298-5310 (2004); Nair, *et al.*, "HIV integrase inhibitors with nucleobase scaffolds: discovery of a highly potent anti-HIV agent," *J. Med. Chem.* 49, 445-447 (2006); Nair, *et al.*, "Conceptually novel HIV integrase inhibitors with nucleobase scaffolds: discovery of a highly potent anti-HIV agent," *Antiviral Res.* 70, A26 (2006); Uchil *et al.*, "Novel strategy to assemble the β -diketone acid pharmacophore of HIV integrase inhibitors on purine nucleobase scaffolds," *J. Org. Chem.* 72, 8577-8579 (2007); Sato, *et al.*, "Novel HIV-1 integrase inhibitors derived from quinolone antibiotics," *J. Med. Chem.* 49, 1506-1508 (2006); Garvey *et al.*, "The Naphthyridinone GSK365735 is a novel, potent human immunodeficiency virus type 1 integrase inhibitor and antiretroviral," *Antimicrob. Agents Chemother.* 52, 901-908 (2008); Min *et al.*, "Pharmacokinetics (PK) and safety in healthy and HIV-infected subjects and short-term antiviral efficacy of S/GSK1265744, a new generation once daily HIV integrase inhibitor," 49th ICAAC Abstract no. H-1228, p249 (2009); Xu *et al.*, "Discovery of GS-9350: A novel pharmacoenhancer without anti-HIV activity," 49th ICAAC Abstract no. H-934, p248 (2009); Min *et al.*, "Pharmacokinetics and safety of S/GSK1349572, a next-generation HIV integrase inhibitor, in healthy volunteers," *Antimicrob. Agents in Chemother.* 54, 254-258 (2010); Johns *et al.*, "Discovery of S/GSK1349572: a once-daily next generation integrase inhibitor with a superior resistance profile," 17th CROI Abstract no. 55, p 86 (2010); Cohen, *et al.*, "Single-

tablet, fixed-dose regimen of elvitegravir/emtricitabine/tenofovir disoproxil fumarate/GS-9350 achieves a high rate of virologic suppression and GS-9350 is an effective booster,” 17th CROI Abstract no. 58LB, p 87 (2010), Nair et al., New Pyridinone Diketo Acid Inhibitors of HIV-1 Integrase: Anti-HIV Data, SAR Analysis, Microsome Stability, 5 Cytochrome P450 Studies and Rodent Pharmacokinetics, 49th ICAAC Abstracts, F1-2023, p211 (2009), Nair *et al.*, “Beta-diketo acids with purine nucleobase scaffolds: novel selective inhibitors of the strand transfer step of HIV integrase,” *Bioorg. Med. Chem. Lett.* 16, 1920-1923 (2006), Chi *et al.*, “A novel diketo phosphonic acid that exhibits specific, strand-transfer inhibition of HIV integrase and anti-HIV activity,” *Bioorg. Med. Chem. Lett.* 17, 10 1266-1269 (2007)]. Other publications in the area are of peripheral relationship to this invention disclosure.

Patents of relevance to this invention disclosure are: Selnick, H. G. *et al.*, (Merck & Co. Inc.), “Preparation of nitrogen-containing 4-heteroaryl-2,4-dioxobutyric acids useful as HIV 15 integrase inhibitors,” WO 9962513; Young, S. D., *et al.*, (Merck & Co. Inc.), “Preparation of aromatic and heteroaromatic 4-aryl-2,4-dioxobutyric acid derivatives useful as HIV integrase inhibitors,” WO 9962897; Fujishita, T., *et al.*, Yoshinaga, T., *et al.* (Shionogi & Co. Ltd.), “Preparation of aromatic heterocycle compounds having HIV integrase inhibiting activities,” WO 0039086; Akihiko, S., (Shionogi & Co. Ltd.), “Medicinal compositions containing 20 propenone derivatives,” WO 0196329; Payne, L. S., *et al.*, (Merck & Co. Inc.; Tularik, Inc.), “Preparation of 1,3-diaryl-1,3-propanediones as HIV integrase inhibitors,” WO 0100578; Egbertson, M., *et al.*, (Merck & Co. Ltd.), “HIV integrase inhibitors,” WO 9962520. Some of the patents cited above are closely related. However, none of the patents or publications describe the class of compounds according to the present invention. Other patents of 25 peripheral relationship to this invention are: Anthony, *et al.*, (Merck & Co. Inc.), “Aza and polyaza-naphthalenyl-carboxamides useful as HIV integrase inhibitors,” WO 02/30426; Sato, *et al.*, (Japan Tobacco Inc.), “Preparation of 4-oxoquinoline derivatives as HIV integrase inhibitors,” WO 2004046115; Sato, *et al.*, (Japan Tobacco Inc.), “Novel 4-oxoquinoline compounds and use thereof as HIV integrase inhibitors,” WO 2005113509; Crescenzi, *et al.*, 30 (Istituto Di Recherche Di Biologia Molecolare P. Angeletti SPA) “Preparation of N-substituted hydroxypyrimidinone carboxamide inhibitors of HIV integrase,” WO 2003035077; Belyk, *et al.*, (Merck & Co. Inc., Istituto Di Recherche Di Biologia Molecolare P. Angeletti SPA), “Preparation of N-(4-fluorobenzyl)-5-hydroxy-1-methyl-2-(1-methyl-1-[[[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl] amino }ethyl)-6-oxo-1,6-dihydropyrimidine-4-

carboxamide potassium salts as HIV integrase inhibitors,” WO 2006060712; Belyk *et al.*, (Merck & Co. Inc.), “Potassium salt of an HIV integrase inhibitor,” US 2006, 0122205 A1; Sato, *et al.*, (Japan Tobacco Inc.), “Preparation of quinolizinone compounds as HIV integrase inhibitors,” WO 2006033422; Yoshida, H., *et al.*, (Shionogi & Co. Ltd.), “Preparation of carbamoyl-pyridinone derivative having HIV integrase inhibitory activity,” WO 2006030807; Dress, *et al.*, (Pfizer, Inc.), “Preparation of N-hydroxy pyrrolopyridinecarboxamides as inhibitors of HIV integrase,” WO 2006027694; Naidu, *et al.*, (Bristol-Myers Squibb Co.), “HIV integrase inhibitors,” US 2005/0261322; Naidu, *et al.*, (Bristol-Myers Squibb Co.), “Bicyclic heterocycles as HIV integrase inhibitors,” US 2005/0267105; Naidu, *et al.*, (Bristol-Myers Squibb Co.), “Bicyclic heterocycles as HIV integrase inhibitors,” US 2006/0199956 and Nair *et al.*, “Diketo acids with nucleobase scaffolds: anti-HIV replication inhibitors targeted at HIV integrase,” US, 2007/7250,421; Nair, *et al.*, “Pyridinone Diketo Acids: Inhibitors of HIV Replication in Combination Therapy, U.S. National Stage Patent Application No. 12/309/017, Filed January 2, 2009. While some of the patents cited above are more related than others, none of the patents or publications describe the class of compounds according to the present invention disclosure.

The class of compounds described in this invention disclosure are chiral and achiral oxy-substituted cyclopentyl pyridinone diketocarboxamides and their derivatives. The compounds have been designed as inhibitors of HIV-1 integrase and have been discovered to possess significant *in vitro* anti-HIV activity. Two examples are shown below (Figure 1a and b). The chiral compound (S,S-isomer, Figure 1a) exhibits anti-HIV activity in cell culture with an EC₅₀ of 25 nM (TI >1,500). The achiral compound (Figure 1b) is more active and has an EC₅₀ of 10 nM (TI >10,000).

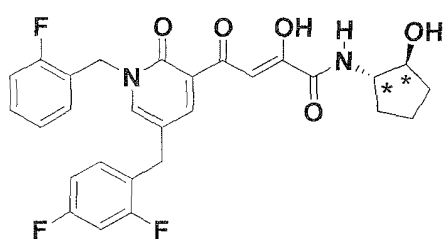


Figure 1a

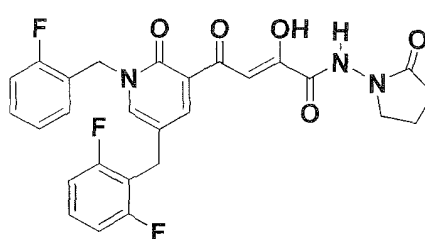


Figure 1b

SUMMARY OF THE INVENTION

Chiral and achiral oxy-substituted cyclopentyl pyridinone diketocarboxamides and their derivatives and methods for their preparations are disclosed. The compounds are represented
5 by formula I and include chiral and achiral compounds, tautomers, regioisomers, geometric isomers, wherein the modified nucleobase scaffold and R, X and Z groups are as otherwise defined in the specification. These complex carboxamides are designed as inhibitors of HIV replication through inhibition of HIV integrase. The compounds are useful in the prevention, inhibition or treatment of infection by HIV and in the treatment of AIDS and ARC, either as
10 the compounds, or as pharmaceutically acceptable salts, with pharmaceutically acceptable carriers, used alone or in combination with antivirals, immunomodulators, antibiotics, vaccines, and other therapeutic agents, especially other anti-HIV compounds (including other anti-HIV integrase agents), which can be used to create combination anti-HIV cocktails. Methods of treating, preventing and/or reducing the likelihood of AIDS and ARC and
15 methods of treating or preventing infection by HIV are also described, the method comprising administering one or more compounds according to the present invention, optionally in combination with additional agents, including anti-HIV agents in effective amounts to a patient or subject in need. .

Compounds according to the present invention exhibit one or more of the following
20 characteristics desired in anti-HIV compounds: increased anti-HIV activity, enhanced bioavailability, enhanced therapeutic index, enhanced stability to metabolic degradation and little drug-to-drug interaction in comparison with prior art compounds of similar (anti-HIV) activity. The present compounds represent a material advance in the treatment and/or prevention of HIV and related secondary conditions and/or disease states.

25 Pharmaceutical compositions which include one or more compounds according to the present invention in combination with a pharmaceutically acceptable carrier, additive or excipient, optionally in combination with at least one additional agent as otherwise described herein represent an additional aspect of the invention. A kit comprising a pharmaceutical composition according to the present invention and instructions on how to administer the
30 composition to a patient in need represent a further aspect of the invention.

DETAILED DESCRIPTION OF THE INVENTION

The following terms are used throughout the specification to describe the present invention. Unless otherwise indicated, a term used to describe the present invention shall be given its ordinary meaning as understood by those skilled in the art.

5

The term “compound”, as used herein, unless otherwise indicated, refers to any specific chemical compound disclosed herein and includes tautomers, regioisomers, geometric isomers, and where applicable, optical isomers thereof, as well as pharmaceutically acceptable saltss thereof. Within its use in context, the term compound generally refers to a single compound, but also may include other compounds such as stereoisomers, regioisomers and/or optical isomers (including racemic mixtures) as well as specific enantiomers or enantiomerically enriched mixtures of disclosed compounds. The breadth of the term “compound” shall be construed within the context of the use of the term. It is noted that in the present invention, where relevant, chiral atoms are represented by an asterisk (*) next to the carbon atom. The symbol ----- is used to signify a single or double bond according to the context in which the bond is used. It is noted that where a substituent should be present in context but is not specifically signified, it is understood that such substituent represents a hydrogen (H) atom.

20

The term “patient” or “subject” is used throughout the specification to describe an animal, generally a mammal and preferably a human, to whom treatment, including prophylactic treatment, with the compositions according to the present invention is provided. For treatment of those infections, conditions or disease states which are specific for a specific animal such as a human patient, the term patient refers to that specific animal.

25

The term “effective” is used herein, unless otherwise indicated, to describe an amount of a compound or composition or component which, in context, is used to produce or effect an intended result, whether that result relates to the treatment of a viral, microbial or other disease state, disorder or condition associated with HIV, ARC or AIDS or alternatively, is used to produce another compound, agent or composition. This term subsumes all other effective amount or effective concentration terms which are otherwise described in the present application.

30

The term “scaffold” is used to mean a pyridinone chemical structure containing at least three substituents on this scaffold, one of which is the diketocarboxamide moiety as otherwise defined herein, and the other two are benzyl groups of which R₁, R₂, R₃ and R₄ are as defined herein.

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The term “prevention” is used within context to mean “reducing the likelihood” of a condition or disease state from occurring as a consequence of administration or concurrent administration of one or more compounds or compositions according to the present invention, alone or in combination with another agent. Thus, the term prevention is used within the context of a qualitative measure and it is understood that the use of a compound according to the present invention to reduce the likelihood of an occurrence of a condition or disease state as otherwise described herein will not be absolute, but will reflect the ability of the compound to reduce the likelihood of the occurrence within a population of patients or subjects in need of such prevention.

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The term “human immunodeficiency virus” or “HIV” shall be used to describe human immunodeficiency viruses 1 and 2 (HIV-1 and HIV-2).

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The terms “ARC” and “AIDS” refer to syndromes of the immune system caused by the human immunodeficiency virus, which are characterized by susceptibility to certain diseases and T cell counts which are depressed compared to normal counts. HIV progresses from Category 1 (Asymptomatic HIV Disease) to Category 2 (ARC), to Category 3 (AIDS), with the severity of the disease.

25

A Category 1 HIV infection is characterized by the patient or subject being HIV positive, asymptomatic (no symptoms) and having never had fewer than 500 CD4 cells. If the patient has had any of the AIDS-defining diseases listed for categories 2 (ARC) or 3 (AIDS), then the patient is not in this category. If the patient’s t-cell count has ever dropped below 500, that patient is considered either Category 2 (ARC) or Category 3 (AIDS).

A Category 2 (ARC) infection is characterized by the following criteria: The patient's T-cells have dropped below 500 but never below 200, and that patient has *never* had any Category 3 diseases (as set forth below) but have had at least one of the following

5 defining illnesses --

- Bacillary angiomatosis
- Candidiasis, oropharyngeal (thrush)
- Candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to therapy
- Cervical dysplasia (moderate or severe)/cervical carcinoma in situ
- 10 ○ Constitutional symptoms, such as fever (38.5 C) or diarrhea lasting longer than 1 month
- Hairy leukoplakia, oral
- Herpes zoster (shingles), involving at least two distinct episodes or more than one dermatome
- 15 ○ Idiopathic thrombocytopenic purpura
- Listeriosis
- Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess
- Peripheral neuropathy

20 According to the U.S. government, in Category 2 ARC, the immune system shows some signs of damage but it isn't life-threatening.

A Category 3 (AIDS) infection is characterized by the following criteria:

your T-cells have dropped below 200 or

25 you have had at least one of the following defining illnesses --

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical cancer, invasive**
- Coccidioidomycosis, disseminated or extrapulmonary
- 30 ○ Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (greater than 1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)

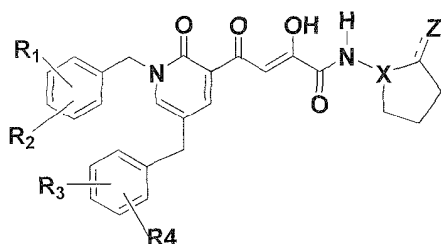
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcer(s) (greater than 1 month's duration); or bronchitis, pneumonitis, or esophagitis
- 5 ○ Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (greater than 1 month's duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- 10 ○ Lymphoma, primary, of brain
- Mycobacterium avium complex or M. kansasii, disseminated or extrapulmonary
- Mycobacterium tuberculosis, any site (pulmonary** or extrapulmonary)
- Mycobacterium, other species or unidentified species, disseminated or
- 15 extrapulmonary
- Pneumocystis carinii pneumonia
- Pneumonia, recurrent**
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent
- 20 ○ Toxoplasmosis of brain
- Wasting syndrome due to HIV

The term “coadministration” shall mean that at least two compounds or compositions are administered to the patient at the same time, such that effective amounts or concentrations of each of the two or more compounds may be found in the patient at a given point in time.

- 25 Although compounds according to the present invention may be co-administered to a patient at the same time, the term embraces both administration of two or more agents at the same time or at different times, provided preferably that effective concentrations of coadministered compounds or compositions are found in the subject at a given time. The term
- coadministration also encompasses, in certain instances, the serial administration of agents
- 30 which are administered serially in a patient to produce an intended effect, regardless of the time of administration and concentration of agent found in the subject.

The term “independently” is used herein to indicate that a variable, which is independently applied, varies independently from application to application.

The present invention is directed to compounds of the general molecular formula I, combinations thereof, or pharmaceutically acceptable salts thereof, in the inhibition of HIV integrase, the inhibition, prevention which reduces the likelihood of or treatment of HIV infections and in the treatment of AIDS and ARC. Compounds of formula I are defined as follows:



Formula I

including chiral isomers, geometric isomers, tautomers, regioisomers, and pharmaceutically acceptable salts thereof, wherein the pyridinone scaffold and R, X, Z groups are as otherwise defined in the specification

Wherein R₁, R₂, R₃ and R₄ are each independently H or a halogen (F, Cl, Br or I, preferably F);

X and Z are each independently represented by the following:

X = CH (carbon center is chiral)

X = N (center is achiral)

Z = -OH (carbon carrying OH which is sp³ hybridized and chiral); and

Z = =O (a keto group; i.e., a carbon carrying oxygen which is sp² hybridized and achiral).

In preferred compounds according to the present the invention, R₁, R₂, R₃ and R₄ are as follows:

R₁ = o-F, R₂ = H, R₃ = p-F, R₄ = o-F (by way of convention, for example, o-F represents an ortho substituted fluorine, p-F represents a para substituted fluorine)

R₁ = p-F, R₂ = H, R₃ = p-F, R₄ = o-F

R₁ = o-F, R₂ = o-F, R₃ = o-F, R₄ = H

R₁ = o-F, R₂ = H, R₃ = o-F, R₄ = o-F

$R_1 = \text{o-F}$, $R_2 = \text{H}$, $R_3 = \text{p-F}$, $R_4 = \text{H}$

$R_1 = \text{o-F}$, $R_2 = \text{p-F}$, $R_3 = \text{p-F}$, $R_4 = \text{o-F}$

$R_1 = \text{o-F}$, $R_2 = \text{o-F}$, $R_3 = \text{o-F}$, $R_4 = \text{o-F}$

5 X is CH or N; and

Z is OH or =O, or a pharmaceutically acceptable salt or ester thereof.

Also embraced by the present invention are pharmaceutical compositions useful for inhibiting HIV integrase, comprising an effective amount of a compound of this invention as described herein, and a pharmaceutically acceptable carrier, additive or excipient.

10 Pharmaceutical compositions useful for treating infection by HIV or for treating AIDS or ARC are also included by the present invention. The present invention also includes methods for inhibiting the viral enzyme, HIV integrase, and a method of inhibiting HIV growth and/or replication, or treating an HIV infection or for treating AIDS or ARC in a patient in need thereof.

15 In addition, the present invention is directed to a pharmaceutical composition comprising, in combination, a therapeutically effective amount of a compound of the present invention in combination with a therapeutically effective amount of an agent for the treatment of AIDS selected from (i) an AIDS or HIV antiviral agent, (ii) an anti-infective agent, (iii) an immunomodulator, (iv) other useful therapeutic agents including antibiotics and other

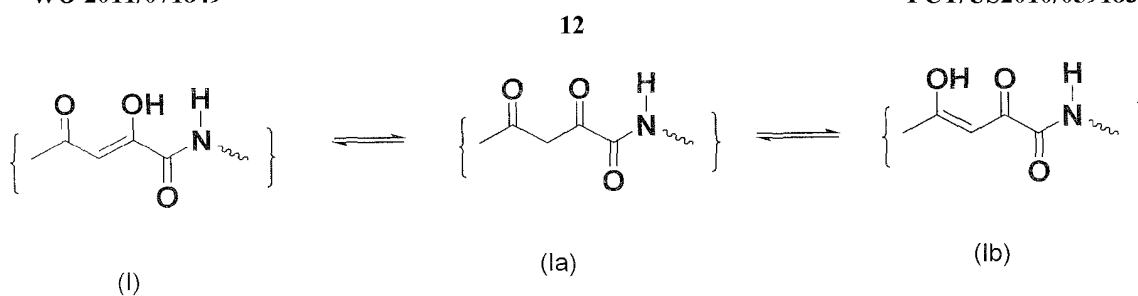
20 antiviral agents.

The compounds of the present invention also embrace regioisomers with respect to the pyridinone scaffold and R_1 , R_2 , R_3 and R_4 and these regioisomeric forms are included in the present invention. The compounds also embrace geometric isomers and these forms are also

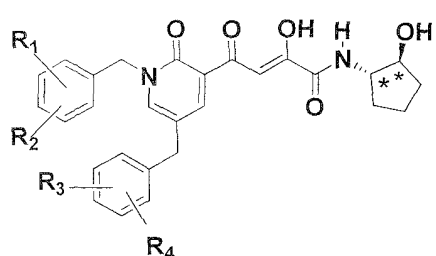
25 included in the present invention.

Tautomeric forms may also exist with compounds of the present invention. Thus, the terminology "and tautomers thereof" is used in describing tautomeric forms of compounds of formula I such as Ia and Ib (shown below). By naming compounds as being represented by

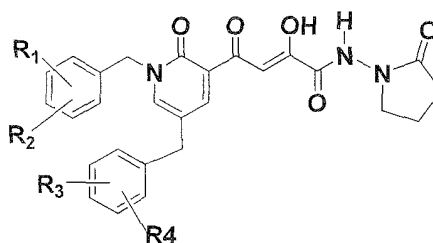
30 the general formula I and tautomers thereof, it is understood that for the purposes of the present invention that tautomers Ia and Ib are also included. Similarly, by referring to compound (Ia), it is understood for the purposes of the present application that tautomers (I) and (Ib) are also intended to be included. The same holds true for references to tautomer (Ib).



The compounds of the present invention have both chiral (asymmetric) and achiral (symmetric) centers. Thus, optical isomers resulting from the presence of asymmetric centers represent a further aspect of the present invention. Examples of both chiral and achiral compounds are shown below in Figure 2.



Chiral – Optically Active



Achiral – Optically Inactive

Figure 2

When the variables involving R_1 , R_2 , R_3 , and R_4 occur more than once in any formula I, the definition on each occurrence is independent of its definition at every other occurrence. Regioisomeric pyridinones, in addition to those structurally identified, are also part of this invention. Combinations of pyridinones and variables are permissible only if, in context, such combinations result in stable compounds.

Particular compounds of structural formula I include:

1. (1S,2S)-4-(5-(2,4-difluorobenzyl)-1-(2-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide
2. (1R,2R)-4-(5-(2,4-difluorobenzyl)-1-(2-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide
3. 4-(5-(2,4-difluorobenzyl)-1-(2-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-4-oxo-N-(2-oxopyrrolidin-1-yl)but-2-enamide
4. (1S,2S)-4-(5-(2,4-difluorobenzyl)-1-(4-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide
5. (1R,2R)-4-(5-(2,4-difluorobenzyl)-1-(4-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide

6. 4-(5-(2,4-difluorobenzyl)-1-(4-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-4-oxo-N-(2-oxopyrrolidin-1-yl)but-2-enamide
7. (1S,2S)-4-(1-(2-fluorobenzyl)-5-(4-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide
- 5 8. (1R,2R)-4-(1-(2-fluorobenzyl)-5-(4-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide
9. 4-(1-(2-fluorobenzyl)-5-(4-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-4-oxo-N-(2-oxopyrrolidin-1-yl)but-2-enamide
- 10 10. (1S,2S)-4-(1-(2,6-difluorobenzyl)-5-(2-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide
11. (1R,2R)-4-(1-(2,6-difluorobenzyl)-5-(2-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide
12. 4-(1-(2,6-difluorobenzyl)-5-(2-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-4-oxo-N-(2-oxopyrrolidin-1-yl)but-2-enamide
- 15 13. (1S,2S)-4-(1,5-bis(2,4-difluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide
14. (1R,2R)-4-(1,5-bis(2,4-difluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide
- 20 15. 4-(1,5-bis(2,4-difluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-4-oxo-N-(2-oxopyrrolidin-1-yl)but-2-enamide
16. (1S,2S)-4-(5-(2,6-difluorobenzyl)-1-(2-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide
17. (1R,2R)-4-(5-(2,6-difluorobenzyl)-1-(2-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide
- 25 18. 4-(5-(2,6-difluorobenzyl)-1-(2-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-4-oxo-N-(2-oxopyrrolidin-1-yl)but-2-enamide
19. (1S,2S)-4-(1,5-bis(2,6-difluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide
20. (1R,2R)-4-(1,5-bis(2,6-difluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide
- 30 21. 4-(1,5-bis(2,6-difluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-4-oxo-N-(2-oxopyrrolidin-1-yl)but-2-enamide

35 The compounds of the present invention are useful in the inhibition of HIV integrase, the prevention, the likelihood of reduction of and/or treatment of infection by HIV and in the treatment of the disease known as AIDS. Treating AIDS or preventing or treating infection by HIV is defined as including the treatment of a wide range of states of HIV infection: AIDS, ARC and actual or potential exposure to HIV (e.g., through blood transfusion,

40 exchange of body fluids, bites, needle punctures, exposure to infected patient blood during medical or dental procedures, and other means, such patients or subjects being considered at risk for HIV infection).

Other applications are also part of this invention. For example, the compounds of this invention are useful in the preparation and execution of screening assays for antiviral compounds including in the isolation of viral enzyme mutants and in further understanding of the enzyme, HIV integrase.

5

The present invention also provides for the use of a compound of structural formula (I) to make a pharmaceutical composition useful for inhibiting HIV integrase and in the treatment of AIDS or ARC.

10 The compounds of the present invention may be administered in the form of well-known “pharmaceutically acceptable” salts. The latter is intended to include all acceptable salts such as acetate, lactobionate, benzenesulfonate, laurate, benzoate, malate, bicarbonate, maleate, bisulfate, mandelate, bitartrate, mesylate, borate, methylbromide, bromide, methylnitrate, calcium edetate, camsylate, mucate, carbonate, napsylate, chloride, nitrate, clavulanate, N-
15 methylglucamine, citrate, ammonium salt, dihydrochloride, oleate, edetate, oxalate, edisylate, pamoate, estolate, palmitate, esylate, fumarate, phosphate, diphosphate, gluceptate, polygalacturonate, gluconate, salicylate, glutamate, stearate, glycolylarsanilate, sulfate, hexylresorcinate, subacetate, hydrabamine, succinate, hydrobromide, tannate, hydrochloride, tartrate, hydroxynaphthoate, teoclate, iodide, tosylate, isothionate, triethiodide, lactate,
20 panoate, valerate, and others which can be used as a dosage form for modifying the solubility or hydrolysis characteristics or can be used in sustained release or pro-drug formulations. The pharmaceutically acceptable salts of this invention include those with counterions such as sodium, potassium, calcium, lithium, magnesium, zinc, and from bases such as ammonia, ethylenediamine, N-methyl-glutamine, lysine, arginine, ornithine, choline, N, N’-
25 dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)aminomethane, and tetramethylammonium hydroxide, among numerous others.

Also, in the case of an alcohol group being present, pharmaceutically acceptable esters
30 may be employed, e.g., acetate, maleate, pivaloyloxymethyl and others, more preferably C₁-C₂₀ esters (preferably C₂ to C₁₂ esters) and those esters known in the art for improving solubility or hydrolysis characteristics for use as sustained release or pro-drug formulations.

