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(54) Title: CHEMICAL COMPOUNDS

(57) Abstract: The present invention relates to a compound that is a non-nucleoside reverse transcriptase inhibitor, and to processes for the preparation and use of the same. Specifically, the present invention includes methods of using such compound in the treatment of human immunodeficiency virus infection.

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CHEMICAL COMPOUNDS

CROSS REFERENCE TO RELATED APPLICATIONS

The present invention claims priority to U.S. Provisional Application Nos. 60/792,434 and 60/863,846 filed on April 17, 2006 and November 1, 2006, respectively.

FIELD OF THE INVENTION

The present invention relates to a compound that is a non-nucleoside reverse transcriptase inhibitor, and to processes for the preparation and use of the same. In particular, the treatment of human immunodeficiency virus infection is disclosed which includes the administration of a benzophenone derivative.

BACKGROUND OF THE INVENTION

The human immunodeficiency virus ("HIV") is the causative agent for acquired immunodeficiency syndrome ("AIDS"), a disease characterized by the destruction of the immune system, particularly of $CD4^+$ T-cells, with attendant susceptibility to opportunistic infections, and its precursor AIDS-related complex ("ARC"), a syndrome characterized by symptoms such as persistent generalized lymphadenopathy, fever and weight loss. HIV is a retrovirus; the conversion of its RNA to DNA is accomplished through the action of the enzyme reverse transcriptase. Compounds that inhibit the function of reverse transcriptase inhibit replication of HIV in infected cells. Such compounds are useful in the prevention or treatment of HIV infection in humans.

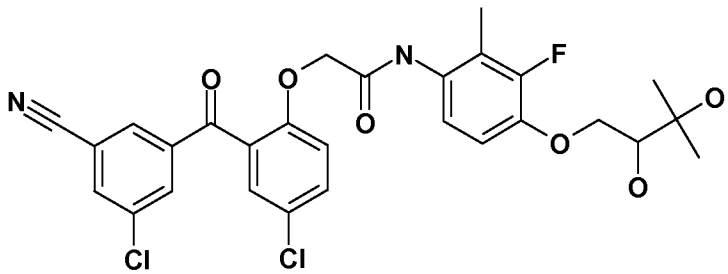
Non-nucleoside reverse transcriptase inhibitors (NNRTIs), in addition to the nucleoside reverse transcriptase inhibitors gained a definitive place in the treatment of HIV-1 infections. The NNRTIs interact with a specific site of HIV-1 reverse transcriptase that is closely associated with, but distinct from, the NRTI binding site. NNRTIs, however, are notorious for rapidly eliciting resistance due to mutations of the amino acids surrounding the NNRTI-binding site (E. De Clercq, *Il Famaco* 54, 26-45, 1999). Failure of long-term efficacy of NNRTIs is often associated with the emergence of drug-resistant virus strains (J. Balzarini, *Biochemical Pharmacology*, Vol 58, 1-27, 1999). Moreover, the mutations that appear in the reverse transcriptase enzyme frequently result in a decreased sensitivity to other reverse transcriptase inhibitors, which results in cross-resistance.

As antiviral use in therapy and prevention of HIV infection continues, the emergence of new resistant new strains is expected to increase. There is therefore an ongoing need for new inhibitors of reverse transcriptase, which have different patterns of effectiveness against the various mutants.

WO 02/070470, WO 01/17982, and US 2006/0025480 disclosed certain benzophenones as non-nucleoside reverse transcriptase inhibitors. We have now discovered that the compounds of the present invention are useful as inhibitors of both wild type and mutant variants of HIV reverse transcriptase.

