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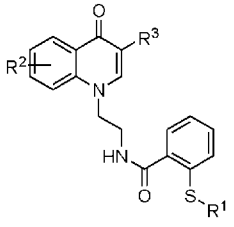
(54) Title: COMPOUNDS AND METHOD FOR TREATING HIV INFECTION

FORMULA (I)



(57) Abstract: Disclosed is a compound of formula (I) or salt thereof: Formula (I) for treating or preventing a human immunodeficiency virus (HIV) infection in a mammal, for inhibiting or preventing maturation of an immature human immunodeficiency virus (HIV) to a mature HIV, and for preventing or inhibiting a human immunodeficiency virus (HIV) infection in a mammal having at least one HIV viral particle on a surface thereof.

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COMPOUNDS AND METHOD FOR TREATING HIV INFECTION

CROSS REFERENCE TO A RELATED APPLICATION

[0001] This application claims the benefit of United States Provisional Patent Application No. 63/437,868 filed January 9, 2023, the disclosure of which is incorporated by reference.

BACKGROUND OF THE INVENTION

[0002] HIV-1 (human immunodeficiency virus-1) infection remains a major medical problem, with approximately 38 million people worldwide living with HIV-1. HIV-1 is a lentivirus which can lead to acquired immunodeficiency syndrome (AIDS). AIDS in humans results in a gradual and persistent decline and failure of the immune system, resulting in heightened risk of life-threatening infection and cancers.

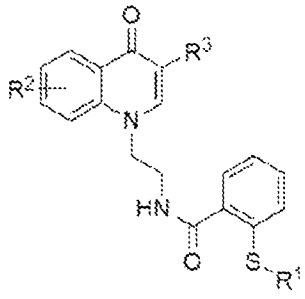
[0003] Currently available drugs for the treatment of HIV infection include a wide variety of agents, with the most common agents including those classified as entry inhibitors, reverse transcriptase inhibitors, integrase inhibitors, and protease inhibitors. Each of these classes of antiviral agents target different pathways of the HIV-1 replication cycle. Typically, combinations of two or more agents selected from different classes of these antiviral agents are administered to patients clinically.

[0004] A key step in the induction of HIV-1 infection is the maturation of HIV-1 from an immature stage to a mature stage. Agents that selectively target the maturation phase of the infection cycle are rare. A key step in HIV-1 maturation requires the dimerization of Gag-pol, which appears to be a necessary step prior to activation of protease from Gag-pol. Protease inhibitors inhibit protease after activation. Blocking dimerization of Gag-pol would prevent activation of protease and thus the HIV-1 virus would remain blocked in an immature state. However, there are few, if any, antiviral agents that block maturation of immature HIV-1 virus.

[0005] Thus, there remains in the art an unmet need for novel agents for the treatment of HIV-1 infection.

BRIEF SUMMARY OF THE INVENTION

[0006] The invention provides a compound of formula (I):



(I),

wherein

R^1 is H, an alkylcarbonyloxyalkyl group, or a substituted heterocyclyl group, wherein the substituted heterocyclyl group includes one or more substituents selected from the group consisting of nitro, alkyl, halo, cycloalkyl, haloalkyl, hydroxyl, carboxyl, formyloxy, hydroxyalkyl, aldehydo, amino, alkylamino, aminoalkyl, alkylaminoalkyl, dialkylamino, mercapto, alkylmercapto, cyano, cyanoalkyl, and azido,

R^2 is halo, alkylenedioxy, or monohalo- or dihalo- alkylenedioxy; and

R^3 is hydrogen or heterocyclylalkylaminocarbonyl, wherein the heterocyclyl moiety is optionally substituted with one or more groups selected from the group consisting of nitro, alkyl, halo, cycloalkyl, haloalkyl, hydroxyl, carboxyl, formyloxy, hydroxyalkyl, aldehydo, amino, alkylamino, aminoalkyl, alkylaminoalkyl, dialkylamino, mercapto, alkylmercapto, cyano, cyanoalkyl, and azido.

[0007] The invention also provides a method for treating or preventing a human immunodeficiency virus (HIV) infection in a mammal in need thereof, comprising administering to the mammal an effective amount of a compound of formula (I).

[0008] The invention further provides a method of inhibiting or preventing maturation of an immature human immunodeficiency virus (HIV) to a mature HIV, comprising exposing the immature HIV to an effective amount of a compound of formula (I).

[0009] The invention additionally provides a method of preventing or inhibiting a human immunodeficiency virus (HIV) infection in a mammal in need thereof, wherein the mammal has at least one HIV viral particle on a surface thereof, comprising topically administering to the surface of the mammal an effective amount of a compound of formula (I).

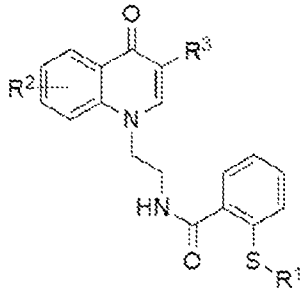
[0010] The compounds of the invention have attractive properties, for example, they provide good cytoprotection with short to moderate half-lives, high volume of distribution rates, and high clearance rates in animals.

BRIEF DESCRIPTION OF THE DRAWING

The Figure displays values of half-life, volume of distribution rate, and clearance rate in male mice for compounds **17**, **18**, and **19**.

DETAILED DESCRIPTION OF THE INVENTION

[0011] In an aspect, the invention provides a compound of formula (I):



(I),

wherein

R^1 is H, an alkylcarbonyloxyalkyl group, or a substituted heterocyclyl group, wherein the substituted heterocyclyl group includes one or more substituents selected from the group consisting of nitro, alkyl, halo, cycloalkyl, haloalkyl, hydroxyl, carboxyl, formyloxy, hydroxyalkyl, aldehydo, amino, alkylamino, aminoalkyl, alkylaminoalkyl, dialkylamino, mercapto, alkylmercapto, cyano, cyanoalkyl, and azido,

R^2 is halo, or alkylenedioxy; and

R^3 is hydrogen or heterocyclylalkylaminocarbonyl, wherein the heterocyclyl moiety is optionally substituted with one or more groups selected from the group consisting of nitro, alkyl, halo, cycloalkyl, haloalkyl, hydroxyl, carboxyl, formyloxy, hydroxyalkyl, aldehydo, amino, alkylamino, aminoalkyl, alkylaminoalkyl, dialkylamino, mercapto, alkylmercapto, cyano, cyanoalkyl, and azido.

[0012] In an aspect, the invention provides a compound of formula (I), wherein R^1 is H or an C_1-C_6 alkylcarbonyloxy C_1-C_3 alkyl group, for example, n-propanoyloxymethyl.

[0013] In an aspect, the invention provides a compound of formula (I), wherein R^1 is a substituted heterocyclyl group wherein the heterocyclyl moiety is selected from the group consisting of imidazolyl, piperidinyl, oxanyl, thianyl, pyridinyl, pyranyl, thiopyranyl, piperazinyl, morpholinyl, thiomorpholinyl, dioxanyl, dithianyl, pyrimidinyl, pyrazinyl, pyridizinyl, oxazinyl, thiazinyl, dioxinyl, dithiinyl, trioxanyl, trithianyl, triazinyl, tetrazinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiaphenyl, pyrrolyl, furanyl, thiophenyl,

imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, dioxolanyl, dithiolanyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, furazanyl, oxadiazolyl, thiadiazolyl, dithiazolyl, and tetrazolyl.

[0014] In a particular aspect, R^1 is imidazolyl substituted with a nitro group and a methyl group.

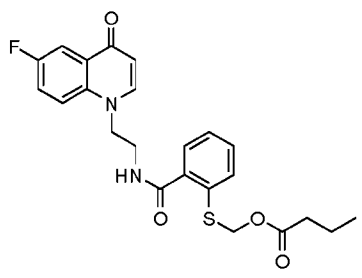
[0015] In an aspect, the invention provides a compound or salt of formula (I), wherein R^2 is fluoro or ethylenedioxy, in particular 6-fluoro or 6,7-ethylenedioxy.

[0016] In any of the above aspects of the compound of formula (I) or salt thereof, R^3 is hydrogen.

[0017] In another aspect of the compound of formula (I) or salt thereof, R^3 is unsubstituted or optionally substituted heterocyclylalkylaminocarbonyl group, wherein the heterocyclyl part of the substituted heterocyclylalkylaminocarbonyl group is selected from the group consisting of imidazolyl, piperidinyl, oxanyl, thianyl, pyridinyl, pyranyl, thiopyranyl, piperazinyl, morpholinyl, thiomorpholinyl, dioxanyl, dithianyl, pyrimidinyl, pyrazinyl, pyridizinyl, oxazinyl, thiazinyl, dioxinyl, dithiinyl, trioxanyl, trithianyl, triazinyl, tetrazinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiaphenyl, pyrrolyl, furanyl, thiophenyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, dioxolanyl, dithiolanyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, furazanyl, oxadiazolyl, thiadiazolyl, dithiazolyl, and tetrazolyl. In particular, R^3 is optionally substituted heterocyclylalkylaminocarbonyl group, wherein the heterocyclyl part of the substituted heterocyclylalkylaminocarbonyl group is pyridinyl.

[0018] In an aspect of the compound of formula (I) or salt thereof, the heterocyclyl part of R^3 is substituted with a C_1-C_6 alkyl group.

[0019] In accordance with an aspect of the invention, the compound of formula (I) is a compound of formulas **1**-**6** and **17**-**19**:



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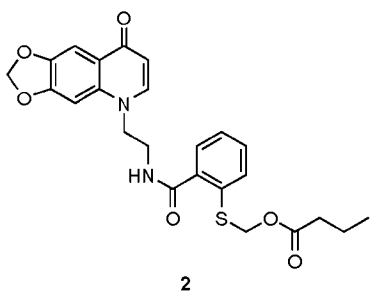

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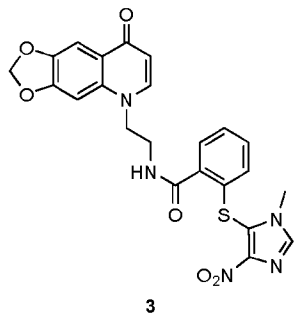

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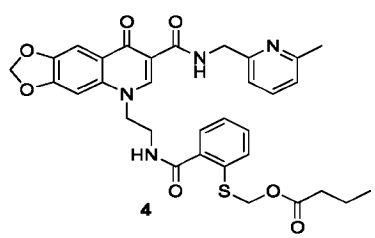

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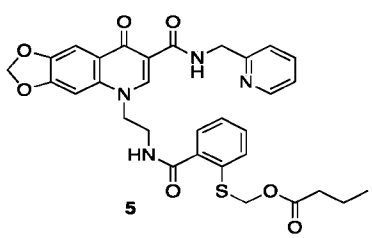

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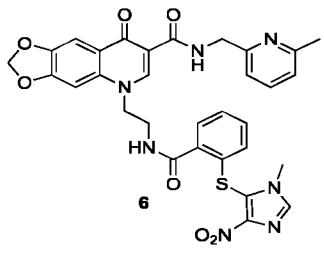

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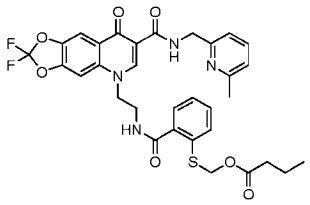
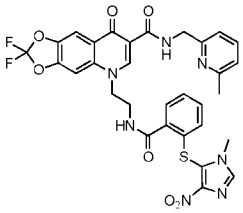


17



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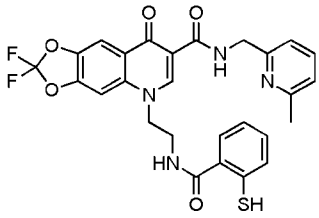
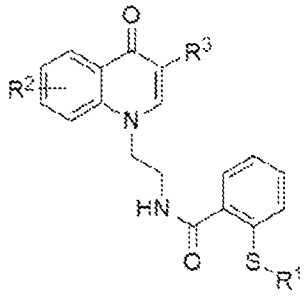


19.

[0020] It is understood that the compound of formula (I) can form solvates, or exist in a substantially uncomplexed form, such as the anhydrous form. As used herein, the term "solvate" refers to a molecular complex wherein the solvent molecule, such as the crystallizing solvent, is incorporated into the crystal lattice. When the solvent incorporated in the solvate is water, the molecular complex is called a hydrate. Pharmaceutically acceptable solvates include hydrates, alcoholates such as methanolates and ethanolates, acetonitrilates and the like. These compounds can also exist in polymorphic forms.

[0021] The present invention also provides a pharmaceutical composition comprising the compound or salt as described above and a pharmaceutically acceptable carrier.

[0022] The present invention further provides a method for treating or preventing a human immunodeficiency virus (HIV) infection in a mammal in need thereof, comprising administering to the mammal an effective amount of a compound of formula (I):



(I).

[0023] In an aspect of the invention, the compound of formula (I) is administered to the subject in combination with a therapeutically effective amount of one or more (e.g., one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents. In certain aspects, the subject is at risk of contracting the HIV virus, such as a subject who has one or more risk factors known to be associated with contracting the HIV virus. In certain aspects, the subject may have not previously received antiviral treatment. In certain aspects, the subject may have previously received antiviral treatment. In certain aspects, the subject may have previously received antiviral treatment and developed resistance to the previously received antiviral treatment.

[0024] In an aspect of the invention, the HIV (e.g., HIV-1) can be a virus selected from the group consisting of HIV Clade A, HIV Clade B, HIV Clade C, HIV Clade D, HIV Clade E, HIV Clade F, HIV Clade G, and HIV Clade O.

[0025] In an aspect of the invention, the compound of formula (I) is administered to the subject in combination with a therapeutically effective amount of one or more (e.g., one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents selected from the group consisting of combination drugs for HIV, other drugs for treating HIV, HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry inhibitors, HIV maturation inhibitors, latency reversing agents, compounds that target the HIV capsid, immune-based therapies, phosphatidylinositol 3-kinase (PI3K) inhibitors, HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins, HIV p17 matrix protein inhibitors, IL-13 antagonists, peptidyl-prolyl cis-trans isomerase A modulators, protein disulfide isomerase inhibitors, complement C5a receptor antagonists, DNA methyltransferase inhibitor, HIV vif gene modulators, Vif dimerization antagonists, HIV-1 viral infectivity factor inhibitors, TAT protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase

modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing inhibitors, Rev protein inhibitors, integrin antagonists, nucleoprotein inhibitors, splicing factor modulators, COMM domain containing protein 1 modulators, HIV ribonuclease H inhibitors, retrocyclin modulators, CDK-9 inhibitors, dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL protein inhibitors, Complement Factor H modulators, ubiquitin ligase inhibitors, deoxycytidine kinase inhibitors, cyclin dependent kinase inhibitors, proprotein convertase PC9 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, G6PD and NADH-oxidase inhibitors, pharmacokinetic enhancers, HIV gene therapy, HIV gene editing, and HIV vaccines, and any combination thereof.