Therapeutically effective amounts of the compounds of the present invention may be administered to patients orally, parenterally, by inhalation spray, topically, or rectally, in dosage unit formulations containing pharmaceutically-acceptable carriers, adjuvants and vehicles including nanoparticle drug delivery approaches. The term “pharmaceutically acceptable” is meant to infer that the carrier, diluent, excipient or other additive is biologically compatible with the other ingredients of the formulation and not deleterious to the patient or recipient. Pharmaceutical compositions are in pharmaceutical dosage form and may be administered in the form of orally-administrable suspensions or tablets, nasal sprays and injectible preparations (injectible aqueous or oleagenous suspensions or suppositories). This method of treatment is part of the invention. The administration approaches used (e.g., orally as solution or suspension, immediate release tablets, nasal aerosol or inhalation, injectible solutions or suspensions or rectally administered in the form of suppositories) involve techniques that are well-known in the art of pharmaceutical formulation.

The compounds of this invention can be administered orally to humans in a preferred form (such as tablets) and in an effective amount within a preferred dosage range of about 0.05 to 200 mg/kg, more preferably about 0.1 to about 25 mg/kg body weight in divided doses. The specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including compound activity, compound metabolism and duration of action, patient age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the condition of the patient undergoing therapy.

The present invention also includes therapeutically effective combinations of the HIV integrase inhibitor compounds of formula I with one or more other therapeutic agents such as AIDS antivirals, other antiviral agents, immunomodulators, antiinfectives, antibiotics, vaccines or other therapeutic agents. Some examples are given below.

**ANTIVIRAL AGENTS, ANTI-INFECTIVES, IMMUNOMODULATORS,
OPPORTUNISTIC INFECTION DRUGS, OTHER RELEVANT DRUGS IN AIDS**

<u>Drug Name</u>	<u>Manufacturer</u>	<u>Therapeutic Use</u>
097	Hoechst/Bayer	HIV infection, AIDS, ARC (NNRT inhibitor)
Amprénivir	Glaxo Wellcome	HIV infection, AIDS,

141W94, GW141		ARC (protease inhibitor)
Abacavir (1592U89) GW 1592	Glaxo Wellcome	HIV infection, AIDS, ARC (RT inhibitor)
Acemannan	Carrington Labs (Irving, TX)	ARC
Acyclovir	Burroughs Wellcome	HIV infection, AIDS, ARC, in combination with AZT
AD-439	Tanox Biosystems	HIV infection, AIDS, ARC
AD-519	Tanox Biosystems	HIV infection, AIDS, ARC
Adefovir dipivoxil AL-721	Gilead Sciences Ethigen (Los Angeles, CA)	HIV infection ARC, PGL HIV positive, AIDS
Alpha Interferon	Glaxo Wellcome	Kaposi's sarcoma, HIV in combination w/Retrovir
Ansamycin LM 427	Adria Laboratories (Dublin, OH) Erbamont (Stamford, CT)	ARC
Antibody which neutralizes pH labile alpha aberrant Interferon AR 177	Advanced Biotherapy Concepts (Rockville, MD)	AIDS, ARC
	Aronex Pharm	HIV infection, AIDS, ARC
Beta-fluoro-ddA	National Cancer Institute	AIDS-associated diseases
BMS-232623 (CGP-73547)	Bristol-Myers Squibb/Novartis	HIV infection, AIDS, ARC (protease inhibitor)
BMS-234475 (CGP-61755)	Bristol-Myers Squibb/Novartis	HIV infection, AIDS, ARC (protease inhibitor)
CI-1012	Warner-Lambert	HIV-1 infection
Cidofovir	Gilead Science	CMV retinitis, herpes, papillomavirus
Curdlan sulfate	AJI Pharma USA	HIV infection
Cytomegalovirus Immune globin	MedImmune	CMV retinitis

Cytovene Ganciclovir	Syntex	Sight threatening CMV Peripheral CMV Retinitis
ddI Dideoxyinosine	Bristol-Myers Squibb	HIV infection, AIDS, ARC; combination with AZT/d4T
DMP-450	AVID (Camden, NJ)	HIV infection, AIDS, ARC (protease inhibitor)
Efavirenz (DMP-266)	DuPont Merck	HIV infection, AIDS, ARC (non-nucleoside RT inhibitor)
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
Famciclovir	Smith Kline	Herpes zoster, herpes simplex
FTC	Emory University	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
GS 840	Gilead	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
HBV097	Hoechst Marion Roussel	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
Hypericin	VIMRx Pharm.	HIV infection, AIDS, ARC
Recombinant Human Interferon Beta	Triton Biosciences (Alameda, CA)	AIDS, Kaposi's sarcoma, ARC
Interferon alfa-n3	Interferon Sciences	ARC, AIDS
Indinavir	Merck	HIV infection, AIDS, ARC, asymptomatic HIV positive; combination with AZT/ddI/ddC
Isentress (Raltegravir)	Merck	HIV infection, AIDS, ARC (integrase inhibitor)
ISIS-2922	ISIS Pharmaceuticals	CMV retinitis
KN1-272	Natl. Cancer Institute	HIV-associated diseases
Lamivudine, 3TC	Glaxo Wellcome	HIV infection, AIDS, ARC (reverse

		transcriptase inhibitor); also with AZT
Lobucavir	Bristol-Myers Squibb	CMV infection
Nelfinavir	Agouron Pharmaceuticals	HIV infection, AIDS, ARC (protease inhibitor)
Nevirapine	Boehringer Ingelheim	HIV infection, AIDS, ARC (RT inhibitor)
Novapren	Novaferon Labs, Inc. (Akron, OH)	HIV inhibitor
Peptide T Octapeptide Sequence	Peninsula Labs (Belmont, CA)	AIDS
Trisodium Phosphonoformate	Astra Pharm. Products, Inc.	CVV retinitis, HIV infection, other CMV
PNU-140690	Pharmacia Upjohn	HIV infection, AIDS, ARC (protease inhibitor)
Probucol	Vyrex	HIV infection, AIDS
RBC-CD4	Sheffield Med. Tech (Houston, TX)	HIV infection, AIDS, ARC
Ritonavir	Abbott	HIV infection, AIDS, ARC (protease inhibitor)
Saquinavir	Hoffmann-LaRoche	HIV infection, AIDS, ARC (protease inhibitor)
Stavudine; d4T Didehydrodeoxythymidine	Bristol-Myers Squibb	HIV infection, AIDS, ARC
Valaciclovir	Glaxo Wellcome	Genital HSV & CMV infections
Virazole Ribavirin	Viratek/ICN (Costa Mesa, CA)	Asymptomatic HIV positive, LAS, ARC
VX-478	Vertex	HIV infection, AIDS, ARC
Zalcitabine	Hoffmann-LaRoche	HIV infection, AIDS, ARC with AZT
Zidovudine; AZT	Glaxo Wellcome	HIV infection, AIDS, ARC, Kaposi's sarcoma,

Tenofovir diisoproxil fumarate salt (Viread [®])	Gilead	in combination with other therapies HIV infection, AIDS, (RT inhibitor)
Combivir [®]	GSK	HIV infection, AIDS, (RT inhibitor)
Abacavir succinate (or Ziagen [®])	GSK	HIV infection, AIDS, (reverse transcriptase inhibitor)
Fuzeon [®] (or T-20)	Roche/Trimeris	HIV infection, AIDS, viral Fusion inhibitor
AS-101	Wyeth-Ayerst	AIDS
Bropirimine Acemannan	Pharmacia Upjohn Carrington Labs, Inc. (Irving, TX)	Advanced AIDS AIDS, ARC
CL246, 738	American Cyanamid Lederle Labs	AIDS, Kaposi's sarcoma
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
FP-21399	Fuki Immuno PHARM	Blocks HIV fusion with CD4+ cells
Gamma Interferon	Genentech	ARC, in combination w/TNF
Granulocyte Macrophage Colony Stimulating Factor	Genetics Institute Sandoz	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Hoeschst-Roussel Immunex	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Schering-Plough	AIDS, combination w/AZT
HIV Core Particle Immunostimulant	Rorer	Seropositive HIV
IL-2 Interleukin-2	Cetus	AIDS, in combination w/AZT

IL-2 Interleukin-2	Hoffman-LaRoche Immunex	AIDS, ARC, HIV, in combination w/AZT
IL-2 Interleukin-2 (aldeslakin)	Chiron	AIDS, increase in CD4 cell counts
Immune Globulin Intravenous (human)	Cutter Biological (Berkeley, CA)	Pediatric AIDS, in combination w/AZT
IMREG-1	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
IMREG-2	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
Imuthiol Diethyl Dithio Carbamate Alpha-2 Interferon	Merieux Institute Schering Plough	AIDS, ARC Kaposi's sarcoma w/AZT, AIDS
Methionine-Enkephalin	TNI Pharmaceutical (Chicago, IL)	AIDS, ARC
MTP-PE Muramyl-Tripeptide	Ciba-Geigy Corp.	Kaposi's sarcoma
Granulocyte Colony Stimulating Factor	Amgen	AIDS, in combination w/AZT
Remune rCD4 Recombinant Soluble Human CD4-IgG rCD4-IgG Hybrids	Immune Response Corp. Genentech	Immunotherapeutic AIDS, ARC AIDS, ARC
Recombinant Soluble Human CD4 Interferon Alfa 2a	Biogen Hoffman-LaRoche	AIDS, ARC Kaposi's sarcoma, AIDS, AR, combination w/AZT
SK&F1-6528 Soluble T4	Smith Kline	HIV infection
Thymopentin	Immunobiology Research Institute (Annandale, NJ)	HIV infection
Tumor Necrosis Factor (TNF)	Genentech	ARC, in combination w/gamma Interferon
AK602	Kumam	HIV infection (entry and

	oto Univers ity Japan Medivir, UK Ltd.	fusion inhibitor)
Alovudine		HIV infection (nucleoside RT inhibitor)
Amdoxovir	RFS Pharma, LLC	Treatment of HIV and HBV infections (nucleoside RT Inhibitor)
AMD070	AnorMED, Inc.	HIV infection (entry and fusion inhibitor)
Atazanavir (Reyataz)	Bristol -Myers Squibb	HIV infection (protease inhibitor)
AVX754 (apricitabine)	Avexa Ltd.	HIV infection (nucleoside RT inhibitor)
Bevirimat	Panacos Pharmaceuticals	HIV infection (maturation inhibitor)
BI-201	BioInvent	HIV infection (gene therapy, blocks HIV tat gene).
BMS-378806	Bristol - Myers Squibb	HIV infection (entry inhibitor)
BMS-488043	Bristol - Myers Squibb	HIV infection (entry and fusion inhibitor)
BMS-707035	Bristol - Myers Squibb	HIV infection (integase inhibitor)
C31G	Cellegy Pharmaceuticals, Inc	HIV infection and other sexually transmitted diseases (STDs)
Carbopol 974P	ReProtect, LLC	Sexual transmission of HIV
Calanolide A	Sarawak MediChem Pharmaceuticals, Inc.	HIV infection (non- nucleoside RT inhibitor)
Carrageenan	FMC Biopolymer	HIV microbicide
Cellulose sulfate	Polydex Pharmaceuticals,	Prevention of HIV

	Ltd.	infection and other sexually transmitted diseases
Cyanovirin-N	Cellegy Pharmaceuticals, Inc.	Prevention of sexual transmission of HIV infection
Darunavir	Tibotec	HIV infection (co-administered with ritonavir)
Delavirdine	Pfizer	HIV infection (non-nucleoside RT inhibitor)
Dextran sulfate	Ueno Fine Chemicals Industry, Ltd.	Prevention of transmission of HIV
Didanosine (Videx, Videx EC)	Bristol - Myers Squibb	HIV infection (nucleoside RT inhibitor)
Efavirenz	Bristol - Myers Squibb	HIV infection (non-nucleoside RT inhibitor)
Elvucitabine	Achillion Pharmaceuticals	HIV infection (nucleoside RT inhibitor)
Emtricitabine	Gilead Sciences	HIV infection (nucleoside RT inhibitor)
Fosamprenavir (Lexiva)	GlaxoSmithKline	HIV infection (protease inhibitor)
Fozivudine tidoxil	Heidelberg Pharma	HIV infection (entry and fusion inhibitor)
GS 9137	Gilead Sciences	HIV infection (integrase inhibitor)
GSK-873,140 (aplaviroc)	GlaxoSmithKline	HIV infection (entry and fusion inhibitor)
GSK- 364735	GlaxoSmithKline	HIV infection (integrase inhibitor)
GW640385 (brecanavir)	GlaxoSmithKline	HIV infection (protease inhibitor)
HG0004	Human Genome Sciences	HIV infection (entry and fusion inhibitor)
HGTV43	Enzo Therapeutics	HIV infection (antisense

		drug)
Hydroxyethyl cellulose	Union Carbide	Prevent sexual transmission of HIV
INCB9471	Incyte Corporation	HIV infection (entry and fusion inhibitor)
KP-1461	Koronis Pharmaceuticals	HIV infection (nucleoside RT inhibitor)
Lopinavir	Abbott Laboratories	HIV infection (protease inhibitor)
Mifepristone (VGX410, RU486)	Viral Genomix	HIV infection (gene therapy, interferes with vpr)
MK-0518	Merck	HIV infection (integrase inhibitor)
PA-457 (bevrimat)	Panacos Pharmaceuticals, Inc.	Treatment of HIV (maturation inhibitor)
Poly(I)-Poly(C12U) (Ampligen)	Hemispherx Biopharma, Inc.	Biological response modifier
PPL-100	Merck	HIV infection (protease inhibitor)
PRO 140	Progenics Pharmaceuticals, Inc.	HIV infection (entry and fusion inhibitor)
PRO 542	Progenics Pharmaceuticals, Inc.	HIV infection (entry and fusion inhibitor)
PRO 2000	Indevus Pharmaceuticals, Inc.	Microbicide
Racivir	Pharmasset, Inc.	HIV infection (nucleoside RT inhibitor)
SCH-D (vicriviroc)	Schering - Plough Corp	HIV infection (entry and fusion inhibitor)
SP01A	Samaritan Pharmaceuticals	HIV infection (entry and fusion inhibitor)
SPL7013 TAK-652	Starpharma Takeda	Microbicide HIV infection (entry and fusion inhibitor)

Tipranavir (Aptivus)	Boehringer Ingelheim Pharmaceuticals	HIV infection (protease inhibitor)
TNX-355	Tanox, Inc.	HIV infection (entry and fusion inhibitor)
TMC125 (etravirine)	Tibotec	HIV infection (non-nucleoside RT inhibitor)
UC-781	Cellegy Pharmaceuticals, Inc	Microbicide
UK-427,857 (Maraviroc) website: aidsinfo.nih.gov/DrugsNew/DrugDetailNT.aspx?MenuItem=Drugs&Search=On&int_id=408	Pfizer	HIV infection (entry and fusion inhibitor)
Valproic acid	Abbott	Treating seizures in HIV infection
VRX496	VIRxSYS	Gene therapy
Zalcitabine (Hivid)	Roche	HIV infection (nucleoside T inhibitor)
Valganciclovir (Valcyte)	Roche	Antiviral (CMV retinitis in AIDS)
Clindamycin with Primaquine	Pharmacia Upjohn	PCP
Fluconazole	Pfizer	Cryptococcal meningitis, candidiasis
Pastille Nystatin Pastille	Squibb Corp.	prevention of oral candidiasis
Ornidyl Eflornithine	Merrell Dow	PCP
Pentamidine Isethionate (IM & IV)	LyphoMed (Rosemont, IL)	PCP treatment
Trimethoprim Trimethoprim/sulfa		Antibacterial Antibacterial
Piritrexim	Burroughs Wellcome	PCP treatment

Pentamidine isethionate	Fisons Corporation	PCP prophylaxis
Spiramycin	Rhone-Poulenc	Cryptosporidial diarrhea
Intraconazole-R51211	Janssen Pharm	Histoplasmosis; cryptococcal meningitis
Trimetrexate	Warner-Lambert	PCP
Daunorubicin	NeXstar, Sequus	Karposi's sarcoma
Recombinant Human Erythropoietin	Ortho Pharm. Corp.	Severe anemia associated w/AZT therapy
Recombinant Human Growth Hormone	Serono	AIDS-related wasting, cachexia
Megestrol Acetate	Bristol-Myers Squibb	Treatment of anorexia associated w/AIDS
Testosterone	Alza, Smith Kline	AIDS-related wasting
Total Enteral Nutrition	Norwich Eaton Pharmaceuticals	Diarrhea and malabsorption in AIDS
Aldesleukin (Proleukin)	Chiron Corp	Biological response modifier
Amphotericin B (Abelecet, AmBisome, Amphocin, Amphotec, Fungizone)	Pfizer, Bristol - Myers Squibb	Antifungal
Azithromycin (Zithromax)	Pfizer	Antibacterial antibiotic
Calcium hydroxyapatite (Radiessse)	Bioform Medical, Inc.	Dermal filler
Doxorubicin (liposomal) (Doxil)	Ortho Biotech, Alza Corporation	Antineoplastic
Dronabinol (Marinol)	Unimed Pharmaceuticals, Inc.	Antiemetics
Entecavir (Baraclude)	Bristol-Myers Squibb	Antiviral
Epoetin alfa (Epogen, Procrit)	Ortho Biotech	Anemia
Etoposide (Etopophos (phosphate salt), Toposar, VePesid)	Pfizer, Bristol-Myers Squibb	Antineoplastic
Fluconazole (Diflucan)	Pfizer	Antifungal

Interferon alfa-2 (Intron A (2b), Roferon-A (2a))	Roche, Schering –Plough	Biological response modifiers
Isoniazid (Nydrazid)	Sandoz, Hoffmann La-Roche	Antimycobacterial
Itraconazole (Sporanox)	Ortho Biotech, Janssen Pharmaceutica	Antifungal
Megestrol (Megace, Megace ES)	Bristol - Myers Squibb	Anticachectic
Paclitaxel (Onxol, Taxol)	Bristol - Myers Squibb, IVAX Pharmaceuticals	Antineoplastic
Peginterferon alfa-2 (PEG-Intron (2b), Pegasys (2a))	Roche, Schering –Plough	Antiviral
Pentamidine (Nebupent)	American Pharmaceutical Partners, Fujisawa Health Care, Inc.	Antiprotozoal
Poly-L-lactic acid (Sculptra)	Dermik Laboratories	Dermal Filler
Rifabutin (Mycobutin)	Pharmacia Corporation	Antimycobacterial
Rifampin (Rifadin, Rimactane)	Aventis Pharmaceuticals	Antimycobacterial
Somatropin	Pharmacia Corporation, Serono Inc	Synthetic human growth hormone
Sulfamethoxazole / Trimethoprim (Bactrim, Septra) (Serostim)	Alpha care Inc, Women First Health Care, King Pharmaceuticals	Antibacterial
Testosterone (Androderm, Androgel, Depo-Testosterone)	Pfizer Inc, Unimed Pharmaceuticals, Inc., Alza Corporation, Watson Laboratories	Androgens
Trimetrexate (Neutrexin)	United States Bioscience Inc, Medimmune, Inc.	Antiprotozoal

The combinations of the compounds of this invention with AIDS antivirals (including anti-HIV integrase-based antivirals), other antivirals, immunomodulators, anti-infectives,

antibiotics, vaccines, other therapeutic agents are not limited to the list in the above Table, but includes, in principle, any combination with any pharmaceutical composition useful for the treatment against infection by HIV or for treating AIDS or ARC. Preferred combinations are simultaneous or alternating treatments of a compound of the present invention and a

5 protease inhibitor (e.g., indinavir, nelfinavir, ritonavir, saquinavir and others), a reverse transcriptase inhibitor [nucleoside (e.g., AZT, 3TC, ddC, ddI, d4T, abacavir and others, and/or non-nucleoside (e.g., efavirenz, nevirapine, and others), or some combination of two or more of these inhibitors (see Table above). A few representative examples of relevant patents citing combinations are: EPO 0,484,071, U.S. 5, 413,999, WO 9962513.

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In such combinations, the compound of the present invention and other active agents may be separately administered or concurrently administered (coadministered). In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

15

- (-)βDioxolane-G; DXG;
- (-)β-Arctigenin; Arctigenin ;
- (-)-Carbovir; (-)-C-D4G; (-)-Carbovir;
- (-)-β-D-2,6-Diaminopurine dioxolane; Amdoxovir; DAPD; APD
- 20 • (+)-2'-Deoxy-3'-oxa-4'-thiocytidine; dOTC (+)
- (+)-2'-Deoxy-3'-oxa-4'-thio-5-fluorocytidine; dOTFC (+)
- (+/-)-Cyclobut-G; A-69992; (+/-)-Lobucavir; C-Oxt-G; Cyclobut-G ; C-Oxetanocin-G
- (R)-2QuinCOAsnPhe[CHOHCH₂]PipCONHtBu
- (R)-3,6-Diamino-N-(aminomethyl)hexanamide; Bellenamine
- 25 • (R)-PMPA; (R)-9-(2-Phosphonylmethoxypropyl)adenine; PMPA-(R); Tenofovir
- (R)-PMPDAP; PMPDAP-(R)
- (S)-PMPA; (S)-9-(2-Phosphonylmethoxypropyl)adenine; PMPA(S)
- (S)-9-(2-Phosphonylmethoxypropyl)adenine; (S)-PMPA
- α-APA; R89439; Loviride
- 30 • α-APA deriv.; R87232
- α-APA deriv.; R88703
- α-APA enantiomer; R90385
- α-L-AZT; AZT-α-L

- α -L-DXC; α -L-Dioxalane-C; DXC- α -L-
- α -L-FTC; FTC- α -L-
- α -Monofluoromethyldehydroornithine methyl ester; MFMOME
- 1,1'-Azobisformamide; ADA; Azodicarbonamide
- 5 • 1-(11-Octylamino-10-hydroxyundecyl)-3,7-dimethylxanthine; CT-2576
- 1-(2',3'-Dideoxy-2'-fluoro- β -D-threo-pentofuranosyl)cytosine; Ro 31-6840
- 1-(2'-Fluoro-2',3'-dideoxy-B-D-erythro-pentofuranosyl)thymine; 2'FddT
- 1-(2OHPr)-4-Substit-piperazine, thienyl carbamate deriv.
- 1-(2OHPr)-4-Substit-piperazine, thienyl carbamate deriv.
- 10 • 1-(2OHPr)-4-Substit-piperazine, thienyl carbamate deriv.
- 1-(2OHPr)-4-Substit-piperazine, thienyl carbamate deriv.
- 1-[(2-Hydroxyethoxy)methyl]-6-(3-methylphenylthio)thymine; HEPT-M
- 1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)-2-thiothymine; HEPT-S
- 1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)thymine; HEPT
- 15 • 1-Deoxynojirimycin ; Deoxynojirimycin
- 141W94; VX-478; Amprenavir; Agenerase®; Approved
- 1592U89 Succinate; Abacavir Succinate; Ziagen® Approved
- 1-Aminooxyethylamine; AEA
- 1-Methoxyoxalyl-3,5-dicaffeoylquinic acid; 1-MO-3,5-DCQA; Dicaffeoylquinic acid deriv.
- 20 • 1OH-2(Cbz-Tle)3PhPr [14]paracyclophane deriv.
- 1OH-2(Cbz-ValNH)3PhPr [13]metacyclophane deriv.
- 1OH-2(Cbz-ValNH)3PhPr [13]paracyclophane deriv.
- 1OH-2(Cbz-ValNH)3PhPr [14]paracyclophane deriv.
- 1OH-2(Cbz-ValNH)3PhPr [17]paracyclophane deriv.
- 25 • 12-Deoxyphorbol-13-(3E,5E-decadienoate); Phorbol deriv.
- 16.alpha.-Bromoepiandrosterone; Epi-Br; ; Inactivin; HE 2000; HE2000; PPB2; DHEA deriv.
- 1- β -D-arabinofuranosyl-5-(2-bromovinyl)uracil; BV-ara-U; BVaraU; BV ara-U; Sorivudine; SQ-32756; Bravavir; Brovavir; Usevir; YN-72; Bromovinyl araU; BVAU
- 30 • 2',3'-Didehydro-3'-deoxycytidine; D4C
- 2',3'-Dideoxydidehydroguanosine; D4G
- 2',3'-Didehydro-3'-deoxythymidine; D4T; Stavudine; Zerit® Approved
- 2',3'-Dideoxy-3'-fluoro-4-thiothymidine; 3'-F-4-Thio-ddT

- 2',3'-Dideoxy-3'-fluoro-5-bromouridine; FddBrU
- 2',3'-Dideoxy-3'-fluoro-5-chlorocytidine; 3'-F-5-Cl-ddC
- 2',3'-Dideoxy-3'-fluoro-5-chlorouridine; 935U83; 5-Chloro-2',3'-dideoxy-3'-fluorouridine; FddCIU; Raluridine
- 5 • 2',3'-Dideoxy-5-ethylcytidine; 5-Et-ddC
- 2',3'-Dideoxyadenosine; D2A; ddAdo; ddA
- 2',3'-Dideoxydidehydroadenosine; d4A
- 2',3'-Dideoxyguanosine; D2G; ddG
- 2',3'-Dideoxy-3'-hydroxymethyl cytidine; 3'-Hydroxymethyl-ddC; BEA-005
- 10 • 2,5'-Anhydro-3'-azido-2',3'-dideoxyuridine; AZU-2,5'-anhydro
- 2,5'-Anhydro-3'-azido-3'-deoxythymidine; AZT-2,5'-anhydro
- 2',5'diSilySpiroT; TSAO-T
- 2',5'diSilySpiroT; TSAO-me³T
- 2,6-Diamino-2',3'-dideoxypurine-9-ribofuranoside; ddDAPR; DAPDDR; 2,6-Diamino-ddP
- 15 • 2,6-Diaminopurine- 2',3'-dideoxydidehydroriboside; ddeDAPR
- 2,6-Diaminopurine-3'-fluoro-2',3'-dideoxyriboside; 3'-F-ddDAPR
- 2-Aminobenzylstatine Valyl Cbz deriv.; Statine deriv.
- 2-Glycine amide-5-chlorophenyl 2-pyrrol ketone; GCPK
- [2-PyridCH₂NCH₃CO-Val-NHCH(Bz)]CHOHCHOH; A-77003
- 20 • 2'-Azido-2',3'-dideoxyadenosine; 9-(2'-Azido-2',3'-dideoxy-β-D-erythropentofuranosyl)adenine; 2'-N3ddA
- 2'-FddA(B-D-threo); F-ddA; 2'-F-dd-ara-A; 9-(2'-Fluoro-2',3'-dideoxy-B-D-threopentafuranosyl)adenine; Lodensine
- 2'-N3ddA (B-D-threo); 9-(2'-Azido-2',3'-dideoxy-β-threopentafuranosyl)adenine
- 25 • 2-NaphCOAsnPhe[CHOHCH₂]Pro-OtBu
- 2-Nitrophenylphenylsulfone; NPPS
- 3-(3-Oxo-1-propenyl)-3'-azido-3'-deoxythymidine; 3-(3-Oxo-1-propenyl)AZT
- 3-(Phenylsulfonyl)-indole deriv. ; L-737,126
- 3,5-DCQA; 3,5-Dicaffeoylquinic acid; Dicaffeoylquinic acid
- 30 • 3'-Azido-2',3'-dideoxy-5-[(cyanomethyl)oxy]uridine; 3'-N3-5-Cyanomethyloxy-ddU
- 3'-Azido-2',3'-dideoxy-5-aminouridine; 3'-N3-5-NH₂-ddU
- 3'-Azido-2',3'-dideoxy-5-aza-6-deazauridine; C-analog of 3'-N3-ddU
- 3'-Azido-2',3'-dideoxy-5-bromouridine; 3'-N3-5-Br-ddU; AZddBrU

