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(54) **PYRIDINONE DIKETO ACIDS: INHIBITORS OF HIV REPLICATION IN COMBINATION THERAPY**

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(57) **ABSTRACT**

A new class of diketo acids constructed on pyridinone scaffolds, designed as inhibitors of HTV replication through inhibition of HIV integrase, is described. These compounds are useful in the prevention or treatment of infection by HIV and in the treatment of AIDS and ARC, either as 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 AIDS and ARC and methods of treating or preventing infection by HIV are also described. Compounds of the present application include those of formula I and include tautomers, regioisomers, geometric isomers, and pharmaceutically acceptable salts thereof, wherein the pyridinone scaffold and R groups are as otherwise defined in the specification. These are combined, with any number of typical other anti-HIV agents (including other integrase-based anti-HIV agents) and other combination therapeutic agents described herein, to provide an effective treatment modality for HIV infections, including AIDS and ARC.

PYRIDINONE DIKETO ACIDS: INHIBITORS OF HIV REPLICATION IN COMBINATION THERAPY

RELATED APPLICATIONS AND GRANT SUPPORT

[0001] This application claims the benefit of priority of provisional application number US60/831,990, filed Jul. 19, 2006, provisional application number US60/920,196, filed Mar. 27, 2007, both entitled, "Pyridinone Diketo Acids: Inhibitors of HIV Replication", and provisional application No. 60/920,197, filed Mar. 27, 2007, entitled, "Pyrinone Diketo Acids: Inhibitors of HIV Replication in Combination Therapy", each of which applications is incorporated by reference in its entirety herein.

[0002] The work leading to the instant patent application was supported in part by a grant from the National Institutes of Health, award number A143181. Consequently, the United States government retains certain rights in the invention.

FIELD OF THE INVENTION

[0003] The present invention relates to the field of antiviral therapy, in particular the treatment of HIV infections in humans, preferably in combination therapy.

BACKGROUND OF THE INVENTION

[0004] 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 [Fauci, *Science,* 239, 617-622 (1988); Katz & Skalka, *Annu. Rev. Biochem.,* 63, 133-173 (1994); Frankel, *Annu. Rev. Biochem.,* 67, 1-25 (1998)]. For this reason, these enzymes of the pol gene have been targeted as potential sites of attack in the development of HIV antiviral chemotherapeutic agents [De Clercq, *J. Med. Chem.* 38, 2491-2517.(1995); *Clin. Microbiol. Rev.,* 10, 674-693 (1997); De Clercq, *Nature Reviews: Drug Discovery,* 11, 13-25 (2002); De Clercq, *J. Med. Chem.* 48, 1297-1313 (2005)]. Drug discovery involving two of these enzymes, HIV reverse transcriptase (RT) and HIV protease (PR), and subsequent clinical applications of some of these therapeutic agents in combination therapy for the treatment of acquired immunodeficiency syndrome (AIDS) and AIDS related complex (ARC) in HAART (highly-active antiretroviral therapy) have suggested that this methodology of targeting key viral enzymes represents a useful approach in antiviral chemotherapy [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); Miller & Hazuda, *Current Opinion in Microbiology,* 4, 535-539 (2001); 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); DeClercq, *Intl. J. Biochem. Cell Biol.* 36, 1800-1822 (2004)]. While HIV RT and HIV PR have been extensively studied with respect to therapeutics, the third enzyme of the pol gene, HIV integrase, has received much less consideration [Miller & Hazuda, *Current Opinion in Microbiology,* 4, 535-539 (2001); Nair, *Rev. Med. Virol.,* 12, 179-193 (2002); Nair, *Current Pharmaceutical Design,* 9, 2553-2565 (2003); Pommier, et al., *Nature Rev. Drug Discovery* 4, 236-248 (2005); Nair, *Frontiers in Med. Chem.* 2, 3-20 (2005)].

[0005] At present there are no drugs in clinical use for HIV/AIDS where the mechanism of action is inhibition of HIV integrase. HIV-1 integrase is a protein of 32 kDa encoded at the 3'-end of the pol gene [Asante-Appiah & Skalka, *Adv. Virus Res.,* 52, 351-369 (1999); Esposito & Craigie, *Adv. Virus Res.,* 52, 319-333 (1999)]. It is involved in the integration of HIV DNA into the host cell chromosome. Because integrase has no human counterpart and because it plays the significant role of completing the invasion of the human cell cell by HIV, it is an attractive target for the discovery of inhibitors of therapeutic potential.

[0006] Incorporation of HIV DNA into host chromosomal DNA in the cell nucleus catalyzed by integrase apparently occurs by a specifically defined sequence of 3'-processing or tailoring and strand transfer/integration reactions [Asante-Appiah & Skalka, *Adv. Virus. Res.,* 52, 351-369 (1999); Esposito & Craigie *Adv. Virus Res.,* 52, 319-333 (1999)]. Prior to the initiation of the integration process, there is assembly of viral DNA, previously produced by reverse transcription, on the integrase. HIV integrase recognizes specific sequences in the LTRs of viral DNA. Following assembly of viral DNA on integrase, the processing of viral DNA occurs where there is site specific endonuclease activity and two nucleotides are cleaved off from each 3'-end of the double helical viral DNA to produce the tailored viral DNA recessed by two nucleotides and bearing a terminal CAOH-3'. For this initial 3'-processing step, integrase apparently activates the phosphodiester bond towards cleavage. The recessed viral DNA thus produced is joined in the next step to host cell DNA in the nucleus through a trans-esterification reaction. In this step, integrase positions the 3'-OH end of the viral DNA for nucleophilic attack on the phosphodiester bond in the host DNA. In the subsequent step, there is cleavage of 4-6 by in host DNA and the coupling involves the joining of processed CAOH-3' viral DNA ends to the 5'-phosphate ends of the host DNA. Finally, there is repair of the resulting gapped intermediate mediated by host cell enzymes, although a role here for the integrase is also possible.

[0007] A variety of compounds are inhibitors of HIV integrase but some of these compounds are non-specific inhibitors of the enzyme while evidence suggests that others may possess some specificity. The various classes include nucleotides, oligonucleotides, dinucleotides, and miscellaneous small molecules including heterocyclic systems, natural products, diketo acids, sulfones and others [Nair, *Rev. Med. Virol.,* 12 179-193 (2002); Nair, *Current Pharmaceutical Design,* 9, 2553-2565 (2003); Chi and Nair, *Bioorg. Med. Chem. Lett.* 14, 4815-4817 (2004); Nair and coworkers, *J. Am. Chem. Soc.,* 122, 5671-5677 (2000)].

[0008] The class of previously studied compounds that are most directly relevant to this patent are diketo acids with aryl or heteroaryl substitutions. Some of these compounds are inhibitors of HIV integrase, but most commonly of only the strand transfer step. The integrase inhibition data have been reported in several scientific publications [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-diketo-containing compounds as HIV-1 integrase inhibitors," *J. Med. Chem.* 45, 3184-3194 (2002); Marchand, C., et al., "Structural determinants for HIV-1 integrase inhibition by β-diketo acids," *J. Biol. Chem.* 277, 12596-12603 (2002); Sethi, M., et al., "Design and synthesis of novel indole beta-diketo acid derivatives as HIV-1 integrase inhibitors," *J. Med.*

Chem. 47, 5298-5310 (2004); Zhang, et al., "Azido-containing aryl β-keto acid HIV-1 integrase inhibitors," *Bioorg. Med. Chem. Lett.* 13, 1215-1219 (2003), 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); Sato, et al., "Novel HIV-1 integrase inhibitors derived from quinolone antibiotics," *J. Med. Chem.* 49, 1506-1508 (2006); 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, 1266-1269 (2007)]. Other publications in the area are of peripheral relationship to this patent application.

[0009] The mechanism of inhibition of HIV integrase by diketo acids may be the result of interaction of the functional groups on these compounds with metal ions in the active site of integrase, resulting in a functional sequestration of these critical metal cofactors [Grobler, J. A., et al., *Proc. Natl. Acad. Sci. USA.* 99, 6661-6666 (2002)].

[0010] Related patents to this application are: Selnick, H. G. et al., (Merck & Co. Inc.), "Preparation of nitrogen-containing 4-heteroaryl-2,4-dioxobutyric acids useful as HIV 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 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 peripheral relationship to this invention are: Anthony, et al., (Merck & Co. Inc.), "Aza and polyazanapthalenyl-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., (Instituto Di Richerche Di Biologia Molecolare P. Angeletti SPA) "Preparation of N-substituted hydroxypyrimidinone carboxamide inhibitors of HIV integrase," WO 2003035077; Belyk, et al., (Merck & Co. Inc., Instituto Di Richerche 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; 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. 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.

[0011] The class of compounds described by us in this invention are inhibitors of HIV-1 integrase and also possess in vitro anti-HIV activity. An example of the anti-HIV data in PBMC for the clinical isolate, HIV_{NL4-3}, in PBMC for one of our compounds, 4-(1,5-dibenzyl-1,2-dihydro-2-oxopyridin-3-yl)-2-hydroxy-4-oxobut-2-enoic acid, (8) and AZT in the same study is given below.

[0012] Compound 8 EC_{95} 0.61 μM, CC_{95}>200 μM, Therapeutic Index (TI)>330

[0013] AZT EC_{95} 9.42 nM, CC_{95}>1 μM, Therapeutic Index (TI)>106

At pH 7.4, the half life ($t_{1/2}$) of compound 8 is >41 hours. The $t_{1/2}$ in pooled human liver microsome for compound 8 is >6 hours.

SUMMARY OF THE INVENTION

[0014] A new class of diketo acids constructed on pyridinone scaffolds, and designed as inhibitors of HIV replication through inhibition of HIV integrase, is described. These compounds can be represented by the general formula I (and includes tautomers, regioisomers and geometric isomers thereof, as well as pharmaceutically acceptable salts thereof, where applicable), in which the moiety illustrated as a square is a molecular scaffold made up of a pyridinone derivative. These compounds have application, inter alia, in the prevention or treatment of infection by HIV and the treatment of AIDS and ARC, either as compounds, or as their 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 AIDS and ARC and methods of treating or preventing infection by HIV are also described.

[0015] The present invention further relates in preferred aspects to the use of at least one of the above compounds in combination with at least one additional anti-HIV agent as otherwise described herein.

DETAILED DESCRIPTION OF THE INVENTION

[0016] The following terms shall be 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.

[0017] 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 salts 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.

[0018] 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.

[0019] 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 inter alia to the treatment of a viral, microbial or other disease state, a 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.

[0020] The term "scaffold" is used throughout the specification to mean a pyridinone chemical structure containing at least four substituents at five substitutable positions on this scaffold, one of which is a ketoacid as otherwise defined herein and the other four of which R^1, R^2, R^3 and R^4 are as defined herein.

[0021] The term "heteroaryl" shall mean a 5 or 6-membered heteroaromatic ring containing 1 to 2 heteroatoms selected from oxygen, nitrogen and sulfur, which heteroaromatic ring is optionally substituted with from 1 to 3 substituents such as halogen, hydroxyl, C_{1-3} alkyl, C_{1-3} alkoxy and CF_3. The terms heteroaryl and "heteroaromatic ring" are used interchangeably herein.

[0022] The term "human immunodeficieincy virus" or "HIV" shall be used to describe human immunodeficiency viruses 1 and 2 (HIV-1 and HIV-2).

[0023] 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.

[0024] 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).

[0025] 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 defining illnesses—

[0026] Bacillary angiomatosis

[0027] Candidiasis, oropharyngeal (thrush)

[0028] Candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to therapy

[0029] Cervical dysplasia (moderate or severe)/cervical carcinoma in situ

[0030] Constitutional symptoms, such as fever (38.5 C) or diarrhea lasting longer than 1 month

[0031] Hairy leukoplakia, oral

[0032] Herpes zoster (shingles), involving at least two distinct episodes or more than one dermatome

[0033] Idiopathic thrombocytopenic purpura

[0034] Listeriosis

[0035] Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess

[0036] Peripheral neuropathy

[0037] According to the U.S. government, in Category 2 ARC, the immune system shows some signs of damage but it isn't life-threatening.

[0038] A Category 3 (AIDS) infection is characterized by the following criteria:

[0039] your T-cells have dropped below 200 or

[0040] you have had at least one of the following defining illnesses—

[0041] Candidiasis of bronchi, trachea, or lungs

[0042] Candidiasis, esophageal

[0043] Cervical cancer, invasive**

[0044] Coccidioidomycosis, disseminated or extrapulmonary

[0045] Cryptococcosis, extrapulmonary

[0046] Cryptosporidiosis, chronic intestinal (greater than 1 month's duration)

[0047] Cytomegalovirus disease (other than liver, spleen, or nodes)

[0048] Cytomegalovirus retinitis (with loss of vision)

[0049] Encephalopathy, HIV-related

[0050] Herpes simplex: chronic ulcer(s) (greater than 1 month's duration); or bronchitis, pneumonitis, or esophagitis

[0051] Histoplasmosis, disseminated or extrapulmonary

[0052] Isosporiasis, chronic intestinal (greater than 1 month's duration)

[0053] Kaposi's sarcoma

[0054] Lymphoma, Burkitt's (or equivalent term)

[0055] Lymphoma, immunoblastic (or equivalent term)

[0056] Lymphoma, primary, of brain

[0057] *Mycobacterium avium* complex or *M. kansasii*, disseminated or extrapulmonary

[0058] *Mycobacterium tuberculosis*, any site (pulmonary** or extrapulmonary)

[0059] *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary

[0060] *Pneumocystis carinii* pneumonia

[0061] Pneumonia, recurrent**

[0062] Progressive multifocal leukoencephalopathy

[0063] *Salmonella* septicemia, recurrent

[0064] Toxoplasmosis of brain

[0065] Wasting syndrome due to HIV

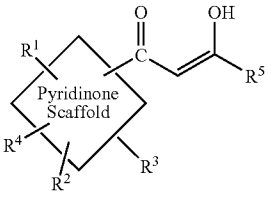
[0066] The term "coadministration" or "combination therapy" shall mean that at least two compounds or compositions are administered to the patient at the same time, such that effective amounts or concentrations of each of the two or more compounds may be found in the patient at a given point in time. 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 that effective concentrations of all coadministered compounds or compositions are found in the subject at a given time. In certain preferred aspects of the present invention, one or more of the diketo acid compounds described above, are coadministered in combination with at least one additional anti-HIV agent as otherwise described herein in a cocktail for the treatment of HIV infections. In particularly preferred aspects of the invention, the co-administration of compounds results in synergistic anti-HIV activity of the therapy.

[0067] The term "independently" is used herein to indicate that the variable, which is independently applied, varies independently from application to application.

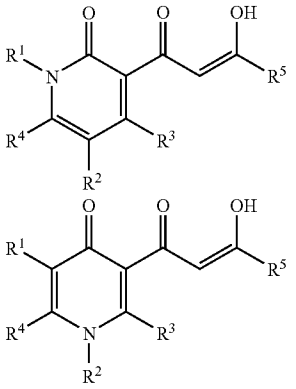
[0068] The present invention is directed to compounds of the general molecular formula I, combinations thereof, or pharmaceutically acceptable salts thereof, in the inhibition of HIV integrase, the prevention or treatment of HIV infections and in the treatment of AIDS and ARC. Compounds of formula I are defined as follows:

I



[0069] including tautomers, regioisomers, and pharmaceutically acceptable salts thereof, wherein two representative pyridinone scaffolds and R groups are defined as:

[0070] diketo acids with the two pyridinone scaffolds shown;



[0071] R^1 and R^2 are independently:

[0072] a) H,

[0073] b) C_{1-6} alkyl,

[0074] c) C_{1-6} fluoroalkyl,

[0075] d) C_{1-6} alkyl $S(O)_nR$, wherein n selected from 0-2, R is selected from C_{1-3} alkyl, phenyl and substituted phenyl with substituents selected from:

[0076] 1) halogen,

[0077] 2) hydroxy,

[0078] 3) C_{1-3} alkyl,

[0079] 4) C_{1-3} alkoxy,

[0080] 5) CF_3,

[0081] e) C_{5-6} cycloalkyl with 1 to 3 substituents selected from:

[0082] 1) halogen,

[0083] 2) hydroxy,

[0084] 3) C_{1-3} alkyl,

[0085] 4) C_{1-3} alkoxy,

[0086] 5) CF_3,

[0087] f) C_{2-6} alkenyl,

[0088] g) C_{1-6} alkyl CO_nR^a, wherein n selected from 1 and 2, R^a selected from:

[0089] 1) C_{1-6} alkyl,

[0090] 2) H,

[0091] h) Phenyl,

[0092] i) Substituted phenyl with 1 to 3 substituents selected from:

[0093] 1) halogen,

[0094] 2) hydroxy,

[0095] 3) C_{1-3} alkyl,

[0096] 4) C_{1-3} alkoxy,

[0097] 5) CF_3,

[0098] j) Benzyl,

[0099] k) Substituted benzyl with 1 to 3 substituents selected from:

[0100] 1) halogen,

[0101] 2) hydroxy,

[0102] 3) C_{1-3} alkyl,

[0103] 4) C_{1-3} alkoxy,

[0104] 5) CF_3,

[0105] l) C_{2-6} alkyl substituted with phenyl,

[0106] m) C_{2-6} alkyl substituted with phenyl, the phenyl group may be substituted with 1 to 3 substituents selected from:

[0107] 1) halogen,

[0108] 2) hydroxy,

[0109] 3) C_{1-3} alkyl,

[0110] 4) C_{1-3} alkoxy,

[0111] 5) CF_3,

[0112] n) R^b,

[0113] o) C_{1-6} alkyl substituted with R^b,

[0114] Wherein each R^b is 5 or 6 membered heteroaromatic ring containing 1 to 2 heteroatoms selected from oxygen, nitrogen and sulfur, the ring could be substituted or not on carbon or nitrogen with 1 to 3 substituents selected from:

[0115] 1) halogen,

[0116] 2) hydroxy,

[0117] 3) C_{1-3} alkyl,

[0118] 4) C_{1-3} alkoxy,

[0119] 5) CF_3,

[0120] R^3 and R^4 are independently selected from:

[0121] a) H,

[0122] b) C_{1-6} alkyl,

[0123] c) Halogen,

[0124] d) Hydroxyl,

[0125] e) Phenylthio,

[0126] f) Substituted phenylthio with 1 to 3 substituents selected from:

[0127] 1) halogen,

[0128] 2) hydroxy,

[0129] 3) C_{1-3} alkyl,

[0130] 4) C_{1-3} alkoxy,

[0131] 5) CF_3,

[0132] g) Benzyl,

[0133] h) Substituted benzyl with 1-3 substituents selected from:

[0134] 1) halogen,

[0135] 2) hydroxy,

[0136] 3) C_{1-3} alkyl,

[0137] 4) C_{1-3} alkoxy,

[0138] 5) CF_3,

[0139] R^5 is selected from:

[0140] a) CO_2R^c, wherein R^c is selected from:

[0141] 1) C_{1-6} alkyl,

[0142] 2) H,

[0143] 3) sodium or other pharmaceutical acceptable salt,

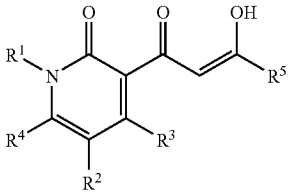
[0144] b) $P(O)(OR^d)(OR^e)$, wherein R^d and R^e could be same or not and that are selected from:

[0145] 1) C_{1-6} alkyl

[0146] 2) H

[0147] 3) sodium or other pharmaceutical acceptable salt.