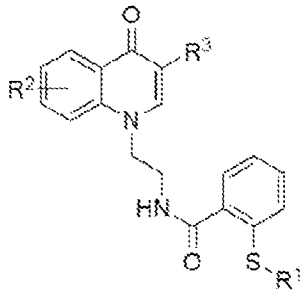
[0026] In an aspect of the invention, the one or more (e.g., one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents are selected from the group consisting of entry inhibitors, HIV non-nucleoside reverse transcriptase inhibitors, HIV non-nucleotide reverse transcriptase inhibitors, HIV nucleoside reverse transcriptase inhibitors, HIV nucleotide reverse transcriptase inhibitors, integrase inhibitors, protease inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, and pharmacokinetic enhancers, and any combination thereof. In certain aspects, the one or more additional therapeutic agents do not include a pharmacokinetic enhancer.

[0027] In an aspect of the invention, the compound of the invention can be administered in combination with highly active antiretroviral therapy (HAART). As used herein, HAART refers to the use of multiple drugs that act on different viral targets (i.e., different pathways within the viral replication cycle).

[0028] In an aspect of the invention, the additional therapeutics agents comprise a combination of antiretroviral agents selected from the group consisting of: tenofovir, emtricitabine, and raltegravir; tenofovir, emtricitabine, and dolutegravir; abacavir, lamivudine, and dolutegravir; tenofovir, emtricitabine, and elvitegravir; tenofovir, emtricitabine, ritonavir, and darunavir; and nipamovir and SAMT-247, which is 3-(S-acetylthiosalicyloyl)aminopropamide or N-[2-ccetylthiobenzoyl]-β-alaninamide. Some of the aforesaid combinations are clinically approved.

[0029] In an aspect of the invention, the invention provides a method for inhibiting or preventing maturation of an immature human immunodeficiency virus (HIV) to a mature

HIV, comprising exposing the immature HIV to an effective amount of a compound of formula (I) or salt thereof:



(I).

[0030] In an aspect of the invention, the method comprises exposing the immature HIV to an effective amount of a compound of formula (I) or salt thereof, to the subject in combination with a therapeutically effective amount of one or more (e.g., one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents. In certain aspects, the subject is at risk of contracting the HIV virus, such as a subject who has one or more risk factors known to be associated with contracting the HIV virus. In certain aspects, the subject may have not previously received antiviral treatment. In certain aspects, the subject may have previously received antiviral treatment. In certain aspects, the subject may have previously received antiviral treatment and developed resistance to the previously received antiviral treatment.

[0031] In an aspect of the invention, the HIV (e.g., HIV-1) can be a virus selected from the group consisting of HIV Clade A, HIV Clade B, HIV Clade C, HIV Clade D, HIV Clade E, HIV Clade F, HIV Clade G, and HIV Clade O.

[0032] In an aspect of the invention, the method further comprises administering a therapeutically effective amount of the compound of formula (I) or salt thereof to the subject in combination with a therapeutically effective amount of one or more (e.g., one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents selected from the group consisting of combination drugs for HIV, other drugs for treating HIV, HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry inhibitors, HIV maturation inhibitors, latency reversing agents, compounds that target the HIV capsid, immune-based therapies, phosphatidylinositol 3-kinase (PI3K) inhibitors, HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins, HIV p17 matrix protein

inhibitors, IL-13 antagonists, peptidyl-prolyl cis-trans isomerase A modulators, protein disulfide isomerase inhibitors, complement C5a receptor antagonists, DNA methyltransferase inhibitor, HIV vif gene modulators, Vif dimerization antagonists, HIV-1 viral infectivity factor inhibitors, TAT protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing inhibitors, Rev protein inhibitors, integrin antagonists, nucleoprotein inhibitors, splicing factor modulators, COMM domain containing protein 1 modulators, HIV ribonuclease H inhibitors, retrocyclin modulators, CDK-9 inhibitors, dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL protein inhibitors, Complement Factor H modulators, ubiquitin ligase inhibitors, deoxycytidine kinase inhibitors, cyclin dependent kinase inhibitors, proprotein convertase PC9 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, G6PD and NADH-oxidase inhibitors, pharmacokinetic enhancers, HIV gene therapy, HIV gene editing, and HIV vaccines, and any combination thereof, is provided.

[0033] In an aspect of the invention, the one or more (e.g., one, two, three, or four; or one or two; or one to three; or one to four) additional therapeutic agents are selected from the group consisting of entry inhibitors, HIV non-nucleoside reverse transcriptase inhibitors, HIV non-nucleotide reverse transcriptase inhibitors, HIV nucleoside reverse transcriptase inhibitors, HIV nucleotide reverse transcriptase inhibitors, integrase inhibitors, protease inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, and pharmacokinetic enhancers, and any combination thereof. In certain aspects, the one or more additional therapeutic agents do not include a pharmacokinetic enhancer.

[0034] In an aspect of the invention, the compound of the invention can be administered in combination with highly active antiretroviral therapy (HAART). As used herein, HAART refers to the use of multiple drugs that act on different viral targets (i.e., different pathways within the viral replication cycle).

[0035] In an aspect of the invention, the additional therapeutic agents comprise a combination of antiretroviral agents selected from the group consisting of: tenofovir, emtricitabine, and raltegravir; tenofovir, emtricitabine, and dolutegravir; abacavir, lamivudine, and dolutegravir; tenofovir, emtricitabine, and elvitegravir; and tenofovir, emtricitabine, ritonavir, and darunavir.

[0036] In any of the above aspects of the invention, the human subject can be infected with the immature HIV and thus the immature HIV can be present in a subject (e.g., a human subject). In these aspects, the exposing of the immature HIV to the compound of formula (I) can be performed by administering the compound of formula (I) or salt thereof, or a composition comprising the compound of formula (I) or salt thereof and a pharmaceutically acceptable carrier, to the subject.

In an aspect, the invention provides a compound of formula (I) or salt thereof for use in treating or preventing a human immunodeficiency virus (HIV) infection in a mammal in need thereof.In certain aspects, the invention provides a compound of formula (I) or salt thereof for use in inhibiting or preventing maturation of an immature human immunodeficiency virus (HIV) to a mature HIV.

[0037] In certain aaspects, the invention provides a compound of formula (I) or salt thereof for use in the manufacture of a medicament for treating or preventing a human immunodeficiency virus (HIV) infection in a mammal in need thereof.

[0038] In certain aspects, the invention provides a compound of formula (I) or salt thereof for use in the manufacture of a medicament inhibiting or preventing maturation of an immature human immunodeficiency virus (HIV) to a mature HIV.

[0039] In an aspect, the invention provides a method of preventing or inhibiting a human immunodeficiency virus (HIV) infection in a mammal in need thereof, wherein the mammal has at least one HIV viral particle on a surface thereof, comprising topically administering to the surface of the mammal an effective amount of a compound of formula (I) or salt thereof.

[0040] In these aspects, the HIV comprises a virus selected from the group consisting of HIV Clade A, HIV Clade B, HIV Clade C, HIV Clade D, HIV Clade E, HIV Clade F, HIV Clade G, and HIV Clade O.

[0041] In certain aspects, the compound of formula (I) or salt thereof is administered in the form of a pharmaceutical composition comprising the compound and a pharmaceutically acceptable carrier.

[0042] In an aspect, the surface can be any surface of the subject. For example, the surface can be the (exterior) skin of the subject. The surface can be an interior surface of the subject, for example, the surface of the vagina or other bodily openings (e.g., ear canal, rectum, nasal passages, and the like). In these aspects, the surface of the subject can be exposed to the immature HIV via interpersonal contact (e.g., via sexual activity), via contact with external surfaces contaminated with samples of infected biological material (e.g., saliva,

semen, vaginal secretions, blood, urine, feces, perspiration, pus, wound exudates, mucus, lymph, tears, ear wax, nasal secretions, secretions exuding from diseased or infected skin, and the like).

[0043] In certain aspects, the invention provides a compound of formula (I) or salt thereof for use in preventing or inhibiting a human immunodeficiency virus (HIV) infection in a mammal in need thereof, wherein the mammal has at least one HIV viral particle on a surface thereof.

[0044] In certain aspects, the invention provides a compound of formula (I) or salt thereof for use in the manufacture of a medicament for preventing or inhibiting a human immunodeficiency virus (HIV) infection in a mammal in need thereof, wherein the mammal has at least one HIV viral particle on a surface thereof. In these aspects, preferably the medicament is adapted for use for topical administration.

[0045] In certain aspects, the compound is administered in the form of a pharmaceutical composition comprising the compound of formula (I) or salt thereof and a pharmaceutically acceptable carrier. Preferably, the pharmaceutical composition is suitable for topical administration, as described herein in connection with the pharmaceutical compositions of the invention.

[0046] Formulations and Dosing

[0047] The present invention further provides a pharmaceutical composition comprising a compound as described above or salt thereof and a pharmaceutically acceptable carrier. The present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount, e.g., a therapeutically effective amount, including a prophylactically effective amount, of the compound of the present invention.

[0048] The pharmaceutically acceptable carrier can be any of those conventionally used and is limited only by chemico-physical considerations, such as solubility and lack of reactivity with the compound, and by the route of administration. It will be appreciated by one of skill in the art that, in addition to the following described pharmaceutical compositions; the compound of the present invention can be formulated as inclusion complexes, such as cyclodextrin inclusion complexes, or liposomes.

[0049] The pharmaceutically acceptable carriers described herein, for example, vehicles, adjuvants, excipients, or diluents, are well known to those who are skilled in the art and are readily available to the public. It is preferred that the pharmaceutically acceptable carrier be

one which is chemically inert to the active compound and one which has no detrimental side effects or toxicity under the conditions of use.

[0050] The choice of carrier will be determined in part by the particular active agent, as well as by the particular method used to administer the composition. Accordingly, there is a wide variety of suitable formulations of the pharmaceutical composition of the present invention. The following formulations for oral, aerosol, parenteral, subcutaneous, intravenous, intraarterial, intramuscular, interperitoneal, intrathecal, rectal, and vaginal administration are merely exemplary and are in no way limiting.

[0051] Formulations suitable for oral administration can consist of (a) liquid solutions, such as an effective amount of the compound dissolved in diluents, such as water, saline, or orange juice; (b) capsules, sachets, tablets, lozenges, and troches, each containing a predetermined amount of the active ingredient, as solids or granules; (c) powders; (d) suspensions in an appropriate liquid; and (e) suitable emulsions. Liquid formulations may include diluents, such as water and alcohols, for example, ethanol, benzyl alcohol, and the polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent, or emulsifying agent. Capsule forms can be of the ordinary hard- or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers, such as lactose, sucrose, calcium phosphate, and cornstarch. Tablet forms can include one or more of lactose, sucrose, mannitol, corn starch, potato starch, alginic acid, microcrystalline cellulose, acacia, gelatin, guar gum, colloidal silicon dioxide, croscarmellose sodium, talc, magnesium stearate, calcium stearate, zinc stearate, stearic acid, and other excipients, colorants, diluents, buffering agents, disintegrating agents, moistening agents, preservatives, flavoring agents, and pharmacologically compatible carriers. Lozenge forms can comprise the active ingredient in a flavor, usually sucrose and acacia or tragacanth, as well as pastilles comprising the active ingredient in an inert base, such as gelatin and glycerin, or sucrose and acacia, emulsions, gels, and the like containing, in addition to the active ingredient, such carriers as are known in the art.

[0052] The compound or salt of the present invention, alone or in combination with other suitable components, can be made into aerosol formulations to be administered via inhalation. These aerosol formulations can be placed into pressurized acceptable propellants, such as dichlorodifluoromethane, propane, nitrogen, and the like. They also may be formulated as pharmaceuticals for non-pressured preparations, such as in a nebulizer or an atomizer.

[0053] Formulations suitable for parenteral administration include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain anti-oxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. The compound can be administered in a physiologically acceptable diluent in a pharmaceutical carrier, such as a sterile liquid or mixture of liquids, including water, saline, aqueous dextrose and related sugar solutions, an alcohol, such as ethanol, isopropanol, or hexadecyl alcohol, glycols, such as propylene glycol or polyethylene glycol, glycerol ketals, such as 2,2-dimethyl-1,3-dioxolane-4-methanol, ethers, such as poly(ethyleneglycol) 400, an oil, a fatty acid, a fatty acid ester or glyceride, or an acetylated fatty acid glyceride with or without the addition of a pharmaceutically acceptable surfactant, such as a soap or a detergent, suspending agent, such as pectin, carbomers, methylcellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agents and other pharmaceutical adjuvants.

[0054] Oils, which can be used in parenteral formulations include petroleum, animal, vegetable, or synthetic oils. Specific examples of oils include peanut, soybean, sesame, cottonseed, corn, olive, petrolatum, and mineral. Suitable fatty acids for use in parenteral formulations include oleic acid, stearic acid, and isostearic acid. Ethyl oleate and isopropyl myristate are examples of suitable fatty acid esters. Suitable soaps for use in parenteral formulations include fatty alkali metal, ammonium, and triethanolamine salts, and suitable detergents include (a) cationic detergents such as, for example, dimethyl dialkyl ammonium halides, and alkyl pyridinium halides, (b) anionic detergents such as, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates, (c) nonionic detergents such as, for example, fatty amine oxides, fatty acid alkanolamides, and polyoxyethylene-polypropylene copolymers, (d) amphoteric detergents such as, for example, alkyl-beta-aminopropionates, and 2-alkyl-imidazoline quaternary ammonium salts, and (3) mixtures thereof.

[0055] The parenteral formulations will typically contain from about 0.5 to about 25% by weight of the active ingredient in solution. Suitable preservatives and buffers can be used in such formulations. In order to minimize or eliminate irritation at the site of injection, such compositions may contain one or more nonionic surfactants having a hydrophile-lipophile balance (HLB) of from about 12 to about 17. The quantity of surfactant in such formulations ranges from about 5 to about 15% by weight. Suitable surfactants include polyethylene

sorbitan fatty acid esters, such as sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol. The parenteral formulations can be presented in unit-dose or multi-dose sealed containers, such as ampoules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, water, for injections, immediately prior to use. Extemporaneous injection solutions and suspensions can be prepared from sterile powders, granules, and tablets of the kind previously described.

[0056] The compound or salt of the present invention may be made into injectable formulations. The requirements for effective pharmaceutical carriers for injectable compositions are well known to those of ordinary skill in the art. See *Pharmaceutics and Pharmacy Practice*, J. B. Lippincott Co., Philadelphia, Pa., Banker and Chalmers, eds., pages 238-250 (1982), and *ASHP Handbook on Injectable Drugs*, Toissel, 4th ed., pages 622-630 (1986).