- 3'-Azido-2',3'-dideoxy-5-chlorocytidine; 3'-Az-5-Cl-ddC
- 3'-Azido-2',3'-dideoxy-5-dimethylaminouridine; 3'-N3-5-NMe2-ddU
- 3'-Azido-2',3'-dideoxy-5-ethyluridine; 3'-N3-5-EtddU; CS-85; AZddEtU
- 3'-Azido-2',3'-dideoxy-5-fluorocytidine; 3'-N3-5-F-ddC
- 5 • 3'-Azido-2',3'-dideoxy-5-fluorouridine; AZddFU
- 3'-Azido-2',3'-dideoxy-5-hydroxyuridine; 3'-N3-5-OH-ddU
- 3'-Azido-2',3'-dideoxy-5-iodouridine; 3'-N3-5-I-ddU; AZddIU
- 3'-Azido-2',3'-dideoxy-5-methylaminouridine; 3'-N3-5-NHMe-ddU
- 3'-Azido-2',3'-dideoxy-5-methylcytidine; CS-92; 3'-N3-5-Me-ddC
- 10 • 3'-Azido-2',3'-dideoxy-5-thiocyanatouridine; 3'-N3-5-SCN-ddU
- 3'-Azido-2',3'-dideoxy-5-trifluoromethyluridine; 3'-N3-5-CF3-ddU
- 3'-Azido-2',3'-dideoxycytidine; CS-91; 3'-N3-ddC
- 3'-Azido-2',3'-dideoxyguanosine; AZG; 3'-N3ddG
- 3'-Azido-2',3'-dideoxy-N4--5-dimethylcytidine; 3'-N3-N4-5-diMe-ddC
- 15 • 3'-Azido-2',3'-dideoxy-N4-OH-5-methylcytidine; 3'-N3-N4-OH-5-Me-ddC
- 3'-Azido-2',3'-dideoxyuridine; CS-87; 3'-N3ddU; AZdU; Uravidine
- 3'-Azido-3'-deoxy-6-azathymidine; 3'AZ-6AzaT
- 3-Azido-3'-deoxythymidyl-(5',5')-2',3'-dideoxy-5'-adenylic acid; AZT-P-ddA
- 3'-Azido-3'-deoxythymidyl-(5',5')-2',3'-dideoxy-5'-adenylic acid, 2-cyanoethyl ester; AZT-
- 20 P(CyE)-ddA
- 3'-Azido-3'-deoxythymidyl-(5',5')-2',3'-dideoxy-5'-inosinic acid; AZT-P-ddI
- 3'-Azido-3'-deoxythymidine-5'-(butylmethoxyvalinyl)phosphate; 5'MeOValPO3(Bu)AZT
- 3'-Azido-5-chloro-2',3'-dideoxyuridine; AzddClUrd; AzddClU
- 3'-Deoxythymidine; ddT
- 25 • 3'-FddA (B-D-Erythro); 9-(3'-Fluoro-2',3'-dideoxy-B-D-erythropentafuranosyl)adenine
- 3'-FddC; 3'-Fluoro-2',3'-dideoxycytidine
- 3'-FddG; 3'-Fluoro-2',3'-dideoxyguanosine
- 3'-FddT; Alovudine; FddT; FddThD; 3'-FLT; FLT
- 3'-FddU; 3'-Fluoro-2',3'-dideoxyuridine
- 30 • 3'-Fluoro-2',3'-dideoxy-5-iodouridine; FddIU
- 3'-N3-ddA; 9-(3'-Azido-2',3'-dideoxy-B-D-erythropentafuranosyl)adenine
- 3TC; Lamivudine; Epivir® Approved;
- Lamivudine & Zidovudine; Combivir® 3TC & AZT; Approved
- 4'-Acetoamidophenyl4-guadinobenzoate; AGB

- 4'-Az-3'-dT; 4'-Azido-3'-deoxythymidine
- 4'-Az-5CldU ; 4'-Azido-5-chloro-2'-deoxyuridine
- 4'-AzdA; 4'-Azido-2'-deoxyadenosine
- 4'-AzdC; 4'-Azido-2'-deoxycytidine
- 5 • 4'-AzdG; 4'-Azido-2'-deoxyguanosine
- 4'-AzdI; 4'-Azido-2'-deoxyinosine
- 4'-AzdU; 4'-Azido-2'-deoxyuridine
- 4'-Azido-2'-deoxy- β -D-erythro-pentofuranosyl-5-methyl-2,4-dioxypyrimidine; 4'-Azidothymidine
- 10 • 4'-Cyanothymidine; 4'-CN-T
- 4-Methyl-5-(pyrazinyl)-3H-1,2-dithiole-3-thione; Oltipraz
- 5'-[(1,4-Dihydro-1-methyl-3-pyridinylcarbonyl)oxy]-3'-azido-2',3'-deoxythymidine; DP-AZT; HP-AZT; AZT Prodrug; AZT-DHP
- 5'-[[(Z)-4-amino-2-butenyl]methylamino]-5'-deoxyadenosine; MDL 73811
- 15 • 5'-Alkylglycosidecarbonate of 3'-azido-3'-deoxythymidine; AcNHGlc-hexyl-CO₃ AZT
- 5Cl3PhS-2IndolCONH₂
- 5-Fluoro-2',3'-dideoxycytidine; 5-F-ddC
- 5-Methyl-3'-azido-2',3'-dideoxyisocytidine; MeAZddIsoC
- 6-O-Butanoylcastanospermine; BuCast; MDL 28,574; Celgosivir
- 20 • 6-Chloro-9-(2,3-dideoxy-b-D-glyceropentofuranosyl)-9H-purine; D2CIP; 6-Chloro-ddP; CPDDR; 6Cl-ddP
- 6-Dimethylaminopurine-2',3'-dideoxyriboside; N-6-dimethylddA; DMAPDDR
- 7-Chloro-N-methyl-5-(1H-pyrrol-2-yl)-3H-1,4-benzodiazepin-2-amine ; Ro 24-7429
- 7-Chloro-5-(2-pyrrolyl)-3H-1,4-benzodiazepin-2(H)-one ; Ro 5-3335
- 25 • 8-Chloro-TIBO; Tivirapine; R86183
- 9-(2,3-Dideoxy- β -D-ribofuranosyl)-6-(methylthio)purine; D2SMeP
- 9-[Bis(OHMe)cBu]A; A-69463; Cyclobutyl-A; Cyclobut-A ; C-oxetanocin A
- A-76890
- A-77212
- 30 • A-80987; Ritonavir deriv., A-81525; Ritonavir deriv., A-83962; Ritonavir deriv.
- A-98881; Azacyclic urea deriv.
- AA; L-ascorbic acid; Calcium Ascorbate
- AAP-BHAP; U-104489; PNU-104489

- Abacavir & Lamivudine & Zidovudine; Trizivir® ABC & (-)-3TC & AZT
- ABT-378; Lopinavir; Component of Kaletra; Aluviran®
- ABT-378 & ABT-538; Kaletra®; Lopinavir & Ritonavir; Aluviran® & Norvir®
- ABT-538; Norvir®; Ritonavir; Component of Kaletra; Approved
- 5 • Acemannan
- Adefovir; PMEAs; GS-0393
- Adefovir dipivoxil; BisPom PMEA; GS-840; Preveon®
- AG-1343; Viracept®; Nelfinavir; Approved
- AG1350; LY316957; Nelfinavir-octahydro-thienopyridine analog
- 10 • AHPBA analog; R-87366
- Alpha-lipoic acid; α -Lipoic acid; Thiocetic acid
- ALX40-4C
- AMD3100; JM3100
- Amprenavir phosphate; VX-175; GW433908; GW433908A (*Sodium Salt*); GW433908G
- 15 (*Calcium Salt*); Fosamprenavir
- Ancer 20; Z-100
- Anti-sense 25-mer phosphorothioate; GEM91
- Atazanavir; CGP-73547; BMS-232632; BMS 232632; Zrivada; Latazanavir; Reyataz®
- Ateviridine; U-87201E; BHAP deriv.
- 20 • Aurintricarboxylic acid; Dupont ATA; Dupont DA639; SD-095345; ATA
- AY 9944; trans-1,4-Bis(2-dichlorobenzylaminoethyl)cyclohexane dichlorhydrate
- AZT; Zidovudine; Azidothymidine; Retrovir®
- AZT-PO₃(CH₃)-AZT; O,O'-Bis(3'-azido-3'-deoxythymidin-5'-yl)methylphosphonate
- Baicalin; TJN-151
- 25 • Betulinic acid; Mairin
- Betulinic acid, 3-O-(3',3'-dimethylsuccinate)
- BHAP deriv.
- BHAP deriv.; Rescriptor® ; Delavirdine; U-90152
- BHAP deriv.; U-88204E
- 30 • BI-RG-587; Nevirapine; Viramune® Approved
- BILA 1906 BS, BILA 2011 BS; Palinavir, BILA 2185 BS
- Bis(2-nitrophenyl)sulfone; Bis(2NO₂Ph)SO₂; NSC633001
- bis-ValHOEt-N₂aza-peptide isostere; CGP 53820

- bis-ValHOEt-N2aza-peptide isostere; CGP 53820 analog
- BMS-186318
- BocPhe[CHOH(CH₂)₃CH=CHPhCO]IleAMBI; L-687,908
- BzOCValPhe[diCHOH(RR)]PheValBzOC
- 5 • BzOCValPhe[diCHOH(SS)]PheValBzOC
C2-Sym Phosphinic amide deriv. (HOECHST AG)
- Calanolide A ; NSC675451, Calanolide B
- Capravirine; S-1153
- Castanospermine
- 10 • CbzAF(CHOHCH₂)AVVOMe
- Cbz-Asn-Apns-Pro-NH-tBu; KNI-102
- CGP 61755; Lasinavir, CGP 64222
- CNI-H0294
- Coactinon;I-EBU; HEPT deriv.; MKC-442; Emivirine
- 15 • Conocurvone; NSC650891
- Coviracil; (-)FTC; (-)-2',3'-Dideoxy-5-fluoro-3'-thiacytidine; Emtricitabine; Emtriva
- C-Oxetanocin-G; A-69992; (+-)Lobucavir; C-Oxt-G; Cyclobut-G; (+-)Cyclobut-G
- Crixivan®; Indinavir; MK639; L-735,524; Approved
- Curdlan Sulfate
- 20 • CV-N; Cyanovirin-N
- Cyclic Urea Amide; SD146
- Cyclosporin A; Sandimmune®
- [Me-Ile-4]Cyclosporin A; SDZ NIM 811
- D4A (L); L-2',3'-Didehydro-2',3'-dideoxyadenosine
- 25 • D4FC; D-D4FC; 2',3'-Didehydro-2',3'-dideoxy-5-fluorocytidine; DPC 817
- D4FC (L); L-2',3'-Didehydro-2',3'-dideoxy-5-fluorocytidine
- D4G (L); L-2',3'-Didehydro-2',3'-dideoxyguanosine
- D4I (L); L-2',3'-Didehydro-2',3'-dideoxyinosine
- DABO
- 30 • ddC; Dideoxycytidine; Zalcitabine; Hivid®
- ddI; Dideoxyinosine; Didanosine; Videx®
- Dehydroepiandrosterone; DHEA; Prasterone; Dehydroisoandrosterone; EL-10
- Dextran Sulfate
- Dicafeic acid ester; L-Chicoric acid

- DMP-266; Sustiva®; Efavirenz; Approved
- DMP-323; XM-323
- DMP-450
- Docosanol; n-Docosanol
- 5 • dOTC (-); (-)-2'-Deoxy-3'-oxa-4'-thiocytidine
- dOTFC (-); (-)-2'-Deoxy-3'-oxa-4'-thio-5-fluorocytidine
- DP-178; Pentafuside; T-20; GP41 127-162 AA; Enfuvirtide; Fuzeon®
- E-BPTU; HEPT deriv.; NSC 648400
- E-EBU; HEPT deriv.; MKC-442 deriv.
- 10 • E-EBU-dM; HEPT deriv.; MKC-442 deriv.
- E-EPSeU; HEPT deriv.; MKC-442 deriv.
- E-EPU; HEPT deriv.; MKC-442 deriv.
- Ebselen
- Etoposide
- 15 • Epoxy steroid deriv.; (4 α ,5 α ,17 β)-17-Hydroxy-3-oxo-4,5-epoxyandrostane-2-carboxamide
- Eulicin
- Fenalamide A1; Phenalamide A1; Stipiamide
- Fleephilone
- Fluoroquinolone deriv.; K-12
- 20 • Fortovase®; Invirase®; Saquinavir; Ro31-8959; Approved
- Foscarnet; Phosphonoformic acid; Foscavir;
- FPMDAP, FPMMPA, FPMPG
- GPGRAF Octomer; SPC3
- Hammerhead anti-gag RNA Ribozyme B
- 25 • Harziphilone
- HBY 097; Quinoxaline deriv.
- HEPT deriv.; MKC-442 deriv.
- HOCH₂CH₂ isostere; ThienopyridCON thienyl urethane deriv.
- HOCH₂CH₂ isostere; ThienopyridCONthienyl urethane deriv.; LY326188
- 30 • HPMPA
- HPMPDAP
- HU; Hydroxyurea; Hydrea
- Hydroxocobalamin

- Hypericin
- Ingenol 3,5,20-triacetate; ITA; RD3-2118
- Ingenol deriv.; RD4-2138
- Inophyllum B, Inophyllum P
- 5 • iQoa-Mta-Apns-Thz-NH-tBu; KNI-272
- Isentress (Raltegravir)
- IsoquinCON furanyl urethane analog
- IsoquinCON thienyl urethane analog
- KNI-154; Noa-Asn-Apns-Thz-NH-tBu, KNI-174; Noa-Asn-Apns-Dmt-NH-tBu
- 10 • KNI-227; Qoa-Mta-Apns-Thz-NH-tBu
- L-685,434, L-685,434-6-Hydroxy derivative, L-685,434-OEtMorphderivative; L-689,502
- L-685,434-OEtNMe₂, L-685,434-OPrMorph derivative, L-697,593; 2-Pyridinone deriv.
- L-697,639; 2-Pyridinone deriv., L-697,661; 2-Pyridinone deriv.
- L-FddC; β-L-5F-ddC
- 15 • Lamivudine & Zidovudine; Combivir® 3TC & AZT; Approved
- LY289612, LY289612 analog, LY289612 analog
- LY-300046-HCl; PETT deriv.; Troviridine
- LY314163; Saquinavir/Nelfinavir deriv..
- LY-73497; N-(2-Phenethyl)-N'-(2-thiazolyl)thiourea; PETT
- 20 MAP; Methyl acetylenic putrescine
- Michellamine A; NSC650898, Michellamine B; NSC649324, Michellamine F
- N-6-Et-ddA; N-Ethyl-2',3'-dideoxyadenosine
- N-6-methyl ddA; N6-Methyl-2',3'-dideoxyadenosine
- Naphthalene 2-sulphonate polymer; PRO 2000
- 25 • Nelfinavir-octahydro-thienopyridine analog
- Nonoxynol 9
- NSC625487; Thiazolobenzimidazole; TBZ
- Oxathiin deriv.; UC-38, Oxathiin deriv.; UC-84
- P9941
- 30 • Penicillin Et(NH)₂ Sym dimer, Penicillin G, ET(NH)₂ deriv.
- Penicillin, 2Isoquin-OHPrNH₂ analog
- Pentosan Sulfate; Elmiron; SP54; Xylan Sulfate;
- PETT Cl, F deriv., PETT deriv.

- Phenoxan
- Phorbol deriv.; Prostratin
- Platanic acid
- PMEDAP, PMEG, PMEHx; PMEI, PMEMAP, PMET
- 5 • PNU-140690; U-140690; Tipranavir
- Pyridinone deriv.
- Quinoxalin2thione deriv; S-2720
- R14458; TIBO deriv..
- R82150; TIBO deriv..
- 10 • R82913; TIBO deriv.
- Resobene
- Ribavirin; Virazole
- Ro 31-8959-bis-thf deriv.
- Saquinavir/Nelfinavir deriv.
- 15 • SB-205569; Val-Phe-Phe-HOCH₂CH₂ isostere analog
- SC-52151; Telinavir
- SDZ PRI 053
- Suramin Sodium
- T22
- 20 • Thalidomide
- Thiangazole; (-)-Thiangazole, Thiazoloisoindol-5-one, Thiazoloisoindol-5-one, deriv.
- Tle-Val-Sta, 5PhBuCOOH deriv.; Statine deriv.
- UC-781
- Val-Val-Sta, 5PhBuCOOH deriv.; Statine deriv.
- 25 • VB-11,328
- Viread®; Tenofovir Disoproxil

30 An alternative list of drugs and/or bioactive agents useful in the treatment of HIV infections, or conditions or disease states which are secondary to HIV infections is set forth hereinbelow. One or more of these agents may be used in combination (coadministered) with at least one anti-HIV agent as otherwise disclosed herein to treat HIV or one of its secondary conditions or disease states, including AIDS/ARC, Kaposi's sarcoma, hepatitis B virus infections, other microbial infections (such as tuberculosis) etc. When used, these compounds are also included in effective amounts.

These include (at the following website):

aidsinfo.nih.gov/DrugsNew/DrugDetailNT.aspx?MenuItem=Drugs&Search=On&int_id=257

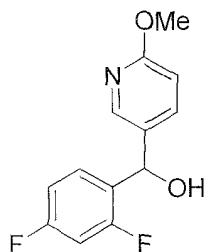
- 5 ACV; AK602; AMD070; APV; ATV; ATZ; AVX754 (apricitabine); AZT; Abacavir; Abacavir / Lamivudine / Zidovudine; Abacavir sulfate; Abacavir sulfate/Lamivudine; Abacavir/Lamivudine; Abelecet; Acyclovir; Adefovir dipivoxil; Adriamycin; Agenerase; Aldesleukin; Alovudine; Aluvia; AmBisome; Amdoxovir; Amphocin; Amphotec; Amphotericin B; Ampligen; Amprenavir; Androderm; Androgel; Apricitabine; Aptivus;
- 10 Atazanavir; Atripla; Azithromycin; BMS-378806; BMS-488043; Bactrim; Baraclude; Bevirimat; Biaxin; Brecanavir; BufferGel; C31G; CD4-IgG2; CS; CV-N; Calanolide A; Calcium hydroxylapatite; Carbopol 974P; Carrageenan; Carraguard; Cellulose sulfate; Clarithromycin; Combivir; Copegus; Cotrimoxazole; Crixivan; Cyanovirin-N; Cytovene; DAPD; DLV; DS; Darunavir; Delavirdine; Depo-Testosterone; Dextran sulfate; Didanosine;
- 15 Diflucan; Doxil; Doxorubicin (liposomal); Dronabinol; EFV; Efavirenz; Elvucitabine; Emtricitabine; Emtricitabine; Tenofovir disoproxil fumarate; Emtriva; Enfuvirtide; Entecavir; Epivir; Epoetin alfa; Epogen; Epzicom; Etopophos (phosphate salt); Etoposide; Etravirine; FTC; Fluconazole; Fortovase; Fosamprenavir; Foxivudine tidoxil; Fungizone; Fuzeon; GS 9137; GSK-873,140 (aplaviroc); GW433908; GW640385 (brecanavir); Ganciclovir;
- 20 Globulin, Immune; Growth hormone (human); Hepsera; Hivid; Human growth hormone; IL-2; INH; Immune Globulin Intravenous (Human); Indinavir; Interferon alfa-2; Interleukin-2, recombinant human; Intron A (2b); Invirase; Isentress; Isoniazid; Itraconazole; KP-1461; Lamivudine/Zidovudine; Lexiva; Lopinavir/Ritonavir; MK-0518; Nebupent; Nelfinavir; Neutrexin; Nevirapine; Norvir; Nydrazid; Peptide T; PMPA Prodrug (Viread)' Prezista
- 25 (Darunavir); PRO 140; PRO 2000; PRO 542 (CD4 IGg2); Procrit (Epoetin); Proleukin; Racivir; Radiesse; Rrebetol; Rescriptor; Retrovir; Reyataz; Ribavirin; Rifabutin; Rifadin; Rifampin; Rimactane; Ritonavir; Roferon-A (2a); Saquinavir; SCH-D (vicriviroc); Somatropin; Stavudine; Sulfamethoxazole / Trimethoprim; Sustanon; Sustiva; TNX-355; Taxol; Tenofovir; Tenofovir disoproxil fumarate; Testosterone; Tipranavir; Toposar;
- 30 Trimetrexate; Trizivir; Truvada (Emtriva and Viread combination); U-90152S (Delavirdine); UC-781; UK-427,857 (maraviroc); Valcyte; Valganciclovir; Valproic acid; VePesid; Vicriviroc; Videx; Viracept (Tenofovir DF); Viramune; Virazole; Viread; Vitrasert; Zalcitabine; Zerit; Ziagen; Zidovudine; Zithromax; Zovirax.

10

Precursor: Example of Synthesis of Diketoacid Precursor, 4-(5-(2,4-difluorobenzyl)-1-(2-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-4-oxobut-2-enoic acid (**8**).



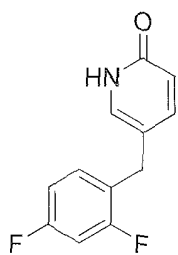
Step 1: Preparation of (2,4-difluorophenyl)(6-methoxypyridin-3-yl)methanol (**2**).



2

To a mixture of 5-bromo-2-methoxypyridine **1** (2.10 g, 10.6 mmol) in anhydrous TBME (20 ml) at -32°C under argon atmosphere was added *n*-BuLi solution (5.8 ml of 2 M solution in cyclohexane, 11.7 mmol) drop wise over 15 min under argon condition. After stirring for 1h, 2,4-difluorobenzaldehyde (1.54 g, 10.6 mmol) was added drop wise over 15 min and the reaction mixture was stirred for 30 min under -32°C under argon atmosphere. Reaction mixture was allowed to warm up to 0°C and quenched with saturated NH₄Cl (20 ml). The phases were separated and the aqueous layer was extracted with TBME (20 ml and 10 ml). All combined organic phases were washed with water (50 ml), and dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo and the residue was purified by flash column chromatography on silica gel (hexanes: ethyl acetate, 85:15). Yield 2.28 g (85%). ¹H NMR (CDCl₃, 500 MHz): δ 8.16 (s, 1H), 7.57-7.52 (m, 2H), 6.93-6.76 (m, 2H), 6.72 (d, 1H, *J* = 9.0 Hz), 6.07 (d, 1H, *J* = 3.5 Hz), 3.92 (s, 3H). ¹³C NMR (CDCl₃, 125 MHz): δ 163.9, 162.4, 159.6, 145.0, 137.2, 131.0, 128.2, 126.5, 111.5, 110.9, 103.9, 67.3, 53.6.

Step 2: Preparation of 5-(2,4-difluorobenzyl)pyridin-2(1*H*)-one (**3**).

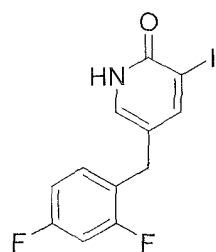


3

A mixture of (2,4-difluoro-phenyl)-(6-methoxy-pyridin-3-yl)methanol **2** (2.28 g, 9.1 mmol), sodium iodide (5.45 g, 36.4 mmol), triethylsilane (2.2 ml, 13.6 mmol) in anhydrous acetonitrile (21 ml) and was stirred at room temperature. TFA (1.1 ml, 14.3 mmol) was added at a rate that maintained the temperature below 30°C; TMSCl (5.8 ml, 45.5 mmol) was added, and the batch was heated at 70°C for 3h. Upon cooling to 55°C, a 0.8 M Na₂SO₃ (11.4

ml) was added, and the reaction mixture was concentrated in vacuo to 20 ml. A solution of 0.15 M Na₂SO₃ (11.4 ml) was added, the mixture was stirred at room temperature overnight. A solution of 1.4 M K₂CO₃ (13.6 ml) was added and cooled to 0°C. The crude product was extracted with ethyl acetate (60 ml) and washed with 0.15 M Na₂SO₃ (20ml) and water (60 ml) and dried over anhydrous sodium sulfate. The mixture was distilled, and the residue was purified by flash column chromatography on silica gel (chloroform: methanol, 90:10). Yield 1.89 g (94 %). ¹H NMR (CDCl₃, 500 MHz): δ 13.35 (s, 1H), 7.36-6.79 (m, 7H), 6.53 (d, 1H, *J* = 9.2 Hz), 3.71 (s, 2H). ¹³C NMR (CDCl₃, 125 MHz): δ 164.7, 162.4, 160.4, 143.2, 132.7, 131.2, 122.3, 120.3, 118.4, 111.4, 104.1, 30.3.

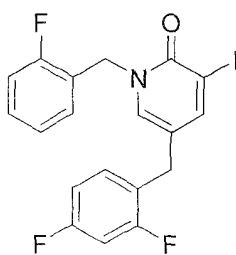
Step 3: Preparation of 5-(2,4-difluorobenzyl)-3-iodopyridin-2(1*H*)-one (4).



4

To a solution of 5-(2,4-difluorobenzyl)pyridin-2(1*H*)-one **3** (1.89 g, 8.5 mmol) in acetic acid (34 ml) was added TFA (2.2 ml), followed by *N*-iodosuccinimide (2.02 g, 8.5 mmol). The red homogeneous solution was allowed to stir overnight at room temperature, poured onto ice and neutralized with conc. NH₄OH. The solid was collected by filtration, rinsed with water, treated with methanol/dichloromethane, dried over sodium sulfate, and evaporated. The resulting brown solid was purified by flash column chromatography on silica gel (hexanes: ethyl acetate, 50: 50). Yield 2.57 g (87 %). ¹H NMR (CDCl₃, 500 MHz): δ 13.20 (s, 1H), 7.98 (d, 1H, *J* = 2.2 Hz), 7.26-6.81 (m, 4H), 3.70 (s, 2H). ¹³C NMR (CDCl₃, 125 MHz): δ 162.5, 161.9, 160.5, 151.9, 133.5, 131.2, 121.8, 120.0, 111.6, 104.3, 91.6, 29.9.

Step 4: Preparation of 5-(2,4-difluorobenzyl)-1-(2-fluorobenzyl)-3-iodopyridin-2(1*H*)-one (5).

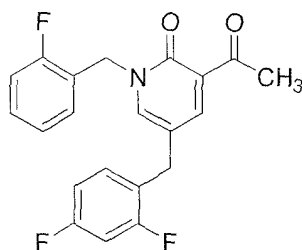


25

5

To a suspension of 5-(2,4-difluorobenzyl)-3-iodopyridin-2(1*H*)-one **4** (5.58 g, 16.1 mmol) in anhydrous DMF (160 ml) was added at room temperature NaH (60% suspension in mineral oil, 0.71 g, 17.7 mmol). After the mixture was stirred for 15 min, *o*-fluorobenzyl bromide (2 ml, 16.1 mmol) was added to the mixture, which was stirred for 2h at RT. The solvent was distilled off and the residue was dissolved in ethyl acetate (200 ml), washed with water (200 ml), brine (200 ml), and dried over anhydrous sodium sulfate and the solvent was distilled off. The residue was purified by flash chromatography on silica gel (hexanes: ethyl acetate, 80:20). Yield 6.61 g (90 %). ¹H NMR (CDCl₃, 500 MHz): δ 7.80 (d, 1H, *J* = 2.2 Hz), 7.55-7.51 (m, 1H), 7.32-7.27 (m, 2H), 7.13-7.04 (m, 3H), 6.86-6.79 (m, 2H), 5.14 (s, 2H), 3.64 (s, 2H). ¹³C NMR (CDCl₃, 125 MHz): δ 162.4, 162.1, 160.5, 160.2, 159.1, 149.8, 136.5, 132.1, 131.1, 130.3, 124.6, 122.5, 121.9, 118.6, 115.4, 111.5, 104.2, 93.5, 48.5, 30.0.