SUMMARY OF THE INVENTION

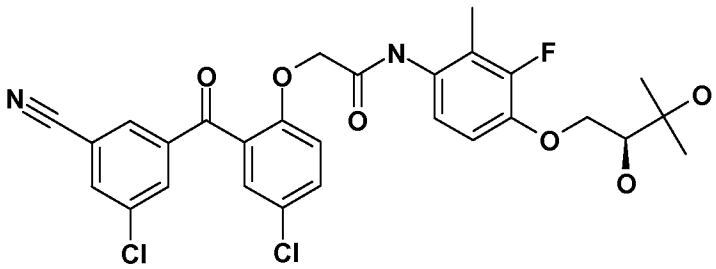
The present invention features a compound of formula (I)



(I)

or a pharmaceutically acceptable derivative thereof.

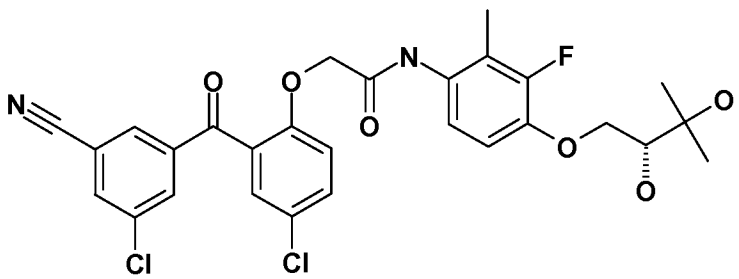
The present invention also features a compound of formula (IA)



(IA)

or a pharmaceutically acceptable derivative thereof.

The present invention features a compound of formula (IB)



(IB)

or a pharmaceutically acceptable derivative thereof.

The present invention features pharmaceutical compositions comprising a compound of the present invention.

The present invention features a compound of the present invention for use in medical therapy, for example, the treatment of viral infections and associated conditions, such as HIV infections and associated conditions.

The present invention also features the use of a compound of the present invention in the manufacture of a medicament for use in the treatment of viral infections and associated conditions, for example, in the treatment of HIV infections and associated conditions.

The present invention features a method for the treatment of viral infections and associated conditions, for example, HIV infections and associated conditions, comprising the administration of a compound of the present invention.

DETAILED DESCRIPTION

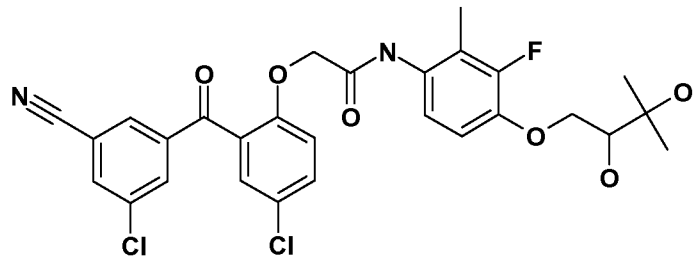
As used herein, the term "treatment" refers to alleviating the specified condition, eliminating or reducing the symptoms of the condition, slowing or eliminating the progression of the condition and preventing or delaying the initial occurrence of the condition in a subject, or reoccurrence of the condition in a previously afflicted subject.

A "pharmaceutically acceptable derivative" means any pharmaceutically acceptable ester, salt of an ester, ether, or other derivative of a compound of this invention which, upon administration to a recipient, is capable of providing directly or indirectly a compound of this invention or an inhibitorily active metabolite or residue thereof. Particularly favored derivatives and prodrugs, and salts thereof, are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a mammal, for example, by allowing an orally administered compound to be more readily absorbed into the blood, or which enhance delivery of the parent compound to a biological compartment, for example, the brain or lymphatic system, relative to the parent species.