[0057] Topical formulations, including those that are useful for transdermal drug release, are well-known to those of skill in the art and are suitable in the context of the invention for application to skin. Topically applied compositions are generally in the form of liquids, creams, pastes, lotions and gels. Topical administration includes application to the skin, mucosal tissue, the oral mucosa, which includes the oral cavity, oral epithelium, palate, gingival, and the nasal mucosa. In some aspects, the composition contains at least one active component and a suitable vehicle or carrier. It may also contain other components, such as an anti-irritant. The carrier can be a liquid, solid or semi-solid. In aspects, the composition is an aqueous solution. Alternatively, the composition can be a dispersion, emulsion, gel, lotion or cream vehicle for the various components. In one aspect, the primary vehicle is water or a biocompatible solvent that is substantially neutral or that has been rendered substantially neutral. The liquid vehicle can include other materials, such as buffers, alcohols, glycerin, and mineral oils with various emulsifiers or dispersing agents as known in the art to obtain the desired pH, consistency and viscosity. It is possible that the compositions can be produced as solids, such as powders or granules. The solids can be applied directly or dissolved in water or a biocompatible solvent prior to use to form a solution that is substantially neutral or that has been rendered substantially neutral and that can then be applied to the target site. In aspects of the invention, the vehicle for topical application to the skin can include water, buffered solutions, various alcohols, glycols such as glycerin, lipid

materials such as fatty acids, mineral oils, phosphoglycerides, collagen, gelatin and silicone based materials.

[0058] Additionally, the compound or salt of the present invention may be made into suppositories by mixing with a variety of bases, such as emulsifying bases or water-soluble bases. Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams, or spray formulas containing, in addition to the active ingredient, such carriers as are known in the art to be appropriate.

[0059] The dose administered to a mammal, particularly, a human, in accordance with the present invention should be sufficient to effect the desired response. Such responses include reversal or prevention of the adverse effects of the disease for which treatment is desired or to elicit the desired benefit. One skilled in the art will recognize that dosage will depend upon a variety of factors, including the age, condition, and body weight of the human, as well as the source, particular type of the disease, and extent of the disease in the human. The size of the dose will also be determined by the route, timing and frequency of administration as well as the existence, nature, and extent of any adverse side effects that might accompany the administration of a particular compound and the desired physiological effect. It will be appreciated by one of skill in the art that various conditions or disease states may require prolonged treatment involving multiple administrations.

[0060] The compound of formula (I), or salt thereof, alone or in combination with one or more additional therapeutic agents, may be administered to a subject in accordance with an effective dosing regimen for a desired period of time or duration, such as at least about one day, at least about one week, at least about one month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 6 months, or at least about 12 months or longer. In one variation, the compound of formula (I) or salt thereof is administered on a daily or intermittent schedule. In one variation, the compound of formula (I) or salt thereof is administered on a monthly schedule. In one variation, the compound is administered every two months. In one variation, the compound of formula (I) or salt thereof is administered every three months. In one variation, the compound of formula (I) or salt thereof is administered every four months. In one variation, the compound of formula (I) or salt thereof is administered every five months. In one variation, the compound of formula (I) or salt thereof is administered every 6 months.

[0061] Suitable doses and dosage regimens can be determined by conventional range-finding techniques known to those of ordinary skill in the art. Generally, treatment is

initiated with smaller dosages that are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. The present inventive method typically will involve the administration of about 0.1 to about 300 mg of the compound or salt thereof described above per kg body weight of the animal or mammal.

[0062] The therapeutically effective amount of the compound administered can vary depending upon the desired effects and the factors noted above. Typically, dosages will be between 0.01 mg/kg and 250 mg/kg of the subject's body weight, and more typically between about 0.05 mg/kg and 100 mg/kg, such as from about 0.2 to about 80 mg/kg, from about 5 to about 40 mg/kg or from about 10 to about 30 mg/kg of the subject's body weight. Thus, unit dosage forms can be formulated based upon the suitable ranges recited above and the subject's body weight. The term "unit dosage form" as used herein refers to a physically discrete unit of therapeutic agent appropriate for the subject to be treated.

[0063] Alternatively, dosages are calculated based on body surface area and from about 1 mg/m^2 to about 200 mg/m^2, such as from about 5 mg/m^2 to about 100 mg/m^2 will be administered to the subject per day. In particular aspects, administration of the therapeutically effective amount of the compound involves administering to the subject from about 5 mg/m^2 to about 50 mg/m^2, such as from about 10 mg/m^2 to about 40 mg/m^2 per day. It is currently believed that a single dosage of the compound is suitable, however a therapeutically effective dosage can be supplied over an extended period of time or in multiple doses per day. Thus, unit dosage forms also can be calculated using a subject's body surface area based on the suitable ranges recited above and the desired dosing schedule.

[0064] In any of the above aspects, the inventive methods further prevent, inhibit, or delay the development or progression of AIDS in a subject infected with an HIV virus, e.g., an immature HIV virus. As used herein, "delaying" development of a disease or condition means to defer, hinder, slow, retard, stabilize and/or postpone development of the disease or condition. This delay can be of varying lengths of time, depending on the history of the disease and/or subject being treated. As is evident to one skilled in the art, a sufficient or significant delay can, in effect, encompass prevention, in that the subject does not develop the disease or condition. For example, a method that "delays" development of AIDS is a method that reduces the probability of disease development in a given time frame and/or reduces extent of the disease in a given time frame, when compared to not using the method. Such comparisons may be based on clinical studies, using a statistically significant number of

subjects. For example, the development of AIDS can be detected using known methods, such as confirming a subject's HIV^+ status and assessing the subject's T-cell count or other indication of AIDS development, such as extreme fatigue, weight loss, persistent diarrhea, high fever, swollen lymph nodes in the neck, armpits or groin, or presence of an opportunistic condition that is known to be associated with AIDS (e.g., a condition that is generally not present in subjects with functioning immune systems but does occur in AIDS patients). Development may also refer to disease progression that may be initially undetectable and includes occurrence, recurrence and onset.

[0065] Examples of combination drugs include tenofovir, emtricitabine, and raltegravir; tenofovir, emtricitabine, and dolutegravir; abacavir, lamivudine, and dolutegravir; tenofovir, emtricitabine, and elvitegravir; emtricitabine, ritonavir, and darunavirefavirenz, tenofovir disoproxil fumarate (ATRIPLA™), and emtricitabine); rilpivirine, tenofovir disoproxil fumarate, and emtricitabine (COMPLERA™); elvitegravir, cobicistat, tenofovir disoproxil fumarate, and emtricitabine (STRIBILD™); tenofovir disoproxil fumarate and emtricitabine (TRUVADA™); tenofovir alafenamide and emtricitabine (DESCOVY™); tenofovir alafenamide, emtricitabine, and rilpivirine (ODEFSEY™); tenofovir alafenamide (GENVOYA™), zidovudine and lamivudine (COMBIVIR™); abacavir sulfate and lamivudine (EPZICOM™); lopinavir and ritonavir (KALETRA™); dolutegravir, abacavir, and lamivudine (TRIUMEQ™); abacavir sulfate, zidovudine, and lamivudine (TRIZIVIR™); emtricitabine, cobicistat, and elvitegravir; darunavir, tenofovir alafenamide hemifumarate, emtricitabine, and cobicistat; efavirenz, lamivudine, and tenofovir disoproxil fumarate; lamivudine and tenofovir disoproxil fumarate; tenofovir and lamivudine; tenofovir alafenamide and emtricitabine; tenofovir alafenamide hemifumarate and emtricitabine; tenofovir alafenamide hemifumarate, emtricitabine, and rilpivirine; tenofovir alafenamide hemifumarate, emtricitabine, cobicistat, and elvitegravir; atazanavir and cobicistat; atazanavir sulfate and cobicistat; atazanavir sulfate and ritonavir; darunavir and cobicistat; dolutegravir and rilpivirine; dolutegravir and rilpivirine hydrochloride; dolutegravir, abacavir sulfate, and lamivudine; lamivudine, nevirapine, and zidovudine; raltegravir and lamivudine; doravirine, lamivudine, and tenofovir disoproxil fumarate; doravirine, lamivudine, and tenofovir disoproxil; dolutegravir+lamivudine, lamivudine+abacavir+zidovudine, lamivudine+abacavir, lamivudine+tenofovir disoproxil fumarate, lamivudine+zidovudine+nevirapine, lopinavir+ritonavir, lopinavir+ritonavir+abacavir+lamivudine, lopinavir+ritonavir+zidovudine+lamivudine,

tenofovir+lamivudine, and tenofovir disoproxil fumarate+emtricitabine+rilpivirine hydrochloride, lopinavir, ritonavir, zidovudine and lamivudine; Vacc-4x and romidepsin; and APH-0812.

[0066] Non-limiting examples of other drugs for treating HIV include acemannan, alisporivir, BanLec, deferiprone, Gamimune, metenkefalin, naltrexone, and Prolastin.

[0067] Non-limiting examples of HIV protease inhibitors include amprenavir, atazanavir, brecanavir, darunavir, fosamprenavir, fosamprenavir calcium, indinavir, indinavir sulfate, lopinavir, nelfinavir, nelfinavir mesylate, ritonavir, saquinavir, saquinavir mesylate, and tipranavir.

[0068] Non-limiting examples of HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase include dapivirine, delavirdine, delavirdine mesylate, doravirine, efavirenz, etravirine, lentinan, nevirapine, and rilpivirine.

[0069] Non-limiting examples of HIV nucleoside or nucleotide inhibitors of reverse transcriptase include adefovir, adefovir dipivoxil, azvudine, emtricitabine, tenofovir, tenofovir alafenamide, tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, didanosine and ddl, abacavir, abacavir sulfate, alovudine, apricitabine, censavudine, didanosine, elvucitabine, festinavir, fosalvudine tidoxil, dapivirine, doravirine, etravirine, tenofovir disoproxil orotate, fozivudine tidoxil, lamivudine, phosphazid, stavudine, zalcitabine, and zidovudine.

[0070] Non-limiting examples of HIV integrase inhibitors include elvitegravir, curcumin, chicoric acid, 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, quercetin, raltegravir, dolutegravir, bictegravir, cabotegravir, integrase-LEDGF inhibitors, ledgins, and cabotegravir.

[0071] Non-limiting examples of HIV non-catalytic site, or allosteric, integrase inhibitors include CX-05045, CX-05168, and CX-14442.

[0072] Non-limiting examples of HIV entry (fusion) inhibitors include cenicriviroc, CCR5 inhibitors, gp41 inhibitors, CD4 attachment inhibitors, gp120 inhibitors, and CXCR4 inhibitors.

[0073] Non-limiting examples of CCR5 inhibitors include aplaviroc, vicriviroc, maraviroc, cenicriviroc, PRO-140, adaptavir (RAP-101), nifeviroc, and anti-GP120/CD4 or CCR5 bispecific antibodies.

[0074] Non-limiting examples of gp41 inhibitors include albuvirtide, enfuvirtide, enfuvirtide biobetter, enfuvirtide biosimilar, HIV-1 fusion inhibitors, and sifuvirtide.

[0075] Non-limiting examples of CD4 attachment inhibitors include ibalizumab and CADA analogs.

[0076] A non-limiting example of a gp120 inhibitor include fostemsavir tromethamine.

[0077] A non-limiting example of a CXCR4 inhibitor includes plerixafor.

[0078] Non-limiting examples of HIV maturation inhibitors include BMS-955176 and GSK-2838232.

[0079] Non-limiting examples of latency reversing agents include histone deacetylase (HDAC) inhibitors, proteasome inhibitors (e.g., velcade), protein kinase C (PKC) activators, BET-bromodomain 4 (BRD4) inhibitors, ionomycin, PMA, SAHA, IL-15, JQ1, disulfram, amphotericin B, and ubiquitin inhibitors such as largazole analogs.

[0080] Non-limiting examples of HDAC inhibitors include romidepsin, vorinostat, and panobinostat.

[0081] Non-limiting examples of PKC activators include indolactam, prostratin, ingenol B, and DAG-lactones.

[0082] Non-limiting examples of capsid inhibitors include capsid polymerization inhibitors or capsid disrupting compounds, HIV nucleocapsid p7 (NCp7) inhibitors such as azodicarbonamide and HIV p24 capsid protein inhibitors,.

[0083] Non-limiting examples of immune-based therapies include toll-like receptors (TLR) modulators such as tlr1, tlr2, tlr3, tlr4, tlr5, tlr6, tlr7, tlr8, tlr9, tlr10, tlr11, tlr12, and tlr13; programmed cell death protein 1 (Pd-1) modulators; programmed death-ligand 1 (Pd-L1) modulators; IL-15 agonists; interleukin-7; plaquenil (hydroxychloroquine); proleukin; interferon alfa; interferon α-2b; interferon α-n3; pegylated interferon α; interferon γ; hydroxyurea; mycophenolate mofetil ribavirin; rintatolimod, polyethyleneimine; gepon; rintatolimod; IL-12; WF-10; VGV-1; MOR-22; interleukin-15/Fc fusion protein, normferon, peginterferon α-2a, peginterferon α-2b, recombinant interleukin-15, and RPI-MN.

[0084] Non-limiting examples of PI3K inhibitors include idelalisib, alpelisib, buparlisib, CAI orotate, copanlisib, duvelisib, gedatolisib, neratinib, panulisib, perifosine, pictilisib, pilaralisib, puquitinib mesylate, rigosertib, rigosertib sodium, sonolisib, and taselisib.

[0085] Non-limiting examples of Integrin α-4/β-7 antagonists include PTG-100, TRK-170, abrilumab, etrolizumab, carotegrast methyl, and vedolizumab.

[0086] Non-limiting examples of HIV antibodies, bispecific antibodies, and antibody-like therapeutic proteins include Fab derivatives, bnABs (broadly neutralizing HIV-1 antibodies), and those targeting HIV gp120 or gp41, antibody-recruiting molecules targeting HIV, anti-CD63 monoclonal antibodies, anti-GB virus C antibodies, anti-GP120/CD4, CCR5 bispecific antibodies, anti-nef single domain antibodies, anti-Rev antibody, camelid derived anti-CD18 antibodies, camelid-derived anti-ICAM-1 antibodies, DCVax-001, gp140 targeted antibodies, gp41-based HIV therapeutic antibodies, human recombinant mAbs, ibalizumab, Immuglo, and MB-66.

[0087] A non-limiting example of those targeting HIV in such a manner include bavituximab.

[0088] Non-limiting examples of pharmacokinetic enhancers include cobicistat and ritonavir.