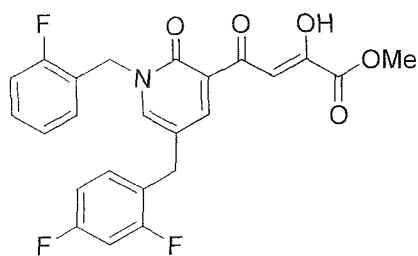
Step 5: Preparation of 3-acetyl-5-(2,4-difluorobenzyl)-1-(2-fluorobenzyl)pyridin-2(1*H*)-one (**6**).



6

A mixture of 5-(2,4-difluorobenzyl)-1-(2-fluorobenzyl)-3-iodopyridin-2(1*H*)-one **5** (6.61 g, 14.5 mmol), bis(triphenylphosphine)palladium(II) chloride (1.02 g, 1.5 mmol), and ethoxyvinyl(tributyl)tin (10.81 g, 29.0 mmol) in anhydrous DMF (145 ml) was heated at 70° under argon condition for 1h. DMF was distilled off and the resulting residue was dissolved in ethyl acetate (145 ml) and filtered through a pad of celite. The filtrate was stirred with 1N HCl (145 ml) for 15 min, washed with water (2 x 145 ml), brine (145 ml), dried over anhydrous sodium sulfate, and distilled off. The residue was purified by flash column chromatography on silica gel (hexanes: ethyl acetate, 80:20). Yield 4.21 g (78%). ¹H NMR (CDCl₃, 500 MHz): δ 7.98 (d, 1H, *J* = 2.6 Hz), 7.49-7.44 (m, 2H), 7.35-7.30 (m, 1H), 7.16-7.07 (m, 3H), 6.85-6.78 (m, 2H), 5.17 (s, 2H), 3.71 (s, 2H), 2.67 (s, 3H). ¹³C NMR (CDCl₃, 125 MHz): δ 197.6, 162.4, 162.1, 160.5, 160.4, 160.2, 144.4, 141.4, 131.4, 131.2, 130.4, 127.7, 124.6, 122.6, 122.1, 116.9, 115.6, 111.5, 104.1, 47.2, 30.9, 30.5.

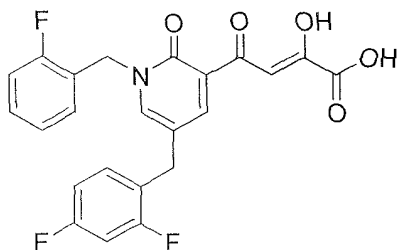
Step 6: Preparation of methyl 4-(5-(2,4-difluorobenzyl)-1-(2-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-4-oxobut-2-enoate (7).



7

To a stirred solution of sodium *t*-butoxide (4.49 g, 45.3 mmol) in anhydrous THF (230 ml) was added dimethyl oxalate (5.41 g, 45.3 mmol) in anhydrous THF (60 ml) under argon condition. The mixture was stirred at room temperature for 30 min and a solution of 3-acetyl-5-(2,4-difluorobenzyl)-1-(2-fluorobenzyl)pyridin-2(1H)-one **6** (4.21 g, 11.3 mmol) in THF (60 ml) was added. The reaction mixture was stirred at room temperature for 3h and then cooled in ice bath, and then 1N HCl (230 ml) was added in one portion. The crude product was extracted with ethyl acetate (2x 230 ml). The combined organic layers were washed with saturated brine (2x 230 ml) and ethyl acetate was distilled off to give a brown residue, which was triturated with methanol. The product was obtained by vacuum filtration. Yield 2.59 g (50 %). ¹H NMR (CDCl₃, 500 MHz): δ 8.18 (d, 1H, *J* = 3.1 Hz), 7.89 (s, 1H), 7.53 (s, 1H), 7.49-7.46 (s, 1H), 7.35-7.31 (s, 1H), 7.16-7.07 (m, 3H), 6.87-6.80 (m, 2H), 5.20 (s, 2H), 3.90 (s, 3H), 3.75 (s, 2H). ¹³C NMR (CDCl₃, 125 MHz): δ 185.0, 171.9, 162.8, 162.6, 162.2, 160.6, 160.2, 159.6, 144.8, 142.0, 131.7, 131.2, 130.6, 124.8, 123.6, 122.4, 121.9, 117.7, 115.7, 111.7, 104.3, 101.8, 53.2, 47.6, 30.6.

Step 7: Preparation of 4-(5-(2,4-difluorobenzyl)-1-(2-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-4-oxobut-2-enoic acid (8).



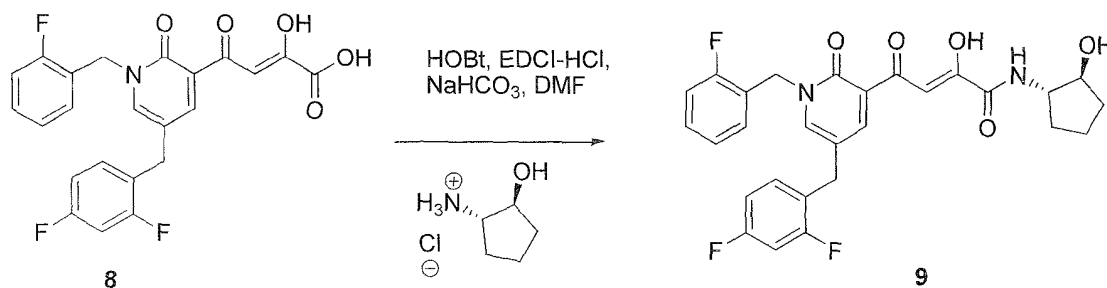
8

To a stirred solution of methyl 4-(5-(2,4-difluorobenzyl)-1-(2-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-4-oxobut-2-enoate **7** (2.59 g, 5.7 mmol) in 1,4-dioxane (125 ml) was added 1N HCl (63 ml). The reaction mixture was allowed to stir at 95°C for 2 h. The crude product was extracted with ethyl acetate (250 ml). The solvent was evaporated under reduced pressure. The solid was crystallized in chloroform and filtered under reduced pressure. Yield 1.61 g (64 %). Yellow solid, mp 187- 189°C, UV (MeOH) 394 nm (ϵ 14,917), 320 (ϵ 5671). ^1H NMR (CDCl_3 -MeOH- d_4 , 500 MHz): δ 8.17 (d, 1H, $J=3.4$ Hz), 7.88 (s, 1H), 7.54 (s, 1H), 7.48-7.45 (m, 1H), 7.36-7.30 (m, 1H), 7.17-7.07 (m, 3H), 6.87-6.81 (m, 2H), 5.19 (s, 2H), 3.76 (s, 2H). ^{13}C NMR (DMSO- d_6 , 125 MHz): δ 184.5, 173.3, 163.2, 161.7, 161.2, 159.8, 158.6, 144.6, 131.9, 130.0, 129.8, 124.5, 123.1, 123.0, 121.5, 116.8, 115.4, 111.6, 103.9, 100.8, 47.3, 29.2. HRMS $[\text{M}+\text{H}]^+$ calculated mass 444.1059 for $\text{C}_{23}\text{H}_{17}\text{F}_3\text{NO}_5$, found 444.1042.

Examples of Synthesis of Carboxamides from Diketoacid Precursor

Representative Example 1

(1S,2S)-4-(5-(2,4-difluorobenzyl)-1-(2-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide (**9**).

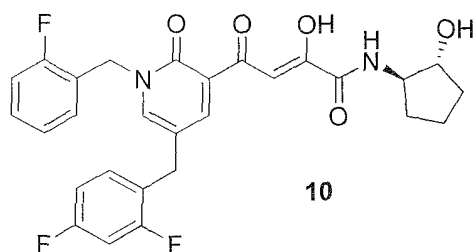


To a chilled solution of the 4-(1-(2-fluorobenzyl)-5-(4-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-4-oxobut-2-enoic acid **8** (150 mg, 0.338 mmol) in dimethylformamide (DMF) (2.0 mL), was added hydroxybenzotriazole (HOBT) (50 mg, 0.372 mmol), followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride EDCI-HCl (71 mg, 0.372 mmol). The resulting mixture was stirred for 30 min. A solution of (1S,2S)-(+)-trans-2-aminocyclopentanol hydrochloride and NaHCO_3 (31 mg, 0.372 mmol) was added. The resulting mixture was stirred for 2h at 0- 5 °C. Thin layer chromatography

(TLC) analysis indicated completion, hence cold water was added to the reaction mixture and then extracted with ethyl acetate (2 x 20mL). The combined organic phase was separated and washed with water twice, then once with 1N HCl solution, then saturated aqueous NaHCO₃ solution. Concentration *in vacuo* afforded the crude product which was passed through a short plug of silica gel eluting with chloroform, the eluent was concentrated and the residual triturated with hexanes affording the product as a yellow solid in 117 mg (66.0%). The residual solvent was removed *in vacuo* affording pure product as a yellow solid, mp 60.0-62.9 °C, $[\alpha]_D^{20} +24.0$ (c 0.01, MeOH), UV (MeOH) 396 nm (ϵ 14,455), 318 nm (ϵ 6327). ¹H NMR (CDCl₃, 500 MHz): δ 15.33 (bs, 1H), 8.16 (d, 1H, J = 2.0Hz), 8.08 (s, 1H), 7.61-6.85 (m, 9H), 5.22 (s, 2H), 4.11 (m, 1H), 3.94 (m, 1H), 3.78 (s, 1H), 2.23 (m, 1H), 2.10 (m, 1H), 1.88 (m, 1H), 1.78 (m, 2H), 1.59 (m, 1H). ¹³C NMR (CDCl₃, 125 MHz): δ 181.3, 180.6, 163.4, 163.3, 162.4, 162.1, 162.0, 161.4, 161.3, 160.4, 160.1, 160.0, 159.2, 145.5, 143.9, 142.3, 141.6, 132.4, 132.4, 132.3, 131.5, 131.4, 131.3, 131.3, 131.2, 130.7, 130.6, 125.0, 124.9, 124.8, 122.8, 122.7, 122.5, 122.2, 122.2, 122.1, 122.1, 117.1, 115.9, 115.7, 115.6, 111.9, 111.9, 111.8, 111.7, 104.7, 104.5, 104.3, 98.3, 79.5, 79.3, 61.0, 60.6, 51.5, 47.7, 47.3, 32.9, 32.8, 32.7, 30.8, 30.7, 30.5, 21.7, 21.5. HRMS (M+H)⁺ calculated mass 527.1794 for C₂₈H₂₆F₃N₂O₅, found 527.1799.

Representative Example 2

(1R,2R)-4-(5-(2,4-difluorobenzyl)-1-(2-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide (**10**).



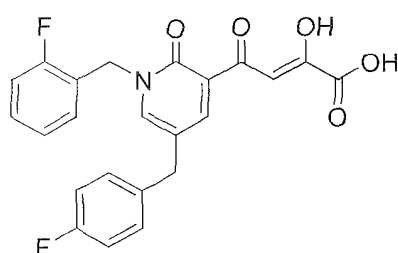
The titled compound was synthesized using the procedure described above using compound **8**. The coupling compound, (1R, 2R)-2-aminocyclopentanol hydrochloride, was synthesized by modification of the following procedure: Overman L.E.; Sugai, S., *J. Org. Chem.* 50, 4154-4155 (1985). The product was a yellow solid, mp 55- 57°C, $[\alpha]_D^{20} -28.5$ (c 0.1, MeOH), UV (MeOH) 396 nm (ϵ 14,100), 319 nm (ϵ 7444). ¹H NMR (CDCl₃, 500 MHz): δ 15.41(bs, 1H), 8.16 (s, 1H), 8.07 (s, 1H), 7.60-6.84 (m, 9H), 5.21 (s, 2H), 4.10-3.76 (m, 5H), 2.25-1.73

(m, 6H). ^{13}C NMR (CDCl_3 , 125 MHz): δ 181.1, 163.0, 162.1, 160.2, 159.0, 143.7, 141.4, 132.1, 132.1, 132.1, 131.2, 131.1, 131.1, 131.0, 130.5, 130.4, 124.7, 124.7, 122.5, 122.4, 122.3, 121.8, 116.9, 115.5, 115.3, 111.7, 111.7, 111.5, 111.5, 104.4, 104.2, 104.0, 98.1, 79.1, 60.2, 47.5, 32.5, 30.5, 30.4, 21.4. HRMS ($\text{M}+\text{H}$) $^+$ calculated mass 527.1794 for

5 $\text{C}_{28}\text{H}_{26}\text{F}_3\text{N}_2\text{O}_5$, found 527.1804.

Representative Example 3

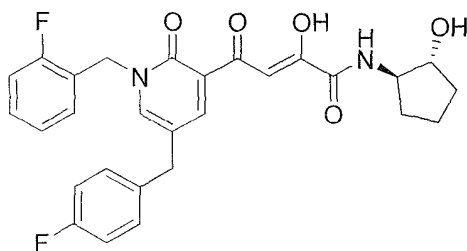
(1R,2R)-4-(1-(2-fluorobenzyl)-5-(4-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide (12).



11 (Precursor)

The precursor, 4-[5-(4-fluoro-benzyl)-1-(2-fluoro-benzyl)-2-oxo-1,2-dihydro-pyridin-3-yl]-2-hydroxy-4-oxo-but-2-enoic acid (11), was prepared following procedure described above for
 15 8 to give 11 as a yellow solid, mp 182-184°C, UV (MeOH) 395 nm (ϵ 14,389), 319 nm (ϵ 6066). ^1H NMR ($\text{CDCl}_3/\text{MeOH}-d_4$, 500 MHz): δ 8.14 (d, 1H, J = 2.6 Hz), 7.88 (s, 1H), 7.48-7.00 (m, 9H), 5.19 (s, 2H), 3.76 (s, 2H). ^{13}C NMR ($\text{CDCl}_3/\text{MeOH}-d_4$, 125 MHz): δ 185.0, 172.7, 163.8, 162.9, 162.2, 160.9, 160.2, 159.7, 144.9, 141.6, 134.4, 131.7, 130.6, 130.2, 124.8, 123.8, 122.4, 119.1, 115.8, 115.7, 101.7, 47.5, 36.8. HRMS ($\text{M}+\text{H}$) $^+$ calculated mass
 20 426.1153 for $\text{C}_{23}\text{H}_{18}\text{F}_2\text{NO}_5$, found 426.1187.

(1R,2R)-4-(1-(2-fluorobenzyl)-5-(4-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide (12)

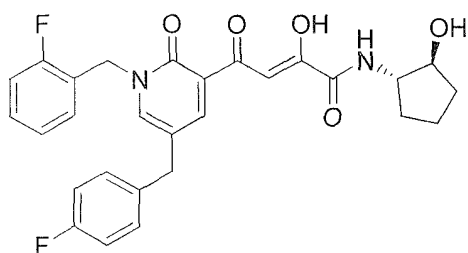


12

Target compound **12** was prepared from **11** using the procedure described above for **9** to give **12** as a yellow solid, mp 67- 69 °C, $[\alpha]_D^{20}$ -28.3, (c 0.12, MeOH), UV (MeOH) 395 nm (ϵ 12,638), 318 nm (ϵ 6759). ^1H NMR (CDCl_3 , 500 MHz): δ 15.35 (bs, 1H), 8.13 (d, 1H, J = 3.0 Hz), 8.08 (s, 1H), 7.61-7.03 (m, 10H), 5.21 (s, 2H), 4.10-3.76 (m, 5H), 2.25-1.57 (m, 6H). ^{13}C NMR (CDCl_3 , 125 MHz): δ 181.1, 163.0, 162.7, 162.1, 160.8, 160.1, 159.0, 143.9, 141.3, 141.3, 134.4, 134.4, 132.1, 132.1, 130.4, 130.4, 130.2, 130.1, 130.1, 124.7, 124.7, 124.7, 122.5, 122.5, 122.4, 118.3, 115.8, 115.6, 115.5, 115.3, 98.1, 79.0, 60.5, 47.4, 36.7, 32.5, 30.3, 21.3. HRMS ($\text{M}+\text{H}$) $^+$ calculated mass 509.1888 for $\text{C}_{28}\text{H}_{27}\text{F}_2\text{N}_2\text{O}_5$, found 509.1893

Representative Example 4

(1S,2S)-4-(1-(2-fluorobenzyl)-5-(4-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide (**13**)

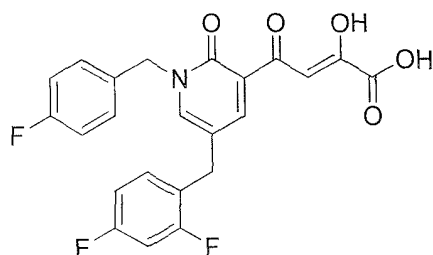


13

Target compound **13** was prepared from **11** using the procedure described above for **9** to give **13** as a yellow solid, mp 79-80 °C, $[\alpha]_D^{20}$ +33.0 (c 0.25, MeOH), UV (MeOH) 395 nm (ϵ 9,000), 318 nm (ϵ 4923). ^1H NMR (CDCl_3 , 500 MHz): δ 15.31 (bs, 1H), 8.12 (s, 1H), 8.05 (s, 1H), 7.57-7.02 (m, 10H), 5.20 (s, 2H), 4.10 (m, 1H), 3.94 (m, 1H), 3.774 (s, 2H), 2.23 (m, 1H), 2.094 (m, 1H), 1.866 (m, 1H), 1.75 (m, 2H), 1.59 (m, 1H). ^{13}C NMR (CDCl_3 , 125 MHz): δ 181.1, 163.1, 162.8, 162.2, 160.9, 160.2, 159.1, 143.9, 141.3, 134.5, 134.4, 132.2, 132.2, 130.5, 130.4, 130.2, 130.1, 124.8, 124.7, 122.6, 122.5, 122.4, 118.3, 115.9, 115.7, 115.6, 115.4, 98.2, 79.2, 77.3, 77.1, 76.8, 60.7, 47.5, 36.8, 32.6, 30.5, 21.4. HRMS ($\text{M}+\text{H}$) $^+$ calculated mass 509.1888 for $\text{C}_{28}\text{H}_{27}\text{F}_2\text{N}_2\text{O}_5$, found 509.1882.

Representative Example 5

(1S,2S)-4-(5-(2,4-difluorobenzyl)-1-(4-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide (**15**)

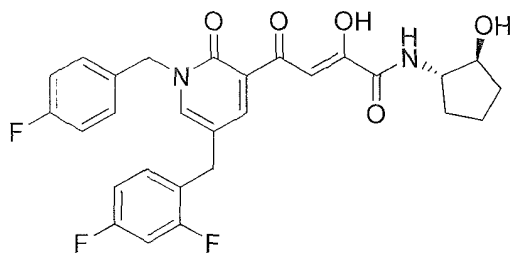
**5 14 (Precursor)**

The precursor compound **14** was synthesized as described above for precursor **8** to give **14** as a yellow solid, mp 197-198°C, UV (MeOH) 396 nm (ϵ 14070), 319 nm (ϵ 6226). ^1H NMR

(DMSO- d_6 , 500 MHz): δ 15.18 (bs, 1H), 14.02 (bs, 1H), 8.33 (d, 1H, $J = 2.0$ Hz), 8.18 (d, 1H, $J = 2.5$ Hz), 7.83 (s, 1H), 7.46-7.07 (m, 7H), 5.19 (s, 1H), 3.84 (s, 2H). ^{13}C NMR

10 (DMSO- d_6 , 125 MHz): δ 185.2, 173.7, 163.7, 163.1, 162.7, 162.6, 161.7, 161.6, 161.1, 160.7, 160.6, 159.8, 159.7, 159.1, 144.9, 144.8, 133.2, 133.2, 132.4, 132.3, 132.3, 132.3, 130.6, 130.6, 130.5, 123.6, 123.6, 123.5, 123.5, 122.0, 117.5, 115.9, 115.7, 112.2, 112.1, 112.0, 112.0, 104.6, 104.4, 104.2, 101.4, 52.1, 29.7.

15 (1S,2S)-4-(5-(2,4-difluorobenzyl)-1-(4-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide (**15**)

**15**

Target compound **15** was prepared from **14** using the procedure described above for **9** to give **15** as a yellow solid, mp 88-90 °C, $[\alpha]^{20}_{\text{D}} +28.8$ (c 0.27, MeOH), UV (MeOH) 399 nm (ϵ 11,600), 318 nm (ϵ 6516).

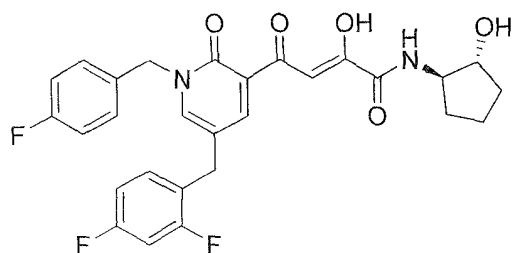
20 ^1H NMR (CDCl_3 , 500 MHz): δ 8.16 (s, 1H), 8.09 (s, 1H), 7.41 (s, 1H), 7.36-6.84 (m, 7H), 5.16 (s, 2H), 4.11-4.08 (m, 1H), 3.96-3.90 (m, 1H), 3.75 (s, 2H), 2.26-2.21 (m, 1H), 2.11-2.06 (m, 1H), 1.90-1.70 m, 4H). ^{13}C NMR (CDCl_3 , 125 MHz): δ 181.3, 180.2, 163.7, 163.2, 163.1, 161.9, 161.8, 161.7, 161.2, 161.2, 160.0, 159.9, 158.9, 145.3, 143.7, 141.6, 140.5, 131.5, 131.5, 131.2,

131.1, 131.1, 131.0, 130.3, 130.2, 130.1, 129.9, 129.9, 122.8, 122.0, 121.9, 121.8, 121.8, 117.1, 116.1, 115.9, 111.8, 111.7, 111.6, 111.6, 104.5, 104.3, 104.1, 98.2, 79.3, 79.1, 60.8, 52.3, 32.7, 32.4, 30.7, 30.5, 30.2, 21.5, 21.2. HRMS (M+H)⁺, calculated mass 527.1794 for C₂₈H₂₆F₃N₂O₅, found 527.1779.

5

Representative Example 6

(1R,2R)-4-(5-(2,4-difluorobenzyl)-1-(4-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide (**16**)

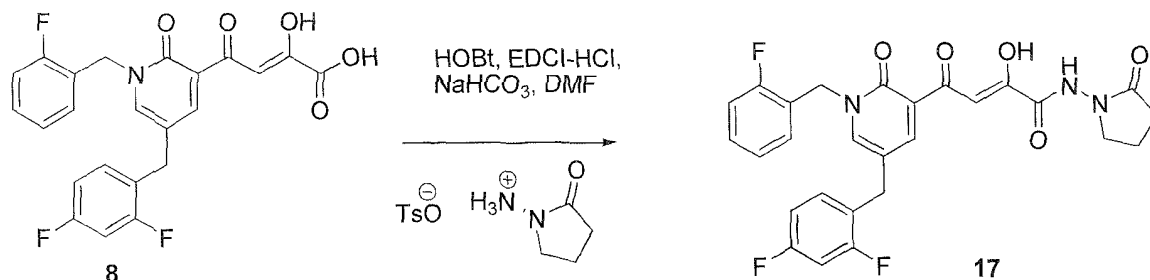
10 **16**

Target compound **16** was prepared from **14** using the procedure described above for **9** to give **16** as a yellow solid, mp 85-86 °C, [α]_D²⁰ -28.9 (c 0.19, MeOH), UV (MeOH) 398nm, (ε 12,800), 321 nm (ε 6459). ¹H NMR (CDCl₃, 500MHz): δ 8.15 (s, 1H), 8.07 (s, 1H), 7.42 (s, 1H), 7.35-6.84 (m, 7H), 5.15 (s, 2H), 4.11 (m, 1H), 3.93 (m, 1H), 3.75 (s, 2H), 2.23 (m, 1H), 2.08 (m, 1H), 1.85-1.58 (m, 4H). ¹³C NMR (CDCl₃, 125 MHz): δ 181.3, 163.7, 163.1, 161.7, 159.0, 143.7, 140.6, 131.5, 131.5, 131.2, 131.1, 131.1, 131.0, 130.3, 130.2, 122.8, 121.9, 117.1, 116.1, 115.9, 111.8, 111.7, 111.6, 111.6, 104.5, 104.3, 104.1, 98.2, 79.2, 77.3, 77.1, 76.8, 60.7, 52.3, 32.6, 30.7, 30.5, 21.4, 21.2. HRMS (M+H)⁺ calculated mass 527.1794 for C₂₈H₂₆F₃N₂O₅, found 527.1794.

20

Representative Example 7

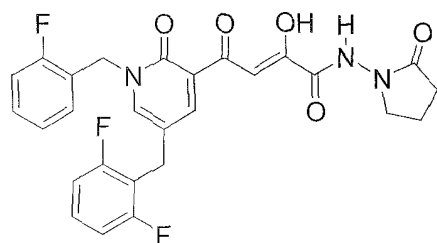
4-(5-(2,4-difluorobenzyl)-1-(2-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-4-oxo-N-(2-oxopyrrolidin-1-yl)but-2-enamide (**17**)



To a chilled solution of the 4-(1-(2-fluorobenzyl)-5-(4-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-4-oxobut-2-enoic acid **8** (150 mg, 0.338 mmol) in dimethylformamide (DMF) (2.0 mL), was added hydroxybenzotriazole (HOBT) (50 mg, 0.372 mmol), followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride EDCI-HCl (71 mg, 0.372 mmol). The resulting mixture was stirred for 30 min. To the above solution was added 1-(amino)-2-pyrrolidinone, *p*-toluene sulfonate (101 mg, 0.372 mmol) and NaHCO₃ (31 mg, 0.372 mmol) was added. The resulting mixture was stirred for 2h at 0-5 °C. Thin layer chromatography (TLC) analysis indicated completion, hence cold water was added to the reaction mixture and then extracted with ethyl acetate (2 x 20mL). The combined organic phase was separated and washed with water twice, then once with 1N HCl solution, then saturated aqueous NaHCO₃ solution. Concentration *in vacuo* afforded the crude product (148 mg, 86%), which was passed through a short plug of silica gel eluting with chloroform, the eluent was concentrated and the residual triturated with pentane, filtered then dried affording the product in 105 mg (61.0%). The product was a yellow solid, mp 86.0-88.0 °C, UV (MeOH) 399 nm (ϵ 8758), 319 nm (ϵ 6,770). ¹H-NMR (CDCl₃, 500 MHz): δ 15.25 (bs, 1H), 8.85 (s, 1H), 8.16 (s, 1H), 8.03 (s, 1H), 7.57-6.85 (m, 9H), 5.21 (s, 2H), 3.78-3.71 (m, 4H), 2.51 (m, 2H), 2.20 (m, 2H). ¹³C-NMR (CDCl₃, 125 MHz): δ 181.4, 179.5, 173.6, 163.4, 162.4, 162.0, 161.4, 161.3, 160.4, 160.1, 160.0, 159.6, 144.2, 141.8, 132.4, 131.4, 131.3, 131.3, 130.7, 130.6, 124.9, 124.9, 122.8, 122.6, 122.5, 122.2, 122.2, 122.0, 117.1, 115.8, 115.6, 111.9, 111.9, 111.7, 104.7, 104.5, 104.3, 98.8, 48.0, 47.7, 30.8, 28.6, 17.0. HRMS (M+H)⁺ calculated mass 526.1590 for C₂₇H₂₃F₃N₃O₅, found 526.1578.