[0148] Certain preferred embodiments include compounds which are based on the 2-pyridinone (pyridin-2-one) scaffold in which the diketo acid moiety is at the 3-position of the pyridinone ring:



wherein R^1 and R^2 are independently benzyl groups or independently substituted benzyl groups with 1 to 3 substituents on the phenyl rings selected from fluorine, chlorine, C_{1-4} alkyl, C_{2-4} alkenyl, methoxy;

wherein R^3 is H, C_{1-3} alkyl, C_{2-3} alkenyl, fluorine, chlorine, methoxy;

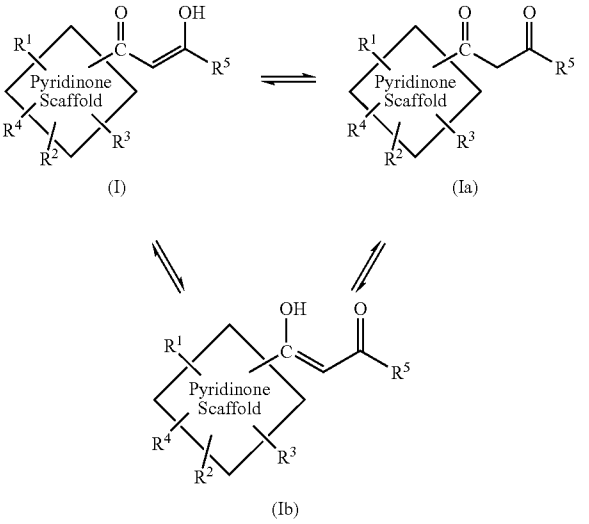
wherein R^4 is H, F, Cl, OH

wherein R^5 is CO_2H or $P(O)(OH)_2$ or a pharmaceutically acceptable salt thereof.

[0149] Also included within the present invention are pharmaceutical compositions preferably useful for inhibiting HIV integrase, comprising of an effective amount of a compound of this invention, and a pharmaceutically acceptable carrier, additive or excipient. Pharmaceutical compositions useful for treating infection such as 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 or replication, or treating an HIV infection or for treating AIDS or ARC. 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 antiviral agents.

[0150] The compounds of the present invention may have 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 may have geometric isomers and these forms are included in the present invention.

[0151] 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 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. The same holds true for references to tautomer (Ib).



[0152] When the variables involving R^1, R^2, R^3, R^4 and R^5 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.

[0153] The compounds of the present invention are useful in the inhibition of HIV integrase, the prevention 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, exchange of body fluids, bites, needle punctures, exposure to infected patient blood during medical or dental procedures, and other means).

[0154] 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.

[0155] 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.

[0156] 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-methylglucamine, citrate, ammonium salt, dihydrochloride, oleate, edetate, oxalate, edisylate, pamoate, estolate, palmitate, esylate, fumarate, phosphate, diphosphate, gluceptate, polygalacturonate, gluconate, salicylate, glutamate, stearate, glycollylarsanilate, sulfate, hexylresorcinate, subacetate, hydrabamine, succinate, hydrobromide, tannate, hydrochloride, tartrate, hydroxynaphthoate, teoclate, iodide, tosylate, isothionate, triethiodide, lactate, 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, e, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)aminomethane, and tetramethylammonium hydroxide.

[0157] Also, in the case of a carboxylic acid (—COOH) or an alcohol group being present, pharmaceutically acceptable esters can be employed, e.g., acetate, maleate, pivaloyloxymethyl and others, more preferably C_1-C_{20} esters and those esters known in the art for improving solubility or hydrolysis characteristics for use as sustained release or pro-drug formulations. Pharmaceutically acceptable esters can also be employed in the case where a phosphonic acid group [$PO(OH)_2$] is present. Diketo phosphonic acids attached to pyridinone scaffolds are also part of this invention.

[0158] Therapeutically effective amounts of the compounds of the present invention may be administered to patients orally, parenterally, by inhalation spray, 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 must be compatible with the other ingredients of the formulation and not deleterious to the patient or recipient. Pharmaceutical compositions may be 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 (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.

[0159] The compounds of this invention can be administered orally to humans in a preferred form (such as tablets) and in a preferred dosage range of about 0.1 to 200 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.

[0160] 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 as otherwise described herein. Some examples are given below.

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

Drug Name	Manufacturer	Therapeutic Use
097	Hoechst/Bayer	HIV infection, AIDS, ARC (NNRT inhibitor)
Amprenivir 141W94, GW141	Glaxo Wellcome	HIV infection, AIDS, 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	Gilead Sciences	HIV infection
AL-721	Ethigen (Los Angeles, CA)	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

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

Drug Name	Manufacturer	Therapeutic Use
Antibody which neutralizes pH labile alpha aberrant Interferon	Advanced Biotherapy Concepts (Rockville, MD)	AIDS, ARC
AR 177	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)
HBY097	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 (Almeda, CA)	AIDS, Kaposi's sarcoma, ARC
Interferon alfa-n3	Interferon Scienes	ARC, AIDS
Indinavir	Merck	HIV infection, AIDS, ARC, asymptomatic HIV positive; combination with AZT/ddI/ddC
ISIS-2922	ISIS Pharmaceuticals	CMV retinitis
KNI-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	Boeheringer Ingleheim	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)

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

Drug Name	Manufacturer	Therapeutic Use
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, in combination with other therapies
Tenofovir diisoproxil fumarate salt (Viread ®)	Gilead	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	Pharmacia Upjohn	Advanced AIDS
Acemannan	Carrington Labs, Inc. (Irving, TX)	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 (aldeslukin)	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	Merieux Institute	AIDS, ARC

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

Drug Name	Manufacturer	Therapeutic Use
Alpha-2 Interferon	Schering Plough	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	Immune Response Corp.	Immunotherapeutic
rCD4 Recombinant Soluble Human CD4-IgG rCD4-IgG Hybrids	Genentech	AIDS, ARC AIDS, ARC
Recombinant Soluble Human CD4	Biogen	AIDS, ARC
Interferon Alfa 2a	Hoffman-LaRoche	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	Kumamoto University Japan	HIV infection (entry and fusion inhibitor)
Alovudine	Medivir, UK Ltd.	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, Ltd.	Prevention of HIV 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)

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

Drug Name	Manufacturer	Therapeutic Use
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 (integase inhibitor)
GSK-873,140 (aplaviroc)	GlaxoSmithKline	HIV infection (entry and fusion inhibitor)
GSK-364735	GlaxoSmithKline	HIV infection (integase 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 (integase inhibitor)
PA-457 (bevirimat)	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	Starpharma	Microbicide
TAK-652	Takeda	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)	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 RT inhibitor)
Valganciclovir (Valcyte)	Roche	Antiviral (CMV retinitis in AIDS)

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

Drug Name	Manufacturer	Therapeutic Use
Clindamycin with Primaquine	Pharmacia Upjohn	PCP
Fluconazole	Pfizer	Cryptococcal meningitis, candidiasis
Pastille	Squibb Corp.	prevention of oral candidiasis
Nystatin Pastille		
Ornidyl	Merrell Dow	PCP
Eflornithine		
Pentamidine Isethionate (IM & IV)	LyphoMed (Rosemont, IL)	PCP treatment
Trimethoprim		Antibacterial
Trimethoprim/sulfa		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 assocated 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 (Radiesse	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

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

Drug Name	Manufacturer	Therapeutic Use
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

[0161] 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 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. Pat. No. 5,413,999, WO 9962513.

[0162] In such combinations the compound of the present invention and other active agents may be separately administered or concurrently administered. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

[0163] The combinations of the compounds of this invention with AIDS antivirals (as described above and as otherwise set forth and described hereinbelow, 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 protease inhibitor (e.g., indinavir, nelfinavir, ritonavir, saquinavir among 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. Pat. No. 5,413,999, WO 9962513.

[0164] In such combinations the compound of the present invention and other active agents, for example as described hereinbelow, may be separately administered or concurrently administered in effective amount. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

[0165] The following examples of drugs or bioactive agents effective against HIV or having benefits when used in the treatment of HIV or secondary indications/conditions of HIV, including AIDS/ARC and secondary conditions or disease states such as Kaposi's sarcoma, hepatitis B virus infections, etc., which may be combined with compounds according to the present invention in providing pharmaceutical compositions and methods of treating HIV infections or their secondary conditions or disease states. When included in pharmaceutical compositions or methods of treatment, these drugs or bioactive agents are included in effective amounts to resolve the condition or disease state for which the compounds have been administered.

[0166] (−)βDioxolane-G; DXG;

[0167] (−)β-Arctigenin; Arctigenin;

[0168] (−)-Carbovir; (−)-C-D4G; (−)-Carbovir;

[0169] (−)-β-D-2,6-Diaminopurine dioxolane; Amdoxovir; DAPD; APD

[0170] (+)-2'-Deoxy-3'-oxa-4'-thiocytidine; dOTC (+)

[0171] (+)-2'-Deoxy-3'-oxa-4'-thio-5-fluorocytidine; dOTFC (+)

[0172] (+/−)-Cyclobut-G; A-69992; (+/−)-Lobucavir; C-Oxt-G; Cyclobut-G; C-Oxetanocin-G

[0173] (R)-2QuinCOAsnPhe[CHOHCH2]PipCONHtBu

[0174] (R)-3,6-Diamino-N-(aminomethyl)hexanamide; Bellenamine

[0175] (R)-PMPA; (R)-9-(2-Phosphonylmethoxypropyl) adenine; PMPA-(R); Tenofovir

[0176] (R)-PMPDAP; PMPDAP-(R)

[0177] (S)-PMPA; (S)-9-(2-Phosphonylmethoxypropyl) adenine; PMPA(S)

[0178] (S)-9-(2-Phosphonylmethoxypropyl)adenine; (S)-PMPA

[0179] α-APA; R89439; Loviride

[0180] α-APA deriv.; R87232

[0181] α-APA deriv.; R88703

[0182] α-APA enantiomer; R90385

[0183] α-L-AZT; AZT-α-L

[0184] α-L-DXC; α-L-Dioxalane-C; DXC-α-L-

[0185] α-L-FTC; FTC-α-L-

[0186] α-Monofluoromethyldehydroomithine methyl ester; MFMOME

[0187] 1,1'-Ambisformamide; ADA; Azodicarbonamide

[0188] 1-(11-Octylamino-10-hydroxyundecyl)-3,7-dimethybcanthine; CT-2576

[0189] 1-(2',3'-Dideoxy-2'-fluoro-β-D-threo-pentofuranosyl)cytosine; Ro 31-6840

[0190] 1-(2'-Fluoro-2',3'-dideoxy-B-D-erythro-pentofumnosyl)thymine; 2'FddT

[0191] 1-(2OHPr)-4-Substit-piperazine, thienyl carbamate deriv.

[0192] 1-(2OHPr)-4-Substit-piperazine, thienyl carbamate deriv.

[0193] 1-(2OHPr)-4-Substit-piperazine, thienyl carbamate deriv.

[0194] 1-(2OHPr)-4-Substit-piperazine, thienyl carbamate deriv.

[0195] 1-[(2-Hydroxyethoxy)methyl]-6-(3-methylphenyl) thio)thymine; HEPT-M

[0196] 1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)-2-thiothymine; HEPT-S

[0197] 1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio) thymine; HEPT

[0198] 1-Deoxynojirimycin; Deoxynojirimycin

[0199] 141 W94; VX-478; Amprenavir; Agenerase®; Approved

[0200] 1592U89 Succinate; Abacavir Succinate; Ziagen® Approved

[0201] 1-Aminooxyethylamine; AEA

[0202] 1-Methoxyoxalyl-3,5-dicaffeoylquinic acid; 1-MO-3,5-DCQA; Dicaffeoylquinic acid deriv.

[0203] 1OH-2(Cbz-Tle)3PhPr [14]paracyclophane deriv.

[0204] 1OH-2(Cbz-VaINH)3PhPr [13]metacyclophane deriv.

[0205] 1OH-2(Cbz-VaINH)3PhPr [13]paracyclophane deriv.

[0206] 1OH-2(Cbz-VaINH)3PhPr [14]paracyclophane deny.

[0207] 1OH-2(Cbz-VaINH)3PhPr [17]paracyclophane deriv.

[0208] 12-Deoxyphorbol-13-(3E,5E-decadienoate); Phorbol deriv.

[0209] 16.alpha.-Bromoepiandrosterone; Epi-Br;; Inactivin; HE 2000; HE2000; PPB2; DHEA deny.

[0210] 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

[0211] 2',3'-Didehydro-3'-deoxycytidine; D4C

[0212] 2',3'-Dideoxydidehydroguanosine; D4G

[0213] 2',3'-Didehydro-3'-deoxythymidine; D4T; Stavudine; Zerit® Approved

[0214] 2',3'-Dideoxy-3'-fluoro-4-thiothymidine; 3'-F-4-Thio-ddT

[0215] 2',3'-Dideoxy-3'-fluoro-5-bromouridine; FddBrU

[0216] 2',3'-Dideoxy-3'-fluoro-5-chlorocytidine; 3'F-5-Cl-ddC

[0217] 2',3'-Dideoxy-3'-fluoro-5-chlorouridine; 935U83; 5-Chloro-2',3'-dideoxy-3'-fluorouridine; FddClU; Raluridine

[0218] 2',3'-Dideoxy-5-ethylcytidine; 5-Et-ddC

[0219] 2',3'-Dideoxyadenosine; D2A; ddAdo; ddA

[0220] 2',3'-Dideoxydidehydroadenosine; d4A

[0221] 2',3'-Dideoxyguanosine; D2G; ddG

[0222] 2',3'-Dideoxy-3'-hydroxymethyl cytidine; 3'-Hydroxymethyl-ddC; BEA-005

[0223] 2,5'-Anhydro-3'-azido-2',3'-dideoxyuridine; AZU-2,5'-anhydro

[0224] 2,5'-Anhydro-3'-azido-3'-deoxythymidine; AZT-2, 5'-anhydro

[0225] 2',5'diSilySpiroT; TSAO-T

[0226] 2',5'diSilySpiroT; TSAO-me^3T

[0227] 2,6-Diamino-2',3'-dideoxypurine-9-ribofuranoside; ddDAPR; DAPDDR; 2,6-Diamino-ddP

[0228] 2,6-Diaminopurine-2',3'-dideoxydidehydroriboside; ddeDAPR

[0229] 2,6-Diaminopurine-3'-fluoro-2',3'-dideoxyriboside; 3'-F-ddDAPR

[0230] 2-Aminobenzylstatine Valyl Cbz deriv.; Statine deriv.