As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal, or human that is being sought, for instance, by a researcher or clinician. The biological or medical response may be considered a prophylactic response or a treatment response. The term "therapeutically effective amount" means any amount which, as

compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

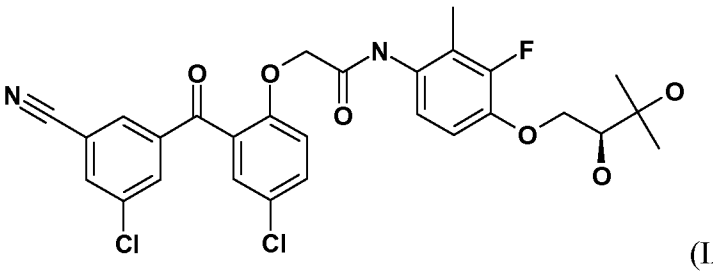
The present invention features a compound of formula (I)



(I)

or a pharmaceutically acceptable derivative thereof. The compound has the name 2-({4-chloro-2-[(3-chloro-5-cyanophenyl)carbonyl]phenyl}oxy)-*N*-{4-[(2,3-dihydroxy-3-methylbutyl)oxy]-3-fluoro-2-methylphenyl}acetamide.

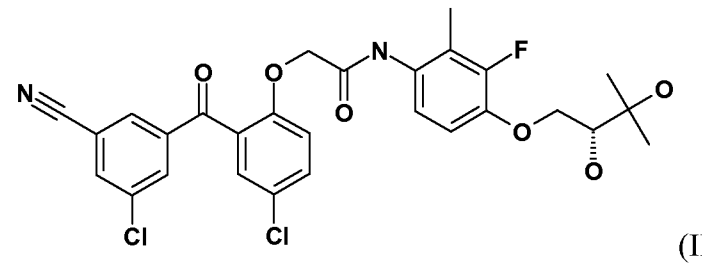
The present invention also features a compound of formula (IA)



(IA)

or a pharmaceutically acceptable derivative thereof. The compound has the name 2-({4-chloro-2-[(3-chloro-5-cyanophenyl)carbonyl]phenyl}oxy)-*N*-(4-{[(2*S*)-2,3-dihydroxy-3-methylbutyl]oxy}-3-fluoro-2-methylphenyl)acetamide.

The present invention further features a compound of formula (IB)



(IB)

or a pharmaceutically acceptable derivative thereof. The compound has the name 2-({4-chloro-2-[(3-chloro-5-cyanophenyl)carbonyl]phenyl}oxy)-*N*-(4-{[(2*R*)-2,3-dihydroxy-3-methylbutyl]oxy}-3-fluoro-2-methylphenyl)acetamide.

Compounds of the present invention may exist in unsolvated forms as well as solvated forms, including hydrated forms. Solvated forms and unsolvated forms are encompassed within the scope of the present invention. Compounds of the present invention may exist in a mixture of forms and/or solvates or as a mixture of amorphous material and one or more forms and/or solvates. In general, all physical forms are intended to be within the scope of the present invention. Forms may be distinguished by various physical characteristics known in the art such as x-ray diffraction patterns, solubility, and melting point.

The compounds described herein contain one or more chiral centers, or may otherwise be capable of existing as multiple stereoisomers. The scope of the present invention includes mixtures of stereoisomers as well as purified enantiomers or enantiomerically/diastereomerically enriched mixtures. Also included within the scope of the invention are the individual isomers of the compounds represented by formula (I), as well as any wholly or partially equilibrated mixtures thereof. The present invention also includes the individual isomers of the compounds represented by the formulas above as mixtures with isomers thereof in which one or more chiral centers are inverted.

Other compounds of this invention may be prepared by one skilled in the art following the teachings of the specification coupled with knowledge in the art using reagents that are readily synthesized or commercially available.

Esters of the compounds of the present invention are independently selected from the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy groups, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, acetyl, n-propyl, t-butyl, or n-butyl), alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted by, for example, halogen, C_{1-4}alkyl, or C_{1-4}alkoxy or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C_{1-20} alcohol or reactive derivative thereof, or by a 2,3-di (C_{6-24})acyl glycerol.

In such esters, unless otherwise specified, any alkyl moiety present advantageously contains from 1 to 18 carbon atoms, particularly from 1 to 6 carbon atoms, more

particularly from 1 to 4 carbon atoms, Any cycloalkyl moiety present in such esters advantageously contains from 3 to 6 carbon atoms. Any aryl moiety present in such esters advantageously comprises a phenyl group.