Representative Example 8

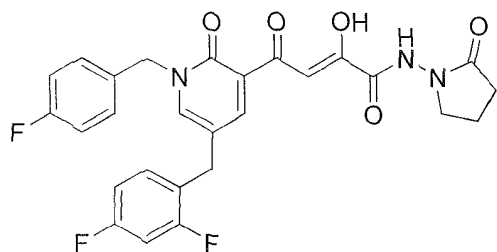
4-(5-(2,6-difluorobenzyl)-1-(2-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-4-oxo-N-(2-oxopyrrolidin-1-yl)but-2-enamide (18)

**18**

Target compound **18** was prepared from the corresponding trifluoro diketo acid using the procedure described above for **17** to give **18** as a yellow solid, mp 175-176°C (amorphous powder), UV (methanol), λ_{max} 401 nm (ϵ 9139), λ_{max} 318 nm (ϵ 6225). $^1\text{H-NMR}$ (CDCl_3 , 500MHz), δ 8.88 (s, 1H), 8.24 (s, 1H), 8.01 (s, 1H), 7.65 (s, 1H), 7.55 (t, $J_1=2\text{Hz}$, $J_2=2.5\text{Hz}$, 1H), 7.33-7.10 (m, 5H), 6.94 (t, $J_1=7.5\text{Hz}$, $J_2=8\text{Hz}$, 2H), 5.21 (s, 2H), 3.83 (s, 2H), 3.71 (t, $J_1=7\text{Hz}$, $J_2=7.5\text{Hz}$, 2H), 2.50 (t, $J_1=7.5\text{Hz}$, $J_2=8\text{Hz}$, 2H), 2.19 (m, 2H); $^{13}\text{C-NMR}$ (CDCl_3 , 125MHz), δ 181.2, 179.3, 173.4, 162.2, 162.1, 162.1, 160.2, 160.2, 160.1, 159.5, 159.0, 144.0, 141.7, 132.1, 132.0, 130.4, 130.4, 128.9, 128.8, 124.7, 124.8, 122.5, 122.4, 122.3, 116.6, 115.6, 115.4, 115.0, 111.7, 111.6, 111.5, 111.4, 98.5, 47.8, 47.4, 28.4, 24.3, 16.8. HRMS $[\text{M}+\text{H}]^+$ calculated mass 526.1590 for $\text{C}_{27}\text{H}_{23}\text{F}_3\text{N}_3\text{O}_5$, found 526.1589.

Representative Example 9

4-(5-(2,4-difluorobenzyl)-1-(4-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-4-oxo-N-(2-oxopyrrolidin-1-yl)but-2-enamide (19)

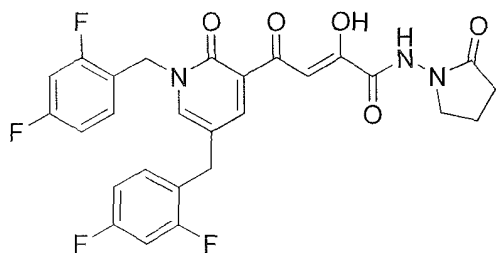
**19**

Target compound **19** was prepared from **14** using the procedure described above for **17** to give **19** as a yellow solid, mp 87-88 °C, UV (MeOH) 400 nm (ϵ 8500), 320 nm (ϵ 6472). ^1H

NMR (CDCl₃, 500 MHz): δ 8.90 (s, 1H), 8.16 (s, 1H), 8.04 (s, 1H), 7.43 (s, 1H), 7.35-6.85 (m, 7H) 5.16 (s, 2H), 3.75 (s, 2H), 3.71 (m, 2H), 2.5 (m, 2H), 2.19 (m, 2H). ¹³C NMR (CDCl₃, 125 MHz): δ 181.0, 179.5, 173.5, 163.7, 163.2, 163.1, 161.9, 161.8, 161.7, 161.2, 161.1, 159.9, 159.8, 159.4, 159.0, 143.9, 140.8, 131.5, 131.4, 131.2, 131.14, 131.11, 131.06, 130.25, 130.19, 122.7, 121.96, 121.94, 121.84, 121.81, 117.2, 116.1, 115.9, 115.8, 111.8, 111.7, 111.6, 111.58, 104.5, 104.3, 104.1, 98.6, 52.3, 47.8, 30.7, 28.4, 28.3, 16.8. HRMS [M+H]⁺ calculated mass 526.1590 for C₂₇H₂₃F₃N₃O₅, found 526.1590.

Representative Example 10

4-(1,5-bis(2,4-difluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-4-oxo-N-(2-oxopyrrolidin-1-yl)but-2-enamide (**20**)

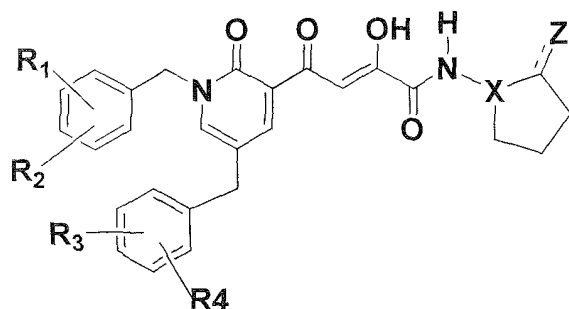


20

Target compound **20** was prepared from the corresponding tetrafluoro diketo acid using the procedure described above for **17** to give **20** as a yellow solid, mp 82-83 °C, UV (MeOH) 400 nm (ϵ 7500), 322 nm (ϵ 5400). ^1H NMR (CDCl_3 , 500 MHz): δ 8.93 (s, 1H), 8.16 (s, 1H), 8.15 (s, 1H), 8.00 (s, 1H), 7.63- 6.85 (m, 6H), 5.15 (s, 2H), 3.78 (s, 2H), 3.72 (m, 2H), 2.50 (m, 2H), 2.19 (m, 2H). ^{13}C NMR (CDCl_3 , 125 MHz): δ 180.9, 179.4, 173.5, 164.1, 164.0, 163.22, 163.12, 162.4, 162.3, 162.1, 162.0, 161.9, 161.8, 161.2, 161.1, 160.4, 160.3, 160.0, 159.9, 159.5, 159.0, 144.0, 141.4, 133.6, 133.5, 133.47, 133.43, 131.2, 131.16, 131.13, 131.1, 122.6, 122.0, 121.9, 121.82, 121.79, 118.5, 118.47, 118.4, 118.35, 117.1, 112.04, 112.01, 111.9, 111.8, 111.77, 111.74, 111.6, 111.57, 104.5, 104.3, 104.15, 104.1, 103.9, 103.7, 98.6, 47.9, 47.2, 30.6, 28.4, 16.8. HRMS $[\text{M}+\text{H}]^+$ calculated mass 544.1496 for $\text{C}_{27}\text{H}_{22}\text{F}_4\text{N}_3\text{O}_5$, found 544.1541.

We claim:

1. A compound according to the general structural formula I (including any chiral isomer, geometric isomer, tautomer, regioisomer or pharmaceutically acceptable salt thereof):



5

Formula I

Wherein R_1 , R_2 , R_3 and R_4 are each independently H or a halogen;

10 X is CH or N; and

Z is OH or =O, or a pharmaceutically acceptable salt or ester thereof.

2. A compound according to claim 1 wherein said halogen is F.

3. A compound according to claim 1 or 2

15 Wherein R_1 , R_2 , R_3 and R_4 are substituted according to the following alternative sequences:

$R_1 = o\text{-F}$, $R_2 = H$, $R_3 = p\text{-F}$, $R_4 = o\text{-F}$

$R_1 = p\text{-F}$, $R_2 = H$, $R_3 = p\text{-F}$, $R_4 = o\text{-F}$

$R_1 = o\text{-F}$, $R_2 = o\text{-F}$, $R_3 = o\text{-F}$, $R_4 = H$

$R_1 = o\text{-F}$, $R_2 = H$, $R_3 = o\text{-F}$, $R_4 = o\text{-F}$

20 $R_1 = o\text{-F}$, $R_2 = H$, $R_3 = p\text{-F}$, $R_4 = H$

$R_1 = o\text{-F}$, $R_2 = p\text{-F}$, $R_3 = p\text{-F}$, $R_4 = o\text{-F}$ or

$R_1 = o\text{-F}$, $R_2 = o\text{-F}$, $R_3 = o\text{-F}$, $R_4 = o\text{-F}$.

4. A compound according to any of claims 1-3 wherein X is CH.

25 5. A compound according to any of claims 1-3 wherein X is N.

6. A compound according to any of claim 1-5 where Z is OH.

7. A compound according to any of claims 1-5 wherein Z is =O.

8. A compound according to any of claims 1-3 wherein the said compound is a pharmaceutically acceptable salt.

9. A pharmaceutical composition for treating an HIV infection, comprising a therapeutically effective amount of a compound according to any of claims 1-8 and a

5 pharmaceutically acceptable carrier, additive or excipient.

10. The pharmaceutical composition of claim 9 wherein said composition treats said HIV infection by inhibiting HIV integrase, both wild type and mutants, in the human host.

11. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any of claims 1-8, a pharmaceutically acceptable carrier, additive or excipient in combination with a therapeutically effective amount of at least one compound selected from the group consisting of i) an additional anti-HIV agent, ii) an anti-infective agent other than an anti-HIV agent, iii) an immunomodulator and iv) a combination agent selected from the group presented in the table shown on pages 27-36, hereof, and a

15 pharmaceutically acceptable carrier, additive or excipient.

12. The composition of claim 11 wherein said anti-infective agent is an antiviral agent selected from the group consisting of a protease inhibitor, a reverse transcriptase inhibitor, an additional integrase inhibitor or a combination thereof.

20

13. The composition of claim 12 wherein said reverse transcriptase inhibitor is a nucleoside compound.

14. The composition of claim 13 wherein said reverse transcriptase inhibitor is a non-nucleoside compound.

25

15. The composition of claim 12 wherein the said additional integrase inhibitor is a compound other than a pyridinone hydroxycyclopentyl carboxamide compound according to claim 1.

30

16. The composition according to any of claims 11-15 in oral or parenteral dosage form.

17. The composition according to any of claims 11-15 formulated for administration as an inhalation spray or a rectal suppository.

18. A method of treating an HIV infection in a patient, said method comprising administering to said patient an effective amount of a composition according to any of claims 11-17.

19. A method of reducing the likelihood of an HIV infection in a patient at risk for said infection, said method comprising administering to said patient an effective amount of a composition according to any of claims 11-17.

20. A method of treating a patient with AIDS or ARC comprising administering to said patient a therapeutically effective amount of the composition according to any of claims 1-17.

21. A method of inhibiting HIV integrase in a subject, said method comprising administering to said subject a therapeutically effective amount of a compound according to any of claims 1-8.

22. The method of claim 21 wherein said subject is a human.

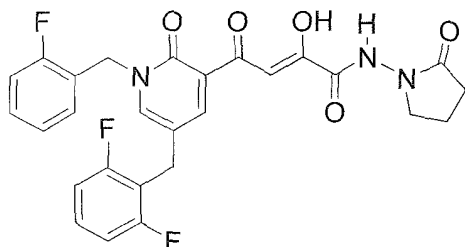
23. The method according to any of the claims 11-14, wherein said anti-HIV or other agent is a compound which is set forth in the table on pages 15-26 herein.

24. A pharmaceutical composition comprising an effective amount of a compound according to any of claim 1-8 in combination with an effective amount of at least one anti-HIV or other compound which is set forth in the table on pages 15-26, herein, in combination with a pharmaceutically acceptable carrier, additive or excipient.

25. A method of treating an HIV infection in a human host comprising administering to said host in combination, an effective amount of at least one compound according to any of claims 1-8 in combination with at least one anti-HIV or other compound, which is set forth which is set forth in the table on any of pages 15-26, herein, in combination with a pharmaceutically acceptable carrier, additive or excipient.

26. A method of treating an HIV infection in a human host comprising administering to said host in combination, an effective amount of a compound according to the structure:

5



in combination with at least one anti-HIV or other compound, which is set forth in the table on any of pages 15-26 herein, in combination with a pharmaceutically acceptable carrier, additive or excipient.

10

27. A pharmaceutical composition according to claim 9 or 10 further comprising at least one additional compound selected from the group consisting of

- (-)βDioxolane-G; DXG;
- 15 • (-)β-Arctigenin; Arctigenin ;
- (-)-Carbovir; (-)-C-D4G; (-)-Carbovir;
- (-)-β-D-2,6-Diaminopurine dioxolane;Amdoxovir; DAPD; APD
- (+)-2'-Deoxy-3'-oxa-4'-thiocytidine; dOTC (+)
- (+)-2'-Deoxy-3'-oxa-4'-thio-5-fluorocytidine; dOTFC (+)
- 20 • (+/-)-Cyclobut-G; A-69992; (+/-)-Lobucavir; C-Oxt-G; Cyclobut-G ; C-Oxetanocin-G
- (R)-2QuinCOAsnPhe[CHOHCH₂]PipCONHtBu
- (R)-3,6-Diamino-N-(aminomethyl)hexanamide; Bellenamine
- (R)-PMPA; (R)-9-(2-Phosphonylmethoxypropyl)adenine; PMPA-(R); Tenofovir
- (R)-PMPDAP; PMPDAP-(R)
- 25 • (S)-PMPA; (S)-9-(2-Phosphonylmethoxypropyl)adenine; PMPA(S)
- (S)-9-(2-Phosphonylmethoxypropyl)adenine; (S)-PMPA
- α-APA; R89439; Loviride
- α-APA deriv.; R87232
- α-APA deriv.; R88703

- α -APA enantiomer; R90385
 - α -L-AZT; AZT- α -L
 - α -L-DXC; α -L-Dioxalane-C; DXC- α -L-
 - α -L-FTC; FTC- α -L-
- 5
- α -Monofluoromethyldehydroornithine methyl ester; MFMOME
 - 1,1'-Azobisformamide; ADA; Azodicarbssomamide
 - 1-(11-Octylamino-10-hydroxyundecyl)-3,7-dimethylxanthine; CT-2576
 - 1-(2',3'-Dideoxy-2'-fluoro- β -D-threo-pentofuranosyl)cytosine; Ro 31-6840
 - 1-(2'-Fluoro-2',3'-dideoxy-B-D-erythro-pentofuranosyl)thymine; 2'FddT
- 10
- 1-(2OHPr)-4-Substit-piperazine, thienyl carbamate deriv.
 - 1-(2OHPr)-4-Substit-piperazine, thienyl carbamate deriv.
 - 1-(2OHPr)-4-Substit-piperazine, thienyl carbamate deriv.
 - 1-(2OHPr)-4-Substit-piperazine, thienyl carbamate deriv.
 - 1-[(2-Hydroxyethoxy)methyl]-6-(3-methylphenylthio)thymine; HEPT-M
- 15
- 1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)-2-thiothymine; HEPT-S
 - 1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)thymine; HEPT
 - 1-Deoxynojirimycin ; Deoxynojirimycin
 - 141W94; VX-478; Amprenavir; Agenerase®; Approved
 - 1592U89 Succinate; Abacavir Succinate; Ziagen® Approved
- 20
- 1-Aminooxyethylamine; AEA
 - 1-Methoxyoxalyl-3,5-dicaffeoylquinic acid; 1-MO-3,5-DCQA; Dicaffeoylquinic acid deriv.
 - 1OH-2(Cbz-Tle)3PhPr [14]paracyclophane deriv.
 - 1OH-2(Cbz-ValNH)3PhPr [13]metacyclophane deriv.
 - 1OH-2(Cbz-ValNH)3PhPr [13]paracyclophane deriv.
- 25
- 1OH-2(Cbz-ValNH)3PhPr [14]paracyclophane deriv.
 - 1OH-2(Cbz-ValNH)3PhPr [17]paracyclophane deriv.
 - 12-Deoxyphorbol-13-(3E,5E-decadienoate); Phorbol deriv.
 - 16.alpha.-Bromoepiandrosterone; Epi-Br; ; Inactivin; HE 2000; HE2000; PPB2; DHEA deriv.
- 30
- 1- β -D-arabinofuranosyl-5-(2-bromovinyl)uracil; BV-ara-U; BVaraU; BV ara-U; Sorivudine; SQ-32756; Bravavir; Brovavir; Usevir; YN-72; Bromovinyl araU; BVAU
 - 2',3'-Didehydro-3'-deoxycytidine; D4C
 - 2',3'-Dideoxydidehydroguanosine; D4G

- 2',3'-Didehydro-3'-deoxythymidine; D4T; Stavudine; Zerit® Approved
- 2',3'-Dideoxy-3'-fluoro-4-thiothymidine; 3'-F-4-Thio-ddT
- 2',3'-Dideoxy-3'-fluoro-5-bromouridine; FddBrU
- 2',3'-Dideoxy-3'-fluoro-5-chlorocytidine; 3'-F-5-Cl-ddC
- 5 • 2',3'-Dideoxy-3'-fluoro-5-chlorouridine; 935U83; 5-Chloro-2',3'-dideoxy-3'-fluorouridine; FddClU; Raluridine
- 2',3'-Dideoxy-5-ethylcytidine; 5-Et-ddC
- 2',3'-Dideoxyadenosine; D2A; ddAdo; ddA
- 2',3'-Dideoxydidehydroadenosine; d4A
- 10 • 2',3'-Dideoxyguanosine; D2G; ddG
- 2',3'-Dideoxy-3'-hydroxymethyl cytidine; 3'-Hydroxymethyl-ddC; BEA-005
- 2,5'-Anhydro-3'-azido-2',3'-dideoxyuridine; AZU-2,5'-anhydro
- 2,5'-Anhydro-3'-azido-3'-deoxythymidine; AZT-2,5'-anhydro
- 2',5'diSilySpiroT; TSAO-T; 2',5'diSilySpiroT; TSAO-me³T
- 15 • 2,6-Diamino-2',3'-dideoxypurine-9-ribofuranoside; ddDAPR; DAPDDR; 2,6-Diamino-ddP
- 2,6-Diaminopurine-2',3'-dideoxydidehydroriboside; ddeDAPR
- 2,6-Diaminopurine-3'-fluoro-2',3'-dideoxyriboside; 3'-F-ddDAPR
- 2-Aminobenzylstatine Valyl Cbz deriv.; Statine deriv.
- 2-Glycine amide-5-chlorophenyl 2-pyrryl ketone; GCPK
- 20 • [2-PyridCH₂NCH₃CO-Val-NHCH(Bz)]CHOHCHOH; A-77003
- 2'-Azido-2',3'-dideoxyadenosine; 9-(2'-Azido-2',3'-dideoxy-β-D-erythropentofuranosyl)adenine; 2'-N3ddA
- 2'-FddA(B-D-threo); F-ddA; 2'-F-dd-ara-A; 9-(2'-Fluoro-2',3'-dideoxy-B-D-threopentafuranosyl)adenine; Lodensine
- 25 • 2'-N3ddA (B-D-threo); 9-(2'-Azido-2',3'-dideoxy-β-threopentafuranosyl)adenine
- 2-NaphCOAsnPhe[CHOHCH₂]Pro-OtBu
- 2-Nitrophenylphenylsulfone; NPPS
- 3-(3-Oxo-1-propenyl)-3'-azido-3'-deoxythymidine; 3-(3-Oxo-1-propenyl)AZT
- 3-(Phenylsulfonyl)-indole deriv. ; L-737,126
- 30 • 3,5-DCQA; 3,5-Dicaffeoylquinic acid; Dicaffeoylquinic acid
- 3'-Azido-2',3'-dideoxy-5-[(cyanomethyl)oxy]uridine; 3'-N3-5-Cyanomethyloxy-ddU
- 3'-Azido-2',3'-dideoxy-5-aminouridine; 3'-N3-5-NH₂-ddU
- 3'-Azido-2',3'-dideoxy-5-aza-6-deazauridine; C-analog of 3'-N3-ddU

- 3'-Azido-2',3'-dideoxy-5-bromouridine; 3'-N3-5-Br-ddU; AZddBrU
- 3'-Azido-2',3'-dideoxy-5-chlorocytidine; 3'-Az-5-Cl-ddC
- 3'-Azido-2',3'-dideoxy-5-dimethylaminouridine; 3'-N3-5-NMe2-ddU
- 3'-Azido-2',3'-dideoxy-5-ethyluridine; 3'-N3-5-EtddU; CS-85; AZddEtU
- 5 • 3'-Azido-2',3'-dideoxy-5-fluorocytidine; 3'-N3-5-F-ddC
- 3'-Azido-2',3'-dideoxy-5-fluorouridine; AZddFU
- 3'-Azido-2',3'-dideoxy-5-hydroxyuridine; 3'-N3-5-OH-ddU
- 3'-Azido-2',3'-dideoxy-5-iodouridine; 3'-N3-5-I-ddU; AZddIU
- 3'-Azido-2',3'-dideoxy-5-methylaminouridine; 3'-N3-5-NHMe-ddU
- 10 • 3'-Azido-2',3'-dideoxy-5-methylcytidine; CS-92; 3'-N3-5-Me-ddC
- 3'-Azido-2',3'-dideoxy-5-thiocyanatouridine; 3'-N3-5-SCN-ddU
- 3'-Azido-2',3'-dideoxy-5-trifluoromethyluridine; 3'-N3-5-CF3-ddU
- 3'-Azido-2',3'-dideoxycytidine; CS-91; 3'-N3-ddC
- 3'-Azido-2',3'-dideoxyguanosine; AZG; 3'-N3ddG
- 15 • 3'-Azido-2',3'-dideoxy-N4--5-dimethylcytidine; 3'-N3-N4-5-diMe-ddC
- 3'-Azido-2',3'-dideoxy-N4-OH-5-methylcytidine; 3'-N3-N4-OH-5-Me-ddC
- 3'-Azido-2',3'-dideoxyuridine; CS-87; 3'-N3ddU; AZdU; Uravidine
- 3'-Azido-3'-deoxy-6-azathymidine; 3'AZ-6AzaT
- 3-Azido-3'-deoxythymidyl-(5',5')-2',3'-dideoxy-5'-adenylic acid; AZT-P-ddA
- 20 • 3'-Azido-3'-deoxythymidyl-(5',5')-2',3'-dideoxy-5'-adenylic acid, 2-cyanoethyl ester; AZT-P(CyE)-ddA
- 3'-Azido-3'-deoxythymidyl-(5',5')-2',3'-dideoxy-5'-inosinic acid; AZT-P-ddI
- 3'-Azido-3'-deoxythymidine-5'-(butylmethoxyvalinyl)phosphate; 5'MeOValPO3(Bu)AZT
- 3'-Azido-5-chloro-2',3'-dideoxyuridine; AzddClUrd; AzddClU
- 25 • 3'-Deoxythymidine; ddT
- 3'-FddA (B-D-Erythro); 9-(3'-Fluoro-2',3'-dideoxy-B-D-erythropentafuranosyl)adenine
- 3'-FddC; 3'-Fluoro-2',3'-dideoxycytidine
- 3'-FddG; 3'-Fluoro-2',3'-dideoxyguanosine
- 3'-FddT; Alovudine; FddT; FddThD; 3'-FLT; FLT
- 30 • 3'-FddU; 3'-Fluoro-2',3'-dideoxyuridine
- 3'-Fluoro-2',3'-dideoxy-5-iodouridine; FddIU
- 3'-N3-ddA; 9-(3'-Azido-2',3'-dideoxy-B-D-erythropentafuranosyl)adenine
- 3TC; Lamivudine; Epivir® Approved;
- Lamivudine & Zidovudine; Combivir® 3TC & AZT; Approved

- 4'-Acetoamidophenyl4-guadinobenzoate; AGB
- 4'-Az-3'-dT; 4'-Azido-3'-deoxythymidine
- 4'-Az-5ClU ; 4'-Azido-5-chloro-2'-deoxyuridine
- 4'-AzdA; 4'-Azido-2'-deoxyadenosine
- 5 • 4'-AzdC; 4'-Azido-2'-deoxycytidine
- 4'-AzdG; 4'-Azido-2'-deoxyguanosine
- 4'-AzdI; 4'-Azido-2'-deoxyinosine
- 4'-AzdU; 4'-Azido-2'-deoxyuridine
- 4'-Azido-2'-deoxy- β -D-erythro-pentofuranosyl-5-methyl-2,4-dioxypyrimidine; 4'-
- 10 Azidothymidine
- 4'-Cyanothymidine; 4'-CN-T
- 4-Methyl-5-(pyrazinyl)-3H-1,2-dithiole-3-thione; Oltipraz
- 5'-[(1,4-Dihydro-1-methyl-3-pyridinylcarbonyl)oxy]-3'-azido-2',3'-deoxythymidine; DP-AZT; HP-AZT; AZT Prodrug; AZT-DHP
- 15 • 5'-[(Z)-4-amino-2-butenyl]methylamino]-5'-deoxyadenosine; MDL 73811
- 5'-Alkylglycosidecarbonate of 3'-azido-3'-deoxythymidine; AcNHGlc-hexyl-CO3 AZT
- 5Cl3PhS-2IndolCONH2
- 5-Fluoro-2',3'-dideoxycytidine; 5-F-ddC
- 5-Methyl-3'-azido-2',3'-dideoxyisocytidine; MeAZddIsoC
- 20 • 6-O-Butanoylcastanospermine; BuCast; MDL 28,574; Celgosivir
- 6-Chloro-9-(2,3-dideoxy-b-D-glyceropentofuranosyl)-9H-purine; D2ClP; 6-Chloro-ddP; CPDDR; 6Cl-ddP
- 6-Dimethylaminopurine-2',3'-dideoxyriboside; N-6-dimethyl-ddA; DMAPDDR
- 7-Chloro-N-methyl-5-(1H-pyrrol-2-yl)-3H-1,4-benzodiazepin-2-amine ; Ro 24-7429
- 25 • 7-Chloro-5-(2-pyrrolyl)-3H-1,4-benzodiazepin-2(H)-one ; Ro 5-3335
- 8-Chloro-TIBO; Tivirapine; R86183
- 9-(2,3-Dideoxy- β -D-ribofuranosyl)-6-(methylthio)purine; D2SMeP
- 9-[Bis(OHMe)cBu]A; A-69463; Cyclobutyl-A; Cyclobut-A ; C-oxetanocin A
- A-76890
- 30 • A-77212
- A-80987; Ritonavir deriv.
- A-81525; Ritonavir deriv.
- A-83962; Ritonavir deriv.