[0231] 2-Glycine amide-5-chlorophenyl 2-pyrryl ketone; GCPK

[0232] [2-PyridCH2NCH3CO-Val-NHCH(Bz)] CHOHCHOH; A-77003

[0233] 2'-Azido-2',3'-dideoxyadenosine; 9-(2'-Azido-2',3'-dideoxy-β-D-erythropentofuranosyl)adenine; 2'-N3ddA

[0234] 2'-FddA(B-D-threo); F-ddA; 2'-F-dd-ara-A; 9-(2'-Fluoro-2',3'-dideoxy-B-D-threopentafuranosyl)adenine; Lodensine

[0235] 2'-N3ddA (B-D-threo); 9-(2'-Azido-2',3'-dideoxy-β-threopentafuranosyl)adenine

[0236] 2-NaphCOAsnPhe[CHOHCH2]Pro-OtBu

[0237] 2-Nitrophenylphenylsulfone; NPPS

[0238] 3-(3-Oxo-1-propenyl)-3'-azido-3'-deoxythymidine; 3-(3-Oxo-1-propenyl)AZT

[0239] 3-(Phenylsulfonyl)-indole denv.; L-737,126

[0240] 3,5-DCQA; 3,5-Dicaffeoylquinic acid; Dicaffeoylquinic acid

[0241] 3'-Azido-2',3'-dideoxy-5-[(cyanomethyl)oxy]uridine; 3'-N3-5-Cyanomethyloxy-ddU

[0242] 3'-Azido-2',3'-dideoxy-5-aminouridine; 3'-N3-5-NH2-ddU

[0243] 3'Azido-2',3'-dideoxy-5-aza-6-deazauridine; C-analog of 3'-N3-ddU

[0244] 3'-Azido-2',3'-dideoxy-5-bromouridine; 3'-N3-5-Br-ddU; AZddBrU

[0245] 3'-Azido-2',3'-dideoxy-5-chlorocytidine; 3'-Az-5-Cl-ddC

[0246] 3'-Azido-2',3'-dideoxy-5-dimethylaminouridine; 3'-N3-5-NMe2-ddU

[0247] 3'-Azido-2',3'-dideoxy-5-ethyluridine; 3'-N3-5-Et-ddU; CS-85; AZddEtU

[0248] 3'-Azido-2',3'-dideoxy-5-fluorocytidine; 3'-N3-5-F-ddC

[0249] 3'-Azido-2',3'-dideoxy-5-fluorouridine; AZddFU

[0250] 3'-Azido-2',3'-dideoxy-5-hydroxyuridine; 3'-N-3-5-OH-ddU

[0251] 3'-Azido-2',3'-dideoxy-5-iodouridine; 3'-N3-5-I-ddU; AZddIU

[0252] 3'-Azido-2',3'-dideoxy-5-methyaminouridine; 3'-N3-5-NHMe-ddU

[0253] 3'Azido-2',3'-dideoxy-5-methylcytidine; CS-92; 3'-N3-5-Me-ddC

[0254] 3'-Azido-2',3'-dideoxy-5-thiocyanatouridine; 3'-N3-5-SCN-ddU

[0255] 3'-Azido-2',3'-dideoxy-5-trifluoromethyluridine; 3'-N3-5-CF3-ddU

[0256] 3'-Azido-2',3'-dideoxycytidine; CS-91; 3'-N3-ddC

[0257] 3'-Azido-2',3'-dideoxyguanosine; AZG; 3'-N3ddG

[0258] 3'-Azido-2',3'-dideoxy-N-4-5-dimethylcytidine; 3'-N3-N4-5-diMe-ddC

[0259] 3'-Azido-2',3'-dideoxy-N4-OH-5-methylcytidine; 3'-N3-N4-OH-5-Me-ddC

[0260] 3'-Azido-2',3'-dideoxyuridine; CS-87; 3'-N3ddU; AZdU; Uravidine

[0261] 3'-Azido-3'-deoxy-6-azathymidine; 3'AZ-6AzaT

[0262] 3-Azido-3'-deoxythymidilyl-(5',5')-2',3'-dideoxy-5'-adenylic acid; AZT-P-ddA

[0263] 3'-Azido-3'-deoxythymidilyl-(5',5')-2',3'-dideoxy-5'-adenylic acid, 2-cyanoethyl ester; AZT-P(CyE)-ddA

[0264] 3'-Azido-3'-deoxythymidilyl-(5',5')-2',3'-dideoxy-5'-inosinic acid; AZT-P-ddI

[0265] 3'-Azido-3'-deoxythymidine-5'-(butylmethoxyvalinyl)phosphate; 5'MeOValPO3(Bu)AZT

[0266] 3'-Azido-5-chloro-2',3'-dideoxyuridine; AzddClUrd; AzddClU

[0267] 3'-Deoxythymidine; ddT

[0268] 3'-FddA (B-D-Erythro); 9-(3'-Fluoro-2',3'-dideoxy-B-D-erythropentafuranosyl)adenine

[0269] 3'-FddC; 3'-Fluoro-2',3'-dideoxycytidine

[0270] 3'-FddG; 3'-Fluoro-2',3'-dideoxyguanosine

[0271] 3'-FddT; Alovudine; FddT; FddThD; 3'-FLT; FLT

[0272] 3'-FddU; 3'-Fluoro-2',3'-dideoxyuridine

[0273] 3'-Fluoro-2',3'-dideoxy-5-iodouridine; FddIU

[0274] 3'-N3-ddA; 9-(3'-Azido-2',3'-dideoxy-B-D-erythropentafuranosyl)adenine

[0275] 3TC; Lamivudine; Epivir® Approved;

[0276] Lamivudine & Zidovudine; Combivir® 3TC & AZT; Approved

[0277] 4'-Acetoamidophenyl4-guadinobenzoate; AGB

[0278] 4'-Az-3'-dT; 4'-Azido-3'-deoxythymidine

[0279] 4'-Az-5CldU; 4'-Azido-5-chloro-2'-deoxyuridine

[0280] 4'-AzdA; 4'-Azido-2'-deoxyadenosine

[0281] 4'-AzdC; 4'-Azido-2'-deoxycytidine

[0282] 4'-AzdG; 4'-Azido-2'-deoxyguanosine

[0283] 4'-AzdI; 4'-Azido-2'-deoxyinosine

[0284] 4'-AzdU; 4'-Azido-2'-deoxyuridine

[0285] 4'-Azido-2'-deoxy-β-D-erythro-pentofuranosyl-5-methyl-2,4-dioxopyrimidine; 4'-Azidothymidine

[0286] 4'-Cyanothymidine; 4'-CN-T

[0287] 4-Methyl-5-(pyrazinyl)-3H-1,2-dithiole-3-thione; Oltipraz

[0288] 5'-[(1,4-Dihydro-1-methyl-3-pyridinylcarbonyl) oxy]-3'-azido-2',3'-deoxythymidine; DP-AZT; HP-AZT; AZT Prodrug; AZT-DHP

[0289] 5'-[[(Z)-4-amino-2-butenyl]methylamino]-5'-deoxyadenosine; MDL 73811

[0290] 5'-Alkylglycosidecarbonate of 3'-azido-3'-deoxythymidine; AcNHGlc-hexyl-CO3 AZT

[0291] 5Cl3PhS-2IndolCONH2

[0292] 5-Fluoro-2',3'-dideoxycytidine; 5-F-ddC

[0293] 5-Methyl-3'-azido-2',3'-dideoxyisocytidine; MeA-ZddIsoC

[0294] 6-O-Butanoylcastanospermine; BuCast; MDL 28,574; Celgosivir

[0295] 6-Chloro-9-(2,3-dideoxy-b-D-glyceropentofuranosyl)-9H-purine; D2ClP; 6-Chloro-ddP; CPDDR; 6Cl-ddP

[0296] 6-Dimethylaminopurine-2',3'-dideoxyriboside; N-6-dimethylddA; DMAPDDR

[0297] 7-Chloro-N-methyl-5-(1H-pyrrol-2-yl)-3H-1,4-benzodiazepin-2-amine; Ro 24-7429

[0298] 7-Chloro-5-(2-pyrryl)-3H-1,4-benzodiazepin-2 (H)-one; Ro 5-3335

[0299] 8-Chloro-TIBO; Tivirapine; R86183

[0300] 9-(2,3-Dideoxy-β-D-ribofuranosyl)-6-(methylthio)purine; D2SMeP

[0301] 9-[Bis(OHMe)cBu]A; A-69463; Cyclobutyl-A; Cyclobut-A; C-oxetanocin A

[0302] A-76890

[0303] A-77212

[0304] A-80987; Ritonavir deriv.

[0305] A-81525; Ritonavir deriv.

[0306] A-83962; Ritonavir deriv.

[0307] A-98881; Azacyclic urea deny.

[0308] AA; L-ascorbic acid; Calcium Ascorbate

[0309] AAP-BHAP; U-104489; PNU-104489

[0310] Abacavir & Lamivudine & Zidovudine; Trizivir® ABC & (−)-3TC & AZT

[0311] ABT-378; Lopinavir; Component of Kaletra; Aluviran®

[0312] ABT-378 & ABT-538; Kaletra®; Lopinavir & Ritonavir; Aluviran® & Norvir®

[0313] ABT-538; Norvir®; Ritonavir; Component of Kaletra; Approved

[0314] Acemannan

[0315] Adefovir; PMEA; GS-0393

[0316] Adefovir dipivoxil; BisPom PMEA; GS-840; Preveon®

[0317] AG-1343; Viracept®; Nelfinavir; Approved

[0318] AG1350; LY316957; Nelfinavir-octahydrothienopyridine analog

[0319] AHPBA analog; R-87366

[0320] Alpha-lipoic acid; α-Lipoic acid; Thioctic acid

[0321] ALX40-4C

[0322] AMD3100; JM3100

[0323] Amprenavir phosphate; VX-175; GW433908; GW433908A (*Sodium Salt*); GW433908G (*Calcium Salt*); Fosamprenavir

[0324] Ancer 20; Z-100

[0325] Anti-sense 25-mer phosphorothioate; GEM91

[0326] Atazanavir; CGP-73547; BMS-232632; BMS 232632; Zrivada; Latazanavir; Reyataz®

[0327] Atevirdine; U-87201E; BHAP deriv.

[0328] Aurintricarboxylic acid; Dupont ATA; Dupont DA639; SD-095345; ATA

[0329] AY 9944; trans-1,4-Bis(2-dichlorobenzylaminoethyl)cyclohexane dichlorhydrate

[0330] AZT; Zidovudine; Azidothymidine; Retrovir®

[0331] AZT-PO3(CH3)-AZT; O,O'-Bis(3'-azido-3'-deoxythymidin-5'-yl)methylphosphonate

[0332] Baicalin; TJN-151

[0333] Betulinic acid; Mairin

[0334] Betulinic acid, 3-O-(3',3'-dimethylsuccinate)

[0335] BHAP deriv.

[0336] BHAP deny.

[0337] BHAP deriv.

[0338] BHAP deriv.

[0339] BHAP deriv.

[0340] BHAP deriv.; Rescriptor®; Delavirdine; U-90152

[0341] BHAP deriv.; U-88204E

[0342] BI-RG-587; Nevirapine; Viramune® Approved

[0343] BILA 1906 BS

[0344] BILA 2011 BS; Palinavir

[0345] BILA 2185 BS

[0346] Bis(2-nitrophenyl)sulfone; Bis(2NO2Ph)SO2; NSC633001

[0347] bis-ValHOEt-N2aza-peptide isostere; CGP 53820

[0348] bis-ValHOEt-N2aza-peptide isostere; CGP 53820 analog

[0349] BMS-186318

[0350] BocPhe[CHOH(CH2)3CH═CHPhCO]IleAMBI; L-687,908

[0351] BzOCValPhe[diCHOH(RR)]PheValBzOC

[0352] BzOCValPhe[diCHOH(SS)]PheValBzOC

[0353] C2-Sym Phosphinic amide deriv. (HOECHST AG)
[0354] Calanolide A; NSC675451
[0355] Calanolide B
[0356] Capravirine; S-1153
[0357] Castanospermine
[0358] CbzAF(CHOHCH2)AVVOMe
[0359] Cbz-Asn-Apns-Pro-NH-tBu; KNI-102
[0360] CGP 61755; Lasinavir
[0361] CGP 64222
[0362] CNI-H0294
[0363] Coactinon; I-EBU; HEPT deriv.; MKC-442; Emivirine
[0364] Conocurvone; NSC650891
[0365] Coviracil; (−)FTC; (−)-2',3'-Dideoxy-5-fluoro-3'-thiacytidine; Emtricitabine; Emtriva
[0366] C-Oxetanocin-G; A-69992; (+−)Lobucavir; C-Oxt-G; Cyclobut-G; (+−)Cyclobut-G
[0367] Crixivan®; Indinavir; MK639; L-735,524; Approved
[0368] Curdlan Sulfate
[0369] CV-N; Cyanovirin-N
[0370] Cyclic Urea Amide; SD146
[0371] Cyclosporin A; Sandimmune®
[0372] [Me-Ile-4]Cyclosporin A; SDZ NIM 811
[0373] D4A (L); L-2',3'-Didehydro-2',3'-dideoxyadenosine
[0374] D4FC; D-D4FC; 2',3'-Didehydro-2',3'-dideoxy-5-fluorocytidine; DPC 817
[0375] D4FC (L); L-2',3'-Didehydro-2',3'-dideoxy-5-fluorocyticline
[0376] D4G (L); L-2',3'-Didehydro-2',3'-dideoxyguanosine
[0377] D4I (L); L-2',3'-Didehydro-2',3'-dideoxyinosine
[0378] DABO
[0379] ddC; Dideoxycytidine; Zalcitabine; Hivid®
[0380] ddI; Dideoxyinosine; Didanosine; Videx®
[0381] Dehydroepiandrosterone; DHEA; Prasterone; Dehydroisoandrosterone; EL-10
[0382] Dextran Sulfate
[0383] Dicaffeic acid ester; L-Chicoric acid
[0384] DMP-266; Sustiva®; Efavirenz; Approved
[0385] DMP-323; XM-323
[0386] DMP-450
[0387] Docosanol; n-Docosanol
[0388] dOTC (−); (−)-2'-Deoxy-3'-oxa-4'-thiocytidine
[0389] dOTFC (−); (−)-2'-Deoxy-3'-oxa-4'-thio-5-fluorocytidine
[0390] DP-178; Pentafuside; T-20; GP41 127-162 AA; Enfuvirtide; Fuzeon®
[0391] E-BPTU; HEPT deriv.; NSC 648400
[0392] E-EBU; HEPT deriv.; MKC-442 deriv.
[0393] E-EBU-dM; HEPT deriv.; MKC-442 deriv.
[0394] E-EPSeU; HEPT deny.; MKC-442 deriv.
[0395] E-EPU; HEPT deriv.; MKC-442 duly.
[0396] Ebselen
[0397] Etoposide
[0398] Epoxy steriod deriv.; (4α,5α,17β)-17-Hydroxy-3-oxo-4,5-epoxyandrostane-2-carboxamide
[0399] Eulicin
[0400] Fenalamide A1; Phenalamide A1; Stipiamide
[0401] Fleephilone
[0402] Fluoroquinolone deriv.; K-12
[0403] Fortovase®; Invirase®; Saquinavir; Ro31-8959; Approved
[0404] Foscarnet; Phosphonoformic acid; Foscavir;
[0405] FPMDAP;
[0406] FPMPA
[0407] FPMPG
[0408] GPGRAF Octomer, SPC3
[0409] Hammerhead anti-gag RNA Ribozyme B
[0410] Harziphilone
[0411] HBY 097; Quinoxaline deriv.
[0412] HEPT deriv.; MKC-442 deriv.
[0413] HEPT deriv.; MKC-442 deriv.
[0414] HOCH2CH2 isostere; ThienopyridCON thienyl urethane deny.
[0415] HOCH2CH2 isostere; ThienopyridCON thienyl urethane duly.
[0416] HOCH2CH2 isostere; ThienopyridCON thienyl urethane deriv.
[0417] HOCH2CH2 isostere, ThienopyridCON thienyl urethane deriv.
[0418] HOCH2CH2 isostere; ThienopyridCON thienyl urethane deny.
[0419] HOCH2CH2 isostere; ThienopyridCONthienyl urethane deriv.; LY326188
[0420] HPMPA
[0421] HPMPDAP
[0422] HU; Hydroxyurea; Hydrea
[0423] Hydroxocobalamin
[0424] Hypericin
[0425] Ingenol 3,5,20-triacetate; ITA; RD3-2118
[0426] Ingenol deriv.; RD4-2138
[0427] Inophyllum B
[0428] Inophyllum P
[0429] iQoa-Mta-Apns-Thz-NH-tBu; KNI-272
[0430] IsoquinCON (uranyl urethane analog
[0431] IsoquinCON thienyl urethane analog
[0432] IsoquinCON thienyl urethane analog
[0433] KNI-154; Noa-Asn-Apns-Thz-NH-tBu
[0434] KNI-174; Noa-Asn-Apns-Dmt-NH-tBu
[0435] KNI-227; Qoa-Mta-Apns-Thz-NH-tBu
[0436] L-685,434
[0437] L-685, 434-6-Hydroxy derivative
[0438] L-685,434-OEtMorphderivative; L-689,502
[0439] L-685,434-OEtNMe2
[0440] L-685,434-OPrMorph derivative
[0441] L-697,593; 2-Pyridinone deriv.
[0442] L-697,639; 2-Pyridinone deriv.
[0443] L-697,661; 2-Pyridinone deriv.
[0444] L-FddC; β-L-5F-ddC
[0445] Lamivudine & Zidovudine; Combivir® 3TC & AZT; Approved
[0446] LY289612
[0447] LY289612 analog
[0448] LY289612 analog
[0449] LY-300046-HCl; PETT deriv.; Trovirdine
[0450] LY314163; Saquinavir/Nelfinavir deriv.
[0451] LY-73497; N-(2-Phenethyl)-N'-(2-thiazolyl)thiourea; PETT
[0452] MAP; Methyl acetylenic putrescine
[0453] Michellamine A; NSC650898
[0454] Michellamine B; NSC649324
[0455] Michellamine F
[0456] N-6-Et-ddA; N-Ethyl-2',3'-dideoxyadenosine
[0457] N-6-methyl ddA; N6-Methyl-2',3'-dideoxyadenosine
[0458] Naphthalene 2-sulphonate polymer; PRO 2000

[0459] Nelfinavir-octahydro-thienopyridine analog
[0460] Nonoxynol 9
[0461] NSC625487; Thiazolobenzimidazole; TBZ
[0462] Oxathiin deriv.; UC-38
[0463] Oxathiin deriv.; UC-84
[0464] P9941
[0465] Penicillin Et(NH)2 Sym dimer
[0466] Penicillin G, ET(NH)2 deriv.
[0467] Penicillin, 2Isoquin-OHPrNH2 analog
[0468] Penicillin, 2Isoquin-OHPrNH2 analog
[0469] Pentosan Sulfate; Elmiron; SP54; Xylan Sulfate;
[0470] PETT Cl, F deriv.
[0471] PETT deriv.
[0472] PETT deriv.
[0473] PETT deriv.
[0474] PETT deriv.
[0475] Phenoxan
[0476] Phorbol deriv.; Prostratin
[0477] Platonic acid
[0478] PMEDAP
[0479] PMEG
[0480] PMEHx; PMEI
[0481] PMEMAP
[0482] PMET
[0483] PNU-140690; U-140690; Tipranavir
[0484] Pyridinone deriv.
[0485] Pyridinone deriv.
[0486] Quinoxalin2thione deriv; S-2720
[0487] R14458; TIBO deriv.
[0488] R82150; TIBO deriv.
[0489] R82913; TIBO deriv.
[0490] Resobene
[0491] Ribavirin; Virazole
[0492] Ro 31-8959-bis-thf deny.
[0493] Saquinavir/Nelfinavir deriv.
[0494] Saquinavir/Nelfinavir deriv.
[0495] SB-205569; Val-Phe-Phe-HOCH2CH2 isostere analog
[0496] SC-52151; Telinavir
[0497] SDZ PR1053
[0498] Suramin Sodium
[0499] T22
[0500] Thalidomide
[0501] Thiangazole; (−)-Thiangazole
[0502] Thiazoloisoindol-5-one
[0503] Thiazoloisoindol-5-one, deriv.
[0504] Tle-Val-Sta, 5PhBuCOOH deriv.; Statine deriv.
[0505] Tle-Val-Sta, 5PhBuCOOH deriv.; Statine deriv.
[0506] UC-781
[0507] Val-Val-Sta, 5PhBuCOOH deriv.; Statine duly.
[0508] Val-Val-Sta, 5PhBuCOOH deny.; Statine deriv.
[0509] Val-Val-Sta, 5PhBuCOOH Statine deriv.
[0510] Val-Val-Sta, 5PhBuCOOH deriv.; Statine deriv.
[0511] Val-Val-Sta, 5PhBuCOOH deriv.; Statine deriv.
[0512] VB-11,328
[0513] Vireada®; Tenofovir Disoproxil

[0514] 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 (coadminstered) with at least one diketo acid 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.