Ethers of the compounds of the present invention include, but are not limited to methyl, ethyl, butyl and the like.

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of the present invention) and a solvent. Such solvents, for the purpose of the invention, should not interfere with the biological activity of the solute. Non-limiting examples of suitable solvents include, but are not limited to water, methanol, ethanol, and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Non-limiting examples of suitable pharmaceutically acceptable solvents include water, ethanol, and acetic acid. Most preferably the solvent used is water.

For use in therapy, therapeutically effective amounts of a compound of the present invention may be administered as the raw chemical. Additionally, the active ingredient may be presented as a pharmaceutical composition. Accordingly, the invention further provides pharmaceutical compositions that include effective amounts of a compound of the present invention and one or more pharmaceutically acceptable carriers, diluents, or excipients. The compounds of the present invention are as herein described. The carrier(s), diluent(s) or excipient(s) must be acceptable, in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient of the pharmaceutical composition.

In accordance with another aspect of the invention there is also provided a process for the preparation of a pharmaceutical composition including admixing a compound of the present invention with one or more pharmaceutically acceptable carriers, diluents or excipients.

A therapeutically effective amount of a compound of the present invention will depend upon a number of factors. For example, the species, age, and weight of the recipient, the precise condition requiring treatment and its severity, the nature of the composition, and the route of administration are all factors to be considered. The therapeutically effective amount ultimately should be at the discretion of the attendant physician or veterinarian. Regardless, an effective amount of a compound of the present

invention for the treatment of humans suffering from frailty, generally, should be in the range of 0.1 to 100 mg/kg body weight of recipient (mammal) per day. More usually the effective amount should be in the range of 0.1 to 10 mg/kg body weight per day. The actual amount per day would usually be from 0.3 to 3,000 mg. This amount may be given in a single dose per day or in a number (such as two, three, four, five, or more) of sub-doses per day such that the total daily dose is the same. An effective amount of a pharmaceutically acceptable derivative thereof may be determined as a proportion of the effective amount of a compound of the present invention *per se*. Similar dosages should be appropriate for treatment of the other conditions referred to herein.

Pharmaceutical compositions may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Such a unit may contain, as a non-limiting example, 0.5 mg to 1 g of a compound of the present invention, depending on the condition being treated, the route of administration, and the age, weight, and condition of the patient. Preferred unit dosage compositions are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Such pharmaceutical compositions may be prepared by any of the methods well known in the pharmacy art.

Pharmaceutical compositions may be adapted for administration by any appropriate route, for example by an oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal, or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such compositions may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s).

Pharmaceutical compositions adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions, each with aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions. For instance, for oral administration in the form of a tablet or capsule, the active drug component may be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Generally, powders are prepared by comminuting the compound to a suitable fine size and mixing with an appropriate pharmaceutical carrier such as an edible carbohydrate,

as, for example, starch or mannitol. Flavorings, preservatives, dispersing agents, and coloring agents may also be present.

Capsules are made by preparing a powder, liquid, or suspension mixture and encapsulating with gelatin or some other appropriate shell material. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate, or solid polyethylene glycol may be added to the mixture before the encapsulation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate may also be added to improve the availability of the medicament when the capsule is ingested. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents may also be incorporated into the mixture. Examples of suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants useful in these dosage forms include, for example, sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

Tablets may be formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant, and pressing into tablets. A powder mixture may be prepared by mixing the compound, suitably comminuted, with a diluent or base as described above. Optional ingredients include binders such as carboxymethylcellulose, aliginates, gelatins, or polyvinyl pyrrolidone, solution retardants such as paraffin, resorption accelerators such as a quaternary salt, and/or absorption agents such as bentonite, kaolin, or dicalcium phosphate. The powder mixture may be wet-granulated with a binder such as syrup, starch paste, acadia mucilage or solutions of cellulosic or polymeric materials, and forcing through a screen. As an alternative to granulating, the powder mixture may be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules may be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention may also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging

steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material, and a polish coating of wax may be provided. Dyestuffs may be added to these coatings to distinguish different unit dosages.