- A-98881; Azacyclic urea deriv.
- AA; L-ascorbic acid; Calcium Ascorbate
- AAP-BHAP; U-104489; PNU-104489
- Abacavir & Lamivudine & Zidovudine; Trizivir® ABC & (-)-3TC & AZT
- 5 • ABT-378; Lopinavir; Component of Kaletra; Aluviran®
- ABT-378 & ABT-538; Kaletra®; Lopinavir & Ritonavir; Aluviran® & Norvir®
- ABT-538; Norvir®; Ritonavir; Component of Kaletra; Approved
- Acemannan
- Adefovir; PMEA; GS-0393
- 10 • Adefovir dipivoxil; BisPom PMEA; GS-840; Preveon®
- AG-1343; Viracept®; Nelfinavir; Approved
- AG1350; LY316957; Nelfinavir-octahydro-thienopyridine analog
- AHPBA analog; R-87366
- Alpha-lipoic acid; α -Lipoic acid; Thioctic acid
- 15 • ALX40-4C
- AMD3100; JM3100
- Amprenavir phosphate; VX-175; GW433908; GW433908A (*Sodium Salt*); GW433908G (*Calcium Salt*); Fosamprenavir
- Ancer 20; Z-100
- 20 • Anti-sense 25-mer phosphorothioate; GEM91
- Atazanavir; CGP-73547; BMS-232632; BMS 232632; Zrivada; Latazanavir; Reyataz®
- Ateviridine; U-87201E; BHAP deriv.
- Aurintricarboxylic acid; Dupont ATA; Dupont DA639; SD-095345; ATA
- AY 9944; trans-1,4-Bis(2-dichlorobenzylaminoethyl)cyclohexane dichlorhydrate
- 25 • AZT; Zidovudine; Azidothymidine; Retrovir®
- AZT-PO₃(CH₃)-AZT; O,O'-Bis(3'-azido-3'-deoxythymidin-5'-yl)methylphosphonate
- Baicalin; TJN-151
- Betulinic acid; Mairin
- Betulinic acid, 3-O-(3',3'-dimethylsuccinate)
- 30 • BHAP deriv.
- BHAP deriv.
- BHAP deriv.
- BHAP deriv.

- BHAP deriv.
- BHAP deriv.; Rescriptor® ; Delavirdine; U-90152
- BHAP deriv.; U-88204E
- BI-RG-587; Nevirapine; Viramune® Approved
- 5 • BILA 1906 BS
- BILA 2011 BS; Palinavir
- BILA 2185 BS
- Bis(2-nitrophenyl)sulfone; Bis(2NO₂Ph)SO₂; NSC633001
- bis-ValHOEt-N2aza-peptide isostere; CGP 53820
- 10 • bis-ValHOEt-N2aza-peptide isostere; CGP 53820 analog
- BMS-186318
- BocPhe[CHOH(CH₂)₃CH=CHPhCO]IleAMBI; L-687,908
- BzOCValPhe[diCHOH(RR)]PheValBzOC
- BzOCValPhe[diCHOH(SS)]PheValBzOC
- 15 C2-Sym Phosphinic amide deriv. (HOECHST AG)
- Calanolide A ; NSC675451
- Calanolide B
- Capravirine; S-1153
- Castanospermine
- 20 • CbzAF(CHOHCH₂)AVVOMe
- Cbz-Asn-Apns-Pro-NH-tBu; KNI-102
- CGP 61755; Lasinavir
- CGP 64222
- CNI-H0294
- 25 • Coactinon;I-EBU; HEPT deriv.; MKC-442; Emivirine
- Conocurvone; NSC650891
- Coviracil; (-)FTC; (-)-2',3'-Dideoxy-5-fluoro-3'-thiacytidine; Emtricitabine; Emtriva
- C-Oxetanocin-G; A-69992; (+-)Lobucavir; C-Oxt-G; Cyclobut-G; (+-)Cyclobut-G
- Crixivan®; Indinavir; MK639; L-735,524; Approved
- 30 • Curdlan Sulfate
- CV-N; Cyanovirin-N
- Cyclic Urea Amide; SD146
- Cyclosporin A; Sandimmune®
- [Me-Ile-4]Cyclosporin A; SDZ NIM 811

- D4A (L); L-2',3'-Didehydro-2',3'-dideoxyadenosine
- D4FC; D-D4FC; 2',3'-Didehydro-2',3'-dideoxy-5-fluorocytidine; DPC 817
- D4FC (L); L-2',3'-Didehydro-2',3'-dideoxy-5-fluorocytidine
- D4G (L); L-2',3'-Didehydro-2',3'-dideoxyguanosine
- 5 • D4I (L); L-2',3'-Didehydro-2',3'-dideoxyinosine
- DABO
- ddC; Dideoxycytidine; Zalcitabine; Hivid®
- ddI; Dideoxyinosine; Didanosine; Videx®
- Dehydroepiandrosterone; DHEA; Prasterone; Dehydroisoandrosterone; EL-10
- 10 • Dextran Sulfate
- Dicafeic acid ester; L-Chicoric acid
- DMP-266; Sustiva®; Efavirenz; Approved
- DMP-323; XM-323
- DMP-450
- 15 • Docosanol; n-Docosanol
- dOTC (-); (-)-2'-Deoxy-3'-oxa-4'-thiocytidine
- dOTFC (-); (-)-2'-Deoxy-3'-oxa-4'-thio-5-fluorocytidine
- DP-178; Pentafuside; T-20; GP41 127-162 AA; Enfuvirtide; Fuzeon®
- E-BPTU; HEPT deriv.; NSC 648400
- 20 • E-EBU; HEPT deriv.; MKC-442 deriv.
- E-EBU-dM; HEPT deriv.; MKC-442 deriv.
- E-EPSeU; HEPT deriv.; MKC-442 deriv.
- E-EPU; HEPT deriv.; MKC-442 deriv.
- Ebselen
- 25 • Etoposide
- Epoxy steroid deriv.; (4 α ,5 α ,17 β)-17-Hydroxy-3-oxo-4,5-epoxyandrostane-2-carboxamide
- Eulicin
- Fenalamide A1; Phenalamide A1; Stipiamide
- *Flephilone*
- 30 • Fluoroquinolone deriv.; K-12
- Fortovase®; Invirase®; Saquinavir; Ro31-8959; Approved
- Foscarnet; Phosphonoformic acid; Foscavir;
- FPMDAP;

- FPMPA
- FPMPG
- GPGRAF Octomer; SPC3
- Hammerhead anti-gag RNA Ribozyme B
- 5 • Harziphilone
- HBY 097; Quinoxaline deriv.
- HEPT deriv.; MKC-442 deriv.
- HEPT deriv.; MKC-442 deriv.
- HOCH₂CH₂ isostere; ThienopyridCON thienyl urethane deriv.
- 10 • HOCH₂CH₂ isostere; ThienopyridCON thienyl urethane deriv.
- HOCH₂CH₂ isostere; ThienopyridCON thienyl urethane deriv.
- HOCH₂CH₂ isostere; ThienopyridCON thienyl urethane deriv.
- HOCH₂CH₂ isostere; ThienopyridCON thienyl urethane deriv.
- HOCH₂CH₂ isostere; ThienopyridCONthienyl urethane deriv.; LY326188
- 15 • HPMPA
- HPMPDAP
- HU; Hydroxyurea; Hydrea
- Hydroxocobalamin
- Hypericin
- 20 • Ingenol 3,5,20-triacetate; ITA; RD3-2118
- Ingenol deriv.; RD4-2138
- Inophyllum B
- Inophyllum P
- iQoa-Mta-Apns-Thz-NH-tBu; KNI-272
- 25 • Isentress (Raltegravir)
- IsoquinCON furanyl urethane analog
- IsoquinCON thienyl urethane analog
- IsoquinCON thienyl urethane analog
- KNI-154; Noa-Asn-Apns-Thz-NH-tBu
- 30 • KNI-174; Noa-Asn-Apns-Dmt-NH-tBu
- KNI-227; Qoa-Mta-Apns-Thz-NH-tBu
- L-685,434
- L-685,434-6-Hydroxy derivative
- L-685,434-sOEtMorphderivative; L-689,502

- L-685,434-OEtNMe₂
- L-685,434-OPrMorph derivative
- L-697,593; 2-Pyridinone deriv.
- L-697,639; 2-Pyridinone deriv.
- 5 • L-697,661; 2-Pyridinone deriv.
- L-FddC; β -L-5F-ddC
- Lamivudine & Zidovudine; Combivir® 3TC & AZT; Approved
- LY289612
- LY289612 analog
- 10 • LY289612 analog
- LY-300046-HCl; PETT deriv.; Troviridine
- LY314163; Saquinavir/Nelfinavir deriv..
- LY-73497; N-(2-Phenethyl)-N'-(2-thiazolyl)thiourea; PETT
- MAP; Methyl acetylenic putrescine
- 15 • Michellamine A; NSC650898
- Michellamine B; NSC649324
- Michellamine F
- N-6-Et-ddA; N-Ethyl-2',3'-dideoxyadenosine
- N-6-methyl ddA; N6-Methyl-2',3'-dideoxyadenosine
- 20 • Naphthalene 2-sulphonate polymer; PRO 2000
- Nelfinavir-octahydro-thienopyridine analog
- Nonoxynol 9
- NSC625487; Thiazolobenzimidazole; TBZ
- Oxathiin deriv.; UC-38
- 25 • Oxathiin deriv.; UC-84
- P9941
- Penicillin Et(NH)₂ Sym dimer
- Penicillin G, ET(NH)₂ deriv.
- Penicillin, 2Isoquin-OHPrNH₂ analog
- 30 • Penicillin, 2Isoquin-OHPrNH₂ analog
- Pentosan Sulfate; Elmiron; SP54; Xylan Sulfate;
- PETT Cl, F deriv.
- PETT deriv.

- PETT deriv.
- PETT deriv.
- PETT deriv.
- Phenoxan
- 5 • Phorbol deriv.; Prostratin
- Platanic acid
- PMEDAP
- PMEG
- PMEHz; PMEI
- 10 • PMEMAP
- PMET
- PNU-140690; U-140690; Tipranavir
- Pyridinone deriv.
- Pyridinone deriv.
- 15 • Quinoxalin2thione deriv; S-2720
- R14458; TIBO deriv..
- R82150; TIBO deriv..
- R82913; TIBO deriv.
- Resobene
- 20 • Ribavirin; Virazole
- Ro 31-8959-bis-thf deriv.
- Saquinavir/Nelfinavir deriv.
- Saquinavir/Nelfinavir deriv.
- SB-205569; Val-Phe-Phe-HOCH₂CH₂ isostere analog
- 25 • SC-52151; Telinavir
- SDZ PRI 053
- Suramin Sodium
- T22
- Thalidomide
- 30 • Thiangazole; (-)-Thiangazole
- Thiazoloisoindol-5-one
- Thiazoloisoindol-5-one, deriv.
- Tle-Val-Sta, 5PhBuCOOH deriv.; Statine deriv.
- Tle-Val-Sta, 5PhBuCOOH deriv.; Statine deriv.

- UC-781
 - Val-Val-Sta, 5PhBuCOOH deriv.; Statine deriv.
 - Val-Val-Sta, 5PhBuCOOH deriv.; Statine deriv.
 - Val-Val-Sta, 5PhBuCOOH deriv.; Statine deriv.
- 5 • Val-Val-Sta, 5PhBuCOOH deriv.; Statine deriv.
- Val-Val-Sta, 5PhBuCOOH deriv.; Statine deriv.
 - VB-11,328 and
 - Viread®; Tenofovir Disoproxil,
- 10 28. A pharmaceutical composition according to claim 9 or 10 further comprising at least one additional compound selected from the group consisting of ACV; AK602; AMD070; APV; ATV; ATZ; AVX754 (apricitabine); AZT; Abacavir; Abacavir / Lamivudine / Zidovudine; Abacavir sulfate; Abacavir sulfate/Lamivudine; Abacavir/Lamivudine; Abelecet; Acyclovir; Adefovir dipivoxil; Adriamycin; Agenerase;
- 15 Aldesleukin; Alovudine; Aluvia; AmBisome; Amdoxovir; Amphocin; Amphotec; Amphotericin B; Ampligen; Amprenavir; Androderm; Androgel; Apricitabine; Aptivus; Atazanavir; Atripla; Azithromycin; BMS-378806; BMS-488043; Bactrim; Baraclude; Bevirimat; Biaxin; Brecanavir; BufferGel; C31G; CD4-IgG2; CS; CV-N; Calanolide A; Calcium hydroxylapatite; Carbopol 974P; Carrageenan; Carraguard; Cellulose sulfate;
- 20 Clarithromycin; Combivir; Copegus; Cotrimoxazole; Crixivan; Cyanovirin-N; Cytovene; DAPD; DLV; DS; Darunavir; Delavirdine; Depo-Testosterone; Dextran sulfate; Didanosine; Diflucan; Doxil; Doxorubicin (liposomal); Dronabinol; EFV; Efavirenz; Elvucitabine; Emtricitabine; Emtricitabine; Tenofovir disoproxil fumarate; Emtriva; Enfuvirtide; Entecavir; Epivir; Epoetin alfa; Epogen; Epzicom; Etopophos (phosphate salt); Etoposide; Etravirine;
- 25 FTC; Fluconazole; Fortovase; Fosamprenavir; Foxivudine tidoxil; Fungizone; Fuzeon; GS 9137; GSK-873,140 (aplaviroc); GW433908; GW640385 (brecanavir); Ganciclovir; Globulin, Immune; Growth hormone (human); Hepsera; Hivid; Human growth hormone; IL-2; INH; Immune Globulin Intravenous (Human); Indinavir; Interferon alfa-2; Interleukin-2, recombinant human; Intron A (2b); Invirase; Isentress; Isoniazid; Itraconazole; KP-1461;
- 30 Lamivudine/Zidovudine; Lexiva; Lopinavir/Ritonavir; MK-0518; Nebupent; Nelfinavir; Neutrexin; Nevirapine; Norvir; Nydrazid; Peptide T; PMPA Prodrug (Viread)'; Prezista (Darunavir); PRO 140; PRO 2000; PRO 542 (CD4 IgG2); Procrit (Epoetin); Proleukin; Racivir; Radiesse; Rrebetol; Rescriptor; Retrovir; Reyataz; Ribavirin; Rifabutin; Rifadin; Rifampin; Rimactane; Ritonavir; Roferon-A (2a); Saquinavir; SCH-D (vicriviroc);

Somatropin; Stavudinie; Sulfamethoxazole / Trimethoprim; Sustanon; Sustiva; TNX-355; Taxol; Tenofovir; Tenofovir disoproxil fumarate; Testosterone; Tipranavir; Toposar; Trimetrexate; Trizivir; Truvada (Emtriva and Viread combination); U-90152S (Delaviridine); UC-781; UK-427,857 (maraviroc); Valcyte; Valganciclovir; Valproic acid; VePesid; 5 Vicriviroc; Videx; Viracept (Tenofovir DF); Viramune; Virazole; Viread; Vitrasert; Zalcitabine; Zerit; Ziagen; Zidovudine; Zithromax; Zovirax, and mixtures thereof.

29. The composition according to any of claims 11-17, 24 and 27-28 wherein said composition treats said HIV infection by inhibiting at least HIV integrase, both wild type and 10 mutants, in the human host.

30. The composition according to claim 24, 27 or 28 in oral or parenteral dosage form.

15 31. The composition according to claim 24, 27 or 28 formulated for administration as an inhalation spray or a rectal suppository.

32. A method of treating an HIV infection in a patient, said method comprising administering to said patient an effective amount of a composition according to claim 24, 27 20 or 28.

33. A method of reducing the likelihood of an HIV infection in a patient at risk of said infection, said method comprising administering to said patient an effective amount of a composition according to claim 24, 27 or 28 to said patient. 25

34. A method of treating a patient with AIDS or ARC comprising administering to said patient a therapeutically effective amount of a composition according to claim 24, 27 or 28.

30 35. A method of inhibiting HIV integrase in a subject, said method comprising administering to said subject a therapeutically effective amount of a composition according to claim 24, 27 or 28.

36. The method according to any claims 32-35 wherein said patient or subject is a human.

37. Use of a composition according to any of claims 9-17, 24, 27 or 28 in the manufacture of medicament for the treatment of HIV in a patient.

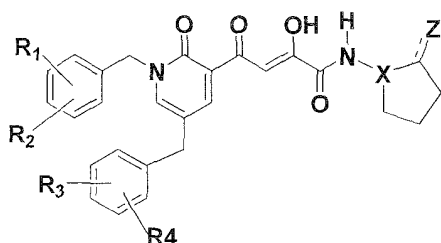
38. Use of a composition according to any of claims 9-17, 24, 27 or 28 in the manufacture of medicament for reducing the likelihood that a patient will contract an HIV infection.

39. Use of a composition according to any of claims 9-17, 24, 27 or 28 in the manufacture of medicament for treating a patient with AIDS or ARC.

40. Use of a composition according to any of claims 9-17, 24, 27 or 28 in the manufacture of medicament for inhibiting HIV integrase in a subject.

41. Use according to any of claims 37-40 wherein said subject is a human patient.

42. A method of treating an HIV infection in a human host comprising administering to said host in combination, an effective amount of a first compound according to the structure:



Formula I

Where $R_1 = o\text{-F}$, $R_2 = H$, $R_3 = p\text{-F}$, $R_4 = o\text{-F}$

$R_1 = p\text{-F}$, $R_2 = H$, $R_3 = p\text{-F}$, $R_4 = o\text{-F}$

$R_1 = o\text{-F}$, $R_2 = o\text{-F}$, $R_3 = o\text{-F}$, $R_4 = H$

$R_1 = o\text{-F}$, $R_2 = H$, $R_3 = o\text{-F}$, $R_4 = o\text{-F}$

$R_1 = o\text{-F}$, $R_2 = H$, $R_3 = p\text{-F}$, $R_4 = H$

$R_1 = o\text{-F}$, $R_2 = p\text{-F}$, $R_3 = p\text{-F}$, $R_4 = o\text{-F}$, or

$R_1 = \text{o-F}$, $R_2 = \text{o-F}$, $R_3 = \text{o-F}$, $R_4 = \text{o-F}$

X is CH or N; and

Z is OH or =O; in combination with an effective amount at least one additional agent set forth below:

- 5
 - (-) β Dioxolane-G; DXG;
 - (-) β -Arctigenin; Arctigenin ;
 - (-)-Carbovir; (-)-C-D4G; (-)-Carbovir;
 - (-)- β -D-2,6-Diaminopurine dioxolane;Amdoxovir; DAPD; APD
 - (+)-2'-Deoxy-3'-oxa-4'-thiocytidine; dOTC (+)
- 10
 - (+)-2'-Deoxy-3'-oxa-4'-thio-5-fluorocytidine; dOTFC (+)
 - (+/-)-Cyclobut-G; A-69992; (+/-)-Lobucavir; C-Oxt-G; Cyclobut-G ; C-Oxetanocin-G
 - (R)-2QuinCOAsnPhe[CHOHCH₂]PipCONHtBu
 - (R)-3,6-Diamino-N-(aminomethyl)hexanamide; Bellenamine
 - (R)-PMPA; (R)-9-(2-Phosphonylmethoxypropyl)adenine; PMPA-(R); Tenofovir
- 15
 - (R)-PMPDAP; PMPDAP-(R)
 - (S)-PMPA; (S)-9-(2-Phosphonylmethoxypropyl)adenine; PMPA(S)
 - (S)-9-(2-Phosphonylmethoxypropyl)adenine; (S)-PMPA
 - α -APA; R89439; Loviride
 - α -APA deriv.; R87232
- 20
 - α -APA deriv.; R88703
 - α -APA enantiomer; R90385
 - α -L-AZT; AZT- α -L
 - α -L-DXC; α -L-Dioxalane-C; DXC- α -L-
 - α -L-FTC; FTC- α -L-
- 25
 - α -Monofluoromethyldehydroornithine methyl ester; MFMOME
 - 1,1'-Azobisformamide; ADA; Azodicarbonamide
 - 1-(11-Octylamino-10-hydroxyundecyl)-3,7-dimethylxanthine; CT-2576
 - 1-(2',3'-Dideoxy-2'-fluoro- β -D-threo-pentofuranosyl)cytosine; Ro 31-6840
 - 1-(2'-Fluoro-2',3'-dideoxy-B-D-erythro-pentofuranosyl)thymine; 2'FddT
- 30
 - 1-(2OHPr)-4-Substit-piperazine, thienyl carbamate deriv.
 - 1-(2OHPr)-4-Substit-piperazine, thienyl carbamate deriv.
 - 1-(2OHPr)-4-Substit-piperazine, thienyl carbamate deriv.
 - 1-(2OHPr)-4-Substit-piperazine, thienyl carbamate deriv.

- 1-[(2-Hydroxyethoxy)methyl]-6-(3-methylphenylthio)thymine; HEPT-M
- 1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)-2-thiothymine; HEPT-S
- 1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)thymine; HEPT
- 1-Deoxynojirimycin ; Deoxynojirimycin
- 5 • 141W94; VX-478; Amprenavir; Agenerase®; Approved
- 1592U89 Succinate; Abacavir Succinate; Ziagen® Approved
- 1-Aminooxyethylamine; AEA
- 1-Methoxyoxalyl-3,5-dicaffeoylquinic acid; 1-MO-3,5-DCQA; Dicaffeoylquinic acid deriv.
- 1OH-2(Cbz-Tle)3PhPr [14]paracyclophane deriv.
- 10 • 1OH-2(Cbz-ValNH)3PhPr [13]metacyclophane deriv.
- 1OH-2(Cbz-ValNH)3PhPr [13]paracyclophane deriv.
- 1OH-2(Cbz-ValNH)3PhPr [14]paracyclophane deriv.
- 1OH-2(Cbz-ValNH)3PhPr [17]paracyclophane deriv.
- 12-Deoxyphorbol-13-(3E,5E-decadienoate); Phorbol deriv.
- 15 • 16.alpha.-Bromoepiandrosterone; Epi-Br; ; Inactivin; HE 2000; HE2000; PPB2; DHEA deriv.
- 1-β-D-arabinofuranosyl-5-(2-bromovinyl)uracil; BV-ara-U; BVaraU; BV ara-U; Sorivudine; SQ-32756; Bravavir; Brovavir; Usevir; YN-72; Bromovinyl araU; BVAU
- 2',3'-Didehydro-3'-deoxycytidine; D4C
- 20 • 2',3'-Dideoxydidehydroguanosine; D4G
- 2',3'-Didehydro-3'-deoxythymidine; D4T; Stavudine; Zerit® Approved
- 2',3'-Dideoxy-3'-fluoro-4-thiothymidine; 3'-F-4-Thio-ddT
- 2',3'-Dideoxy-3'-fluoro-5-bromouridine; FddBrU
- 2',3'-Dideoxy-3'-fluoro-5-chlorocytidine; 3'-F-5-Cl-ddC
- 25 • 2',3'-Dideoxy-3'-fluoro-5-chlorouridine; 935U83; 5-Chloro-2',3'-dideoxy-3'-fluorouridine; FddCIU; Raluridine
- 2',3'-Dideoxy-5-ethylcytidine; 5-Et-ddC
- 2',3'-Dideoxyadenosine; D2A; ddAdo; ddA
- 2',3'-Dideoxydidehydroadenosine; d4A
- 30 • 2',3'-Dideoxyguanosine; D2G; ddG
- 2',3'-Dideoxy-3'-hydroxymethyl cytidine; 3'-Hydroxymethyl-ddC; BEA-005
- 2,5'-Anhydro-3'-azido-2',3'-dideoxyuridine; AZU-2,5'-anhydro
- 2,5'-Anhydro-3'-azido-3'-deoxythymidine; AZT-2,5'-anhydro

- 2',5'diSilySpiroT; TSAO-T
- 2',5'diSilySpiroT; TSAO-me³T
- 2,6-Diamino-2',3'-dideoxypurine-9-ribofuranoside; ddDAPR; DAPDDR; 2,6-Diamino-ddP
- 2,6-Diaminopurine- 2',3'-dideoxydidehydroriboside; ddeDAPR
- 5 • 2,6-Diaminopurine-3'-fluoro-2',3'-dideoxyriboside; 3'-F-ddDAPR
- 2-Aminobenzylstatine Valyl Cbz deriv.; Statine deriv.
- 2-Glycine amide-5-chlorophenyl 2-pyrryl ketone; GCPK
- [2-PyridCH₂NCH₃CO-Val-NHCH(Bz)]CHOHCHOH; A-77003
- 2'-Azido-2',3'-dideoxyadenosine; 9-(2'-Azido-2',3'-dideoxy-β-D-
- 10 erythropentofuranosyl)adenine; 2'-N3ddA
- 2'-FddA(B-D-threo); F-ddA; 2'-F-dd-ara-A; 9-(2'-Fluoro-2',3'-dideoxy-B-D-
- threopentafuranosyl)adenine; Lodensine
- 2'-N3ddA (B-D-threo); 9-(2'-Azido-2',3'-dideoxy-β-threopentafuranosyl)adenine
- 2-NaphCOAsnPhe[CHOHCH₂]Pro-OtBu
- 15 • 2-Nitrophenylphenylsulfone; NPPS
- 3-(3-Oxo-1-propenyl)-3'-azido-3'-deoxythymidine; 3-(3-Oxo-1-propenyl)AZT
- 3-(Phenylsulfonyl)-indole deriv. ; L-737,126
- 3,5-DCQA; 3,5-Dicaffeoylquinic acid; Dicaffeoylquinic acid
- 3'-Azido-2',3'-dideoxy-5-[(cyanomethyl)oxy]uridine; 3'-N3-5-Cyanomethyloxy-ddU
- 20 • 3'-Azido-2',3'-dideoxy-5-aminouridine; 3'-N3-5-NH₂-ddU
- 3'-Azido-2',3'-dideoxy-5-aza-6-deazauridine; C-analog of 3'-N3-ddU
- 3'-Azido-2',3'-dideoxy-5-bromouridine; 3'-N3-5-Br-ddU; AZddBrU
- 3'-Azido-2',3'-dideoxy-5-chlorocytidine; 3'-Az-5-Cl-ddC
- 3'-Azido-2',3'-dideoxy-5-dimethylaminouridine; 3'-N3-5-NMe₂-ddU
- 25 • 3'-Azido-2',3'-dideoxy-5-ethyluridine; 3'-N3-5-EtddU; CS-85; AZddEtU
- 3'-Azido-2',3'-dideoxy-5-fluorocytidine; 3'-N3-5-F-ddC
- 3'-Azido-2',3'-dideoxy-5-fluorouridine; AZddFU
- 3'-Azido-2',3'-dideoxy-5-hydroxyuridine; 3'-N3-5-OH-ddU
- 3'-Azido-2',3'-dideoxy-5-iodouridine; 3'-N3-5-I-ddU; AZddIU
- 30 • 3'-Azido-2',3'-dideoxy-5-methylaminouridine; 3'-N3-5-NHMe-ddU
- 3'-Azido-2',3'-dideoxy-5-methylcytidine; CS-92; 3'-N3-5-Me-ddC
- 3'-Azido-2',3'-dideoxy-5-thiocyanatouridine; 3'-N3-5-SCN-ddU
- 3'-Azido-2',3'-dideoxy-5-trifluoromethyluridine; 3'-N3-5-CF₃-ddU