[0515] These include: 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; 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; Tenofovir disoproxil fumarate; Emtriva; 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, Interferon alfa-2; Interleukin-2, recombinant human; Intron A (2b); Invirase; Isoniazid; Itraconazole; KP-1461; Lamivudine/Zidovudine; Lexiva; Lopinavir/Ritonavir; MK-0518; Nebupent; Nelfinavir; Neutrexin; Nevirapine; Norvir; Nydrazid; Peptide T; PMPA Prodrug (Viread)' Prezista (Darunavir); PRO140; PRO2000; PRO542 (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; Vicriviroc; Videx; Viracept (Tennofovir DF); Viramune; Virazole; Viread; Vitrasert; Zalcitabine; Zerit; Ziagen; Zidovudine; Zithromax; Zovirax.

[0516] 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 (coadminstered) with at least one diketo acid 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.

[0517] These include: 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; Atazsmavir; 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; 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; Isoniazid; Itraconazole; KP-1461; Lamivudine/Zidovudine; Lexiva; Lopinavir/Ritonavir; MK-0518; Nebupent; Nelfinavir; Neutrexin; Nevirapine; Norvir; Nydrazid; Peptide T; PMPA Prodrug (Viread)' Prezista (Darunavir); PRO140; PRO2000; PRO542 (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; Vicriviroc; Videx; Viracept (Tennofovir DF); Viramune; Virazole; Viread; Vitrasert; Zalcitabine; Zerit; Ziagen; Zidovudine; Zithromax; Zovirax.

[0518] The following representative examples are provided to illustrate, details for the preparation of the compounds of the present invention. The examples are not intended to be limitations on the scope of the present invention and they should not be so construed. Furthermore, the compounds described in the following examples are not to be viewed as forming the only set of compounds that is considered as the invention, and any combination of components of the compounds or their moieties may itself form a set. This has been addressed previously in this patent document. Those skilled in the art will readily comprehend that known variations of reaction conditions and synthetic conversions described in the following preparative procedures can be used to prepare these other compounds.

[0519] The following representative examples are provided to illustrate details for the preparation of the compounds of the present invention. The examples are not intended to be limitations on the scope of the present invention and they should not be so construed. Furthermore, the compounds described in the following examples are not to be viewed as forming the only set of compounds that is considered as the invention, and any combination of components of the compounds or their moieties may itself form a set. This has been addressed previously in this patent document. Those skilled in the art will readily comprehend that known variations of reaction conditions and synthetic conversions described in the following preparative procedures can be used to prepare these other compounds.

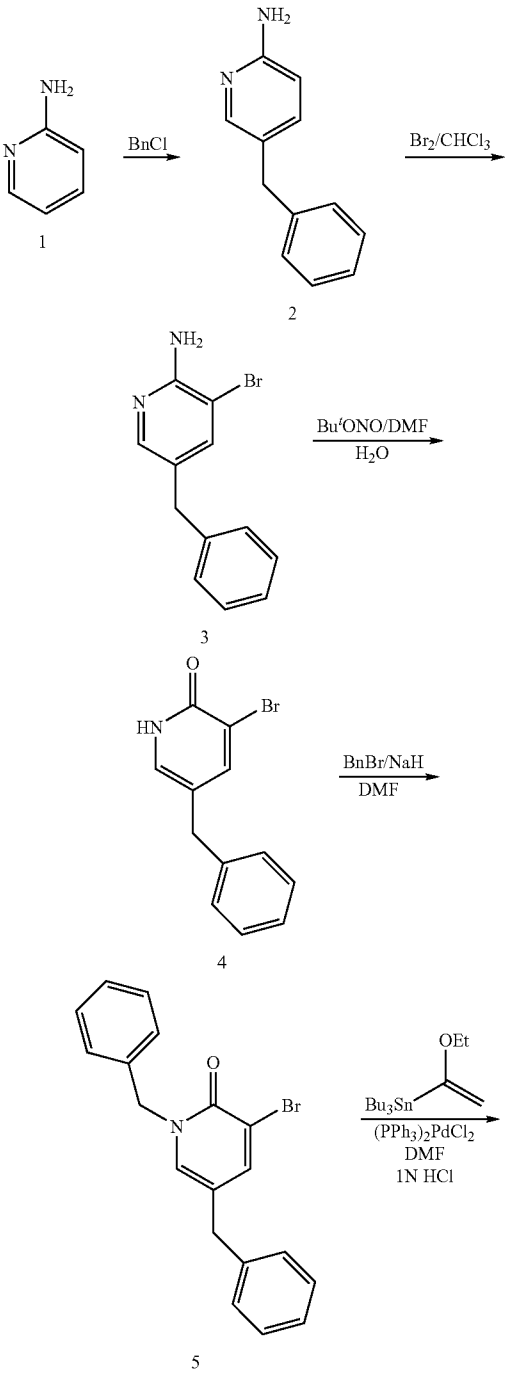
Chemical Synthesis

Representative Example 1

4-(1,5-dibenzyl-1,2-dihydro-2-oxopyridin-3-yl)-2-hydroxy-4-oxobut-2-enoic acid (8)

[0520] The relevant scheme (1) is shown below.

Scheme 1



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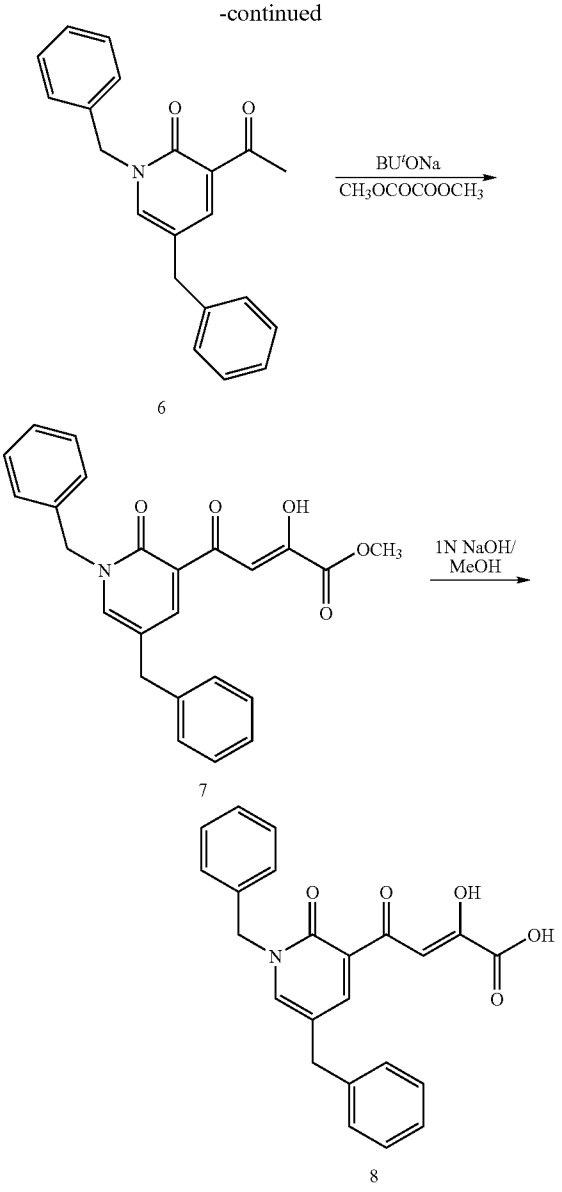
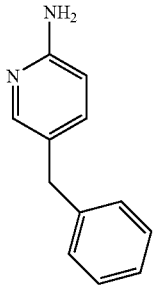


Step 1: 5-Benzylpyridin-2-amine (2)

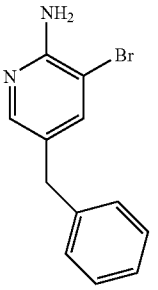
[0521]



[0522] A mixture of pyridine-2-amine 1 (14.1 g, 149.8 mmol) and benzylchloride (36.0 g, 284.6 mmol) was heated to 180° C. until the mixture began to boil [Kowalski, *J. Heterocycl. Chem.* 28, 875-879 (1991)]. The temperature was then gradually raised during 3 h to 250° C. and maintained for 24 h. After cooling, the reaction mixture was washed out from the flask with MeOH (60 mL) and treated with 10% aqueous NH_4OH (40 mL). After addition of water (200 mL), the resulting oil was extracted with $CHCl_3$ (2×200 mL), dried over anhydrous Na_2SO_4, and $CHCl_3$ distilled off. The residue was separated by distillation under reduced pressure. The fraction collected at 130-135° C./1 mm Hg was further purified by flash chromatography on silica gel (EtOAc:hexane, 7:3). Yield 9.2 g (34%), white solid, mp 79-80° C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.87 (s, 2H, CH_2), 4.43 (bs, 2H, NH_2), 6.48 (d, 1H, CH J=8.5 Hz), 7.19-7.33 (m, 6H, Ar—H and CH), 7.99 (d, 1H, CH, J=1.5 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 38.2, 108.7, 126.1, 126.4, 128.5, 128.7, 128.9, 128.9, 138.6, 140.9, 147.7, 156.8.

Step 2: 5-Benzyl-3-bromopyridin-2-amine (3)

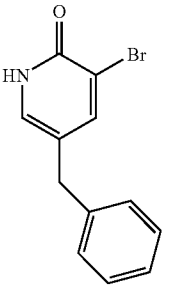
[0523]



[0524] To a stirred solution of 5-benzylpyridin-2-amine 2 (6.0 g, 32.3 mmol) in CH_2Cl_2 (100 mL) cooled to 0° C. was added bromine (5.1 g, 32.3 mmol) dropwise [Kelly, et al., *J. Am. Chem. Soc.* 112, 8024-8034 (1990)]. The bromine decolorized immediately and the mixture was left stirring for 30 min. The mixture was shaken with saturated $NaHCO_3$ solution (100 mL), the organic layer was then dried over anhydrous Na_2SO_4, and distilled off to give a yellow residue which was purified by flash chromatography on silica gel (EtOAc:hexane, 3:7). Yield 7.3 g (86%), white solid, mp 110-111° C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.86 (s, 2H, CH_2), 4.88 (bs, 2H, NH_2), 7.19-7.35 (m, 5H, Ar—H), 7.50 (d, 1H, CH, J=1.5 Hz), 7.94 (d, 1H, CH, J=1.0 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 37.7, 104.6, 126.4, 126.4, 128.1, 128.6, 128.6, 128.7, 140.2, 140.8, 146.7, 154.0; HRMS $(M+H)^+$ calcd for $C_{12}H_{13}BrN_2$ 263.0184, found 263.0184.

Step 3: 5-Benzyl-3-bromopyridin-2(1H)-one (4)

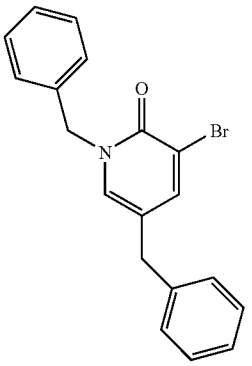
[0525]



[0526] To a stirred solution of 5-benzyl-3-bromopyridin-2-amine 3 (0.2 g, 0.7 mmol) in DMF (4 mL) was added water (2 drops) followed by t-butyl nitrite (0.378 g, 3.6 mmol) and the reaction mixture stirred at RT for 30 min. DMF and the excess reagent were distilled off, and the residue purified by flash chromatography on silica gel (EtOAc:hexane, 1:1). Yield 7.3 g (86%), white solid, mp 151-152° C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.77 (s, 2H, CH_2), 7.17-7.36 (m, 611, Ar—H and CH), 7.76 (d, 1H, CH, J=1.5 Hz) 13.25 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 37.3, 115.4, 121.0, 126.9, 128.8, 128.8, 128.9, 128.9, 132.4, 138.5, 145.3, 161.0; HRMS $(M+H)^+$calcd for $C_{12}H_{11}BrNO$ 264.0024, found 264.0014.

Step 4: 1,5-Dibenzyl-3-bromopyridin-2(1H)-one (5)

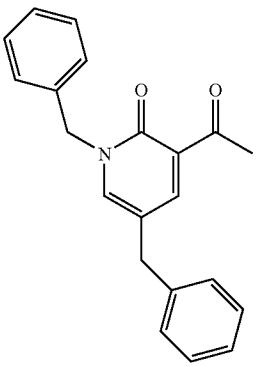
[0527]



[0528] To a suspension of 5-benzyl-3-bromopyridin-2 (1H)-one 4 (3.5 g, 13.5 mmol) in dry DMF (100 mL) was added NaH 60% suspension in mineral oil (0.5 g, 16.2 mmol) and stirred for 30 min, followed by the addition of benzyl bromide (0.1.36 g, 7.9 mmol) and mixture further stirred for 1 h at RT. DMF was distilled off and the residue redissolved in EtOAc (250 mL), washed with brine solution (2×100 mL), dried over anhydrous Na_2SO_4 and EtOAc distilled off to give a yellow syrup, which was purified by column chromatography on silica gel (EtOAc:Hexane, 4:6) to give 5. Yield 3.8 g (83%), yellow solid, mp 89-90° C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.69 (s, 2H, CH_2), 5.18 (s, 2H, CH_2), 7.11 (d, 1H, CH, J=2 Hz), 7.12-7.39 (m, 10H, Ar—H), 7.60 (d, 1H, CH, J=2 Hz), ^{13}C NMR ($CDCl_3$, 125 MHz): δ 37.4, 53.5, 117.1, 119.1, 126.9, 128.2, 128.2, 128.3, 128.3, 128.6, 128.8, 128.8, 128.9, 128.9, 134.6, 135.8, 138.7, 143.0, 158.3. HRMS $(M+H)^+$calcd for $C_{19}H_{17}BrNO$ 354.0494, found 354.0455.

Step 5: 3-Acetyl-1,5-dibenzyl-3-pyridin-2(1H)-one (6)

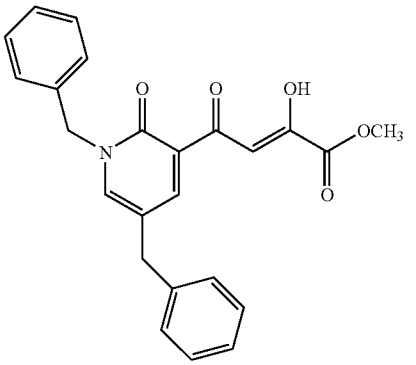
[0529]



[0530] A mixture of 1,5-dibenzyl-3-bromopyridin-2(1H)-one 5 (1.0 g, 2.8 mmol) bis(triphenylphosphine)palladium(II) chloride (0.19 g, 0.28 mmol) and ethoxyvinyl(tributyl)tin (2.03 g, 5.6 mmol) in dry DMF (50 mL) was heated under N_2 at 70° C. for 1 h. DMF was distilled off and the resulting residue redissolved in EtOAc (50 mL) and filtered through a pad of celite EtOAc fraction was stirred with 1 N HCl (30 mL) for 15 min, washed with water (2×30 mL), and dried over anhydrous Na_2SO_4 and distilled off to give a yellow residue which was purified by flash chromatography on silica gel (EtOAc:hexane, 2:8). Yield 0.86 g (97%), yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.73 (s, 3H, CH_3), 3.75 (s, 2H, CH_2), 5.19 (s, 2H, CH_2), 7.14-7.40 (m, 11H, Ar—H and CH), 8.04 (d, 1H, CH, J=3 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 31.1, 37.5, 52.5, 118.6, 126.8, 127.8, 127.8, 127.9, 128.2, 128.2, 128.6, 128.6, 128.8, 128.8, 129.0, 135.8, 138.8, 140.7, 144.8, 160.4, 198.0; HRMS (M+calcd for $C_{21}H_{20}NO_2$ 318. 1494, found 318.1461.

Step 6: Methyl-4-(1,5-dibenzyl-1,2-dihydro-2-oxopyridin-3-yl)-2-hydroxy-4-oxobut-2-enoate (7)

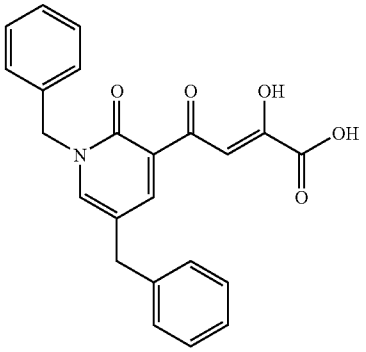
[0531]



[0532] To a stirred solution of 3-acetyl-1,5-dibenzyl-3-pyridin-2(1H)-one 6 (0.1 g, 0.31 mmol) in THF (5 mL) was added Na-t-butoxide (0.30 g, 3.1 mmol) and the reaction mixture stirred for 15 min. A solution of dimethyl oxalate (0.37 g, 3.1 mmol) in THF (5 mL) was added at RT and stirred for 2 h. THF was distilled off and 1 N HCl (1 mL) was added and extracted with EtOAc (2×10 mL), washed with saturated brine solution (4×20 mL), dried over anhydrous sodium sulfate and EtOAc distilled off to give a brown residue which was purified first by ion exchange chromatography (Diethylamino sephadex anion exchange resin, (CH_3CN:H_2O, 1:1) and then by flash chromatography on silica gel ($CHCl_3$:MeOH, 9.9:0. 1). Yield 0.054 g (44%), yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.79 (s, 2H, CH_2), 3.91 (s, 3H, CH_3), 5.21 (s, 2H, CH_2), 7.15-7.42 (m 11H, Ar—H and CH), 7.98 (s, 1H, olefenic CH), 8.24 (d, 1H, CH, J=2.5 Hz), ^{13}C NMR ($CDCl_3$, 100 MHz): δ 37.5, 52.7, 53.0, 101.8, 119.0, 123.4, 126.9, 128.0, 128.0, 128.3, 128.6, 128.6, 128.9, 129.0, 129.0, 129.1, 135.6, 138.6, 141.4, 145.0, 159.5, 162.6, 172.2, 185.5; HRMS $(M+H)^4$ calcd for $C24H_{22}NO_5$ 404.1498, found 404. 1411.