[0089] Non-limiting examples of HIV vaccines include peptide vaccines, recombinant subunit protein vaccines, live vector vaccines, DNA vaccines, CD4-derived peptide vaccines, vaccine combinations, rgp120, monomeric gp120 HIV-1 subtype C vaccine, Remune, ITV-1, Contre Vir, Ad5-ENVA-48, DCVax-001, Vacc-4x, Vacc-C5, VAC-3S, multiclade DNA recombinant adenovirus-5, Pennvax-G, Pennvax-GP, HIV-TriMix-mRNA vaccine, HIV-LAMP-vax, Ad35, Ad35-GRIN, NAcGM3/VSSP ISA-51, poly-ICLC adjuvanted vaccines, TatImmune, GTU-multiHIV, gp140[delta]V2.TV1+MF-59, rVSVIN HIV-1 gag vaccine, SeV-Gag vaccine, and virus-like particle vaccines such as pseudovirion vaccine, CombiVICHvac, LFn-p24 B/C fusion vaccine, GTU-based DNA vaccine, HIV gag/pol/nef/env DNA vaccine, anti-TAT HIV vaccine, conjugate polypeptides vaccine, dendritic-cell vaccines, gag-based DNA vaccine, gp41 HIV-1 vaccine, HIV vaccine (PIKA adjuvant), I i-key/MHC class II epitope hybrid peptide vaccines, ITV-2, ITV-3, ITV-4, LIPO-5, multiclade Env vaccine, MVA vaccine, Pennvax-GP, pp71-deficient HCMV vector HIV gag vaccine, recombinant peptide vaccine, rgp160 HIV vaccine, RNActive HIV vaccine, SCB-703, Tat Oyi vaccine, TBC-M4, therapeutic HIV vaccine, UBI HIV gp120, variant gp120 polypeptide vaccine, and rAd5 gag-pol env A/B/C vaccine.

[0090] A particular example of HIV vaccine is the ΔV1DNA-ALVAC/gp120/alum vaccine. When this vaccine was administed in combination with SAMT-247 (S-acyl-2-mercaptobenzamide thioester), it was found that 16 out of 20 female macaques were protected against vaginal acquisition of the highly pathogenic simian immunodeficiency virus

(SIV). See Rahman et al., *Nature Microbiology* **8**, 767–768 and its Editorial (both published online April 06, 2023).

[0091] It will be appreciated by one of skill in the art that the additional therapeutic agents listed above may be included in more than one of the classes listed above. The particular classes are not intended to limit the functionality of those compounds listed in those classes.

[0092] In a specific aspect, the compound of formula (I) or salt thereof can be combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase and an HIV non-nucleoside inhibitor of reverse transcriptase. In another specific aspect, the compound of formula (I) or salt thereof can be combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, and an HIV protease inhibiting compound. In an additional aspect, the compound of formula (I) can be combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, an HIV non-nucleoside inhibitor of reverse transcriptase, and a pharmacokinetic enhancer. In certain aspects, the compound of formula (I) can be combined with at least one HIV nucleoside inhibitor of reverse transcriptase, an integrase inhibitor, and a pharmacokinetic enhancer. In another aspect, the compound of formula (I) is combined with two HIV nucleoside or nucleotide inhibitors of reverse transcriptase.

[0093] In a particular aspect, the compound of formula (I) is combined with tenofovir, emtricitabine, and raltegravir. In a particular aspect, the compound of formula (I) is combined with tenofovir, emtricitabine, and dolutegravir, In a particular aspect, the compound of formula (I) is combined with abacavir, lamivudine, and dolutegravir. In a particular aspect the compound of formula (I) is combined with tenofovir, emtricitabine, and elvitegravir; emtricitabine, ritonavir, and darunavir. In any of the above aspects, any of the additional therapeutic agents may be in the form of pharmaceutically acceptable salts thereof.

[0094] A compound of formula (I) may be combined with one or more additional therapeutic agents in any dosage amount of the compound of Formula (I) (e.g., from 1 mg to 1000 mg of compound).

[0095] In a particular aspect, the compound of formula (I) or salt thereof is combined with tenofovir, emtricitabine, and raltegravir; tenofovir, emtricitabine, and dolutegravir; abacavir, lamivudine, and dolutegravir; tenofovir, emtricitabine, and elvitegravir; or emtricitabine, ritonavir, and darunavir, wherein the additional therapeutic agent can be present in any suitable amount. In any of the above aspects, any of the additional therapeutic

agents may be in the form of pharmaceutically acceptable salts thereof, particularly any clinically approved pharmaceutically acceptable salts thereof.

[0096] The compound of formula (I) or salt thereof may be combined with one or more additional therapeutic agents in any dosage amount of the compound of Formula (I) (e.g., from 0.01 mg/kg to 250 mg/kg of compound based on the subject's body weight or 5 mg to 500 mg (e.g., 5 mg to 250 mg, or 5 mg to 200 mg, or 5 mg to 100 mg) per unit dosage form). In certain aspects, the compound of formula (I) is combined with 5-30 mg tenofovir, 5-300 mg emtricitabine, and 5-30 mg raltegravir; 5-30 mg tenofovir, 5-300 mg emtricitabine, and 5-30 mg dolutegravir; 5-30 mg abacavir, 5-30 mg lamivudine, and 5-30 mg dolutegravir; 5-30 mg tenofovir, 5-300 mg emtricitabine, and 5-30 mg elvitegravir; or 5-300 mg emtricitabine, 5-30 mg ritonavir, and 5-30 mg darunavir; or 5-300 or 5-30 mg nipamovir; or 5-300 or 5-30 mg of SAMT-247.

[0097] Gene therapy and cell therapy includes the genetic modification to silence a gene; genetic approaches to directly kill the infected cells; the infusion of immune cells designed to replace most of the patient's own immune system to enhance the immune response to infected cells, or activate the patient's own immune system to kill infected cells, or find and kill the infected cells; genetic approaches to modify cellular activity to further alter endogenous immune responsiveness against the infection.

[0098] Examples of dendritic cell therapy include AGS-004.

[0099] Non-limiting examples of genome editing systems (gene editors) are a CRISPR/Cas9 system, a zinc finger nuclease system, a TALEN system, a homing endonucleases system, and a meganuclease system.

[0100] Examples of HIV targeting CRISPR/Cas9 systems include EBT101.

[0101] CAR-T Cell Therapy refers to a population of immune effector cells engineered to express a chimeric antigen receptor (CAR), wherein the CAR comprises an HIV antigen-binding domain. The HIV antigen include an HIV envelope protein or a portion thereof, gp120 or a portion thereof, a CD4 binding site on gp120, the CD4-induced binding site on gp120, N glycan on gp120, the V2 of gp120, the membrane proximal region on gp41. The immune effector cell is a T cell or an NK cell. In some aspects, the T cell is a CD4+ T cell, a CD8+ T cell, or a combination thereof. A non-limiting example of CAR-T includes VC-CAR-T.

[0102] TCR-T cells are engineered to target HIV derived peptides present on the surface of virus-infected cells. The following examples further illustrate the invention but, of course, should not be construed as in any way limiting its scope.

EXAMPLE 1

[0103] This Example illustrates the biological activity of compounds of the present invention.

[0104] **(a) Anti-HIV Cytoprotection Evaluation:** Inhibition of virus-induced cytopathic effects (CPE) and cell viability following HIV replication in CEM-SS cells were measured by the use of XTT tetrazolium dye. CEM-SS cells (2.5 x 10^3 cells per well) were seeded in 96-well U-bottomed tissue culture plates in RPMI medium supplemented with 10% FBS, 2 mM L-glutamine, 100 U/ml penicillin and 100 µg/ml streptomycin. Serially diluted compounds (6 concentrations) and HIV-1_{RF} diluted to a pre-determined titer to yield 85 to 95% cell killing at 6 days post-infection were be added to the plate. AZT was evaluated in parallel as a positive control. Following incubation at 37°C, 5% CO_2 for six days, cell viability was measured by XTT staining. The optical density of the cell culture plate will be determined spectrophotometrically at 450 and 650 nm using Softmax Pro 4.6 software. Percent CPE reduction of the virus-infected wells and the percent cell viability of uninfected drug control wells was calculated to define the EC_{50}, TC_{50} and therapeutic index (TI_{50}) using Microsoft Excel Xlfit4.

[0105] **(b) Anti-HIV-1 Cytoprotection Assay in PBMCs:** PHA-P stimulated PBMCs from three donors were pooled together and re-suspended in fresh tissue culture medium at 1 x 10^6 cells/ml and plated in the interior wells of a 96 well round bottom microplate at 50 µL/well. A 100 µL volume of 2X concentrations of compound-containing media were transferred to the round-bottom 96-well plate containing the cells in triplicate. Fifty microliters (50 µL) of HIV-1 at a pre-determined dilution was added. Each plate contained cell control wells and virus control wells in parallel with the experimental wells. After 7 days in culture, efficacy was evaluated by measuring the reverse transcriptase in the culture supernatants and the cells were stained with the tetrazolium dye XTT to evaluate cytotoxicity.

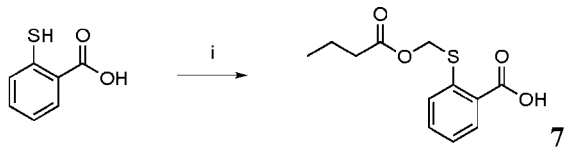
[0106] The results of biological activity tests are set forth in Table 1.

Table 1. Results of Cytoprotection Evaluation and Cytoprotection Assay in PBMCs

Compound	**CEM-SS**			**PBMC**		
	HIV-1_{RF}			**HIV-$1_{92RW009}$**		
	EC_{50} [μM]	*TC_{50} [μM]*	*TI*	*EC_{50} [μM]*	*TC_{50} [μM]*	*TI*
1	0.56	56.2	100	2.48	>100	>40.3
2	1.15	32.2	28	0.48	>100	>209
3				17.7	>100	>5.65
4	0.48	>100	>208	1.09	>100	>91.7
5	0.54	>100	>185	0.91	>100	>110
6				30.9	>100	>3.24

EXAMPLE 2

[0107] This Example illustrates a method of synthesis of 2-(((butyryloxy)methyl)thio)benzoic acid **7**, an intermediate in the synthesis of a compound of formula (I):



7

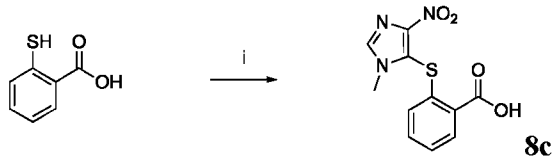
i. CH_3ONa, chloromehylbutyrate, DIPEA, anhydrous DMF, 60°C, overnight.

[0108] Thiosalicylic acid (5.00 g, 32.4 mmol, 1.00 eq) was dissolved in anhydrous DMF (0.5 M), then cooled to 0°C. Sodium methoxide (1.93 g, 35.7 mmol, 1.10 eq) and chloromethylbutyrate (5.36 mL, 42.1 mmol, 1.30 eq) were added and the mixture was heated at 60°C overnight. After cooling, mixture was filtered through Celite and filtrate evaporated. Crude was washed with Et_2O to obtain desired product **7** as a white solid (5.31 g, 20.9 mmol, 65%).

[0109] ^1H NMR (400 MHz, DMSO) δ 13.17 (bs, 1H), 7.89 (d, 1H, J = 7.5 Hz), 7.63 – 7.56 (m, 2H), 7.31 (t, 1H, J = 7.5 Hz), 5.54 (s, 2H), 2.32 (t, 2H, J = 7.2 Hz), 1.53 (sex, 2H, J = 7.6 Hz), 0.85 (t, 3H, J = 7.3 Hz).

EXAMPLE 3

[0110] This Example illustrates a method of synthesis of 2-((1-methyl-4-nitro-1H-imidazol-5-yl)thio)benzoic acid **8c**, which is another intermediate in the synthesis of a compound of formula (I).



8c

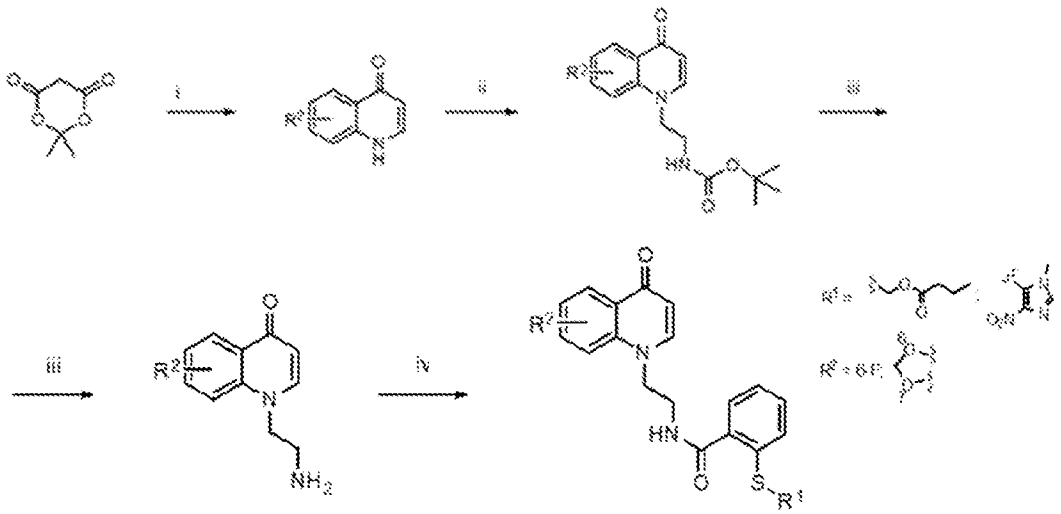
i. AcONa, EtOH, reflux, 3h.

[0111] Thiosalicylic acid (500 mg, 3.24 mmol, 1.00 eq) was dissolved in EtOH (0.5 M), then sodium acetate (266 mg, 6.48 mmol, 2.00 eq) and 5-chloro-1-methyl-4-nitro-1H-imidazole (419 mg, 2.59 mmol, 0.80 eq) were added and the mixture was refluxed for 3h. After cooling, precipitate was filtered and washed with EtOH and H_2O to obtain the desired product **8** as a yellow solid (603 mg, 2.16 mmol, 67%).

[0112] ^{1}H NMR (400 MHz, DMSO) δ 8.21 (s, 1H), 8.00 (d, 1H, J = 7.3 Hz), 7.37 (t, 1H, J = 7.5 Hz), 7.28 (t, 1H, J = 7.4 Hz), 6.55 (d, 1H, J = 8.0 Hz), 3.61 (s, 3H).

EXAMPLE 4

[0113] This Example illustrates a method of synthesis of compounds **1-6** in accordance with formula (I), as illustrated in the reaction scheme, Scheme 1, below:

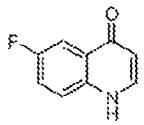


Scheme 1

[0114] i. a) trimethylorthoformate, reflux, 2h. b) aniline, reflux, overnight. c) Ph_2O, 250°C, 2h. ii) tert-butyl (2-bromoethyl)carbamate, NaH, anhydrous DMF, 70°C, 6h. iii) TFA/DCM 1:1, RT, 2h. iv) **7** or **8**, HATU, DIPEA, anhydrous DMF, RT, overnight.

[0115] Synthesis of ((2-((2-(6-fluoro-4-oxoquinolin-1(4H)-yl)ethyl)carbamoyl)phenyl)thio)methyl butyrate **1** was carried out as follows.