- 3'-Azido-2',3'-dideoxycytidine; CS-91; 3'-N3-ddC
- 3'-Azido-2',3'-dideoxyguanosine; AZG; 3'-N3ddG
- 3'-Azido-2',3'-dideoxy-N4--5-dimethylcytidine; 3'-N3-N4-5-diMe-ddC
- 3'-Azido-2',3'-dideoxy-N4-OH-5-methylcytidine; 3'-N3-N4-OH-5-Me-ddC
- 5 • 3'-Azido-2',3'-dideoxyuridine; CS-87; 3'-N3ddU; AZdU; Uravidine
- 3'-Azido-3'-deoxy-6-azathymidine; 3'AZ-6AzaT
- 3-Azido-3'-deoxythymidyl-(5',5')-2',3'-dideoxy-5'-adenylic acid; AZT-P-ddA
- 3'-Azido-3'-deoxythymidyl-(5',5')-2',3'-dideoxy-5'-adenylic acid, 2-cyanoethyl ester; AZT-P(CyE)-ddA
- 10 • 3'-Azido-3'-deoxythymidyl-(5',5')-2',3'-dideoxy-5'-inosinic acid; AZT-P-ddI
- 3'-Azido-3'-deoxythymidine-5'-(butylmethoxyvalinyl)phosphate; 5'MeOValPO3(Bu)AZT
- 3'-Azido-5-chloro-2',3'-dideoxyuridine; AzddClUrd; AzddClU
- 3'-Deoxythymidine; ddT
- 3'-FddA (B-D-Erythro); 9-(3'-Fluoro-2',3'-dideoxy-B-D-erythropentafuranosyl)adenine
- 15 • 3'-FddC; 3'-Fluoro-2',3'-dideoxycytidine
- 3'-FddG; 3'-Fluoro-2',3'-dideoxyguanosine
- 3'-FddT; Alovudine; FddT; FddThD; 3'-FLT; FLT
- 3'-FddU; 3'-Fluoro-2',3'-dideoxyuridine
- 3'-Fluoro-2',3'-dideoxy-5-iodouridine; FddIU
- 20 • 3'-N3-ddA; 9-(3'-Azido-2',3'-dideoxy-B-D-erythropentafuranosyl)adenine
- 3TC; Lamivudine; Epivir® Approved;
- Lamivudine & Zidovudine; Combivir® 3TC & AZT; Approved
- 4'-Acetoamidophenyl4-guadinobenzoate; AGB
- 4'-Az-3'-dT; 4'-Azido-3'-deoxythymidine
- 25 • 4'-Az-5ClU ; 4'-Azido-5-chloro-2'-deoxyuridine
- 4'-AzdA; 4'-Azido-2'-deoxyadenosine
- 4'-AzdC; 4'-Azido-2'-deoxycytidine
- 4'-AzdG; 4'-Azido-2'-deoxyguanosine
- 4'-AzdI; 4'-Azido-2'-deoxyinosine
- 30 • 4'-AzdU; 4'-Azido-2'-deoxyuridine
- 4'-Azido-2'-deoxy-β-D-erythro-pentofuranosyl-5-methyl-2,4-dioxypyrimidine; 4'-Azidothymidine
- 4'-Cyanothymidine; 4'-CN-T

- 4-Methyl-5-(pyrazinyl)-3H-1,2-dithiole-3-thione; Oltipraz
- 5'-[(1,4-Dihydro-1-methyl-3-pyridinylcarbonyl)oxy]-3'-azido-2',3'-deoxythymidine; DP-AZT; HP-AZT; AZT Prodrug; AZT-DHP
- 5'-[(Z)-4-amino-2-butenyl]methylamino]-5'-deoxyadenosine; MDL 73811
- 5 • 5'-Alkylglycosidecarbonate of 3'-azido-3'-deoxythymidine; AcNHGlc-hexyl-CO₃ AZT
- 5Cl₃PhS-2IndolCONH₂
- 5-Fluoro-2',3'-dideoxycytidine; 5-F-ddC
- 5-Methyl-3'-azido-2',3'-dideoxyisocytidine; MeAZddIsoC
- 6-O-Butanoylcastanospermine; BuCast; MDL 28,574; Celgosivir
- 10 • 6-Chloro-9-(2,3-dideoxy-β-D-glyceropentofuranosyl)-9H-purine; D2CIP; 6-Chloro-ddP; CPDDR; 6Cl-ddP
- 6-Dimethylaminopurine-2',3'-dideoxyriboside; N-6-dimethyl-ddA; DMAPDDR
- 7-Chloro-N-methyl-5-(1H-pyrrol-2-yl)-3H-1,4-benzodiazepin-2-amine ; Ro 24-7429
- 7-Chloro-5-(2-pyrrolyl)-3H-1,4-benzodiazepin-2(H)-one ; Ro 5-3335
- 15 • 8-Chloro-TIBO; Tivirapine; R86183
- 9-(2,3-Dideoxy-β-D-ribofuranosyl)-6-(methylthio)purine; D2SMeP
- 9-[Bis(OHMe)cBu]A; A-69463; Cyclobutyl-A; Cyclobut-A ; C-oxetanocin A
- A-76890
- A-77212
- 20 • A-80987; Ritonavir deriv.
- A-81525; Ritonavir deriv.
- A-83962; Ritonavir deriv.
- A-98881; Azacyclic urea deriv.
- AA; L-ascorbic acid; Calcium Ascorbate
- 25 • AAP-BHAP; U-104489; PNU-104489
- Abacavir & Lamivudine & Zidovudine; Trizivir® ABC & (-)-3TC & AZT
- ABT-378; Lopinavir; Component of Kaletra; Aluviran®
- ABT-378 & ABT-538; Kaletra®; Lopinavir & Ritonavir; Aluviran® & Norvir®
- ABT-538; Norvir®; Ritonavir; Component of Kaletra; Approved
- 30 • Acemannan
- Adefovir; PMEAs; GS-0393
- Adefovir dipivoxil; BisPom PMEAs; GS-840; Preveon®
- AG-1343; Viracept®; Nelfinavir; Approved

- AG1350; LY316957; Nelfinavir-octahydro-thienopyridine analog
- AHPBA analog; R-87366
- Alpha-lipoic acid; α -Lipoic acid; Thiocetic acid
- ALX40-4C
- 5 • AMD3100; JM3100
- Amprenavir phosphate; VX-175; GW433908; GW433908A (*Sodium Salt*); GW433908G (*Calcium Salt*); Fosamprenavir
- Ancer 20; Z-100
- Anti-sense 25-mer phosphorothioate; GEM91
- 10 • Atazanavir; CGP-73547; BMS-232632; BMS 232632; Zrivada; Latazanavir; Reyataz®
- Ateviridine; U-87201E; BHAP deriv.
- Aurintricarboxylic acid; Dupont ATA; Dupont DA639; SD-095345; ATA
- AY 9944; trans-1,4-Bis(2-dichlorobenzylaminoethyl)cyclohexane dichlorhydrate
- AZT; Zidovudine; Azidothymidine; Retrovir®
- 15 • AZT-PO₃(CH₃)-AZT; O,O'-Bis(3'-azido-3'-deoxythymidin-5'-yl)methylphosphonate
- Baicalin; TJN-151
- Betulinic acid; Mairin
- Betulinic acid, 3-O-(3',3'-dimethylsuccinate)
- BHAP deriv.
- 20 • BHAP deriv.
- BHAP deriv.
- BHAP deriv.
- BHAP deriv.
- BHAP deriv.; Rescriptor® ; Delavirdine; U-90152
- 25 • BHAP deriv.; U-88204E
- BI-RG-587; Nevirapine; Viramune® Approved
- BILA 1906 BS
- BILA 2011 BS; Palinavir
- BILA 2185 BS
- 30 • Bis(2-nitrophenyl)sulfone; Bis(2NO₂Ph)SO₂; NSC633001
- bis-ValHOEt-N₂aza-peptide isostere; CGP 53820
- bis-ValHOEt-N₂aza-peptide isostere; CGP 53820 analog
- BMS-186318

- BocPhe[CHOH(CH₂)₃CH=CHPhCO]IleAMBI; L-687,908
- BzOCValPhe[diCHOH(RR)]PheValBzOC
- BzOCValPhe[diCHOH(SS)]PheValBzOC
- C2-Sym Phosphinic amide deriv. (HOECHST AG)
- 5 • Calanolide A ; NSC675451
- Calanolide B
- Capravirine; S-1153
- Castanospermine
- CbzAF(CHOHCH₂)AVVOMe
- 10 • Cbz-Asn-Apns-Pro-NH-tBu; KNI-102
- CGP 61755; Lasinavir
- CGP 64222
- CNI-H0294
- Coactinon;I-EBU; HEPT deriv.; MKC-442; Emivirine
- 15 • Conocurvone; NSC650891
- Coviracil; (-)FTC; (-)-2',3'-Dideoxy-5-fluoro-3'-thiacytidine; Emtricitabine; Emtriva
- C-Oxetanocin-G; A-69992; (+-)Lobucavir; C-Oxt-G; Cyclobut-G; (+-)Cyclobut-G
- Crixivan®; Indinavir; MK639; L-735,524; Approved
- Curdlan Sulfate
- 20 • CV-N; Cyanovirin-N
- Cyclic Urea Amide; SD146
- Cyclosporin A; Sandimmune®
- [Me-Ile-4]Cyclosporin A; SDZ NIM 811
- D4A (L); L-2',3'-Didehydro-2',3'-dideoxyadenosine
- 25 • D4FC; D-D4FC; 2',3'-Didehydro-2',3'-dideoxy-5-fluorocytidine; DPC 817
- D4FC (L); L-2',3'-Didehydro-2',3'-dideoxy-5-fluorocytidine
- D4G (L); L-2',3'-Didehydro-2',3'-dideoxyguanosine
- D4I (L); L-2',3'-Didehydro-2',3'-dideoxyinosine
- DABO
- 30 • ddC; Dideoxycytidine; Zalcitabine; Hivid®
- ddI; Dideoxyinosine; Didanosine; Videx®
- Dehydroepiandrosterone; DHEA; Prasterone; Dehydroisoandrosterone; EL-10
- Dextran Sulfate
- Dicafeic acid ester; L-Chicoric acid

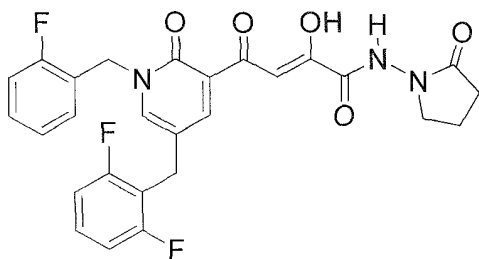
- DMP-266; Sustiva®; Efavirenz; Approved
- DMP-323; XM-323
- DMP-450
- Docosanol; n-Docosanol
- 5 • dOTC (-); (-)-2'-Deoxy-3'-oxa-4'-thiocytidine
- dOTFC (-); (-)-2'-Deoxy-3'-oxa-4'-thio-5-fluorocytidine
- DP-178; Pentafuside; T-20; GP41 127-162 AA; Enfuvirtide; Fuzeon®
- E-BPTU; HEPT deriv.; NSC 648400
- E-EBU; HEPT deriv.; MKC-442 deriv.
- 10 • E-EBU-dM; HEPT deriv.; MKC-442 deriv.
- E-EPSeU; HEPT deriv.; MKC-442 deriv.
- E-EPU; HEPT deriv.; MKC-442 deriv.
- Ebselen
- Etoposide
- 15 • Epoxy steroid deriv.; (4 α ,5 α ,17 β)-17-Hydroxy-3-oxo-4,5-epoxyandrostane-2-carboxamide
- Eulicin
- Fenalamide A1; Phenalamide A1; Stipiamide
- Flephilone
- Fluoroquinolone deriv.; K-12
- 20 • Fortovase®; Invirase®; Saquinavir; Ro31-8959; Approved
- Foscarnet; Phosphonoformic acid; Foscavir;
- FPMDAP;
- FPMPA
- FPMPG
- 25 • GPGRAF Octomer; SPC3
- Hammerhead anti-gag RNA Ribozyme B
- Harziphilone
- HBY 097; Quinoxaline deriv.
- HEPT deriv.; MKC-442 deriv.
- 30 • HEPT deriv.; MKC-442 deriv.
- HOCH₂CH₂ isostere; ThienopyridCON thienyl urethane deriv.
- HOCH₂CH₂ isostere; ThienopyridCON thienyl urethane deriv.
- HOCH₂CH₂ isostere; ThienopyridCON thienyl urethane deriv.

- HOCH₂CH₂ isostere; ThienopyridCON thienyl urethane deriv.
- HOCH₂CH₂ isostere; ThienopyridCON thienyl urethane deriv.
- HOCH₂CH₂ isostere; ThienopyridCONthienyl urethane deriv.; LY326188
- HPMPA
- 5 • HPMPDAP
- HU; Hydroxyurea; Hydrea
- Hydroxocobalamin
- Hypericin
- Ingenol 3,5,20-triacetate; ITA; RD3-2118
- 10 • Ingenol deriv.; RD4-2138
- Inophyllum B
- Inophyllum P
- iQoa-Mta-Apns-Thz-NH-tBu; KNI-272
- Isentress (Raltegravir)
- 15 • IsoquinCON furanyl urethane analog
- IsoquinCON thienyl urethane analog
- IsoquinCON thienyl urethane analog
- KNI-154; Noa-Asn-Apns-Thz-NH-tBu
- KNI-174; Noa-Asn-Apns-Dmt-NH-tBu
- 20 • KNI-227; Qoa-Mta-Apns-Thz-NH-tBu
- L-685,434
- L-685,434-6-Hydroxy derivative
- L-685,434-OEtMorphderivative; L-689,502
- L-685,434-OEtNMe₂
- 25 • L-685,434-OPrMorph derivative
- L-697,593; 2-Pyridinone deriv.
- L-697,639; 2-Pyridinone deriv.
- L-697,661; 2-Pyridinone deriv.
- L-FddC; β-L-5F-ddC
- 30 • Lamivudine & Zidovudine; Combivir® 3TC & AZT; Approved
- LY289612
- LY289612 analog
- LY289612 analog

- LY-300046-HCl; PETT deriv.; Trovirdine
- LY314163; Saquinavir/Nelfinavir deriv..
- LY-73497; N-(2-Phenethyl)-N'-(2-thiazolyl)thiourea; PETT
- MAP; Methyl acetylenic putrescine
- 5 • Michellamine A; NSC650898
- Michellamine B; NSC649324
- Michellamine F
- N-6-Et-ddA; N-Ethyl-2',3'-dideoxyadenosine
- N-6-methyl ddA; N6-Methyl-2',3'-dideoxyadenosine
- 10 • Naphthalene 2-sulphonate polymer; PRO 2000
- Nelfinavir-octahydro-thienopyridine analog
- Nonoxynol 9
- NSC625487; Thiazolobenzimidazole; TBZ
- Oxathiin deriv.; UC-38
- 15 • Oxathiin deriv.; UC-84
- P9941
- Penicillin Et(NH)₂ Sym dimer
- Penicillin G, ET(NH)₂ deriv.
- Penicillin, 2Isoquin-OHPrNH₂ analog
- 20 • Penicillin, 2Isoquin-OHPrNH₂ analog
- Pentosan Sulfate; Elmiron; SP54; Xylan Sulfate;
- PETT Cl, F deriv.
- PETT deriv.
- PETT deriv.
- 25 • PETT deriv.
- PETT deriv.
- Phenoxan
- Phorbol deriv.; Prostratin
- Platanic acid
- 30 • PMEDAP
- PMEG
- PMEH_x; PMEI
- PMEMAP
- PMET

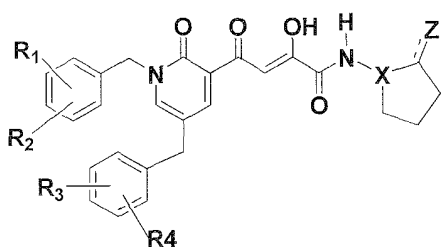
- PNU-140690; U-140690; Tipranavir
 - Pyridinone deriv.
 - Pyridinone deriv.
 - Quinoxalin2thione deriv; S-2720
 - 5 • R14458; TIBO deriv..
 - R82150; TIBO deriv..
 - R82913; TIBO deriv.
 - Resobene
 - Ribavirin; Virazole
 - 10 • Ro 31-8959-bis-thf deriv.
 - Saquinavir/Nelfinavir deriv.
 - Saquinavir/Nelfinavir deriv.
 - SB-205569; Val-Phe-Phe-HOCH₂CH₂ isostere analog
 - SC-52151; Telinavir
 - 15 • SDZ PRI 053
 - Suramin Sodium
 - T22
 - Thalidomide
 - Thiangazole; (-)-Thiangazole
 - 20 • Thiazoloisoindol-5-one
 - Thiazoloisoindol-5-one, deriv.
 - Tle-Val-Sta, 5PhBuCOOH deriv.; Statine deriv.
 - Tle-Val-Sta, 5PhBuCOOH deriv.; Statine deriv.
 - UC-781
 - 25 • Val-Val-Sta, 5PhBuCOOH deriv.; Statine deriv.
 - Val-Val-Sta, 5PhBuCOOH deriv.; Statine deriv.
 - Val-Val-Sta, 5PhBuCOOH deriv.; Statine deriv.
 - Val-Val-Sta, 5PhBuCOOH deriv.; Statine deriv.
 - Val-Val-Sta, 5PhBuCOOH deriv.; Statine deriv.
 - 30 • VB-11,328
 - Viread®; Tenofovir Disoproxil
- and mixtures thereof.

43. A method according to claim 42, wherein said first compound is



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44. A method of treating an HIV infection in a human host comprising administering to said host in combination, an effective amount of a first compound according to the structure:



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Formula I

Where $R_1 = o\text{-F}$, $R_2 = \text{H}$, $R_3 = p\text{-F}$, $R_4 = o\text{-F}$

$R_1 = p\text{-F}$, $R_2 = \text{H}$, $R_3 = p\text{-F}$, $R_4 = o\text{-F}$

15 $R_1 = o\text{-F}$, $R_2 = o\text{-F}$, $R_3 = o\text{-F}$, $R_4 = \text{H}$

$R_1 = o\text{-F}$, $R_2 = \text{H}$, $R_3 = o\text{-F}$, $R_4 = o\text{-F}$

$R_1 = o\text{-F}$, $R_2 = \text{H}$, $R_3 = p\text{-F}$, $R_4 = \text{H}$

$R_1 = o\text{-F}$, $R_2 = p\text{-F}$, $R_3 = p\text{-F}$, $R_4 = o\text{-F}$ or

$R_1 = o\text{-F}$, $R_2 = o\text{-F}$, $R_3 = o\text{-F}$, $R_4 = o\text{-F}$;

20 X is CH or N; and

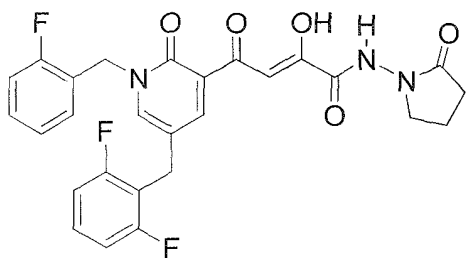
Z is OH or =O;

and pharmaceutically acceptable salts thereof, in combination with at least one additional compound selected from the group consisting of ACV; AK602; AMD070; APV; ATV; ATZ; AVX754 (apricitabine); AZT; Abacavir; Abacavir / Lamivudine / Zidovudine; Abacavir sulfate; Abacavir sulfate/Lamivudine; Abacavir/Lamivudine; Abelecet; Acyclovir; Adefovir

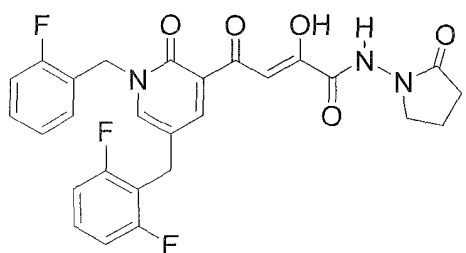
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dipivoxil; Adriamycin; Agenerase; Aldesleukin; Alovudine; Aluvia; AmBisome; Amdoxovir; Amphocin; Amphotec; Amphotericin B; Ampligen; Amprenavir; Androderm; Androgel; Apricitabine; Aptivus; Atazanavir; Atripla; Azithromycin; BMS-378806; BMS-488043; Bactrim; Baraclude; Bevirimat; Biaxin; Brecanavir; BufferGel; C31G; CD4-IgG2; CS; CV-
5 N; Calanolide A; Calcium hydroxylapatite; Carbopol 974P; Carrageenan; Carraguard; Cellulose sulfate; Clarithromycin; Combivir; Copegus; Cotrimoxazole; Crixivan; Cyanovirin-N; Cytovene; DAPD; DLV; DS; Darunavir; Delavirdine; Depo-Testosterone; Dextran sulfate; Didanosine; Diflucan; Doxil; Doxorubicin (liposomal); Dronabinol; EFV; Efavirenz; Elvucitabine; Emtricitabine; Emtricitabine; Tenofovir disoproxil fumarate; Emtriva;
10 Enfufirtide; Entecavir; Epivir; Epoetin alfa; Epogen; Epzicom; Etopophos (phosphate salt); Etoposide; Etravirine; FTC; Fluconazole; Fortovase; Fosamprenavir; Foxivudine tidoxil; Fungizone; Fuzeon; GS 9137; GSK-873,140 (aplaviroc); GW433908; GW640385 (brecanavir); Ganciclovir; Globulin, Immune; Growth hormone (human); Hepsera; Hivid; Human growth hormone; IL-2; INH; Immune Globulin Intravenous (Human); Indinavir;
15 Interferon alfa-2; Interleukin-2, recombinant human; Intron A (2b); Invirase; Isentress; Isoniazid; Itraconazole; KP-1461; Lamivudine/Zidovudine; Lexiva; Lopinavir/Ritonavir; MK-0518; Nebupent; Nelfinavir; Neutrexin; Nevirapine; Norvir; Nydrazid; Peptide T; PMPA Prodrug (Viread)'; Prezista (Darunavir); PRO 140; PRO 2000; PRO 542 (CD4 IGg2); Procrit (Epoetin); Proleukin; Racivir; Radiesse; Rrebetol; Rescriptor; Retrovir; Reyataz; Ribavirin;
20 Rifabutin; Rifadin; Rifampin; Rimactane; Ritonavir; Roferon-A (2a); Saquinavir; SCH-D (vicriviroc); Somatropin; Stavudinie; Sulfamethoxazole / Trimethoprim; Sustanon; Sustiva; TNX-355; Taxol; Tenofovir; Tenofovir disoproxil fumarate; Testosterone; Tipranavir; Toposar; Trimetrexate; Trizivir; Truvada (Emtriva and Viread combination); U-90152S (Delaviridine); UC-781; UK-427,857 (maraviroc); Valcyte; Valganciclovir; Valproic acid;
25 VePesid; Vicriviroc; Videx; Viracept (Tenofovir DF); Viramune; Virazole; Viread; Vitrasert; Zalcitabine; Zerit; Ziagen; Zidovudine; Zithromax; Zovirax and mixtures thereof, further in combination with a pharmaceutically acceptable carrier, additive or excipient.

45. A method according to claim 44 wherein the first compound is



46. A pharmaceutical composition comprising an effective amount of a compound
5 according to the structure:



in combination with an effective amount of at least one additional compound selected from
10 the group

- (-)-β-Dioxolane-G; DXG;
- (-)-β-Arctigenin; Arctigenin ;
- (-)-Carbovir; (-)-C-D4G; (-)-Carbovir;
- (-)-β-D-2,6-Diaminopurine dioxolane; Amdoxovir; DAPD; APD
- 15 • (+)-2'-Deoxy-3'-oxa-4'-thiocytidine; dOTC (+)
- (+)-2'-Deoxy-3'-oxa-4'-thio-5-fluorocytidine; dOTFC (+)
- (+/-)-Cyclobut-G; A-69992; (+/-)-Lobucavir; C-Oxt-G; Cyclobut-G ; C-Oxetanocin-G
- (R)-2QuinCOAsnPhe[CHOHCH₂]PipCONHtBu
- (R)-3,6-Diamino-N-(aminomethyl)hexanamide; Bellenamine
- 20 • (R)-PMPA; (R)-9-(2-Phosphonylmethoxypropyl)adenine; PMPA-(R); Tenofovir
- (R)-PMPDAP; PMPDAP-(R)
- (S)-PMPA; (S)-9-(2-Phosphonylmethoxypropyl)adenine; PMPA(S)
- (S)-9-(2-Phosphonylmethoxypropyl)adenine; (S)-PMPA
- α-APA; R89439; Loviride
- 25 • α-APA deriv.; R87232

- α -APA deriv.; R88703
- α -APA enantiomer; R90385
- α -L-AZT; AZT- α -L
- α -L-DXC; α -L-Dioxalane-C; DXC- α -L-
- 5 • α -L-FTC; FTC- α -L-
- α -Monofluoromethyldehydroornithine methyl ester; MFMOME
- 1,1'-Azobisformamide; ADA; Azodicarbonamide
- 1-(11-Octylamino-10-hydroxyundecyl)-3,7-dimethylxanthine; CT-2576
- 1-(2',3'-Dideoxy-2'-fluoro- β -D-threo-pentofuranosyl)cytosine; Ro 31-6840
- 10 • 1-(2'-Fluoro-2',3'-dideoxy-B-D-erythro-pentofuranosyl)thymine; 2'FddT
- 1-(2OHPr)-4-Substit-piperazine, thienyl carbamate deriv.
- 1-(2OHPr)-4-Substit-piperazine, thienyl carbamate deriv.
- 1-(2OHPr)-4-Substit-piperazine, thienyl carbamate deriv.
- 1-(2OHPr)-4-Substit-piperazine, thienyl carbamate deriv.
- 15 • 1-[(2-Hydroxyethoxy)methyl]-6-(3-methylphenylthio)thymine; HEPT-M
- 1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)-2-thiothymine; HEPT-S
- 1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)thymine; HEPT
- 1-Deoxynojirimycin ; Deoxynojirimycin
- 141W94; VX-478; Amprenavir; Agenerase®; Approved
- 20 • 1592U89 Succinate; Abacavir Succinate; Ziagen® Approved
- 1-Aminooxyethylamine; AEA
- 1-Methoxyoxalyl-3,5-dicaffeoylquinic acid; 1-MO-3,5-DCQA; Dicafeoylquinic acid deriv.
- 1OH-2(Cbz-Tle)3PhPr [14]paracyclophane deriv.
- 1OH-2(Cbz-ValNH)3PhPr [13]metacyclophane deriv.
- 25 • 1OH-2(Cbz-ValNH)3PhPr [13]paracyclophane deriv.
- 1OH-2(Cbz-ValNH)3PhPr [14]paracyclophane deriv.
- 1OH-2(Cbz-ValNH)3PhPr [17]paracyclophane deriv.
- 12-Deoxyphorbol-13-(3E,5E-decadienoate); Phorbol deriv.
- 16.alpha.-Bromoepiandrosterone; Epi-Br; ; Inactivin; HE 2000; HE2000; PPB2; DHEA
- 30 deriv.
- 1- β -D-arabinofuranosyl-5-(2-bromovinyl)uracil; BV-ara-U; BVaraU; BV ara-U;
- Sorivudine; SQ-32756; Bravavir; Brovavir; Usevir; YN-72; Bromovinyl araU; BVAU
- 2',3'-Didehydro-3'-deoxycytidine; D4C