Step 7: 4-(1,5-Dibenzyl-1,2-dihydro-2-oxopyridin-3-yl)-2-hydroxy-4-oxobut-2-enoic acid (8)

[0533]



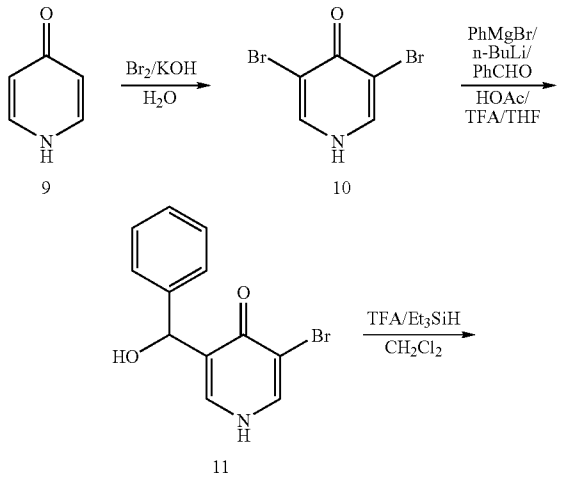
[0534] To a stirred solution of methyl-4-(1,5-dibenzyl-1,2-dihydro-2-oxopyridin-3-yl)-2-hydroxy-4-oxobut-2-enoate 7 (0.069 g, 0.17 mmol) in MeOH (5 mL) at 0° C. was added a solution of 1N NaOH (0.5 mL) and reaction mixture allowed to stir at 0° C. for 30 min. Reaction was then allowed to stir at ambient temperature for 1 h. The reaction mixture was neutralized with 1 N HCl, the solid separated was filtered and dried under vacuum. Recrystallization with EtOAc/Hexane gave yellow solid. Yield 0.034 g (52%), yellow solid, mp: 158-159° C. NMR ($CDCl_3$, 500 MHz): δ 3.82 (s, 2H, CH_2), 5.26 (s, 2H, CH_2), 7.16-7.39 (m, 10H, Ar—H), 7.45 (d, 1H, CH, J=2 Hz), 7.98 (s, 1H, olefenic CH), 8.26 (d, 1H, CH, J=2 Hz), ^{13}C NMR ($CDCl_3$, 125 MHz): δ 37.5, 53.3, 100.8, 119.8, 123.1, 127.0, 128.2, 128.5, 128.5, 128.6, 128.6, 128.9, 128.9, 129.0, 129.1, 129.1, 135.2, 138.4, 141.3, 145.1, 159.5, 162.3, 173.7; HRMS $(M+H)^+$calcd for $C_{23}H_{20}NO_5$ 390.1341, found 390.1342.

Representative Example 2

4-(1,5-dibenzyl-1,4-dihydro-4-oxopyridin-3-yl)-2-hydroxy-4-oxobut-2-enoic acid (16)

[0535] The relevant scheme (2) is shown below.

Scheme 2



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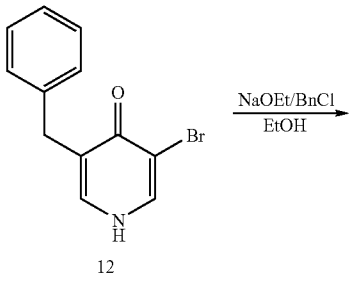

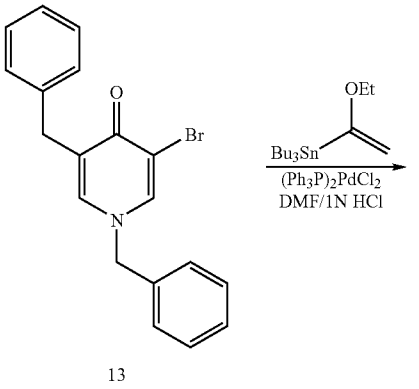

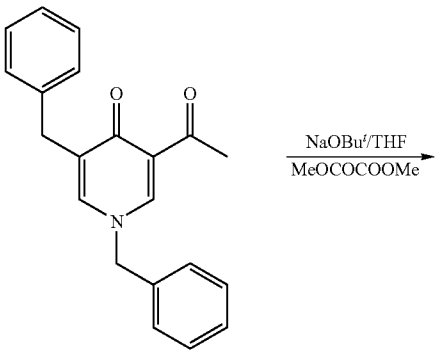

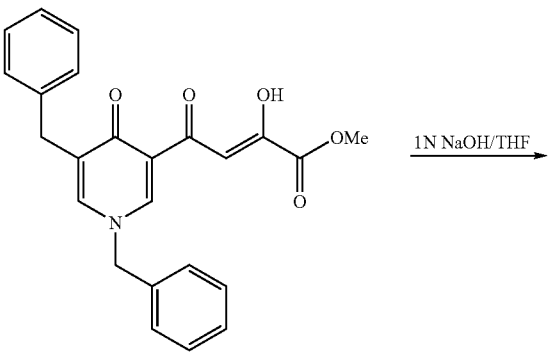

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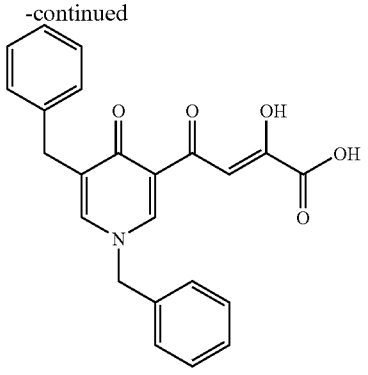
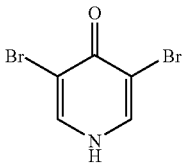


16

Step 1: 3,5-Dibromo-pyridin-4-one (10)

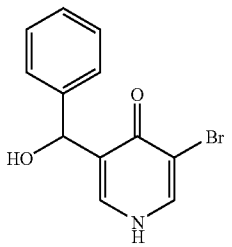
[0536]



[0537] To an ice-cooled solution of pyridine-4-one 9 (6.98 g, 73.4 mmol) and KOH (9.52 g, 146.8 mmol) in water (140 mL) was added bromine (7.58 mL, 147.5 mmol) dropwise over 30 min [Spivey, et al., *J. Org. Chem.* 65, 3154-3159 (2000)]. After an additional 30 min, the precipitate was filtered off, washed with a copious amount of water, and dried in vacuo. Yield 16.17 g (87%), yellow solid, mp 320° C. (sublimes). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 12.3 (s, 1H), 8.26 (s, 21-1). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 167.5, 138.2, 138.2, 111.8, 111.8.

Step 2: 3-Bromo-5-(hydroxy-phenyl-methyl)-pyridin-4-one (11)

[0538]

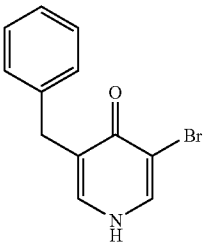


[0539] To a heterogeneous mixture of 3,5-dibromo-pyridin-4-one 10 (0.313 g, 1.24 mmol) in anhydrous THF (4 mL) at −78° C. under nitrogen atmosphere was added phenylmagnesium bromide solution (1.36 mL of 1 M solution in THF, 1.36 mmol) [Borzilleri, et al., US Pat. 20050245530]. After stirring for 15 min, n-BuLi solution (0.68 mL of 2 M solution in cyclohexane, 1.36 mmol) was added and the reaction mixture stirred for 15 min at −78° C. under nitrogen atmosphere. To this mixture was added benzaldehyde (0.26 mL, 2.6 mmol) and the mixture was stirred for 2 h at −78° C. The reaction mixture was quenched by adding HOAc (0.38 mL) and TFA (0.38 mL), concentrated in vacuo and the residue was purified by flash column chromatography on silica gel (dichloromethane: methanol, 95:5). Yield 0.125 g (36%), white solid, 123-124° C. ^{1}H NMR (MeOH-d_4, 500 MHz): δ 8.09 (s, 1H), 7.81 (s, 1H), 7.38-7.17 (m, 5H), 5.92 (s, 1H), 3.83 (s, 2H). ^{13}C NMR (MeOH-d_4, 125 MBz): δ 174.3, 144.4, 139.7, 135.8, 133.6, 129.4, 129.3, 128.6, 128.0, 128.0, 114.8, 70.8.

Step 3: 3-Benzyl-5-bromopyridin-4-one (12)

[0540]

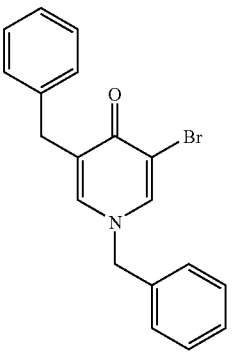
12



[0541] A mixture of 3-bromo-5-(hydroxyl-phenyl-methyl) pyridin-4-one 11 (0.125 g, 91 mmol), TFA (16 mL) and Et_3SiH in anhydrous dichloromethane (30 mL) was stirred at rt for 10 h [Borzilleri, et al., US Pat. 20050245530]. The reaction mixture was concentrated in vacuo and the residue purified by flash column chromatography on silica gel (dichloromethane: methanol, 98:2). Yield 0.081 g (69%), white solid. ^{1}H NMR (MeOH-d_4, 500 MHz): δ 8.12 (s, 1H), 7.47 (s, 1H), 7.29-7.17 (m, 5H), 3.83 (s, 2H). ^{13}C NMR (MeOH-d_4, 125 MHz): δ 175.2, 140.7, 139.5, 136.9, 130.8, 130.0, 130.0, 129.5, 129.5, 127.3, 114.1, 34.9.

Step 4: 1,3-Dibenzyl-5-bromo-1H-pyridin-4-one (13)

[0542]

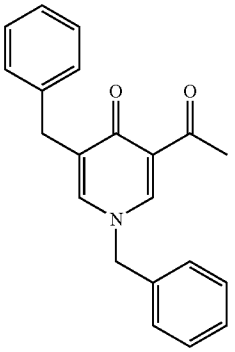


[0543] A mixture of 3-benzyl-5-bromopyridin-4-one 12 (0.57 g, 2.16 mmol) and NaOEt (0.89 mL, 2.37 mmol) in absolute ethanol (20 mL) was refluxed with benzyl chloride (0.30 ml), 2.59 mmol) for 1 h under nitrogen. The solvent was

distilled off to give a yellow residue which was purified by flash column chromatography on silica gel (dichloromethane: methanol, 98:2). Yield 1:31 g (96.7%), yellow solid, mp 120-121° C. ^{1}H NMR ($CDCl_3$. 500 MHz): δ 7.67 (d, 1H, J=2.4), 7.32-7.07 (m, 10H), 4.83 (s, 1H), 3.78 (s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.2, 139.6, 139.1, 137.6, 134.7, 129.9, 129.9, 129.3, 129.3, 129.2, 129.0, 128.6, 128.6, 127.5, 127.6, 126.4, 114.1, 60.3, 34.4. HRMS (M+H)$^+$calcd for $C_{19}H_{16}BrNO$ 354.0494, found 354.0499.

Step 5: 3-Acetyl-1,5-dibenzyl-1H-pyridin-4-one (14)

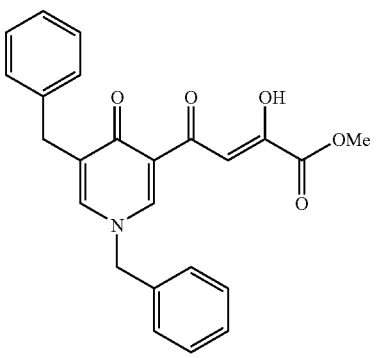
[0544]



[0545] A mixture of 1,3-dibenzyl-5-bromo-1H-pyridin-4-one 13 (1.31 g, 2.70 mmol), tributyl-(1-ethoxyvinyl)tin (1.80 mL, 5.18 mmol) and dichlorobis(triphenylphosphine)-palladium(II) (0.26 g, 0.37 mmol) in anhydrous DMF (20 mL) was stirred under nitrogen atmosphere at 95° C. for 8 h. The reaction mixture was extracted with ethyl acetate (3×50 mL), washed with 1N HCl (3×50 mL), and solvent distilled off. The residue was purified by flash column chromatography on silica gel (dichloromethane methanol, 98:2). Yield 1.06 g (90%), yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.19 (d, 1H, J=2.6), 7.39-7.10 (m, 10H), 6.90 (d, 1H, J=2.5), 4.89 (s, 2H), 3.81 (s, 2H), 2.74 (s, 3H). HRMS (M+calcd for $C_{21}H_{19}NO_2$ 318.1494, found 318.1493.

Step 6: Methyl 4-(1,5-dibenzyl-4-oxo-1,4-dihydro-pyridin-3-yl)-2-hydroxy-4-oxo-but-2-enoate (15)

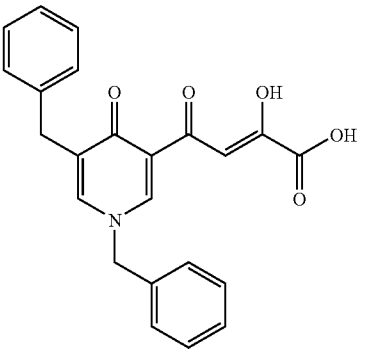
[0546]



[0547] To a stirred solution of sodium t-butoxide (0.52 g, 5.23 mmol) in anhydrous THF (13 mL) at room temperature was added dropwise dimethyl oxalate (0.42 g, 3.48 mmol) in THF (6 mL) followed by 3-acetyl-1,5-dibenzyl-1H-pyridin-4-one 14 (0.55 g, 1.74 mmol) in THF (8 mL). The resulting mixture was stirred at room temperature for 4 h and then acidified (pH=6). The crude product was extracted with ethyl acetate (100 mL), washed with water (2×100 mL) and brine (2×100 mL), and dried over anhydrous sodium sulfate and the solvent was distilled off. The residue was purified by ion exchange chromatography (diethylamino sephadex anion exchange resin (CH_3CN: H_2O, 1:1) and then by flash chromatography on silica gel (chloroform, 100%). Yield 0.44 g (63%), mp 148-150° C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.34 (d, J=2.5, 1H), 8.12 (s, 1H), 7.40-7.12 (m, 10H), 6.91 (d, J=2.3, 1H), 4.94 (s, 2H), 3.88 (s, 3H), 3.82 (s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 187.2, 175.2, 170.3, 162.7, 143.9, 138.4, 136.9, 136.1, 133.8, 129.4, 129.5, 129.3, 129.1, 129.1, 128.7, 128.6, 127.5, 127.4, 126.5, 120.2, 102.4, 61.2, 53.0, 33.5. HRMS (M+H)$^+$calcd for C24$H_{22}NO_5$ 404.1498, found 404.1497.

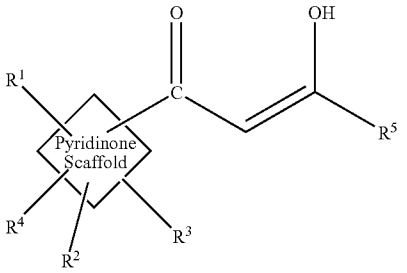
Step 7: 4-(1,5-dibenzyl-1,4-dihydro-4-oxopyridin-3-yl)-2-hydroxy-4-oxobut-2-enoic acid (16)

[0548]



[0549] A mixture of methyl-4-(1,5-dibenzyl-1,4-dihydro-4-oxopyridin-3-yl)-2-hydroxy-4-oxobut-2-enoate 15, (0.080 g, 0.19 mmol) and 1 N NaOH (4 mL) in THF (12 mL) was stirred at 0° C. for 4 h. THF was distilled off and the residue acidified with 1 N HCl and extracted with EtOAc (2×25 mL), washed with brine solution (1×25 mL), dried over anhydrous Na_2SO_4 and EtOAc distilled off to give a yellow solid. The crude solid was triturated with diethylether, filtered and dried under vacuum. Finally the solid was triturated with chloroform, filtered and dried under vacuum for 24 h. Yield 0.065 g (84%), yellow solid, mp 140-142° C. ^{1}H NMR ($CDCl_3$+ MeOH-d_4, 500 MHz): δ 3.80 (s, 211, CH_2), 4.97 (s, 2H, CH_2), 6.95 (t, 1H, CH, J=1 Hz), 7.13-7.40 (m, 11H, Ar—H and olefenic CH), 8.36 (d, 1H, CH, J=2.5 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 33.4, 61.2, 120.5, 126.5, 127.5, 127.6, 128.6, 128.7, 128.7, 129.1, 129.1, 129.2, 129.2, 129.2, 129.4, 133.8, 135.9, 137.2, 138.2, 143.8, 163.8, 175.4. HRMS (M+H)$^+$ calcd for $C_{23}H_{20}NO_5$ 390.1341, found 390.1343.

1. A compound according to the general structure of formula I:



I

wherein the scaffold is independently the 2- and 4-pyridinones identified herein and their regioisomers;

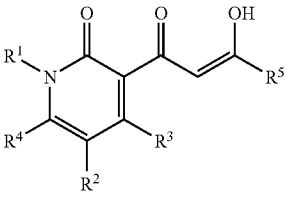
R^1 and R^2 are each independently H, C_{1-6} alkyl, C_{1-6} fluoroalkyl, unsubstituted or substituted C_{5-6} cycloalkyl, C_{1-6} alkenyl, unsubstituted or substituted phenyl, unsubstituted or substituted benzyl, C_{2-6} alkyl phenyl which phenyl moiety may be optionally substituted, unsubstituted or substituted heteroaryl, C_{1-6} alkyl substituted with a heteroaryl group which heteroaryl group is optionally substituted, C_{1-6} alkyl S(O)R or alkyl $(SO_2)R$ where R is alkyl, phenyl or substituted phenyl, C_{1-6} alkyl CO_2R^a where R^a is C_{1-6} alkyl or H, C_{1-6} alkyl $COR^{a'}$ where $R^{a'}$ is Cl_{1-6} alkyl;

R^3 and R^4 are independently selected from H, C_{1-6} alkyl, halogen, hydroxyl, unsubstituted or substituted benzyl, or unsubstituted or substituted phenylthio;

R^5 is CO_2R^c or $P(O)(OR^c)(OR^c)$, where each R^c is independently from H and C_{1-6} alkyl,

Or a pharmaceutically acceptable salt thereof.

2. A compound of claim **1** according to the structure:



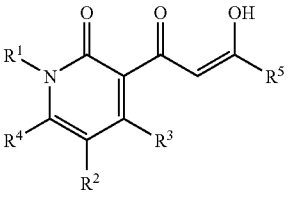
wherein R^1 and R^2 are each independently a benzyl group or a substituted benzyl group with 1 to 3 substituents on the aromatic ring selected from halogen, hydroxyl, methoxy, methyl, ethyl, propyl, CF_3, or a $—CH_2 R^b$ group where R^b is a 5- or 6-membered heteroaryl group;

R^3 and R^4 are independently H, C_{1-6} alkyl, halogen, benzyl, substituted benzyl, phenylthio, or substituted phenylthio with 1 to 3 substitutents on the phenyl ring selected from halogen, hydroxyl, methoxy, methyl, ethyl, propyl, CF_3;

wherein R^5 is CO_2R where R is selected from H and C_{1-6} alkyl,

or a pharmaceutically acceptable salt thereof.