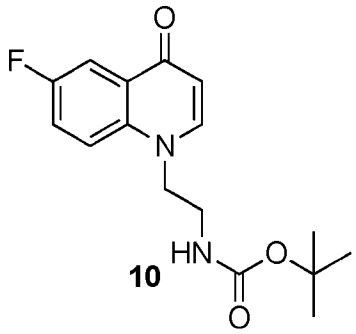
[0116] Step 1: A solution of Meldrum's acid (973 mg, 6.75 mmol, 1.50 eq) in trimethylorthoformate (12.3 mL, 112 mmol, 25.0 eq) was refluxed for 2h. After cooling, 4-fluoroaniline (0.33 mL, 4.50 mmol, 1.00 eq) was added and the mixture refluxed overnight. After cooling, precipitate was filtered and suspended in diphenyl ether (1.43 mL, 9.00 mmol, 2.00 eq). Then, mixture was heated at 250°C for 2h. After cooling, precipitate was filtered and washed with hexane. Crude was purified by flash chromatography with gradient 0 to 10% MeOH in DCM to obtain compound **9** as a light brown solid (196 mg, 1.20 mmol, 27%). Ref: Rotzoll, S. *et al. Synthesis* **2009**, 1, 69–78.



9

^{1}H NMR (400 MHz, DMSO) δ 11.9 (s, 1H), 7.94 (d, 1H, J = 7.4 Hz), 7.72 (dd, 1H, J = 9.2, 2.8 Hz), 7.62 (dd, 1H, J = 9.0, 4.8 Hz), 7.56 (td, 1H, J = 9.0, 2.9 Hz), 6.03 (d, 1H, J = 7.5 Hz).

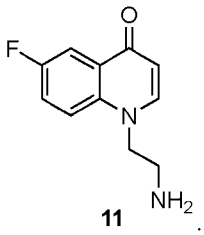
[0117] Step 2: Compound **9** (96.2 mg, 0.59 mmol, 1.00 eq) was dissolved in anhydrous DMF (0.1 M), then NaH 60% in mineral oil (26.0 mg, 0.65 mmol, 1.10 eq) and tert-butyl (2-bromoethyl)carbamate (132 mg, 0.59 mmol, 1.00 eq) were added. The reaction mixture was heated at 70°C for 6h. After cooling and removal of the solvent, crude was diluted in DCM and washed with aq. sat. $NaHCO_3$ (x1), H_2O (x1), and brine (x1). The organic phase was dried over Na_2SO_4. The resulting crude was purified by flash chromatography with gradient 0 to 10% MeOH in DCM to obtain compound **10** as a brown solid (33.9 mg, 0.11 mmol, 20%). Ref: Mori, S. *et al. Eur. J. Med. Chem.* **2019**, 179, 837-848.



10

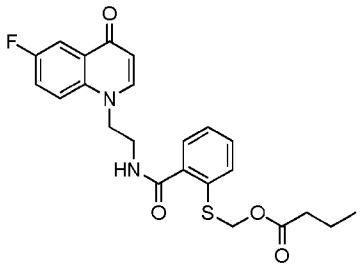
^{1}H NMR (400 MHz, DMSO) δ 7.90 – 7.80 (m, 3H), 7.66 – 7.61 (m, 1H), 6.99 (t, 1H, J = 5.3 Hz), 6.04 (d, 1H, J = 7.7 Hz), 4.27 (t, 2H, J = 5.6 Hz), 1.29 (s, 9H).

[0118] Step 3: Compound **10** (33.9 mg, 0.11 mmol) was stirred in a TFA/DCM 1:1 solution (4.0 mL) for 2h. After evaporation of the solvents, the crude product containing compound **11** was used in the subsequent step without further purification.



11

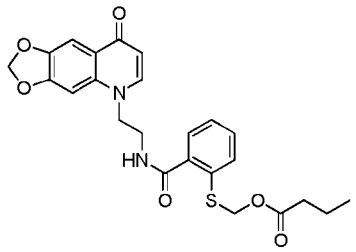
[0119] Step 4: 2-(((butyryloxy)methyl)thio)benzoic acid **7** (28.0 mg, 0.11 mmol, 1.00 eq) was dissolved in anhydrous DMF (0.1 M), then HATU (42.0 mg, 0.11 mmol, 1.00 eq) and DIPEA (0.04 mL, 0.22 mmol, 2.00 eq) were added. After 10 mins, a solution of **11** (0.11 mmol, 1.00 eq) and DIPEA (0.04 mL, 0.22 mmol, 2.00 eq) in anhydrous DMF (0.1 M) was added. The mixture was stirred at RT overnight. After removal of solvents, the crude was diluted in DCM and washed with aq. sat. $NaHCO_3$ (x1), H_2O (x1), and brine (x1). Organic phase was dried over Na_2SO_4. The crude product was purified by flash chromatography with gradient 0 to 10% MeOH in DCM to afford final product **1** as a white solid (14.5 mg, 0.03 mmol, 30%).



1

[0120] ^{1}H NMR (500 MHz, DMSO) δ 8.55 (t, 1H, J = 5.7 Hz), 7.97 (dd, 1H, J = 9.4, 4.3 Hz), 7.94 (d, 1H, J = 7.6 Hz), 7.82 (dd, 1H, J = 9.2, 3.1 Hz), 7.68 – 7.64 (m, 1H), 7.58 (d, 1H, J = 7.9 Hz), 7.47 – 7.43 (m, 1H), 7.30 (d, 2H, J = 4.3 Hz), 6.05 (d, 1H, J = 7.3 Hz), 5.45 (s, 2H), 4.42 (t, 1H, J = 5.6 Hz), 3.59 (q, 2H, J = 5.8 Hz), 2.31 (t, 2H, J = 7.2 Hz), 1.54 (sex, 2H, J = 7.3 Hz), 0.86 (3H, J = 7.3 Hz). ^{13}C NMR (125 MHz, DMSO) δ 176.13, 172.74, 168.36, 159.74, 157.81, 145.45, 137.13, 137.06, 134.36, 131.00, 129.11, 128.70, 128.65, 128.06, 126.68, 120.95, 120.76, 120.06, 120.00, 110.44, 110.26, 108.43, 66.57, 51.57, 38.53, 35.79, 18.29, 13.76. ^{19}F NMR (376 MHz, DMSO) δ -118.41. HRMS-ESI+ (m/z): $[M + H]^+$ calcd for $C_{23}H_{24}N_2O_4F^{32}S$, 443.1441; found, 443.1443.

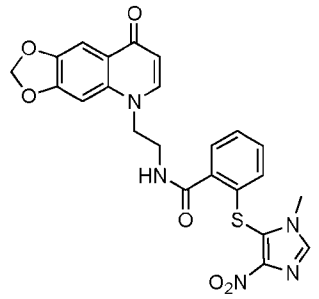
[0121] Synthesis of ((2-((2-(8-oxo-[1,3]dioxolo[4,5-g]quinolin-5(8H)-yl)ethyl)carbamoyl)phenyl)thio)methyl butyrate **2**: Compound **2** was synthesized following the method for compound **1**, where in step 1**,** 3,4-(methylenedioxy)aniline was used instead of 4-fluoroaniline.



2

[0122] Compound **2** was a white solid. ^{1}H NMR (600 MHz, DMSO) δ 8.56 (t, 1H, J = 5.8 Hz), 7.79 (d, 1H, J = 7.6 Hz), 7.59 (d, 1H, J = 8.0 Hz), 7.49 (d, 2H, J = 2.6 Hz), 7.48 – 7.45 (m, 1H), 7.33 – 7.31 (m, 2H), 6.18 (s, 2H), 5.96 (d, 1H, J = 7.7 Hz), 5.45 (s, 2H), 4.34 (t, 1H, J = 6.0 Hz), 3.56 (q, 2H, J = 5.8 Hz), 2.32 (t, 2H, J = 7.3 Hz), 1.55 (sex, 2H, J = 7.4 Hz), 0.87 (t, 3H, J = 7.4 Hz). ^{13}C NMR (150 MHz, DMSO) δ 175.64, 172.73, 168.38, 152.07, 145.26, 143.90, 137.42, 137.24, 134.32, 130.97, 129.26, 128.03, 126.73, 122.94, 108.49, 102.79, 102.55, 96.54, 66.68, 51.73, 38.46, 35.80, 18.28, 13.76. HRMS-ESI+ (m/z): $[M + H]^+$ calcd. for $C_{24}H_{25}N_2O_6^{32}S$, 469.1433; found, 469.1435.

[0123] Synthesis of 2-((1-methyl-4-nitro-1H-imidazol-5-yl)thio)-N-(2-(8-oxo-[1,3]dioxolo[4,5-g]quinolin-5(8H)-yl)ethyl)benzamide, **3**

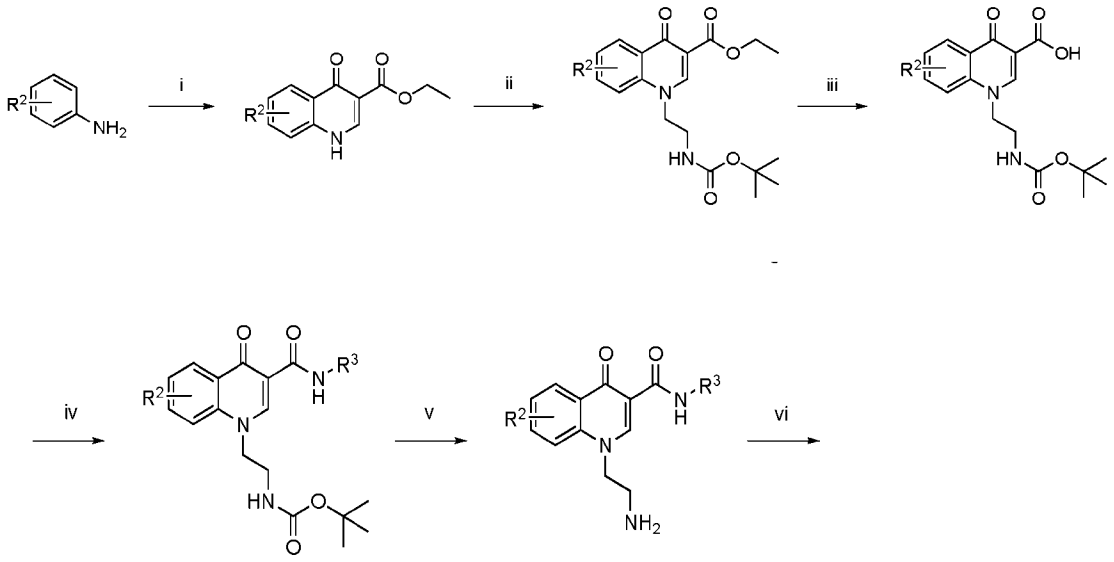


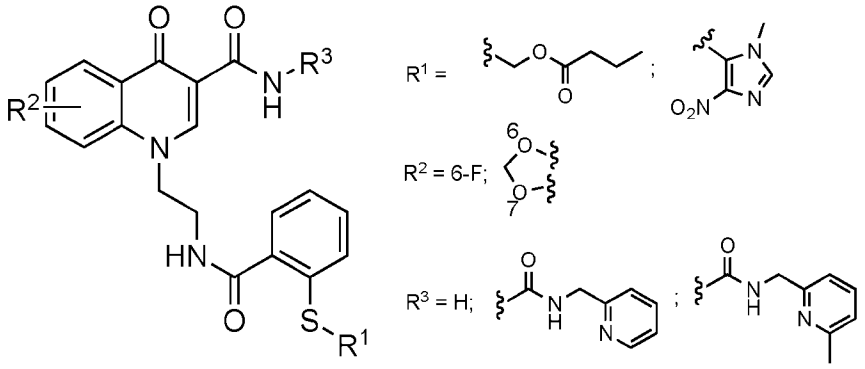
3

[0124] Compound **3** was synthesized following the method for compound **2**, where in step **4** compound **8** was used instead of **7**.

[0125] Yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 8.81 (t, 1H, J = 5.3 Hz), 8.15 (s, 1H), 7.77 (d, 1H, J = 7.2 Hz), 7.54 – 7.49 (m, 2H), 7.35 – 7.27 (m, 2H), 6.71 (d, 1H, J = 7.5 Hz), 6.17 (s, 2H), 5.94 (d, 1H, J = 7.8 Hz), 4.38 (t, 2H, J = 5.3 Hz), 3.62 (q, 2H, J = 5.9 Hz), 3.58 (s, 3H). ^{13}C NMR (150 MHz, DMSO) δ 175.65, 167.68, 152.09, 149.46, 145.28, 143.84, 139.77, 137.43, 135.26, 133.38, 131.98, 128.67, 127.35, 126.46, 123.43, 122.95, 108.53, 102.82, 102.57, 96.56, 51.78, 38.55, 33.18. HRMS-ESI+ (m/z): $[M + H]^{+}$ calcd for $C_{23}H_{20}N_5O_6{}^{32}S$, 494.1134; found, 494.1141.

[0126] Scheme 2.

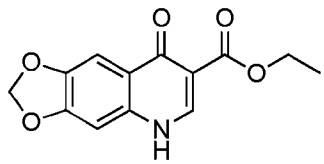




[0127] i. a) diethyl ethoxyethylenemalonate, EtOH, reflux, overnight. b) Ph_2O, 250°C, 2h. ii) tert-butyl (2-bromoethyl)carbamate, K_2CO_3, KI, anhydrous DMF, 50°C, 4 days. iii) aq. NaOH 2M/EtOH 3:1, 80°C, 2h. iv) amine, HATU, DIPEA, anhydrous DMF, RT, overnight. v) TFA/DCM 1:1, RT, 2h. vi) **7** or **8**, HATU, DIPEA, anhydrous DMF, RT, overnight.

[0128] Synthesis of ((2-((2-(7-(((6-methylpyridin-2-yl)methyl)carbamoyl)-8-oxo-[1,3]dioxolo[4,5-g]quinolin-5(8H)-yl)ethyl)carbamoyl)phenyl)thio)methyl butyrate **4**

[0129] Step 1: 3,4-(methylenedioxy)aniline (2.00 g, 14.6 mmol, 1.00 eq) and diethyl ethoxyethylenemalonate (2.95 mL, 14.6 mmol,1.00 eq) were dissolved in EtOH (20.0 mL) and the mixture was refluxed overnight. After cooling and removal of solvent, the crude was suspended in diphenyl ether (29.0 mL, 2.00 eq) and heated at 250°C for 2h. After cooling, the precipitate was filtered and washed with hexane. The crude was purified by flash chromatography with gradient 0 to 10% MeOH in DCM to obtain compound **12** as a light brown solid (1.49 g, 5.70 mmol, 39%). Ref: Mori, S. *et al. Eur. J. Med. Chem.* **2019**, 179, 837-848:

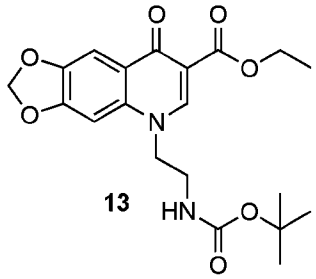


12

[0130] ^{1}H NMR (500 MHz, DMSO) δ 12.15 (s, 1H), 8.42 (s, 1H), 7.45 (s, 1H), 7.06 (s, 1H), 6.17 (s, 2H), 4.20 (q, 2H, J = 7.1 Hz), 1.27 (t, 3H, J = 7.1 Hz).