- 2',3'-Dideoxydidehydroguanosine; D4G
- 2',3'-Didehydro-3'-deoxythymidine; D4T; Stavudine; Zeret® Approved
- 2',3'-Dideoxy-3'-fluoro-4-thiothymidine; 3'-F-4-Thio-ddT
- 2',3'-Dideoxy-3'-fluoro-5-bromouridine; FddBrU
- 5 • 2',3'-Dideoxy-3'-fluoro-5-chlorocytidine; 3'-F-5-Cl-ddC
- 2',3'-Dideoxy-3'-fluoro-5-chlorouridine; 935U83; 5-Chloro-2',3'-dideoxy-3'-fluorouridine; FddClU; Raluridine
- 2',3'-Dideoxy-5-ethylcytidine; 5-Et-ddC
- 2',3'-Dideoxyadenosine; D2A; ddAdo; ddA
- 10 • 2',3'-Dideoxydidehydroadenosine; d4A
- 2',3'-Dideoxyguanosine; D2G; ddG
- 2',3'-Dideoxy-3'-hydroxymethyl cytidine; 3'-Hydroxymethyl-ddC; BEA-005
- 2,5'-Anhydro-3'-azido-2',3'-dideoxyuridine; AZU-2,5'-anhydro
- 2,5'-Anhydro-3'-azido-3'-deoxythymidine; AZT-2,5'-anhydro
- 15 • 2',5'diSilySpiroT; TSAO-T
- 2',5'diSilySpiroT; TSAO-me³T
- 2,6-Diamino-2',3'-dideoxypurine-9-ribofuranoside; ddDAPR; DAPDDR; 2,6-Diamino-ddP
- 2,6-Diaminopurine- 2',3'-dideoxydidehydroriboside; ddeDAPR
- 2,6-Diaminopurine-3'-fluoro-2',3'-dideoxyriboside; 3'-F-ddDAPR
- 20 • 2-Aminobenzylstatine Valyl Cbz deriv.; Statine deriv.
- 2-Glycine amide-5-chlorophenyl 2-pyrryl ketone; GCPK
- [2-PyridCH₂NCH₃CO-Val-NHCH(Bz)]CHOHCHOH; A-77003
- 2'-Azido-2',3'-dideoxyadenosine; 9-(2'-Azido-2',3'-dideoxy-β-D-erythropentofuranosyl)adenine; 2'-N3ddA
- 25 • 2'-FddA(B-D-threo); F-ddA; 2'-F-dd-ara-A; 9-(2'-Fluoro-2',3'-dideoxy-B-D-threopentafuranosyl)adenine; Lodensine
- 2'-N3ddA (B-D-threo); 9-(2'-Azido-2',3'-dideoxy-β-threopentafuranosyl)adenine
- 2-NaphCOAsnPhe[CHOHCH₂]Pro-OtBu
- 2-Nitrophenylphenylsulfone; NPPS
- 30 • 3-(3-Oxo-1-propenyl)-3'-azido-3'-deoxythymidine; 3-(3-Oxo-1-propenyl)AZT
- 3-(Phenylsulfonyl)-indole deriv. ; L-737,126
- 3,5-DCQA; 3,5-Dicaffeoylquinic acid; Dicaffeoylquinic acid
- 3'-Azido-2',3'-dideoxy-5-[(cyanomethyl)oxy]uridine; 3'-N3-5-Cyanomethyloxy-ddU

- 3'-Azido-2',3'-dideoxy-5-aminouridine; 3'-N3-5-NH₂-ddU
- 3'-Azido-2',3'-dideoxy-5-aza-6-deazauridine; C-analog of 3'-N3-ddU
- 3'-Azido-2',3'-dideoxy-5-bromouridine; 3'-N3-5-Br-ddU; AZddBrU
- 3'-Azido-2',3'-dideoxy-5-chlorocytidine; 3'-Az-5-Cl-ddC
- 5 • 3'-Azido-2',3'-dideoxy-5-dimethylaminouridine; 3'-N3-5-NMe₂-ddU
- 3'-Azido-2',3'-dideoxy-5-ethyluridine; 3'-N3-5-EtddU; CS-85; AZddEtU
- 3'-Azido-2',3'-dideoxy-5-fluorocytidine; 3'-N3-5-F-ddC
- 3'-Azido-2',3'-dideoxy-5-fluorouridine; AZddFU
- 3'-Azido-2',3'-dideoxy-5-hydroxyuridine; 3'-N3-5-OH-ddU
- 10 • 3'-Azido-2',3'-dideoxy-5-iodouridine; 3'-N3-5-I-ddU; AZddIU
- 3'-Azido-2',3'-dideoxy-5-methylaminouridine; 3'-N3-5-NHMe-ddU
- 3'-Azido-2',3'-dideoxy-5-methylcytidine; CS-92; 3'-N3-5-Me-ddC
- 3'-Azido-2',3'-dideoxy-5-thiocyanatouridine; 3'-N3-5-SCN-ddU
- 3'-Azido-2',3'-dideoxy-5-trifluoromethyluridine; 3'-N3-5-CF₃-ddU
- 15 • 3'-Azido-2',3'-dideoxycytidine; CS-91; 3'-N3-ddC
- 3'-Azido-2',3'-dideoxyguanosine; AZG; 3'-N3ddG
- 3'-Azido-2',3'-dideoxy-N₄--5-dimethylcytidine; 3'-N3-N₄-5-diMe-ddC
- 3'-Azido-2',3'-dideoxy-N₄-OH-5-methylcytidine; 3'-N3-N₄-OH-5-Me-ddC
- 3'-Azido-2',3'-dideoxyuridine; CS-87; 3'-N3ddU; AZdU; Uravidine
- 20 • 3'-Azido-3'-deoxy-6-azathymidine; 3'AZ-6AzaT
- 3-Azido-3'-deoxythymidyl-(5',5')-2',3'-dideoxy-5'-adenylic acid; AZT-P-ddA
- 3'-Azido-3'-deoxythymidyl-(5',5')-2',3'-dideoxy-5'-adenylic acid, 2-cyanoethyl ester; AZT-P(CyE)-ddA
- 3'-Azido-3'-deoxythymidyl-(5',5')-2',3'-dideoxy-5'-inosinic acid; AZT-P-ddI
- 25 • 3'-Azido-3'-deoxythymidine-5'-(butylmethoxyvalinyl)phosphate; 5'MeOValPO₃(Bu)AZT
- 3'-Azido-5-chloro-2',3'-dideoxyuridine; AzddClUrd; AzddClU
- 3'-Deoxythymidine; ddT
- 3'-FddA (B-D-Erythro); 9-(3'-Fluoro-2',3'-dideoxy-B-D-erythropentafuranosyl)adenine
- 3'-FddC; 3'-Fluoro-2',3'-dideoxycytidine
- 30 • 3'-FddG; 3'-Fluoro-2',3'-dideoxyguanosine
- 3'-FddT; Alovudine; FddT; FddThD; 3'-FLT; FLT
- 3'-FddU; 3'-Fluoro-2',3'-dideoxyuridine
- 3'-Fluoro-2',3'-dideoxy-5-iodouridine; FddIU
- 3'-N3-ddA; 9-(3'-Azido-2',3'-dideoxy-B-D-erythropentafuranosyl)adenine

- 3TC; Lamivudine; Epivir® Approved;
- Lamivudine & Zidovudine; Combivir® 3TC & AZT; Approved
- 4'-Acetoamidophenyl4-guadinobenzoate; AGB
- 4'-Az-3'-dT; 4'-Azido-3'-deoxythymidine
- 5 • 4'-Az-5CldU ; 4'-Azido-5-chloro-2'-deoxyuridine
- 4'-AzdA; 4'-Azido-2'-deoxyadenosine
- 4'-AzdC; 4'-Azido-2'-deoxycytidine
- 4'-AzdG; 4'-Azido-2'-deoxyguanosine
- 4'-AzdI; 4'-Azido-2'-deoxyinosine
- 10 • 4'-AzdU; 4'-Azido-2'-deoxyuridine
- 4'-Azido-2'-deoxy- β -D-erythro-pentofuranosyl-5-methyl-2,4-dioxypyrimidine; 4'-Azidothymidine
- 4'-Cyanothymidine; 4'-CN-T
- 4-Methyl-5-(pyrazinyl)-3H-1,2-dithiole-3-thione; Oltipraz
- 15 • 5'-[(1,4-Dihydro-1-methyl-3-pyridinylcarbonyl)oxy]-3'-azido-2',3'-deoxythymidine; DP-AZT; HP-AZT; AZT Prodrug; AZT-DHP
- 5'-[[*(Z)*-4-amino-2-butenyl]methylamino]-5'-deoxyadenosine; MDL 73811
- 5'-Alkylglycosidecarbonate of 3'-azido-3'-deoxythymidine; AcNHGlc-hexyl-CO3 AZT
- 5Cl3PhS-2IndolCONH2
- 20 • 5-Fluoro-2',3'-dideoxycytidine; 5-F-ddC
- 5-Methyl-3'-azido-2',3'-dideoxyisocytidine; McAZddIsoC
- 6-O-Butanoylcastanospermine; BuCast; MDL 28,574; Celgosivir
- 6-Chloro-9-(2,3-dideoxy- β -D-glyceropentofuranosyl)-9H-purine; D2ClP; 6-Chloro-ddP; CPDDR; 6Cl-ddP
- 25 • 6-Dimethylaminopurine-2',3'-dideoxyriboside; N-6-dimethyl-ddA; DMAPDDR
- 7-Chloro-N-methyl-5-(1H-pyrrol-2-yl)-3H-1,4-benzodiazepin-2-amine ; Ro 24-7429
- 7-Chloro-5-(2-pyrryl)-3H-1,4-benzodiazepin-2(H)-one ; Ro 5-3335
- 8-Chloro-TIBO; Tivirapine; R86183
- 9-(2,3-Dideoxy- β -D-ribofuranosyl)-6-(methylthio)purine; D2SMcP
- 30 • 9-[Bis(OHMe)cBu]A; A-69463; Cyclobutyl-A; Cyclobut-A ; C-oxetanocin A
- A-76890
- A-77212
- A-80987; Ritonavir deriv.

- A-81525; Ritonavir deriv.
- A-83962; Ritonavir deriv.
- A-98881; Azacyclic urea deriv.
- AA; L-ascorbic acid; Calcium Ascorbate
- 5 • AAP-BHAP; U-104489; PNU-104489
- Abacavir & Lamivudine & Zidovudine; Trizivir® ABC & (-)-3TC & AZT
- ABT-378; Lopinavir; Component of Kaletra; Aluviran®
- ABT-378 & ABT-538; Kaletra®; Lopinavir & Ritonavir; Aluviran® & Norvir®
- ABT-538; Norvir®; Ritonavir; Component of Kaletra; Approved
- 10 • Acemannan
- Adefovir; PMEA; GS-0393
- Adefovir dipivoxil; BisPom PMEA; GS-840; Preveon®
- AG-1343; Viracept®; Nelfinavir; Approved
- AG1350; LY316957; Nelfinavir-octahydro-thienopyridine analog
- 15 • AHPBA analog; R-87366
- Alpha-lipoic acid; α -Lipoic acid; Thiocetic acid
- ALX40-4C
- AMD3100; JM3100
- Amprenavir phosphate; VX-175; GW433908; GW433908A (*Sodium Salt*); GW433908G
- 20 (*Calcium Salt*); Fosamprenavir
- Ancer 20; Z-100
- Anti-sense 25-mer phosphorothioate; GEM91
- Atazanavir; CGP-73547; BMS-232632; BMS 232632; Zrivada; Latazanavir; Reyataz®
- Ateviridine; U-87201E; BHAP deriv.
- 25 • Aurintricarboxylic acid; Dupont ATA; Dupont DA639; SD-095345; ATA
- AY 9944; trans-1,4-Bis(2-dichlorobenzylaminoethyl)cyclohexane dichlorhydrate
- AZT; Zidovudine; Azidothymidine; Retrovir®
- AZT-PO₃(CH₃)-AZT; O,O'-Bis(3'-azido-3'-deoxythymidin-5'-yl)methylphosphonate
- Baicalin; TJN-151
- 30 • Betulinic acid; Mairin
- Betulinic acid, 3-O-(3',3'-dimethylsuccinate)
- BHAP deriv.
- BHAP deriv.

- BHAP deriv.
- BHAP deriv.
- BHAP deriv.
- BHAP deriv.; Rescriptor® ; Delavirdine; U-90152
- 5 • BHAP deriv.; U-88204E
- BI-RG-587; Nevirapine; Viramune® Approved
- BILA 1906 BS
- BILA 2011 BS; Palinavir
- BILA 2185 BS
- 10 • Bis(2-nitrophenyl)sulfone; Bis(2NO₂Ph)SO₂; NSC633001
- bis-ValHOEt-N₂aza-peptide isostere; CGP 53820
- bis-ValHOEt-N₂aza-peptide isostere; CGP 53820 analog
- BMS-186318
- BocPhe[CHOH(CH₂)₃CH=CHPhCO]IleAMBI; L-687,908
- 15 • BzOCValPhe[diCHOH(RR)]PheValBzOC
- BzOCValPhe[diCHOH(SS)]PheValBzOC
- C₂-Sym Phosphinic amide deriv. (HOECHST AG)
- Calanolide A ; NSC675451
- Calanolide B
- 20 • Capravirine; S-1153
- Castanospermine
- CbzAF(CHOHCH₂)AVVOMe
- Cbz-Asn-Apns-Pro-NH-tBu; KNI-102
- CGP 61755; Lasinavir
- 25 • CGP 64222
- CNI-H0294
- Coactinon; I-EBU; HEPT deriv.; MKC-442; Emivirine
- Conocurvone; NSC650891
- Coviracil; (-)FTC; (-)-2',3'-Dideoxy-5-fluoro-3'-thiacytidine; Emtricitabine; Emtriva
- 30 • C-Oxetanocin-G; A-69992; (+-)Lobucavir; C-Oxt-G; Cyclobut-G; (+-)Cyclobut-G
- Crixivan®; Indinavir; MK639; L-735,524; Approved
- Curdlan Sulfate
- CV-N; Cyanovirin-N
- Cyclic Urea Amide; SD146

- Cyclosporin A; Sandimmune®
- [Me-Ile-4]Cyclosporin A; SDZ NIM 811
- D4A (L); L-2',3'-Didehydro-2',3'-dideoxyadenosine
- D4FC; D-D4FC; 2',3'-Didehydro-2',3'-dideoxy-5-fluorocytidine; DPC 817
- 5 • D4FC (L); L-2',3'-Didehydro-2',3'-dideoxy-5-fluorocytidine
- D4G (L); L-2',3'-Didehydro-2',3'-dideoxyguanosine
- D4I (L); L-2',3'-Didehydro-2',3'-dideoxyinosine
- DABO
- ddC; Dideoxycytidine; Zalcitabine; Hivid®
- 10 • ddI; Dideoxyinosine; Didanosine; Videx®
- Dehydroepiandrosterone; DHEA; Prasterone; Dehydroisoandrosterone; EL-10
- Dextran Sulfate
- Dicaaffeic acid ester; L-Chicoric acid
- DMP-266; Sustiva®; Efavirenz; Approved
- 15 • DMP-323; XM-323
- DMP-450
- Docosanol; n-Docosanol
- dOTC (-); (-)-2'-Deoxy-3'-oxa-4'-thiocytidine
- dOTFC (-); (-)-2'-Deoxy-3'-oxa-4'-thio-5-fluorocytidine
- 20 • DP-178; Pentafuside; T-20; GP41 127-162 AA; Enfuvirtide; Fuzeon®
- E-BPTU; HEPT deriv.; NSC 648400
- E-EBU; HEPT deriv.; MKC-442 deriv.
- E-EBU-dM; HEPT deriv.; MKC-442 deriv.
- E-EPSeU; HEPT deriv.; MKC-442 deriv.
- 25 • E-EPU; HEPT deriv.; MKC-442 deriv.
- Ebselen
- Etoposide
- Epoxy steroid deriv.; (4 α ,5 α ,17 β)-17-Hydroxy-3-oxo-4,5-epoxyandrostane-2-carboxamide
- Eulicin
- 30 • Fenalamide A1; Phenalamide A1; Stipiamide
- Fleephilone
- Fluoroquinolone deriv.; K-12
- Fortovase®; Invirase®; Saquinavir; Ro31-8959; Approved

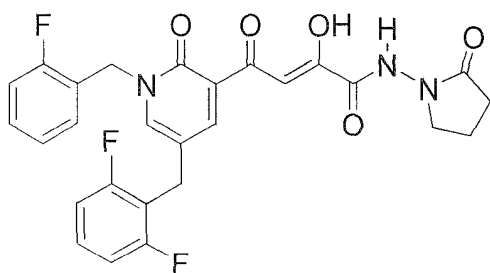
- Foscarnet; Phosphonoformic acid; Foscavir;
- FPMDAP;
- FPMPA
- FPMPG
- 5 • GPGRAF Octomer; SPC3
- Hammerhead anti-gag RNA Ribozyme B
- Harziphilone
- HBY 097; Quinoxaline deriv.
- HEPT deriv.; MKC-442 deriv.
- 10 • HEPT deriv.; MKC-442 deriv.
- HOCH₂CH₂ isostere; ThienopyridCON thienyl urethane deriv.
- HOCH₂CH₂ isostere; ThienopyridCON thienyl urethane deriv.
- HOCH₂CH₂ isostere; ThienopyridCON thienyl urethane deriv.
- HOCH₂CH₂ isostere; ThienopyridCON thienyl urethane deriv.
- 15 • HOCH₂CH₂ isostere; ThienopyridCON thienyl urethane deriv.
- HOCH₂CH₂ isostere; ThienopyridCONthienyl urethane deriv.; LY326188
- HPMPA
- HPMPDAP
- HU; Hydroxyurea; Hydrea
- 20 • Hydroxocobalamin
- Hypericin
- Ingenol 3,5,20-triacetate; ITA; RD3-2118
- Ingenol deriv.; RD4-2138
- Inophyllum B
- 25 • Inophyllum P
- iQoa-Mta-Apns-Thz-NH-tBu; KNI-272
- Isentress (Raltegravir)
- IsoquinCON furanyl urethane analog
- IsoquinCON thienyl urethane analog
- 30 • IsoquinCON thienyl urethane analog
- KNI-154; Noa-Asn-Apns-Thz-NH-tBu
- KNI-174; Noa-Asn-Apns-Dmt-NH-tBu
- KNI-227; Qoa-Mta-Apns-Thz-NH-tBu
- L-685,434

- L-685,434-6-Hydroxy derivative
- L-685,434-OEtMorphderivative; L-689,502
- L-685,434-OEtNMe₂
- L-685,434-OPrMorph derivative
- 5 • L-697,593; 2-Pyridinone deriv.
- L-697,639; 2-Pyridinone deriv.
- L-697,661; 2-Pyridinone deriv.
- L-FddC; β -L-5F-ddC
- Lamivudine & Zidovudine; Combivir® 3TC & AZT; Approved
- 10 • LY289612
- LY289612 analog
- LY289612 analog
- LY-300046-HCl; PETT deriv.; Troviridine
- LY314163; Saquinavir/Nelfinavir deriv..
- 15 • LY-73497; N-(2-Phenethyl)-N'-(2-thiazolyl)thiourea; PETT
- MAP; Methyl acetylenic putrescine
- Michellamine A; NSC650898
- Michellamine B; NSC649324
- Michellamine F
- 20 • N-6-Et-ddA; N-Ethyl-2',3'-dideoxyadenosine
- N-6-methyl ddA; N6-Methyl-2',3'-dideoxyadenosine
- Naphthalene 2-sulphonate polymer; PRO 2000
- Nelfinavir-octahydro-thienopyridine analog
- Nonoxynol 9
- 25 • NSC625487; Thiazolobenzimidazole; TBZ
- Oxathiin deriv.; UC-38
- Oxathiin deriv.; UC-84
- P9941
- Penicillin Et(NH)₂ Sym dimer
- 30 • Penicillin G, ET(NH)₂ deriv.
- Penicillin, 2Isoquin-OHPrNH₂ analog
- Penicillin, 2Isoquin-OHPrNH₂ analog
- Pentosan Sulfate; Elmiron; SP54; Xylan Sulfate;

- PETT Cl, F deriv.
- PETT deriv.
- PETT deriv.
- PETT deriv.
- 5 • PETT deriv.
- Phenoxan
- Phorbol deriv.; Prostratin
- Platonic acid
- PMEDAP
- 10 • PMEG
- PMEHx; PMEI
- PMEMAP
- PMET
- PNU-140690; U-140690; Tipranavir
- 15 • Pyridinone deriv.
- Pyridinone deriv.
- Quinoxalin2thione deriv; S-2720
- R14458; TIBO deriv..
- R82150; TIBO deriv..
- 20 • R82913; TIBO deriv.
- Resobene
- Ribavirin; Virazole
- Ro 31-8959-bis-thf deriv.
- Saquinavir/Nelfinavir deriv.
- 25 • Saquinavir/Nelfinavir deriv.
- SB-205569; Val-Phe-Phe-HOCH₂CH₂ isostere analog
- SC-52151; Telinavir
- SDZ PRI 053
- Suramin Sodium
- 30 • T22
- Thalidomide
- Thiangazole; (-)-Thiangazole
- Thiazoloisoindol-5-one
- Thiazoloisoindol-5-one, deriv.

- Tle-Val-Sta, 5PhBuCOOH deriv.; Statine deriv.
 - Tle-Val-Sta, 5PhBuCOOH deriv.; Statine deriv.
 - UC-781
 - Val-Val-Sta, 5PhBuCOOH deriv.; Statine deriv.
 - 5 • Val-Val-Sta, 5PhBuCOOH deriv.; Statine deriv.
 - Val-Val-Sta, 5PhBuCOOH deriv.; Statine deriv.
 - Val-Val-Sta, 5PhBuCOOH deriv.; Statine deriv.
 - Val-Val-Sta, 5PhBuCOOH deriv.; Statine deriv.
 - VB-11,328
 - 10 • Viread®; Tenofovir Disoproxil,
- and mixtures thereof, further in combination with a pharmaceutically acceptable carrier, additive or excipient.

47. A pharmaceutical composition comprising an effective amount of a compound
- 15 according to the structure:



- 20 in combination with at least one additional compound selected from the group consisting of
- ACV; AK602; AMD070; APV; ATV; ATZ; AVX754 (apricitabine); AZT; Abacavir;
- Abacavir / Lamivudine / Zidovudine; Abacavir sulfate; Abacavir sulfate/Lamivudine;
- Abacavir/Lamivudine; Abelecet; Acyclovir; Adefovir dipivoxil; Adriamycin; Agenerase;
- Aldesleukin; Alovudine; Aluvia; AmBisome; Amdoxovir; Amphocin; Amphotec;
- 25 Amphotericin B; Ampligen; Amprenavir; Androderm; Androgel; Apricitabine; Aptivus;
- Atazanavir; Atripla; Azithromycin; BMS-378806; BMS-488043; Bactrim; Baraclude;
- Bevirimat; Biaxin; Brecanavir; BufferGel; C31G; CD4-IgG2; CS; CV-N; Calanolide A;
- Calcium hydroxylapatite; Carbopol 974P; Carrageenan; Carraguard; Cellulose sulfate;
- Clarithromycin; Combivir; Copegus; Cotrimoxazole; Crixivan; Cyanovirin-N; Cytovene;

DAPD; DLV; DS; Darunavir; Delavirdine; Depo-Testosterone; Dextran sulfate; Didanosine; Diflucan; Doxil; Doxorubicin (liposomal); Dronabinol; EFV; Efavirenz; Elvucitabine; Emtricitabine; Emtricitabine; Tenofovir disoproxil fumarate; Emtriva; Enfuvirtide; Entecavir; Epivir; Epoetin alfa; Epogen; Epzicom; Etopophos (phosphate salt); Etoposide; Etravirine; 5 FTC; Fluconazole; Fortovase; Fosamprenavir; Foxivudine tidoxil; Fungizone; Fuzeon; GS 9137; GSK-873,140 (aplaviroc); GW433908; GW640385 (brecanavir); Ganciclovir; Globulin, Immune; Growth hormone (human); Hepsera; Hivid; Human growth hormone; IL-2; INH; Immune Globulin Intravenous (Human); Indinavir; Interferon alfa-2; Interleukin-2, recombinant human; Intron A (2b); Invirase; Isentress; Isoniazid; Itraconazole; KP-1461; 10 Lamivudine/Zidovudine; Lexiva; Lopinavir/Ritonavir; MK-0518; Nebupent; Nelfinavir; Neutrexin; Nevirapine; Norvir; Nydrazid; Peptide T; PMPA Prodrug (Viread)'; Prezista (Darunavir); PRO 140; PRO 2000; PRO 542 (CD4 IGg2); Procrit (Epoetin); Proleukin; Racivir; Radiesse; Rrebetol; Rescriptor; Retrovir; Reyataz; Ribavirin; Rifabutin; Rifadin; Rifampin; Rimactane; Ritonavir; Roferon-A (2a); Saquinavir; SCH-D (vicriviroc); 15 Somatropin; Stavudinie; Sulfamethoxazole / Trimethoprim; Sustanon; Sustiva; TNX-355; Taxol; Tenofovir; Tenofovir disoproxil fumarate; Testosterone; Tipranavir; Toposar; Trimetrexate; Trizivir; Truvada (Emtriva and Viread combination); U-90152S (Delaviridine); UC-781; UK-427,857 (maraviroc); Valcyte; Valganciclovir; Valproic acid; VePesid; Vicriviroc; Videx; Viracept (Tenofovir DF); Viramune; Virazole; Viread; Vitrasert; 20 Zalcitabine; Zerit; Ziagen; Zidovudine; Zithromax; Zovirax and mixtures thereof, further in combination with a pharmaceutically acceptable carrier, additive or excipient.

48. The compound:

- 25 • (1S,2S)-4-(5-(2,4-difluorobenzyl)-1-(2-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide
- (1R,2R)-4-(5-(2,4-difluorobenzyl)-1-(2-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide
- 4-(5-(2,4-difluorobenzyl)-1-(2-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-4-oxo-N-(2-oxopyrrolidin-1-yl)but-2-enamide
- 30 • (1S,2S)-4-(5-(2,4-difluorobenzyl)-1-(4-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide
- (1R,2R)-4-(5-(2,4-difluorobenzyl)-1-(4-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide

- 4-(5-(2,4-difluorobenzyl)-1-(4-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-4-oxo-N-(2-oxopyrrolidin-1-yl)but-2-enamide
- (1S,2S)-4-(1-(2-fluorobenzyl)-5-(4-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide
- 5 • (1R,2R)-4-(1-(2-fluorobenzyl)-5-(4-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide
- 4-(1-(2-fluorobenzyl)-5-(4-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-4-oxo-N-(2-oxopyrrolidin-1-yl)but-2-enamide
- (1S,2S)-4-(1-(2,6-difluorobenzyl)-5-(2-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide
- 10 • (1R,2R)-4-(1-(2,6-difluorobenzyl)-5-(2-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide
- 4-(1-(2,6-difluorobenzyl)-5-(2-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-4-oxo-N-(2-oxopyrrolidin-1-yl)but-2-enamide
- 15 • (1S,2S)-4-(1,5-bis(2,4-difluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide
- (1R,2R)-4-(1,5-bis(2,4-difluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide
- 4-(1,5-bis(2,4-difluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-4-oxo-N-(2-oxopyrrolidin-1-yl)but-2-enamide
- 20 • (1S,2S)-4-(5-(2,6-difluorobenzyl)-1-(2-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide
- (1R,2R)-4-(5-(2,6-difluorobenzyl)-1-(2-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide
- 25 • 4-(5-(2,6-difluorobenzyl)-1-(2-fluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-4-oxo-N-(2-oxopyrrolidin-1-yl)but-2-enamide
- (1S,2S)-4-(1,5-bis(2,6-difluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide
- (1R,2R)-4-(1,5-bis(2,6-difluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-N-(2-hydroxycyclopentyl)-4-oxobut-2-enamide, or
- 30 • 4-(1,5-bis(2,6-difluorobenzyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-hydroxy-4-oxo-N-(2-oxopyrrolidin-1-yl)but-2-enamide.

49. A pharmaceutical composition comprising a compound according to claim 48 in combination with a pharmaceutically acceptable carrier, additive or excipient.

50. The composition according to claim 49 in oral or parenteral dosage form.

5 51. Use of a compound according to any of claims 1-8 in the manufacture of a medicament for a first medical use.

52. A kit comprising a pharmaceutical composition according to any of claims 11-17, 24, 27-31, 46-47 and 49 and instructions for a medical professional and/or a patient on how to administer said composition.