3. The compound of claim **1** according to the structure:



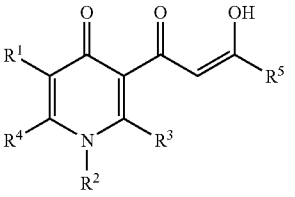
wherein R^1 and R^2 are each independently a benzyl group or substituted benzyl group with 1 to 3 substituents on the aromatic ring selected from halogen, hydroxyl, methoxy, methyl, ethyl, propyl, CF_3 or wherein R^1 and R^2 are independently $—CH_2R^b$ where R^b is a 5- or 6-membered heteroaromatic ring;

wherein R^3 and R^4 are independently H, C_{1-6} alkyl, halogen, benzyl, substituted benzyl, phenylthio, or substituted phenylthio with 1 to 3 substitutents on the phenyl ring selected from halogen, methoxy, methyl, ethyl, propyl, CF_3;

wherein R^5 is P(O)(OR)(OR), where the R groups could be the same or not and are selected from H or C_{1-6} alkyl,

or a pharmaceutically acceptable salt thereof.

4. A compound of claim **1** according to the structure:



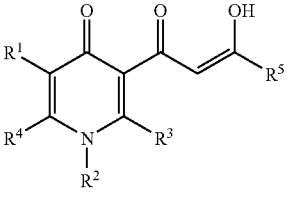
wherein R^1 and R^2 are each independently a benzyl group or a substituted benzyl group with 1 to 3 substituents on the aromatic ring selected from halogen, hydroxyl, methoxy, methyl, ethyl, propyl, CF_3, or a $CH_2 R^b$ group where R^b is a 5- or 6-membered heteroaryl group;

R^3 and R^4 are independently H, Cl_6 alkyl, halogen, benzyl, substituted benzyl, phenylthio, or substituted phenylthio with 1 to 3 substitutents on the phenyl ring selected from halogen, hydroxyl, methoxy, methyl, ethyl, propyl, CF_3;

wherein R^5 is CO_2R where R is selected from H and C_{1-6} alkyl,

or a pharmaceutically acceptable salt thereof.

5. A compound of claim **1** according to the structure:



wherein R^1 and R^2 are each independently a benzyl group or substituted benzyl group with 1 to 3 substituents on the aromatic ring selected from halogen, hydroxyl, methoxy, methyl, ethyl, propyl, CF_3 or wherein R^1 and R^2 are independently CH_2R^b where R^b is a 5- or 6-membered heteroaromatic ring;

wherein R^3 and R^4 are independently H, C_{1-6} alkyl, halogen, benzyl, substituted benzyl, phenylthio, or substituted phenylthio with 1 to 3 substitutents on the phenyl ring selected from halogen, methoxy, methyl, ethyl, propyl, CF_3;

wherein R^5 is P(O)(OR)(OR), where the R groups could be the same or not and are selected from H or C_{1-6} alkyl,

or a pharmaceutically acceptable salt thereof.

6. A compound of claim **1** selected from the group consisting of

4-(1,5-dibenzyl-1,2-dihydro-2-oxopyridin-3-yl)-2-hydroxy-4-oxobut-2-enoic acid;

4-(1,5-dibenzyl-1,4-dihydro-4-oxopyridin-3-yl)-2-hydroxy-4-oxobut-2-enoic acid;

3-Acetyl-1,5-dibenzyl-3-pyridin-2(1H)-one;

3-Acetyl-1,5-dibenzyl-1H-pyridin-4-one;

Methyl-4-(1,5-dibenzyl-1,2-dihydro-2-oxopyridin-3-yl)-2-hydroxy-4-oxobut-2-enoate; and

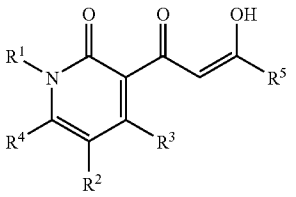
Methyl 4-(1,5-dibenzyl-4-oxo-1,4-dihydro-pyridin-3-yl)-2-hydroxy-4-oxo-but-2-enoate, or a pharmaceutically acceptable salt thereof.

7. A compound according to claim **1** selected from the group consisting of

4-(1,5-dibenzyl-1,2-dihydro-2-oxopyridin-3-yl)-2-hydroxy-4-oxobut-2-enoic acid; and

4-(1,5-dibenzyl-1,4-dihydro-4-oxopyridin-3-yl)-2-hydroxy-4-oxobut-2-enoic acid, or a pharmaceutically acceptable salt thereof.

8. A compound according to claim **1** according to the structure:



wherein R^1 and R^2 are independently benzyl groups or substituted benzyl groups with 1 to 3 substituents on the phenyl rings selected from the group consisting of fluorine, chlorine, C_{1-4} alkyl, C_{2-4} alkenyl and methoxy;

R^3 is H, C_{1-3} alkyl, C_{2-3} alkenyl, fluorine, chlorine or methoxy;

R^4 is H, F, Cl or OH; and

R^5 is CO_2H or $P(O)(OH)_2$,

or a pharmaceutically acceptable salt thereof.

9. The compound according to claim **1** wherein at least one of R^1 and R^2 is a benzyl group.

10. The compound according to claim **1** wherein both R^1 and R^2 are benzyl groups.

11. The compound according to claim **8** wherein both R^1 and R^2 are benzyl groups.

12. The compound according to any of claims **1-5** and **8-11** wherein R^3 and R^4 are independently H, methyl, fluorine or chlorine.

13. The compound according to any of claims **1-5** and **8-12** wherein R^3 and R^4 are independently H, fluorine or chlorine.

14. The compound according to any of claims **1-5** and **8-13** wherein R^3 and R^4 are each H.

15. The compound according to claim any of claims **1-5** and **8-14** wherein R^5 is CO_2H or a pharmaceutically acceptable salt thereof.

16. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any of claims **1-15** and a pharmaceutically acceptable carrier, additive or excipient.

17. The pharmaceutical composition of claim **16** wherein said composition inhibits HIV integrase, both wild type and mutants, in a human host.

18. A pharmaceutical composition comprising a therapeutically effective amount of a first compound according to claim **1** in combination with a therapeutically effective amount of at least one additional 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, iv) other combination agent selected from the table shown on pages 17-28, herein, and a pharmaceutically acceptable carrier, additive or excipient.

19. The composition according to claim **18** 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. The composition of claim **19** wherein said reverse transcriptase inhibitor is a nucleoside compound.

21. The composition of claim **19** wherein said reverse transcriptase inhibitor is a non-nucleoside compound.

22. The composition of claim **19** wherein the said additional integrase inhibitor is a compound other than a pyrimidinone compound.

23. The composition according to claim **16** in oral or parenteral dosage form.

24. The composition according to claim **16** formulated for administration as an inhalation spray or a rectal suppository.

25. A method of preparing a pharmaceutical composition comprising combining a compound of claim **1** with a pharmaceutically-acceptable carrier, additive or excipient to produce a mixture and preparing an oral or parenteral dosage form from said mixture.

26. 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 **16** to said patient.

27. 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 claim **16** to said patient.

28. 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 **16**.

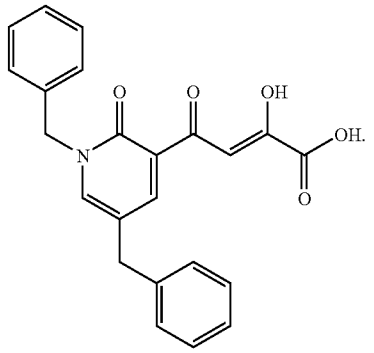
29. A method of inhibiting HIV integrase in a subject, said method comprising administering to said subject a therapeutically effective amount of a composition according to claim **16** to said subject.

30. The method according to claim **26** wherein said subject is a human.

31. The method according to any of the claim **26** wherein said anti-HIV or other agent is a compound which is set forth in the table on any of pages 17-28, herein.

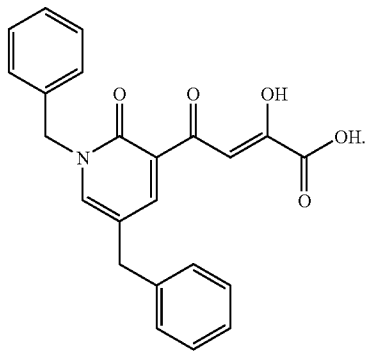
32. A method of treating an HIV infection in a human host comprising administering to said host the composition of claim **27**.

33. The method according to claim **32** wherein said composition comprises an effective amount of the compound



34. A pharmaceutical composition comprising an effective amount of a first compound according to claim **1** in combination with an effective amount of at least one anti-HIV or other compound which is set forth in the table on any of pages 17-28, herein, in combination with a pharmaceutically acceptable carrier, additive or excipient.

35. The pharmaceutical composition according to claim **16** wherein said compound is



36. A pharmaceutical composition according to claim **16** further comprising at least one additional compound is selected from the group consisting of (−)β-Dioxolane-G (DXG); (−)β-Arctigenin (Arctigenin); (−)-Carbovir (−)-CD4G; (−)-2',3'-Dideoxy-5-fluoro-3'-thiacytidine (FTC); (−)-β-D-2,6-Diaminopurine dioxolane (DAPD); (+)-2'-Deoxy-3'-oxa-4'-thiocytidine (dOTC+); (+)-2'-Deoxy-3'-oxa-4'-thio-5-fluorocytidine (dOTFC+); (+/−)-Lobucavir; (R)-2QuinCOAsnPhe[CHOHCH2]PipCONHtBu; (R)-3,6-Diamino-N-(aminomethyl)hexanamide (Bellenamine); (R)-9-(2-Phosphonylmethoxypropyl)adenine (Tenofovir); (R)-PMPDAP; (S)-9-(2-Phosphonylmethoxypropyl)adenine ((S)-PMPA); PMPA(S); α-APA (Loviride); R87232; R88703; α-APA enantiomer (R90385); α-L-AZT; α-L-Dioxalane-C (α-L-DXC); α-L-FTC; α-Monofluoromethyldehydroornithine methyl ester (MFMOME); 1,1'-Azobisformamide (ADA); 1-(11-Octylamino-10-hydroxyundecyl)-3,7-dimethylxanthine (CT-2576); 1-(2',3'-Dideoxy-2'-fluoro-(3-D-threo-pentofuranosyl)cytosine (Ro 31-6840); 1-(2'-Fluoro-2',3'-dideoxy-β-D-erythro-pentofuranosyl)thymine (2'FddT); 1-[(2-Hydroxyethoxy)methyl]-6-(3-methylphenyl)thio)thymine (HEPT-M); 1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)-2-thiothymine (HEPT-S); 1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT); Deoxynojirimycin (1-Deoxynojirimycin); Amprenavir; Abacavir Succinate(Ziagen); 1-Aminooxyethylamine (AEA); 1-Methoxyoxalyl-3,5-dicaffeoylquinic acid (1-MO-3,5-DCQA); 1OH-2(Cbz-Tle)$_3$PhPr [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)$_3$PhPr [17]paracyclophane deriv.; 12-Deoxyphorbol-13-(3E,5E-decadienoate); 16.alpha.-Bromoepiandrosterone (Epi-Br) or (Inactivin); 1-β-D-arabinofuranosyl-5-(2-bromovinyl)uracil (Sorivudine); 2',3'-Didehydro-3'-deoxycytidine (D4C); 2',3'-Dideoxydidehydroguanosine (D4G); 2',3'-Didehydro-3'-deoxythymidine (D4T) (Stavudine); 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) (Raluridine); 2',3'-Dideoxy-5-ethylcytidine (5-Et-ddC); 2',3'-Dideoxyadenosine (ddA); 2',3'-Dideoxydidehydroadenosine (d4A); 2',3'-Dideoxyguanosine (ddG); 2',3'-Dideoxy-3'-hydroxymethyl cytidine (3'-Hydroxymethyl-ddC); 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-me^3T); 2,6-Diamino-2',3'-dideoxypurine-9-ribofuranoside (ddDAPR)(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; 2-Glycine amide-5-chlorophenyl 2-pyrryl ketone (GCPK); [2-PyridCH2NCH3CO-Val-NHCH(Bz)] CHOHCHOH (A-77003); 2'-Azido-2',3'-dideoxyadenosine (2'-N3ddA); 2'-F-dd-ara-A (Lodensine); 2'-FddT; 2'-N3ddA; 2'-N3ddA (3-D-threo); 2-NaphCOAsnPhe[CHOHCH2]Pro-OtBu; 2-Nitrophenylphenylsulfone (NPPS); 3-(3-Oxo-1-propenyl)-3'-azido-3'-deoxythymidine (3-(3-Oxo-1-propenyl)AZT); 3-(3-Oxo-1-propenyl)AZT; L-737,126; 3,5-Dicaffeoylquinic acid (3,5-DCQA); 3'-Azido-3'-deoxy-6-azathymidine; 3'-Azido-2',3'-dideoxy-5-[(cyanomethyl)oxy] uridine; 3'-Azido-2',3'-dideoxy-5-aminouridine; 3'-Azido-2',3'-dideoxy-5-aza-6-deazauridine; 3'-Azido-2',3'-dideoxy-5-bromouridine; 3'-Azido-2',3'-dideoxy-5-chlorocytidine (3'-Az-5-Cl-ddC); 3'-Azido-2',3'-dideoxy-5-dimethylaminouridine; 3'-Azido-2',3'-dideoxy-5-ethyluridine; 3'-Azido-2',3'-dideoxy-5-fluorocytidine; 3'-Azido-2',3'-dideoxy-5-fluorouridine; 3'-Azido-2',3'-dideoxy-5-hydroxyuridine; 3'-Azido-2',3'-dideoxy-5-iodouridine; 3'-Azido-2',3'-dideoxy-5-methyaminouridine; 3'-Azido-2',3'-dideoxy-5-methylcytidine; 3'-Azido-2',3'-dideoxy-5-thiocyanatouridine; 3'-Azido-2',3'-dideoxy-5-trifluoromethyluridine; 3'-Azido-2',3'-dideoxycytidine; 3'-Azido-2',3'-dideoxyguanosine; 3'-Azido-2',3'-dideoxy-N4-5-dimethylcytidine; 3'-Azido-2',3'-dideoxy-N4-OH-5-methylcytidine; 3'-Azido-2',3'-dideoxyuridine (Uravidine); 3'-Azido-3'-deoxy-6-azathymidine; 3-Azido-3'-deoxythymidilyl-(5',5')-2',3'-dideoxy-5'-adenylic acid; 3'-Azido-3'-deoxythymidilyl-(5',5')-2',3'-dideoxy-5'-adenylic acid, 2-cyanoethyl ester; 3'-Azido-3'-deoxythymidilyl-(5',5')-2',3'-dideoxy-5'-inosinic acid (AZT-P-ddI); 3'-Azido-3'-deoxythymidine-5'-(butylmethoxyvalinyl)phosphate; 3'-Azido-5-chloro-2',3'-dideoxyuridine; 3'-Deoxythymidine (ddT); 9-(3'-Fluoro-2',