[0131] Step 2: Compound **12** (1.49 g, 5.70 mmol, 1.00 eq) was dissolved in anhydrous DMF (0.1 M), then K_2CO_3 (15.8 g, 114 mmol, 20.0 eq), KI (9.46 g, 57 mmol, 10.0 eq), and tert-butyl (2-bromoethyl)carbamate (5.20 g, 23.2 mmol, 4.00 eq) were added. Mixture was

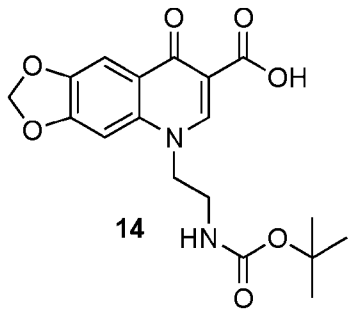
heated at 50°C for 4 days. After cooling and removal of solvent, credo was diluted in DCM and washed H_2O (x1) and brine (x1). Organic phase was dried over Na_2SO_4. Crude was then purified by flash chromatography with gradient 0 to 10% MeOH in DCM to obtain compound **13** as a brown solid (1.06 g, 2.63 mmol, 46%):



13

[0132] ^1H NMR (500 MHz, DMSO) δ 8.34 (s, 1H), 7.54 (s, 1H), 7.46 (s, 1H), 7.01 (t, 1H, J = 5.6 Hz), 6.21 (s, 2H), 4.31 – 4.26 (m, 2H), 4.20 (q, 2H, J = 7.1 Hz), 3.29 – 3.25 (m, 2H), 1.30 – 1.24 (m, 12H).

[0133] Step 3: Compound **13** (1.06 g, 2.63 mmol) was dissolved in aq. NaOH 2M/EtOH 3:1 (14.0 mL) and heated at 80°C for 2h. After cooling, pH was adjusted to ~3 with aq. 20% citric acid solution. Precipitate was filtered and washed with H_2O to obtain compound **14** as a light-yellow solid (825 mg, 2.19 mmol, 83%):

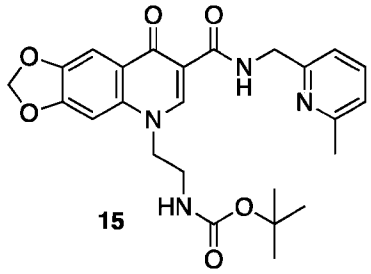


14

[0134] ^1H NMR (400 MHz, DMSO) δ 8.67 (s, 1H), 7.69 (s, 1H), 7.64 (s, 1H), 7.01 (t, 1H, J = 5.9 Hz), 6.31 (s, 2H), 4.49 (t, 2H, J = 4.8 Hz), 1.22 (s, 9H).

[0135] Step 4: Compound **14** (150 mg, 0.40 mmol, 1.00 eq) was dissolved in anhydrous DMF (0.5 M), then HATU (152 mg, 0.40 mmol, 1.00 eq) and DIPEA (0.42 mL, 2.40 mmol, 6.00 eq) were added. After 30 mins, (6-methylpyridin-2-yl)methanamine (0.07 mL, 0.60 mmol, 1.50 eq) was added and reaction stirred at RT overnight. After removal of solvent, crude was diluted in DCM and washed with aq. sat. $NaHCO_3$ (x1), H_2O (x1), and brine (x1). The organic phase was dried over Na_2SO_4. The crude product was purified by flash

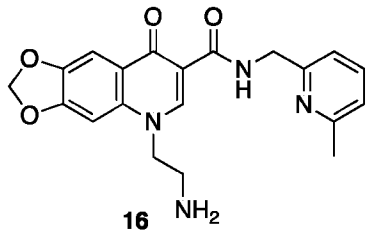
chromatography with gradient 0 to 10% MeOH in DCM to obtain compound **15** as a white solid (61.0 mg, 0.13 mmol, 32%):



15

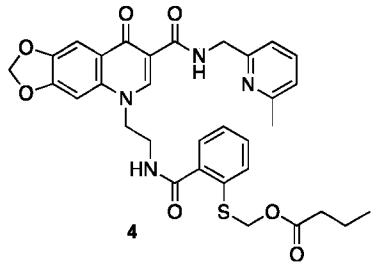
[0136] ^{1}H NMR (500 MHz, DMSO) δ 10.6 (t, 1H, J = 5.5 Hz), 8.59 (s, 1H), 7.64 (t, 2H, J = 7.8 Hz), 7.54 (s, 1H), 7.13 (t, 2H, J =8.0 Hz), 6.99 (t, 1H, J = 5.9 Hz), 6.24 (s, 2H), 4.59 (d, 2H, J = 5.8 Hz), 4.39 (t, 2H, J = 5.7 Hz), 2.48 (s, 3H), 1.23 (s, 9H).

[0137] Step 5: Compound **15** (60 mg, 0.12 mmol) was stirred in a TFA/DCM 1:1 solution (4.00 mL) for 2h. After evaporation of solvents, crude product **16** was used in the subsequent step without further purification.



16

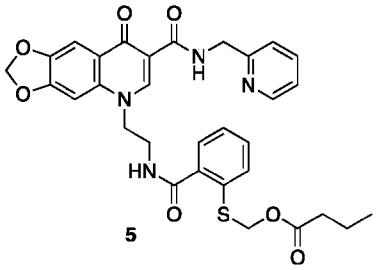
[0138] Step 6: 2-(((butyryloxy)methyl)thio)benzoic acid, **7** (31.3 mg, 0.12 mmol, 1.00 eq) was dissolved in anhydrous DMF (0.2 M), then HATU (46.8 mg, 0.12 mmol, 1.00 eq) and DIPEA (0.09 mL, 0.49 mmol, 4.00 eq) were added. After 10 mins, a solution of **16** (0.12 mmol, 1.00 eq) and DIPEA (0.09 mL, 0.49 mmol, 4.00 eq) in anhydrous DMF (0.2 M) was added. Mixture was stirred at RT overnight. After removal of the solvents, the crude was diluted in DCM and washed with aq. sat. $NaHCO_3$ (x1), H_2O (x1), and brine (x1). The organic phase was dried over Na_2SO_4. The crude was purified by flash chromatography with gradient 0 to 10% MeOH in DCM to obtain compound **4** as a white solid (42.9 mg, 0.07 mmol, 57% over two steps).



4

[0139] ^{1}H NMR (500 MHz, DMSO) δ 10.61 (t, 1H, J = 5.8 Hz), 8.68 (s, 1H), 8.53 (t, 1H, J = 6.0 Hz), 7.65 (s, 1H), 7.64 (s, 1H), 7.62 (t, 1H, J = 7.7 Hz), 7.54 (d, 1H, J = 8.0 Hz), 7.42 (dt, 1H, J = 8.0, 1.2 Hz), 7.29 (dd, 1H, J = 7.8, 1.3 Hz), 7.17 (d, 1H, J = 7.7 Hz), 7.14 (d, 1H, J = 7.7 Hz), 7.09 (d, 1H, J = 7.7 Hz), 6.25 (s, 2H), 5.37 (s, 2H), 4.59 (d, 2H, J = 5.8 Hz), 4.54 (t, 2H, J = 5.4 Hz), 3.61 (q, 2H, J = 5.5 Hz), 2.47 (s, 3H), 2.29 (t, 2H, J = 7.3 Hz), 1.52 (sex, 2H, J = 7.4 Hz), 0.85 (t, 3H, J = 7.4 Hz). ^{13}C NMR (125 MHz, DMSO) δ 174.80, 172.68, 168.34, 164.92, 158.16, 157.79, 152.92, 147.82, 146.60, 137.47, 137.32, 136.92, 134.31, 130.90, 129.20, 128.04, 126.66, 123.64, 121.84, 118.51, 110.53, 103.19, 103.05, 97.18, 66.84, 53.39, 44.71, 38.13, 35.77, 24.49, 18.27, 13.76. HRMS-ESI+ (m/z): $[M + H]^+$ calcd for $C_{32}H_{33}N_4O_7{}^{32}S$, 617.2070; found, 617.2073.

[0140] Synthesis of ((2-((2-(8-oxo-7-((pyridin-2-ylmethyl)carbamoyl)-[1,3]dioxolo[4,5-g]quinolin-5(8H)-yl)ethyl)carbamoyl)phenyl)thio)methyl butyrate **5**: Compound **5** was synthesized following method for **4**, where in step **4** pyridin-2-ylmethanamine was used instead of (6-methylpyridin-2-yl)methanamine.

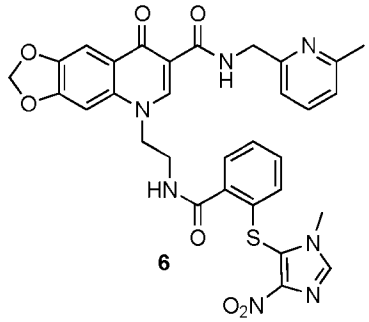


5

[0141] White solid. ^{1}H NMR (600 MHz, DMSO) δ 10.66 (t, 1H, J = 5.7 Hz), 8.70 (s, 1H), 8.55 – 8.54 (m, 2H), 7.75 (dt, 1H, J = 7.7, 1.8 Hz), 7.66 (s, 1H), 7.65 (s, 1H), 7.55 (d, 1H, J = 7.8 Hz), 7.43 (dt, 1H, J = 7.6, 1.3 Hz), 7.33 (d, 1H, J = 7.8 Hz), 7.31 – 7.28 (m, 2H), 7.17 (dt, 1H, J = 7.5, 0.8 Hz), 6.26 (s, 2H), 5.38 (s, 2H), 4.66 (d, 2H, J = 5.7 Hz), 4.55 (t, 2H, J = 5.6 Hz), 3.62 (q, 2H, J = 5.6 Hz), 2.30 (t, 2H, J = 7.3 Hz), 1.53 (sex, 2H, J = 7.4 Hz), 0.86 (t, 3H, J = 7.4 Hz). ^{13}C NMR (150 MHz, DMSO) δ 174.79, 172.67, 168.35, 164.93, 158.66, 152.91, 149.47, 147.80, 146.60, 137.39, 137.18, 136.92, 134.26, 130.88, 129.26, 128.04,

126.68, 123.66, 122.59, 121.70, 110.55, 103.18, 103.07, 97.17, 66.87, 53.37, 44.66, 38.15, 35.77, 18.26, 13.75. HRMS-ESI+ (m/z): $[M + H]^+$ calcd for $C_{31}H_{31}N_4O_7{}^{32}S$, 603.1913; found, 603.1920.

[0142] Synthesis of 5-(2-(2-((1-methyl-4-nitro-1H-imidazol-5-yl)thio)benzamido)ethyl)-N-((6-methylpyridin-2-yl)methyl)-8-oxo-5,8-dihydro-[1,3]dioxolo[4,5-g]quinoline-7-carboxamide, **6**. Compound **6** was synthesized following method for **4**, where in step **6** compound **8** was used instead of **7**.



6

[0143] Yellow solid. ^{1}H NMR (500 MHz, DMSO) δ 10.55 (t, 1H, J = 5.8 Hz), 8.79 (t, 1H, J = 5.8 Hz), 8.71 (s, 1H), 8.10 (s, 1H), 7.67 (s, 1H), 7.64 (s, 1H), 7.60 (t, 1H, J = 7.7 Hz), 7.50 (dd, 1H, J = 7.9, 1.1 Hz), 7.29 (dt, 1H, J = 7.7, 1.2 Hz), 7.15 (t, 1H, J = 7.4 Hz), 7.12 (d, 1H, J = 7.7 Hz), 7.06 (d, 1H, J = 7.8 Hz), 6.70 (d, 1H, J = 7.8 Hz), 6.25 (s, 2H), 4.58 (t, 1H, J = 5.5 Hz), 4.54 (d, 2H, J = 5.8 Hz), 3.67 (q, 2H, J = 5.4 Hz), 3.50 (s, 3H), 2.46 (s, 3H). ^{13}C NMR (125 MHz, DMSO) δ 174.76, 167.70, 164.85, 158.09, 157.79, 152.95, 149.47, 147.80, 146.63, 139.68, 137.47, 136.94, 134.69, 133.85, 131.84, 128.75, 127.54, 126.50, 123.63, 123.33, 121.85, 118.48, 110.52, 103.21, 103.06, 97.19, 53.38, 44.65, 38.28, 33.15, 24.49. HRMS-ESI+ (m/z): $[M + H]^+$ calcd for $C_{31}H_{28}N_7O_7{}^{32}S$, 642.1771; found, 642.1765.

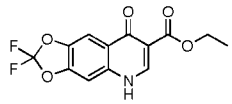
EXAMPLE 4

[0144] This Example illustrates a method of synthesis of compounds **17-19** in accordance with formula (I).

[0145] Example 4-1: synthesis of ((2-((2-(2,2-difluoro-7-(((6-methylpyridin-2-yl)methyl)carbamoyl)-8-oxo-[1,3]dioxolo[4,5-g]quinolin-5(8H)-yl)ethyl)carbamoyl)phenyl)thio)methyl butyrate 6'.

[0146] Step 1: 5-amino-2,2-difluorobenzodioxole (500 mg, 2.89 mmol, 1.00 eq) and diethyl ethoxyethylenemalonate (0.58 mL, 2.89 mmol,1.00 eq) were dissolved in absolute EtOH (5.00 mL) and the mixture was refluxed overnight. After cooling and removal of

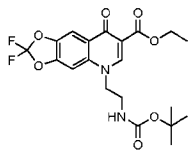
solvent, the crude material was suspended in diphenyl ether (10.0 mL, 2.00 eq) and heated at 250°C for 2h. After cooling, precipitate was filtered and washed with hexane to obtain compound 1' as a light yellow solid (405 mg, 1.36 mmol, 47%).



1'

[0147] ^{1}H NMR (500 MHz, DMSO) δ 12.46 (s, 1H), 8.57 (s, 1H), 7.96 (s, 1H), 7.59 (s, 1H), 4.22 (q, 2H, J = 7.2 Hz), 1.28 (t, 3H, J = 7.1 Hz). ^{19}F NMR (376 MHz, DMSO) δ -49.58.