3'-dideoxy-β-D-erythropentafuranosyl)adenine; 3'-Fluoro-2',3'-dideoxy-5-iodouridine (FddIU); 3'-Fluoro-2',3'-dideoxycytidine (3'-FddC); 3'-Fluoro-2',3'-dideoxyguanosine (3'-FddG); 3'-Fluoro-2',3'-dideoxyuridine (3'-FddU); 9-(3'-Azido-2',3'-dideoxy-β-D-erythropentafuranosyl)adenine; 3TC (Lamivudine); 3TC & AZT (Combivir); 4'-Acetoamidophenyl4-guadinobenzoate; 4'-Azido-3'-deoxythymidine; 4'-Azido-5-chloro-2'-deoxyuridine; 4'-Azido-2'-deoxyadenosine; 4'-Azido-2'-deoxycytidine; 4'-Azido-2'-deoxyguanosine; 4'-Azido-2'-deoxyinosine; 4'-Azido-2'-deoxyuridine; 4'-Azidothymidine; 4'-Cyanothymidine; 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); 5'-[[(Z)-4-amino-2-butenyl]methylamino]-5'-deoxyadenosine (MDL 73811); 5'-Alkylglycosidecarbonate of 3'-azido-3'-deoxythymidine; 5Cl3PhS-2IndolCONH2; 5-Fluoro-2',3'-dideoxycytidine; 5-Methyl-3'-azido-2',3'-dideoxyisocytidine; Celgosivir; 6-Chloro-9-(2,3-dideoxy-β-D-glyceropentofuranosyl)-9H-purine; 6-Dimethylaminopurine-2',3'-dideoxyriboside; Ro 24-7429; Ro 5-3335; Tivirapine; 9-(2,3-Dideoxy-β-D-ribofuranosyl)-6-(methylthio)purine; 9-(2'-Azido-2',3'-dideoxy-B-D-threopentafuranosyl)adenine; C-oxetanocin A; (+−) Lobucavir; A-76890; A-77003; A-77212; A-80987; A-81525; A-83962; A-98881; PNU-104489; Trizivir; Lopinavir; Kaletra; Lopinavir & Ritonavir; Aluviran®& Norvir; Azodicarbonamide; Adefovir; Adefovir dipivoxil (Preveon®); Nelfinavir; AG1350 (LY316957); R-87366; Alpha-lipoic acid; Alovudine (3'-FddT); ALX40-4C; AMD3100 (JM3100); Amdoxovir (APD); Amprenavir phosphate (Fosamprenavir); Ancer 20 (Z-100); Atazanavir (Latazanavir); Atevirdine; Aurintricarboxylic acid; AY 9944; 3'-Azido-5-chloro-2',3'-dideoxyuridine; AZT; α-L-AZT; O,O'-Bis(3'-azido-3'-deoxythymidin-5'-yl)methylphosphonate; Baicalin (TJN-151); Betulinic acid (Mairin); Betulinic acid, 3-O-(3',3'-dimethylsuccinate); Delavirdine (U-90152); U-88204E; Nevirapine; BILA 1906 BS; BILA 2011 BS (Palinavir); BILA 2185 BS; NSC633001; CGP 53820; bis-ValHOEt-N2aza-peptide isostere (CGP 53820 analog); BMS-186318; L-687,908; Brovavir; BzOCValPhe[diCHOH(RR)]PheValBzOC; BzOCValPhe[diCHOH(SS)]PheValBzOC; C2-Sym Phosphinic amide deriv. (HOECHST AG); NSC675451; Calanolide B; Capravirine (S-1153); Carbovir; Castanospermine; CGP 61755 (Lasinavir); CGP 64222; CNI-H0294; Emivirine; Conocurvone (NSC650891); Emtricitabine; C-Oxetanocin-G; Indinavir; Curdlan Sulfate; Cyanovirin-N; SD146; Cyclosporin A; SDZ NIM 811; L-2',3'-Didehydro-2',3'-dideoxyadenosine (L-D4A); 2',3'-Didehydro-2',3'-dideoxy-5-fluorocytidine (DD4C); L-2',3'-Didehydro-2',3'-dideoxy-5-fluorocytidine (LD4C); L-2',3'-Didehydro-2',3'-dideoxyguanosine (LD4G); L-2',3'-Didehydro-2',3'-dideoxyinosine (LD4I); DABO; ddI; ddC; DMP-323; DMP-450; (−)-2'-Deoxy-3'-oxa-4'-thiocytidine; (−)-2'-Deoxy-3'-oxa-4'-thio-5-fluorocytidine; Pentafuside (Enfuvirtide); Etoposide; Efavirenz; Emtriva; K-12 (fluoroquinoline derivative); Saquinavir; Foscarnet; Phosphonoformic acid; Foscavir; FPMDAP; FPMPA; FPMPG; Gene Expression Modulator 91 (GEM91); Hammerhead anti-gag RNA Ribozyme B; Harziphilone; HBY 097 (Quinoxaline deriv); E-EBU; E-EP-SeU; E-EPU; NSC 648400; E-EBU-dM; Zalcitabine; LY326188; ingenol 3,5,20-triacetate (ITA); Inophyllum B; KNI-272; RD3-2118; KNI-102; KNI-154; KNI-174; KNI-227; L-685,434; L-689,502; L-697,593; L-697,639; L-697,661; LY289612; Trovirdine; LY-73497; L-735,524; N-Ethyl-2',3'-dideoxyadenosine; N6-Methyl-2',3'-dideoxyadenosine; Noa-Asn-Apns-Thz-NH-tBu; Nonoxynol 9; Ritonavir; NSC625487; NSC649324; NSC650898; UC-38; UC-84; P9941; Palinavir; Pentosan Sulfate; Elmiron; SP54; PNU-140690 (Tipranavir); S-2720; R14458; R82150; R82913; R86183; RD4-2138; Resobene; Reyataz; Ribavirin; 7-Chloro-N-methyl-5-(1H-pyrrol-2-yl)-3H-1,4-benzodiazepin-2-amine; 7-Chloro-5-(2-pyrryl)-3H-1,4-benzodiazepin-2(H)-one; LY314163; SB-205569; Telinavir; SD-095345SD146; SDZ PR1 053; SPC3; Suram in Sodium; T22; Thalidomide; Thiangazole; Thiazoloisoindol-5-one; U-104489; U-140690; U-87201E; U-88204E; UC-781; VB-11,328; VX-478; 141W94; XM-323 and mixtures thereof.

37. The composition according to claim **16** further comprising an 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; 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; Tenofovir disoproxil fumarate; Emtriva; 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; Interferon alfa-2; Interleukin-2, recombinant human; Intron A (2b); Invirase; Isoniazid; Itraconazole; KP-1461; Lamivudine/Zidovudine; Lexiva; Lopinavir/Ritonavir; MK-0518; Nebupent; Nelfinavir; Neutrexin; Nevirapine; Norvir; Nydrazid; Peptide T; PMPA Prodrug (Viread)' Prezista (Darunavir); PRO140; PRO2000; PRO542 (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; Vicriviroc; Videx; Viracept (Tennofovir DF); Viramune; Virazole; Viread; Vitrasert; Zalcitabine; Zerit; Ziagen; Zidovudine; Zithromax; Zovirax and mixtures thereof.

38. The composition according to claim **34** wherein said composition treats said HIV infection by inhibiting at least HIV integrase, both wild type and mutants, in the human host.

39. The composition according to claim **34** in oral or parenteral dosage form.

40. The composition according to claim **34** formulated for administration as an inhalation spray or a rectal suppository.

41. 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 **34** to said patient.

42. A method of reducing the likelihood of an HIV infection in a patient at risk said infection, said method comprising administering to said patient an effective amount of a composition according to claim **34** to said patient.

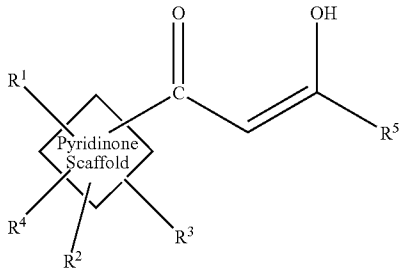
43. A method of treating a patient with AIDS or ARC comprising administering to said patient a therapeutically effective amount of a composition according to claim **34**.

44. 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 **34**.

45. The method according to claim **41** wherein said subject is a human.

46-50. (canceled)

51. 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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wherein the scaffold is independently the 2- and 4-pyridinones identified herein and their regioisomers;

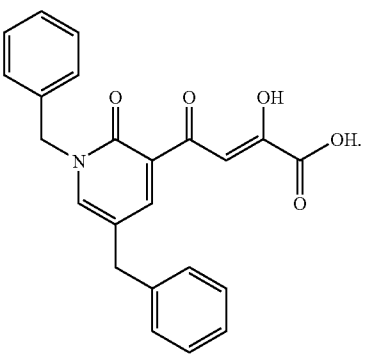
R^1 and R^2 are each independently H, C_{1-6} alkyl, C_{1-6} fluoroalkyl, unsubstituted or substituted C_{5-6} cycloalkyl, C_{1-6} alkenyl, unsubstituted or substituted phenyl, unsubstituted or substituted benzyl, C_{2-6} alkyl phenyl which phenyl moiety may be optionally substituted, unsubstituted or substituted heteroaryl, C_{1-6} alkyl substituted with a heteroaryl group which heteroaryl group is optionally substituted, C_{1-6} alkyl S(O)R or alkyl $(SO_2)R$ where R is alkyl, phenyl or substituted phenyl, C_{1-6} alkyl CO_2R^a where R^a is C_{1-6} alkyl or H, C_{1-6} alkyl $COR^{a'}$ where $R^{a'}$ is C_{1-6} alkyl;

R^3 and R^4 are independently selected from H, C_{1-6} alkyl, halogen, hydroxyl, unsubstituted or substituted benzyl, or unsubstituted or substituted phenylthio;

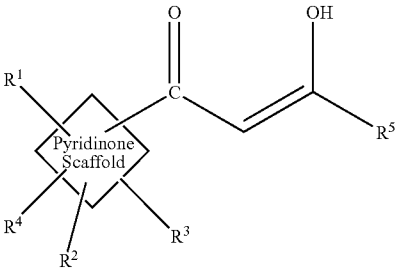
R^5 is CO_2R^c or $P(O)(OR^c)(OR^c)$, where each R^c is independently from H and C_{1-6} alkyl, and pharmaceutically acceptable salts thereof, in combination with at least one additional compound selected from the group consisting of (−)β-Dioxolane-G (DXG); Arctigenin (Arctigenin); (−)-Carbovir (−)-C-D4G; (−)-2',3'-Dideoxy-5-fluoro-3'-thiacytidine (FTC); (−)-β-D-2,6-Diaminopurine dioxolane (DAPD); (+)-2'-Deoxy-3'-oxa-4'-thiocytidine (dOTC+); (+)-2'-Deoxy-3'-oxa-4'-thio-5-fluorocytidine (dOTFC+); (+/−)-Lobucavir; (R)-2QuinCOAsnPhe [CHOHCH2]PipCONHtBu; (R)-3,6-Diamino-N-(aminomethyl)hexanamide (Bellenamine); (R)-9-(2-Phosphonylmethoxypropyl)adenine (Tenofovir); (R)-PMPDAP; (S)-9-(2-Phosphonylmethoxypropyl) adenine ((S)-PMPA); PMPA(S); α-APA (Loviride); R87232; R88703; α-APA enantiomer (R90385); α-L-AZT; α-L-Dioxalane-C (α-L-DXC); α-L-FTC; α-Monofluoromethyldehydroornithine methyl ester (MFMOME); 1,1'-Azobisformamide (ADA); 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-β-D-erythro-pentofuranosyl)thymine (2'FddT); 1-[(2-Hydroxyethoxy)methyl]-6-(3-methylphenyl)thio)thymine (HEPT-M); 1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)-2-thiothymine (HEPT-S); 1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio) thymine (HEPT); Deoxynojirimycin (1-Deoxynojirimycin); Amprenavir; Abacavir Succinate(Ziagen); 1-Aminooxyethylamine (AEA); 1-Methoxyoxalyl-3,5-dicaffeoylquinic acid (1-MO-3,5-DCQA); 1OH-2(Cbz-Tle)$_3$PhPr [14]paracyclophane deriv; 1OH-2(Cbz-ValNH)3PhPr [13]metacyclophane deriv.; 1OH-2(Cbz-ValNH)$_3$PhPr [13]paracyclophane deriv.; 1OH-2(Cbz-ValNH)$_3$PhPr [14]paracyclophane deriv.; 1OH-2(Cbz-ValNH)3PhPr [17]paracyclophane deriv.; 12-Deoxyphorbol-13-(3E,5E-decadienoate); 16.alpha.-Bromoepiandrosterone (Epi-Br) or (Inactivin); 1-β-D-arabinofuranosyl-5-(2-bromovinyl)uracil (Sorivudine); 2',3'-Didehydro-3'-deoxycytidine (D4C); 2',3'-Dideoxydidehydroguanosine (D4G); 2',3'-Didehydro-3'-deoxythymidine (D4T) (Stavudine); 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) (Raluridine); 2',3'-Dideoxy-5-ethylcytidine (5-Et-ddC); 2',3'-Dideoxyadenosine (ddA); 2',3'-Dideoxydidehydroadenosine (d4A); 2',3'-Dideoxyguanosine (ddG); 2',3'-Dideoxy-3'-hydroxymethyl cytidine (3'-Hydroxymethyl-ddC); 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-me^3T); 2,6-Diamino-2',3'-dideoxypurine-9-ribofuranoside (ddDAPR)(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; 2-Glycine amide-5-chlorophenyl 2-pyrryl ketone (GCPK); [2-PyridCH2NCH3CO-Val-NHCH(Bz)] CHOHCHOH (A-77003); 2'-Azido-2',3'-dideoxyadenosine (2'-N3ddA); 2'-F-dd-ara-A (Lodensine); 2'-FddT; 2'-N3ddA; 2'-N3ddA ((3-D-threo); 2-NaphCOAsnPhe[CHOHCH2]Pro-OtBu; 2-Nitrophenylphenylsulfone (NPPS); 3-(3-Oxo-1-propenyl)-3'-azido-3'-deoxythymidine (3-(3-Oxo-1-propenyl)AZT); 3-(3-Oxo-1-propenyl)AZT; L-737,126; 3,5-Dicaffeoylquinic acid (3,5-DCQA); 3'-Azido-3'-deoxy-6-azathymidine; 3'-Azido-2',3'-dideoxy-5-[(cyanomethyl)oxy]uridine; 3'-Azido-2',3'-dideoxy-5-aminouridine; 3'-Azido-2',3'-dideoxy-5-aza-6-deazauridine; 3'-Azido-2',3'-dideoxy-5-bromouridine; 3'-Azido-2',3'-dideoxy-5-chlorocytidine (3'-Az-5-Cl-ddC); 3'-Azido-2',3'-dideoxy-5-dimethylaminouridine;

3'-Azido-2',3'-dideoxy-5-ethyluridine; 3'-Azido-2',3'-dideoxy-5-fluorocytidine; 3'-Azido-2',3'-dideoxy-5-fluorouridine; 3'-Azido-2',3'-dideoxy-5-hydroxyuridine; 3'-Azido-2',3'-dideoxy-5-iodouridine; 3'-Azido-2',3'-dideoxy-5-methyaminouridine; 3'-Azido-2',3'-dideoxy-5-methylcytidine; 3'-Azido-2',3'-dideoxy-5-thiocyanatouridine; 3'-Azido-2',3'-dideoxy-5-trifluoromethyluridine; 3'-Azido-2',3'-dideoxycytidine; 3'-Azido-2',3'-dideoxyguanosine; 3'-Azido-2',3'-dideoxy-N4-5-dimethylcytidine; 3'-Azido-2',3'-dideoxy-N4-OH-5-methylcytidine; 3'-Azido-2',3'-dideoxyuridine (Uravidine); 3'-Azido-3'-deoxy-6-azathymidine; 3-Azido-3'-deoxythymidilyl-(5',5')-2',3'-dideoxy-5'-adenylic acid; 3'-Azido-3'-deoxythymidilyl-(5',5')-2',3'-dideoxy-5'-adenylic acid, 2-cyanoethyl ester; 3'-Azido-3'-deoxythymidilyl-(5',5')-2',3'-dideoxy-5'-inosinic acid (AZT-P-ddI); 3'-Azido-3'-deoxythymidine-5'-(butylmethoxyvalinyl)phosphate; 3'-Azido-5-chloro-2',3'-dideoxyuridine; 3'-Deoxythymidine (ddT); 9-(3'-Fluoro-2',3'-dideoxy-β-D-erythropentafuranosyl)adenine; 3'-Fluoro-2',3'-dideoxy-5-iodouridine (FddIU); 3'-Fluoro-2',3'-dideoxycytidine (3'-FddC); 3'-Fluoro-2',3'-dideoxyguanosine (3'-FddG); 3'-Fluoro-2',3'-dideoxyuridine (3'-FddU); 9-(3'-Azido-2',3'-dideoxy-β-D-erythropentafuranosyl)adenine; 3TC (Lamivudine); 3TC & AZT (Combivir); 4'-Acetoamidophenyl4-guadinobenzoate; 4'-Azido-3'-deoxythymidine; 4'-Azido-5-chloro-2'-deoxyuridine; 4'-Azido-2'-deoxyadenosine; 4'-Azido-2'-deoxycytidine; 4'-Azido-2'-deoxyguanosine; 4'-Azido-2'-deoxyinosine; 4'-Azido-2'-deoxyuridine; 4'-Azidothymidine; 4'-Cyanothymidine; 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); 5'-[[(Z)-4-amino-2-butenyl]methylamino]-5'-deoxyadenosine (MDL 73811); 5'-Alkylglycosidecarbonate of 3'-azido-3'-deoxythymidine; 5Cl3PhS-2IndolCONH2; 5-Fluoro-2',3'-dideoxycytidine; 5-Methyl-3'-azido-2',3'-dideoxyisocytidine; Celgosivir; 6-Chloro-9-(2,3-dideoxy-β-D-glycero-pentofuranosyl)-9H-purine; 6-Dimethylaminopurine-2',3'-dideoxyriboside; Ro 24-7429; Ro 5-3335; Tivirapine; 9-(2,3-Dideoxy-13-D-ribofuranosyl)-6-(methylthio)purine; 9-(2'-Azido-2',3'-dideoxy-B-D-threopentafuranosyl)adenine; C-oxetanocin A; (+−) Lobucavir; A-76890; A-77003; A-77212; A-80987; A-81525; A-83962; A-98881; PNU-104489; Trizivir; Lopinavir; Kaletra; Lopinavir & Ritonavir; Aluviran®& Norvir; Azodicarbonamide; Adefovir; Adefovir dipivoxil (Preveon®); Nelfinavir; AG1350 (LY316957); R-87366; Alpha-lipoic acid; Alovudine (3'-FddT); ALX40-4C; AMD3100 (JM3100); Amdoxovir (APD); Amprenavir phosphate (Fosamprenavir); Ancer 20 (Z-100); Atazanavir (Latazanavir); Atevirdine; Aurintricarboxylic acid; AY 9944; 3'-Azido-5-chloro-2',3'-dideoxyuridine; AZT; α-L-AZT; O,O'-Bis(3'-azido-3'-deoxythymidin-5'-yl)methylphosphonate; Baicalin (TJN-151); Betulinic acid (Mairin); Betulinic acid, 3-O-(3',3'-dimethylsuccinate); Delavirdine (U-90152); U-88204E; Nevirapine; BILA 1906 BS; BILA 2011 BS (Palinavir); BILA 2185 BS; NSC633001; CGP 53820; bis-ValHOEt-N2aza-peptide isostere (CGP 53820 analog); BMS-186318; L-687,908; Brovavir; BzOCValPhe [diCHOH(RR)]PheValBzOC; BzOCValPhe[diCHOH (SS)]PheValBzOC; C2-Sym Phosphinic amide deriv. (HOECHST AG); NSC675451; Calanolide B; Capravirine (S-1153); Carbovir; Castanospermine; CGP 61755 (Lasinavir); CGP 64222; CNI-H0294; Emivirine; Conocurvone (NSC650891); Emtricitabine; C-Oxetanocin-G; Indinavir; Curdlan Sulfate; Cyanovirin-N; SD146; Cyclosporin A; SDZ NIM 811; L-2',3'-Didehydro-2',3'-dideoxyadenosine (L-D4A); 2',3'-Didehydro-2',3'-dideoxy-5-fluorocytidine (DD4C); L-2',3'-Didehydro-2',3'-dideoxy-5-fluorocytidine (LD4C); L-2',3'-Didehydro-2',3'-dideoxyguanosine (LD4G); L-2',3'-Didehydro-2',3'-dideoxyinosine (LD4I); DABO; ddI; ddC; DMP-323; DMP-450; (−)-2'-Deoxy-3'-oxa-4'-thiocytidine; (+2'-Deoxy-3'-oxa-4'-thio-5-fluorocytidine; Pentafuside (Enfuvirtide); Etoposide; Efavirenz; Emtriva; K-12 (fluoroquinoline derivative); Saquinavir; Foscarnet; Phosphonoformic acid; Foscavir; FPMDAP; FPMPA; FPMPG; Gene Expression Modulator 91 (GEM91); Hammerhead anti-gag RNA Ribozyme B; Harziphilone; HBY 097 (Quinoxaline deriv); E-EBU; E-EPSeU; E-EPU; NSC 648400; E-EBU-dM; Zalcitabine; LY326188; Ingenol 3,5,20-triacetate (ITA); Inophyllum B; KNI-272; RD3-2118; KNI-102; KNI-154; KNI-174; KNI-227; L-685,434; L-689,502; L-697,593; L-697,639; L-697,661; LY289612; Trovirdine; LY-73497; L-735,524; N-Ethyl-2',3'-dideoxyadenosine; N6-Methyl-2',3'-dideoxyadenosine; Noa-Asn-Apns-Thz-NH-tBu; Nonoxynol 9; Ritonavir; NSC625487; NSC649324; NSC650898; UC-38; UC-84; P9941; Palinavir; Pentosan Sulfate; Elmiron; SP54; PNU-140690 (Tipranavir); S-2720; R14458; R82150; R82913; R86183; RD4-2138; Resobene; Reyataz; Ribavirin; 7-Chloro-N-methyl-5-(1H-pyrrol-2-yl)-3H-1,4-benzodiazepin-2-amine; 7-Chloro-5-(2-pyrryl)-3H-1,4-benzodiazepin-2(H)-one; LY314163; SB-205569; Telinavir; SD-095345SD146; SDZ PR1 053; SPC3; Suram in Sodium; T22; Thalidomide; Thiangazole; Thiazoloisoindol-5-one; U-104489; U-140690; U-87201E; U-88204E; UC-781; VB-11,328; VX-478; 141W94; XM-323 and mixtures thereof, further in combination with a pharmaceutically acceptable carrier, additive or excipient.