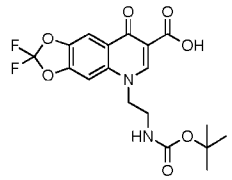
[0148] Step 2: Compound 1' (404 mg, 1.36 mmol, 1.00 eq) was dissolved in anhydrous DMF (0.1 M), then K_2CO_3 (3.76 g, 27.2 mmol, 20.0 eq), KI (2.26 g, 13.6 mmol, 10.0 eq), and tert-butyl (2-bromoethyl)carbamate (1.22 g, 5.44 mmol, 4.00 eq) were added. Mixture was heated at 50 °C for 4 days. After cooling and removal of solvent, crude was diluted in DCM and washed with H_2O (x1) and brine (x1). The organic phase was dried over Na_2SO_4. Crude was then purified by flash chromatography with a gradient of 0 to 10% MeOH in DCM to obtain compound 2' as a light-yellow solid (157 mg, 0.36 mmol, 26%).



2'

[0149] ^{1}H NMR (500 MHz, DMSO) δ 8.48 (s, 1H), 8.04 (s, 1H), 8.04 (s, 1H), 7.00 (t, 1H, J = 5.5 Hz), 4.37 (t, 2H, J = 4.9 Hz), 4.31 – 4.25 (m, 2H), 4.23 (q, 2H, J = 7.2 Hz), 1.28 (t, 3H, J = 7.2 Hz), 1.23 (s, 9H). ^{19}F NMR (376 MHz, DMSO) δ -49.42.

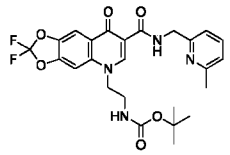
[0150] Step 3: Compound 2' (157 mg, 0.36 mmol) was dissolved in aq. NaOH 2M/EtOH 3:1 (10.0 mL) and heated at 80°C for 2h. After cooling, the pH was adjusted to ~3 with aq. 20% citric acid solution. The precipitate was filtered and washed with H_2O to obtain compound 3' as a white solid (89.7 mg, 0.22 mmol, 60%).



3'

[0151] ^{1}H NMR (400 MHz, DMSO) δ 8.84 (s, 1H), 8.29 (s, 1H), 8.24 (s, 1H), 7.02 (t, 1H, J = 5.9 Hz), 4.57 (t, 2H, J = 5.2 Hz), 3.35 (q, 2H, J = 5.3 Hz), 1.18 (s, 9H). ^{19}F NMR (376 MHz, DMSO) δ -49.20.

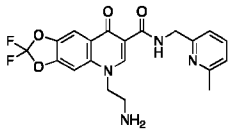
[0152] Step 4: Compound 3' (89.7 mg, 0.22 mmol, 1.00 eq) was dissolved in anhydrous DMF (0.5 M), then HATU (83.6 mg, 0.22, 1.00 eq) and DIPEA (0.15 mL, 0.88 mmol, 6.00 eq) were added. After 30 mins, (6-methylpyridin-2-yl)methanamine (0.03 mL, 0.22 mmol, 1.00 eq) was added and the reaction was stirred at RT overnight. After removal of solvent, crude was diluted in DCM and washed with aq. sat. $NaHCO_3$ (x1), H_2O (x1), and brine (x1). The organic phase was dried over Na_2SO_4. The crude material was then purified by flash chromatography with a gradient 0 to 10% MeOH in DCM to obtain compound 4' as a white solid (50.7 mg, 0.10 mmol, 45%).



4'

[0153] ^{1}H NMR (500 MHz, DMSO) δ 10.4 (t, 1H, J = 5.8 Hz), 8.73 (s, 1H), 8.17 (s, 1H), 8.14 (s, 1H) 7.64 (t, 1H, J = 7.5 Hz), 7.13 (t, 2H, J = 7.4 Hz), 7.02 (t, 1H, J = 5.9 Hz), 4.50 (d, 2H, J = 5.8 Hz), 4.47 (t, 2H, J = 5.2 Hz), 2.48 (s, 3H), 1.17 (s, 9H). ^{19}F NMR (376 MHz, DMSO) δ -49.42.

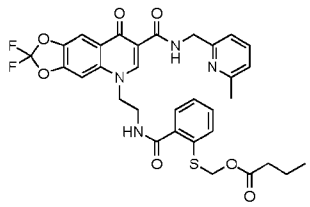
[0154] Step 5: Compound 4' (50.7 mg, 0.10 mmol) was stirred in a TFA/DCM 1:1 solution (2.00 mL) for 2h. After evaporation of solvents, crude product 5' was used in the subsequent step without further purification.



5'

[0155] Step 6: Compound 10, 2-(((butyryloxy)methyl)thio)benzoic acid (25.4 mg, 0.10 mmol, 1.00 eq) was dissolved in anhydrous DMF (0.2 M), then HATU (38.0 mg, 0.10 mmol, 1.00 eq) and DIPEA (0.07 mL, 0.40 mmol, 4.00 eq) were added. After 10 mins, a solution of 5' (0.10 mmol, 1.00 eq) and DIPEA (0.07 mL, 0.40 mmol, 4.00 eq) in anhydrous DMF (0.2 M) was added. Mixture was stirred at RT overnight. After removal of solvents, crude was diluted in DCM and washed with aq. sat. $NaHCO_3$ (x1), H_2O (x1), and brine (x1). Organic phase was dried over Na_2SO_4. Crude was then purified by flash chromatography with

gradient 0 to 10% MeOH in DCM to obtain compound **17** as a white solid (36.5 mg, 0.06 mmol, 56% over two steps).

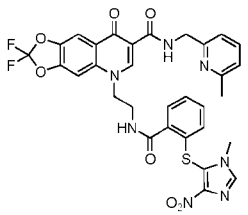


17

[0156] ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.41 (t, 1H, J = 5.7 Hz), 8.82 (s, 1H), 8.53 (t, 1H, J = 5.9 Hz), 8.23 (s, 1H), 8.18 (s, 1H), 7.62 (t, 1H, J = 7.7 Hz), 7.53 (dd, 1H, J = 8.1, 0.7 Hz), 7.42 (dt, 1H, J = 7.37, 1.1 Hz), 7.26 (dd, 1H, J = 7.6, 1.4 Hz), 7.15 (dt, 2H, J = 7.7, 0.7 Hz), 7.10 (d, 1H, J = 7.7 Hz), 5.34 (s, 2H), 4.62 – 4.59 (m, 4H), 3.65 (q, 2H, J = 5.4 Hz), 2.28 (t, 2H, J = 7.2 Hz), 1.51 (sex, 2H, J = 7.3 Hz), 0.84 (t, 3H, J = 7.3 Hz). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 174.98, 172.65, 168.36, 164.42, 157.90, 157.82, 149.36, 147.10, 141.43, 137.71, 137.48, 137.21, 134.31, 131.76 (t, J_F = 255.3 Hz), 130.94, 129.19, 127.97, 126.63, 125.16, 121.89, 118.57, 111.08, 106.44, 100.00, 66.82, 53.78, 44.76, 38.02, 35.75, 24.50, 18.25, 13.74. ^{19}F NMR (376 MHz, DMSO) δ -49.38. HRMS-ESI+ (m/z): $[M + H]^+$ calcd for $C_{32}H_{31}N_4O_7F_2{}^{32}S$, 635.1882; found, 635.1877.

[0157] Example 4-2: synthesis of 2,2-difluoro-5-(2-(2-((1-methyl-4-nitro-1H-imidazol-5-yl)thio)benzamido)ethyl)-N-((6-methylpyridin-2-yl)methyl)-8-oxo-5,8-dihydro-[1,3]dioxolo[4,5-g]quinoline-7-carboxamide **18**.

[0158] Compound **18** was synthesized following method for **17**, where in step 6 compound 11 was used instead of compound 10.



18

[0159] Compound **18** was a pale yellow solid. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.36 (t, 1H, J = 5.7 Hz), 8.84 (s, 1H), 8.78 (t, 1H, J = 5.9 Hz), 8.25 (s, 1H), 8.17 (s, 1H), 8.10 (s ,1H), 7.61 (t, 1H, J = 7.7 Hz), 7.47 (dd, 1H, J = 7.6, 1.2 Hz), 7.29 (dt, 1H, J = 7.6, 1.2 Hz), 7.16 – 7.12 (m, 2H), 7.07 (d, 1H, J = 7.8 Hz), 6.69 (dd, 1H, J = 8.0, 0.7 Hz), 4.66 (t, 2H, J = 5.4

Hz), 4.55 (d, 2H, J = 5.7 Hz), 3.71 (q, 2H, J = 5.4 Hz), 3.50 (s, 3H), 2.46 (s, 3H). ^{13}C NMR (DMSO-d_6, 150 MHz) δ 174.93, 167.76, 164.35, 157.82, 149.43, 147.14, 141.46, 139.67, 137.73, 137.49, 134.69, 133.81, 131.76 (t, J_F = 255.0 Hz), 131.87, 128.67, 127.56, 126.46, 125.15, 123.30, 121.89, 118.52, 111.08, 106.46, 100.02, 53.73, 44.70, 38.20, 33.14, 24.50. ^{19}F NMR (DMSO-d_6, 376 MHz) δ -49.37. HRMS-ESI+ (m/z): $[M + H]^+$ calcd for $C_{32}H_{31}N_4O_7F_2{}^{32}S$, 678.1582; found, 678.1578.

EXAMPLE 5

[0160] This Example illustrates anti-HIV cytoprotection provided by compounds in accordance with an aspect of the invention.

[0161] Inhibition of virus-induced cytopathic effects (CPE) and cell viability following HIV replication in CEM-SS cells were measured by XTT tetrazolium dye. CEM-SS cells (2.5 x 10^3 cells per well) were seeded in 96-well U-bottomed tissue culture plates in RPMI medium supplemented with 10% FBS, 2 mM L-glutamine, 100 U/ml penicillin and 100 µg/ml streptomycin. Serially diluted compounds (6 concentrations) and HIV-1RF diluted to a pre-determined titer to yield 85 to 95% cell killing at 6 days post-infection were be added to the plate. AZT was evaluated in parallel as a positive control. Following incubation at 37°C, 5% CO_2 for six days, cell viability was measured by XTT staining. The optical density of the cell culture plate will be determined spectrophotometrically at 450 and 650 nm using Softmax Pro 4.6 software. Percent CPE reduction of the virus-infected wells and the percent cell viability of uninfected drug control wells were calculated to define the EC_{50}, TC_{50} and therapeutic index (TI_{50}) using Microsoft Excel Xlfit4. The results obtained are set forth in Table 2.

[0162] Table 2. Anti-HIV cytoprotection Results

Compound	HIV-1_{RF}		
	EC_{50} [µM]	*TC_{50} [µM]*	*TI*
17	1.48	>100	>67.6

EXAMPLE 6

[0163] This Example illustrates anti-HIV cytoprotection provided by compounds in accordance with another aspect of the invention, namely in PBMCs. PHA-P stimulated PBMCs from three donors were pooled together and re-suspended in fresh tissue culture

medium at 1 x 10^6 cells/ml and plated in the interior wells of a 96 well round bottom microplate at 50 µL/well. A 100 µL volume of 2X concentrations of compound-containing media were transferred to the round-bottom 96-well plate containing the cells in triplicate. Fifty microliters (50 µL) of HIV-1 at a pre-determined dilution was added. Each plate contained cell control wells and virus control wells in parallel with the experimental wells. After 7 days in culture, efficacy was evaluated by measuring the reverse transcriptase in the culture supernatants and the cells were stained with the tetrazolium dye XTT to evaluate cytotoxicity. The results obtained are set forth in Table 3.

Table 3. Anti-HIV-1 Cytoprotection Assay in PBMCs

HIV-1 Virus Isolate	***Co-Receptor Usage***	***17***		
		EC_{50} [µM]	*TC_{50} [µM]*	*TI*
RW92009 (A)	CXCR4/CCR5	4.26	>100	>23.5
HT92599 (B)	CXCR4	6.52	>100	>15.3
ZA97009 (C)	CCR5	10.7	>100	>9.35
UG92001 (D)	CXCR4/CCR5	5.14	>100	>19.5
CMU08 (E)	CXCR4	5.23	>100	>19.1
BR93020 (F)	CCR5	2.01	>100	>49.8
RU132 (G)	CCR5	6.85	>100	>14.6
BCF01 (O)	CCR5	7.79	>100	>12.8

EXAMPLE 7

[0164] This Example illustrates results of a pharmacokinetic study on compounds **17-19** in male CD-1 mice in accordance with an aspect of the invention.

[0165] Male CD-1 mice weighing between 250-260 grams were dosed via orbital sinus injection and blood was collected via submandibular vein. IV dosing solutions were prepared in DMSO:PEG400:Saline (5:35:60, v/v/v) at 1 mg/mL concentration of the prodrug. Blood samples (50 µL each time point) were obtained via Culex at predetermined time points (0, 5, 15, 30, 60, 120, 240, 360, 480 and 1440 min) after dosing. Plasma was obtained by centrifugation within 30 minutes after collection and aliquots of dosing solutions were taken and analyzed at the same time with plasma samples using a validated LC-MS/MS method developed on a Shimadzu HPLC system interfaced to a Sciex QTRAP 5500 mass

spectrometer. Eluents were gradient mixtures of water and acetonitrile with 0.1% formic acid. HPLC column was ACE 5 C8, 50 x 2.1 mm, 5 µM. PK parameters of the analytes were obtained using Phoenix® WinNonlin® software (version 8.1).

[0166] The results obtained are set forth in Tables 4 and 5 and in Fig. 1.

Table 4. Pharmacokinetic data obtained on compounds **17-19**

Compound	$t_{1/2}$ [h]	t_{max} [h]	t_{last} [h]	C_0 [ng/mL]	C_{max} [ng/mL]
17	1.36	NA	8.00	1910	NA
18	2.73	0.083	8.00	NA	75.6
19	0.35	0.083	2.00	NA	46.9

Table 5. Furtehr pharmacokinetic data obtained on compounds **17-19**

Compound	AUC_{0-t} [h*ng/mL]	AUC_{0-inf} [h*ng/mL]	V_{ss} [L/kg]	CL [mL/min/kg]	MRT_{inf} [h]
17	590	600	9.6	136	1.18
18	34.8	34.8	NA	NA	3.73
19	12.8	12.8	NA	NA	0.33

[0167] The Figure displays the pharmacokinetic properties of compounds **17-19**.

[0168] The study was performed in male CD-1 mice to assess pharmacokinetics (PK) of prodrug **17** and its metabolites **18** and **19**. Following a single IV bolus dose of 5 mg/kg of compound **17** to male CD-1 mice, the PK of compound **17** was characterized by a moderate half-life (1.36 h), a high volume of distribution (9.6 L/kg) and a high clearance (136 mL/min/kg).

[0169] A moderate elimination half-life (2.73 h) characterized the PK of **18** following a single IV bolus dose of 5 mg/kg **17** to male mice. Mean t_{max}, C_{max} and AUC_{0-inf} were 0.083 h, 75.6 ng/mL and 42.5 h*ng/mL, respectively. Exposure (AUC_{0-t}) of **18** was approximately 17-fold lower than that of **17**.