52. The method according to claim **51** wherein said first compound is



53. 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:



I

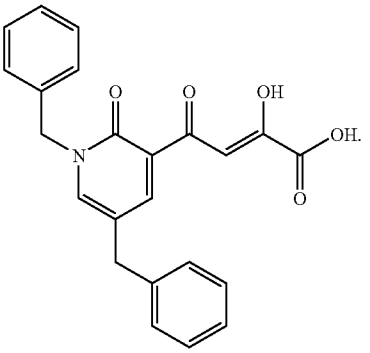
wherein the scaffold is independently the 2- and 4-pyridinones identified herein and their regioisomers;

R^1 and R^2 are each independently H, C_{1-6} alkyl, C_{1-6} fluoroalkyl, unsubstituted or substituted C_{5-6} cycloalkyl, C_{1-6} alkenyl, unsubstituted or substituted phenyl, unsubstituted or substituted benzyl, C_{2-6} alkyl phenyl which phenyl moiety may be optionally substituted, unsubstituted or substituted heteroaryl, C_{1-6} alkyl substituted with a heteroaryl group which heteroaryl group is optionally substituted, C_{1-6} alkyl S(O)R or alkyl $(SO_2)R$ where R is alkyl, phenyl or substituted phenyl, C_{1-6} alkyl CO_2R^a where R^a is C_{1-6} alkyl or H, C_{1-6} alkyl $COR^{a'}$ where $R^{a'}$ is C_{1-6} alkyl;

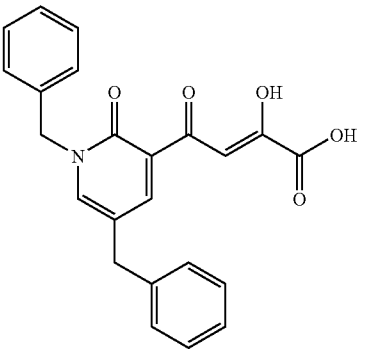
R^3 and R^4 are independently selected from H, C_{1-6} alkyl, halogen, hydroxyl, unsubstituted or substituted benzyl, or unsubstituted or substituted phenylthio;

R^5 is CO_2R^c or $P(O)(OR^c)(OR^c)$, where each R^c is independently from H and C_{1-6} alkyl, 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 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-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; Tenofovir disoproxil fumarate; Emtriva; 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; Interferon alfa-2; Interleukin-2, recombinant human; Intron A (2b); Invirase; Isoniazid; Itraconazole; KP-1461; Lamivudine/Zidovudine; Lexiva; Lopinavir/Ritonavir; MK-0518; Nebupent; Nelfinavir; Neutrexin; Nevirapine; Norvir; Nydrazid; Peptide T; PMPA Prodrug (Viread)' Prezista (Darunavir); PRO140; PRO2000; PRO542 (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; Vicriviroc; Videx; Viracept (Tennofovir 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.

54. The method according to claim **53** wherein said first compound is



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

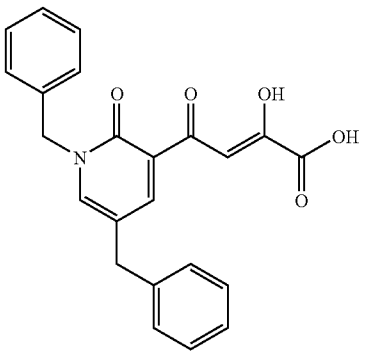


in combination with an effective of at least one additional compound selected from the group (−)β-Dioxolane-G (DXG); (−)β-Arctigenin (Arctigenin); (−)-Carbovir (−)-C-D4G; (−)-2',3'-Dideoxy-5-fluoro-3'-thiacytidine (FTC); (−)-β-D-2,6-Diaminopurine dioxolane (DAPD); (+)-2'-Deoxy-3'-oxa-4'-thiocytidine (dOTC+); (+)-2'-Deoxy-3'-oxa-4'-thio-5-fluorocytidine (dOTFC+); (+/−)-Lobucavir; (R)-

2QuinCOAsnPhe[CHOHCH2]PipCONHtBu; (R)-3,6-Diamino-N-(aminomethyl)hexanamide (Bellenamine); (R)-9-(2-Phosphonylmethoxypropyl)adenine (Tenofovir); (R)-PMPDAP; (S)-9-(2-Phosphonylmethoxypropyl)adenine ((S)-PMPA); PMPA(S); α-APA (Loviride); R87232; R88703; α-APA enantiomer (R90385); α-L-AZT; α-L-Dioxalane-C (α-L-DXC); α-L-FTC; α-Monofluoromethyldehydroornithine methyl ester (MFMOME); 1,1'-Azobisformamide (ADA); 1-(11-Octylamino-10-hydroxyundecyl)-3,7-dimethylxanthine (CT-2576); 1-(2',3'-Dideoxy-2'-fluoro-(3-D-threo-pentofuranosyl)cytosine (Ro 31-6840); 1-(2'-Fluoro-2',3'-dideoxy-(3-D-erythro-pentofuranosyl)thymine (2'FddT); 1-[(2-Hydroxyethoxy)methyl]-6-(3-methylphenyl)thio)thymine (HEPT-M); 1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)-2-thiothymine (HEPT-S); 1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT); Deoxynojirimycin (1-Deoxynojirimycin); Amprenavir; Abacavir Succinate(Ziagen); 1-Aminooxyethylamine (AEA); 1-Methoxyoxalyl-3,5-dicaffeoylquinic acid (1-MO-3,5-DCQA); 1OH-2(Cbz-Tle)$_3$PhPr [14]paracyclophane deriv; 1OH-2(Cbz-ValNH)$_3$PhPr [13]metacyclophane deriv.; 1OH-2(Cbz-ValNH)$_3$PhPr [13]paracyclophane deriv.; 1OH-2 (Cbz-ValNH)$_3$PhPr [14]paracyclophane deriv.; 1OH-2(Cbz-ValNH)$_3$PhPr [17]paracyclophane deriv.; 12-Deoxyphorbol-13-(3E,5E-decadienoate); 16.alpha.-Bromoepiandrosterone (Epi-Br) or (Inactivin); 1-β-D-arabinofuranosyl-5-(2-bromovinyl)uracil (Sorivudine); 2',3'-Didehydro-3'-deoxycytidine (D4C); 2',3'-Dideoxydidehydroguanosine (D4G); 2',3'-Didehydro-3'-deoxythymidine (D4T) (Stavudine); 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) (Raluridine); 2',3'-Dideoxy-5-ethylcytidine (5-Et-ddC); 2',3'-Dideoxyadenosine (ddA); 2',3'-Dideoxydidehydroadenosine (d4A); 2',3'-Dideoxyguanosine (ddG); 2',3'-Dideoxy-3'-hydroxymethyl cytidine (3'-Hydroxymethyl-ddC); 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-meˆ3T); 2,6-Diamino-2',3'-dideoxypurine-9-ribofuranoside (ddDAPR)(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; 2-Glycine amide-5-chlorophenyl 2-pyrryl ketone (GCPK); [2-PyridCH2NCH3CO-Val-NHCH(Bz)]CHOHCHOH (A-77003); 2'-Azido-2',3'-dideoxyadenosine (2'-N3ddA); 2'-F-dd-ara-A (Lodensine); 2'-FddT; 2'-N3ddA; 2'-N3ddA ((3-D-threo), 2-NaphCOAsnPhe[CHOHCH2]Pro-OtBu; 2-Nitrophenylphenylsulfone (NPPS); 3-(3-Oxo-1-propenyl)-3'-azido-3'-deoxythymidine (3-(3-Oxo-1-propenyl) AZT); 3-(3-Oxo-1-propenyl)AZT; L-737,126; 3,5-Dicaffeoylquinic acid (3,5-DCQA); 3'-Azido-3'-deoxy-6-azathymidine; 3'-Azido-2',3'-dideoxy-5-[(cyanomethyl)oxy] uridine; 3'-Azido-2',3'-dideoxy-5-aminouridine; 3'-Azido-2',3'-dideoxy-5-aza-6-deazauridine; 3'-Azido-2',3'-dideoxy-5-bromouridine; 3'-Azido-2',3'-dideoxy-5-chlorocytidine (3'-Az-5-Cl-ddC); 3'-Azido-2',3'-dideoxy-5-dimethylaminouridine; 3'-Azido-2',3'-dideoxy-5-ethyluridine; 3'-Azido-2',3'-dideoxy-5-fluorocytidine; 3'-Azido-2',3'-dideoxy-5-fluorouridine; 3'-Azido-2',3'-dideoxy-5-hydroxyuridine; 3'-Azido-2',3'-dideoxy-5-iodouridine; 3'-Azido-2',3'-dideoxy-5-methyaminouridine; 3'-Azido-2',3'-dideoxy-5-methylcytidine; 3'-Azido-2',3'-dideoxy-5-thiocyanatouridine; 3'-Azido-2',3'-dideoxy-5-trifluoromethyluridine; 3'-Azido-2',3'-dideoxycytidine; 3'-Azido-2',3'-dideoxyguanosine; 3'-Azido-2',3'-dideoxy-N4-5-dimethylcytidine; 3'-Azido-2',3'-dideoxy-N4-OH-5-methylcytidine; 3'-Azido-2',3'-dideoxyuridine (Uravidine); 3'-Azido-3'-deoxy-6-azathymidine; 3-Azido-3'-deoxythymidilyl-(5',5)-2',3'-dideoxy-5'-adenylic acid; 3'-Azido-3'-deoxythymidilyl-(5',5')-2',3'-dideoxy-5'-adenylic acid, 2-cyanoethyl ester; 3'-Azido-3'-deoxythymidilyl-(5',5')-2',3'-dideoxy-5'-inosinic acid (AZT-P-ddI); 3'-Azido-3'-deoxythymidine-5'-(butylmethoxyvalinyl)phosphate; 3'-Azido-5-chloro-2',3'-dideoxyuridine; 3'-Deoxythymidine (ddT); 9-(3'-Fluoro-2',3'-dideoxy-β-D-erythropentafuranosyl)adenine; 3'-Fluoro-2',3'-dideoxy-5-iodouridine (FddIU); 3'-Fluoro-2',3'-dideoxycytidine (3'-FddC); 3'-Fluoro-2',3'-dideoxyguanosine (3'-FddG); 3'-Fluoro-2',3'-dideoxyuridine (3'-FddU); 9-(3'-Azido-2',3'-dideoxy-13-D-erythropentafuranosyl)adenine; 3TC (Lamivudine); 3TC & AZT (Combivir); 4'-Acetoamidophenyl4-guadinobenzoate; 4'-Azido-3'-deoxythymidine; 4'-Azido-5-chloro-2'-deoxyuridine; 4'-Azido-2'-deoxyadenosine; 4'-Azido-2'-deoxycytidine; 4'-Azido-2'-deoxyguanosine; 4'-Azido-2'-deoxyinosine; 4'-Azido-2'-deoxyuridine; 4'-Azidothymidine; 4'-Cyanothymidine; 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); 5'-[[(Z)-4-amino-2-butenyl]methylamino]-5'-deoxyadenosine (MDL 73811); 5'-Alkylglycosidecarbonate of 3'-azido-3'-deoxythymidine; 5Cl3PhS-2IndolCONH2; 5-Fluoro-2',3'-dideoxycytidine; 5-Methyl-3'-azido-2',3'-dideoxyisocytidine; Celgosivir; 6-Chloro-9-(2,3-dideoxy-β-D-glyceropentofuranosyl)-9H-purine;
6-Dimethylaminopurine-2',3'-dideoxyriboside; Ro 24-7429; Ro 5-3335; Tivirapine; 9-(2,3-Dideoxy-β-D-ribofuranosyl)-6-(methylthio)purine; 9-(2'-Azido-2',3'-dideoxy-B-D-threo-pentofuranosyl)adenine; C-oxetanocin A; (+−)Lobucavir; A-76890; A-77003; A-77212; A-80987; A-81525; A-83962; A-98881; PNU-104489; Trizivir; Lopinavir; Kaletra; Lopinavir & Ritonavir; Aluviran®& Norvir; Azodicarbonamide; Adefovir; Adefovir dipivoxil (Preveon®); Nelfinavir; AG1350 (LY316957); R-87366; Alpha-lipoic acid; Alovudine (3'-FddT); ALX40-4C; AMD3100 (JM3100); Amdoxovir (APD); Amprenavir phosphate (Fosamprenavir); Ancer 20 (Z-100); Atazanavir (Latazanavir); Atevirdine; Aurintricarboxylic acid; AY 9944; 3'-Azido-5-chloro-2',3'-dideoxyuridine; AZT; α-L-AZT; O,O'-Bis(3'-azido-3'-deoxythymidin-5'-yl)methylphosphonate; Baicalin (TJN-151); Betulinic acid (Mairin); Betulinic acid, 3-O-(3',3'-dimethylsuccinate); Delavirdine (U-90152); U-88204E; Nevirapine; BILA 1906 BS; BILA 2011 BS (Palinavir); BILA 2185 BS; NSC633001; CGP 53820; bis-ValHOEt-N2aza-peptide isostere (CGP 53820 analog); BMS-186318; L-687,908; Brovavir; BzOCValPhe[diCHOH(RR)]PheValBzOC; BzOCValPhe [diCHOH(SS)]PheValBzOC; C2-Sym Phosphinic amide deriv. (HOECHST AG); NSC675451; Calanolide B; Capravirine (S-1153); Carbovir; Castanospermine; CGP 61755 (Lasinavir); CGP 64222; CNI-H0294; Emivirine; Conocurvone (NSC650891); Emtricitabine; C-Oxetanocin-G; Indinavir; Curdlan Sulfate; Cyanovirin-N; SD146; Cyclosporin A; SDZ NIM 811; L-2',3'-Didehydro-2',3'-dideoxyadenosine (L-D4A); 2',3'-Didehydro-2',3'-dideoxy-5-fluorocytidine (DD4C); L-2',3'-Didehydro-2',3'-dideoxy-5-fluorocytidine (LD4C); L-2',3'-Didehydro-2',3'-dideoxyguanosine (LD4G); L-2',3'-Didehydro-2',3'-dideoxyinosine (LD4I); DABO; ddI; ddC; DMP-323; DMP-450; (−)-2'-Deoxy-3'-oxa-4'-thiocytidine; (−)-2'-Deoxy-3'-oxa-4'-thio-5-fluorocytidine; Pentafuside (Enfuvirtide); Etoposide; Efavirenz; Emtriva; K-12 (fluoroquinoline derivative); Saquinavir; Foscarnet; Phosphonoformic acid; Foscavir; FPMDAP; FPMPA; FPMPG; Gene Expression Modulator 91 (GEM91); Hammerhead anti-gag RNA Ribozyme B; Harziphilone; HBY 097 (Quinoxaline deriv); E-EBU; E-EP-SeU; E-EPU; NSC 648400; E-EBU-dM; Zalcitabine; LY326188; Ingenol 3,5,20-triacetate (ITA); Inophyllum B; KNI-272; RD3-2118; KNI-102; KNI-154; KNI-174; KNI-

227; L-685,434; L-689,502; L-697,593; L-697,639; L-697,661; LY289612; Trovirdine; LY-73497; L-735,524; N-Ethyl-2',3'-dideoxyadenosine; N6-Methyl-2',3'-dideoxyadenosine; Noa-Asn-Apns-Thz-NH-tBu; Nonoxynol 9; Ritonavir; NSC625487; NSC649324; NSC650898; UC-38; UC-84; P9941; Palinavir; Pentosan Sulfate; Elmiron; SP54; PNU-140690 (Tipranavir); S-2720; R14458; R82150; 882913; R86183; RD4-2138; Resobene; Reyataz; Ribavirin; 7-Chloro-N-methyl-5-(1H-pyrrol-2-yl)-3H-1,4-benzodiazepin-2-amine; 7-Chloro-5-(2-pyrryl)-3H-1,4-benzodiazepin-2(H)-one; LY314163; SB-205569; Telinavir; SD-095345SD146; SDZ PR1 053; SPC3; Suramin Sodium; T22; Thalidomide; Thiangazole; Thiazoloisoindol-5-one; U-104489; U-140690; U-87201E; U-88204E; UC-781; VB-11,328; VX-478; 141W94; XM-323 and mixtures thereof, further in combination with a pharmaceutically acceptable carrier, additive or excipient.

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



in combination with an effective of at least one additional compound selected from the group 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; 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; Tenofovir disoproxil fumarate; Emtriva; 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; Interferon alfa-2; Interleukin-2, recombinant human; Intron A (2b); Invirase; Isoniazid; Itraconazole; KP-1461; Lamivudine/Zidovudine; Lexiva; Lopinavir/Ritonavir; MK-0518; Nebupent; Nelfinavir; Neutrexin; Nevirapine; Norvir; Nydrazid; Peptide T; PMPA Prodrug (Viread)' Prezista (Darunavir); PRO140; PRO2000; PRO542 (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; Vicriviroc; Videx; Viracept (Tennofovir 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.

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