[0170] A short elimination half-life (0.35 h) characterized the PK of **19** following a single IV bolus dose of 5 mg/kg **17** to male mice. Mean t_{max}, C_{max} and AUC_{0-inf} were 0.083 h, 46.9 ng/mL and 13.1 h*ng/mL, respectively. Exposure (AUC_{0-t}) of 9` was approximately 46-fold lower than that of **17**.

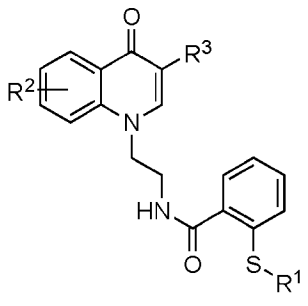
[0171] All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

[0172] The use of the terms "a" and "an" and "the" and "at least one" and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The use of the term "at least one" followed by a list of one or more items (for example, "at least one of A and B") is to be construed to mean one item selected from the listed items (A or B) or any combination of two or more of the listed items (A and B), unless otherwise indicated herein or clearly contradicted by context. The terms "comprising," "having," "including," and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to,") unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

[0173] Preferred aspects of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred aspects may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

CLAIM(S):

1. A compound of formula (I) or a salt thereof:



(I),

wherein

R^1 is H, an alkylcarbonyloxyalkyl group, or a substituted heterocyclyl group, wherein the substituted heterocyclyl group includes one or more substituents selected from the group consisting of nitro, alkyl, halo, cycloalkyl, haloalkyl, hydroxyl, carboxyl, formyloxy, hydroxyalkyl, aldehydo, amino, alkylamino, aminoalkyl, alkylaminoalkyl, dialkylamino, mercapto, alkylmercapto, cyano, cyanoalkyl, and azido,

R^2 is halo, alkylenedioxy, or monohalo- or dihalo- alkylenedioxy; and

R^3 is hydrogen or heterocyclylalkylaminocarbonyl, wherein the heterocyclyl moiety is optionally substituted with one or more groups selected from the group consisting of nitro, alkyl, halo, cycloalkyl, haloalkyl, hydroxyl, carboxyl, formyloxy, hydroxyalkyl, aldehydo, amino, alkylamino, aminoalkyl, alkylaminoalkyl, dialkylamino, mercapto, alkylmercapto, cyano, cyanoalkyl, and azido.

2. The compound or salt of claim 1, wherein R^1 is H or an C_1-C_6 alkylcarbonyloxy C_1-C_3 alkyl group.

3. The compound or salt of claim 1 or 2, wherein R^1 is H or n-propanoyloxymethyl.

4. The compound or salt of claim 1, wherein R^1 is a substituted heterocyclyl group wherein the heterocyclyl moiety is selected from the group consisting of imidazolyl, piperidinyl, oxanyl, thianyl, pyridinyl, pyranyl, thiopyranyl, piperazinyl, morpholinyl, thiomorpholinyl, dioxanyl, dithianyl, pyrimidinyl, pyrazinyl, pyridizinyl, oxazinyl, thiazinyl, dioxinyl, dithiinyl, trioxanyl, trithianyl, triazinyl, tetrazinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiaphenyl, pyrrolyl, furanyl, thiophenyl, imidazolidinyl, pyrazolidinyl,

oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, dioxolanyl, dithiolanyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, furazanyl, oxadiazolyl, thiadiazolyl, dithiazolyl, and tetrazolyl.

5. The compound or salt of claim 4, wherein R^1 is imidazolyl substituted with a nitro group and a methyl group.

6. The compound or salt of any one of claims 1-5, wherein R^2 is fluoro, ethylenedioxy, or difluoroethylenedioxy.

7. The compound or salt of claim 6, wherein R^2 is 6-fluoro, 6,7-ethylenedioxy, or 6,7-difluoroethylenedioxy.

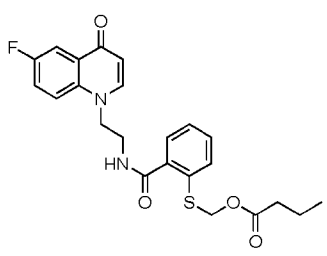
8. The compound or salt of any one of claims 1-7, wherein R^3 is hydrogen.

9. The compound or salt of any one of claims 1-7, wherein R^3 is unsubstituted or optionally substituted heterocyclylalkylaminocarbonyl group, wherein the heterocyclyl part of the substituted heterocyclylalkylaminocarbonyl group is selected from the group consisting of imidazolyl, piperidinyl, oxanyl, thianyl, pyridinyl, pyranyl, thiopyranyl, piperazinyl, morpholinyl, thiomorpholinyl, dioxanyl, dithianyl, pyrimidinyl, pyrazinyl, pyridizinyl, oxazinyl, thiazinyl, dioxinyl, dithiinyl, trioxanyl, trithianyl, triazinyl, tetrazinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiaphenyl, pyrrolyl, furanyl, thiophenyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, dioxolanyl, dithiolanyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, furazanyl, oxadiazolyl, thiadiazolyl, dithiazolyl, and tetrazolyl.

10. The compound or salt of any one of claims 1-7 and 9, wherein R^3 is optionally substituted heterocyclylalkylaminocarbonyl group, wherein the heterocyclyl part of the optionally substituted heterocyclylalkylaminocarbonyl group is pyridinyl or imidazolyl.

11. The compound or salt of claim 9 or 10, wherein the heterocyclyl part of R^3 is substituted with a C_1-C_6 alkyl group and/or a nitro group.

12. The compound or salt of claim 1, wherein the compound is a compound of formulas 1-9:



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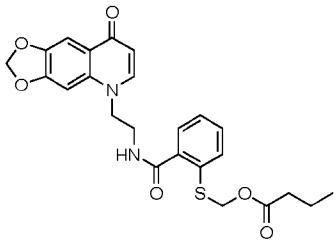

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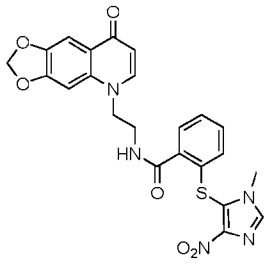

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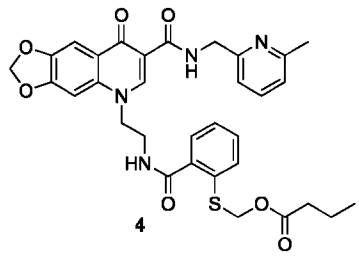

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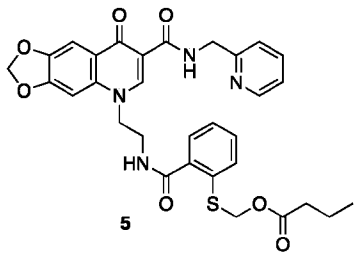

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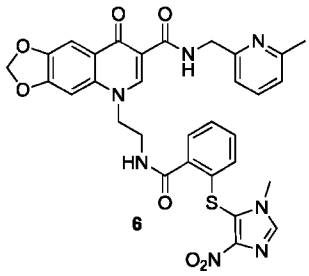

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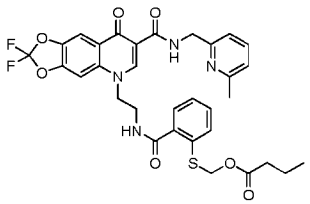

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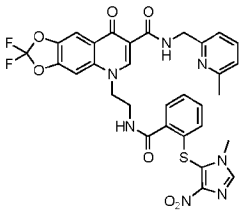

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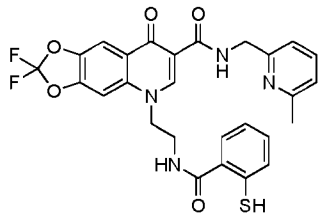


19.

13. A pharmaceutical composition comprising the compound or salt of any one of claims 1-12 and a pharmaceutically acceptable carrier.

14. A method of treating or preventing a human immunodeficiency virus (HIV) infection in a mammal in need thereof comprising administering to the mammal an effective amount of a compound or salt according to any one of claims 1-12 or a pharmaceutical composition according to claim 13.

15. The method according to claim 14, wherein the HIV comprises a virus selected from the group consisting of HIV Clade A, HIV Clade B, HIV Clade C, HIV Clade D, HIV Clade E, HIV Clade F, HIV Clade G, and HIV Clade O.

16. The method according to claim 14 or 15, wherein the compound or salt or composition is administered orally.

17. The method according to any one of claims 14-16, further comprising administering to the mammal one, two, three, or four additional therapeutic agents.

18. The method according to claim 17, wherein the one, two, three, or four additional therapeutic agents are selected from the group consisting of combination drugs for HIV, HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site integrase inhibitors, HIV entry inhibitors, HIV maturation inhibitors, latency reversing agents, compounds that target the HIV capsid, immune-based therapies, phosphatidylinositol 3-kinase (PI3K) inhibitors, HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins, HIV p17 matrix protein inhibitors, IL-13 antagonists, peptidyl-prolyl cis-trans isomerase A modulators, protein disulfide isomerase inhibitors, complement C5a receptor antagonists, DNA methyltransferase inhibitor, HIV vif gene modulators, Vif dimerization antagonists, HIV-1 viral infectivity factor inhibitors, TAT protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing inhibitors, Rev protein inhibitors, integrin antagonists, nucleoprotein inhibitors, splicing factor modulators, COMM domain containing protein 1 modulators, HIV ribonuclease H inhibitors, retrocyclin modulators, CDK-9 inhibitors, dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL protein inhibitors, Complement Factor H modulators, ubiquitin ligase inhibitors, deoxycytidine kinase inhibitors, cyclin dependent kinase inhibitors, proprotein convertase PC9 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, G6PD and NADH-oxidase inhibitors, pharmacokinetic enhancers, HIV gene therapy, HIV gene editing, and HIV vaccines, and any combination thereof.

19. The method according to claim 18, wherein the one, two, three, or four additional therapeutic agents are selected from the group consisting of entry inhibitors, HIV non-nucleoside reverse transcriptase inhibitors, HIV non-nucleotide reverse transcriptase inhibitors, HIV nucleoside reverse transcriptase inhibitors, HIV nucleotide reverse transcriptase inhibitors, integrase inhibitors, protease inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, and pharmacokinetic enhancers, and any combination thereof.

20. The method according to claim 17, wherein the additional therapeutic agents comprise a combination of antiretroviral agents selected from the group consisting of:

tenofovir, emtricitabine, and raltegravir;

tenofovir, emtricitabine, and dolutegravir;

abacavir, lamivudine, and dolutegravir;

tenofovir, emtricitabine, and elvitegravir;

tenofovir, emtricitabine, ritonavir, and darunavir; and

nipamovir and SAMT-247.

21. The method according to any one of claims 14-20, which inhibits or prevents maturation of an immature human immunodeficiency virus (HIV) to a mature HIV.

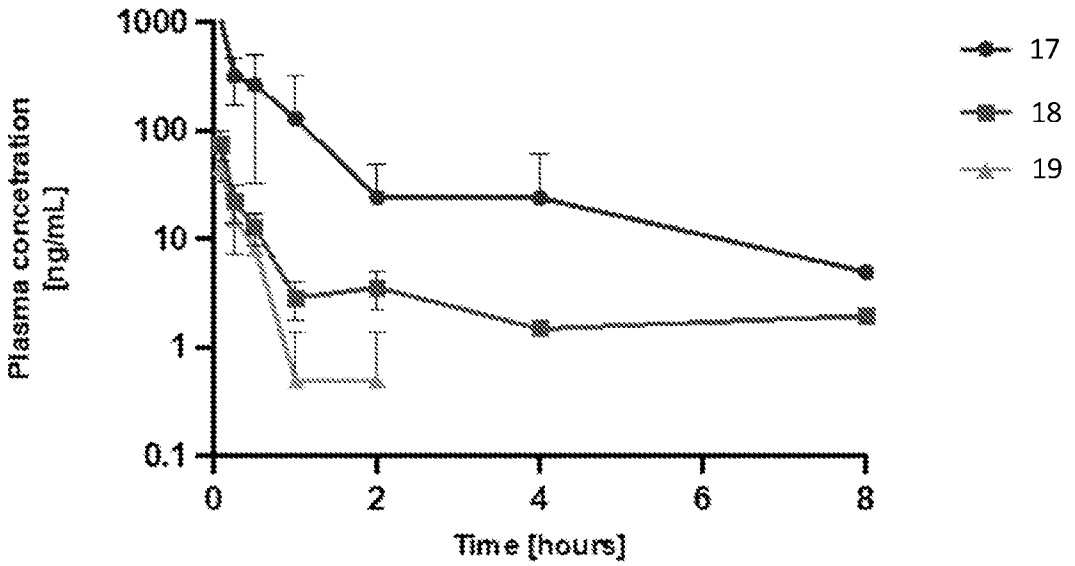
22. A compound or salt according to any one of claims 1-12 or a pharmaceutical composition according to claim 13, for use in treating or preventing a human immunodeficiency virus (HIV) infection in a mammal in need thereof.

23. The method according to claim 17, wherein the one, two, three, or four additional therapeutic agent is a HIV vaccine.

24. The method according to claim 23, wherein the HIV vaccine is ΔV1DNA-ALVAC/gp120/alum vaccine.

25. The compound or salt for use according to claim 22, wherein the compound or salt is used in combination with an additional therapeutic agent.

26. The compound or salt for use according to claim 23, wherein the additional therapeutic agent is ΔV1DNA-ALVAC/gp120/alum vaccine.


1000
100
10
1
0.1
Plasma concetration [ng/mL]
0
2
4
6
8
Time [hours]
17
18
19

Figure

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2023/085968

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4355 A61K31/47
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2019/046778 A1 (MAVUPHARMA INC [US]) 7 March 2019 (2019-03-07) Sulfamide, N-[2-[1-(1,3-dioxolo[4,5-g]quinolin-8-yl)- 4-piperidinyl]ethyl]-; claims 1-97; compound 221 -----	1-26
A	AIZIKOVICH A YA ET AL: "Novel 1-Trifluoromethyl Substituted 1,2-Ethylenediamines and Their use for the Synthesis of Fluoroquinolones", TETRAHEDRON, ELSEVIER SIENCE PUBLISHERS, AMSTERDAM, NL, vol. 56, no. 13, 24 March 2000 (2000-03-24), pages 1923-1927, XP027199965, ISSN: 0040-4020 [retrieved on 2000-03-24] compound 11a -----	1-26

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 March 2024	19/03/2024

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sáez Díaz, R

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2023/085968

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		CA 3074013 A1	07-03-2019
		CL 2020000501 A1	10-07-2020
		CN 111315723 A	19-06-2020
		CO 2020003478 A2	13-04-2020
		CR 20200140 A	15-05-2020
		DO P2020000050 A	15-08-2020
		EC SP20020410 A	30-06-2020
		EP 3676254 A1	08-07-2020
		IL 272910 A	30-04-2020
		JP 2020532526 A	12-11-2020
		KR 20200047627 A	07-05-2020
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		US 2020291024 A1	17-09-2020
		US 2023183239 A1	15-06-2023
		WO 2019046778 A1	07-03-2019