Oral fluids such as solutions, syrups, and elixirs may be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups may be prepared, for example, by dissolving the compound in a suitably flavored aqueous solution, while elixirs may be prepared through the use of a non-toxic alcoholic vehicle. Suspensions may be formulated generally by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives; flavor additives such as peppermint oil, or natural sweeteners, saccharin, or other artificial sweeteners; and the like may also be added.

Where appropriate, dosage unit compositions for oral administration may be microencapsulated. The composition may also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax or the like.

The compounds of the present invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes may be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

The compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled.

The compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers may include polyvinylpyrrolidone (PVP), pyran copolymer, polyhydroxypropylmethacrylamide–phenol, polyhydroxyethyl-aspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug; for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates, and cross-linked or amphipathic block copolymers of hydrogels.

Pharmaceutical compositions adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of

the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in *Pharmaceutical Research*, 3(6), 318 (1986), incorporated herein by reference as related to such delivery systems.

Pharmaceutical compositions adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols, or oils.

For treatments of the eye or other external tissues, for example mouth and skin, the compositions may be applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical compositions adapted for topical administrations to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

Pharmaceutical compositions adapted for topical administration in the mouth include lozenges, pastilles, and mouthwashes.

Pharmaceutical compositions adapted for nasal administration, where the carrier is a solid, include a coarse powder having a particle size for example in the range 20 to 500 microns. The powder is administered in the manner in which snuff is taken, i.e., by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable compositions wherein the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oil solutions of the active ingredient.

Pharmaceutical compositions adapted for administration by inhalation include fine particle dusts or mists, which may be generated by means of various types of metered dose pressurized aerosols, nebulizers, or insufflators.

Pharmaceutical compositions adapted for rectal administration may be presented as suppositories or as enemas.

Pharmaceutical compositions adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams, or spray formulations.

Pharmaceutical compositions adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may 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 which may include suspending agents and thickening agents. The compositions may be presented in unit-dose or multi-dose containers, for example sealed ampules and vials, and may 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 may be prepared from sterile powders, granules, and tablets.

In addition to the ingredients particularly mentioned above, the compositions may include other agents conventional in the art having regard to the type of formulation in question. For example, compositions suitable for oral administration may include flavoring or coloring agents.

In another embodiment of the invention there is provided a compound according to the invention for use in medical therapy particularly for the treatment of viral infections such as an HIV infection. Compounds according to the invention have been shown to be active against HIV infections, although these compounds may be active against HBV infections as well.

The compound according to the invention is particularly suited to the treatment of HIV infections and associated conditions. Reference herein to treatment extends to treatment of established infections, symptoms, and associated clinical conditions such as AIDS related complex (ARC), Kaposi's sarcoma, and AIDS dementia.

The present invention provides a method of treatment of HIV mutant viruses that exhibit NNRTI drug resistance by administering a therapeutically effective amount of a compound of the present invention or a pharmaceutically acceptable derivative thereof to a mammal, in particular a human. In particular, the compounds of the present invention may be used to treat wild-type HIV-1 as well as several resistance mutations, for example, K103N, L100I, or Y181C.

The present invention provides a method for the treatment of the symptoms or effects of a viral infection in an infected animal, for example, a mammal including a human, which comprises treating said animal with a therapeutically effective amount of a compound according to the invention. According to a particular embodiment of this aspect of the invention, the viral infection is a retroviral infection, in particular an HIV

infection. A further aspect of the invention includes a method for the treatment of the symptoms or effects of an HBV infection.

The compounds of the present invention may also be used in adjuvant therapy in the treatment of HIV infections or HIV-associated symptoms or effects, for example Kaposi's sarcoma.

The compounds of the present invention and any pharmaceutically acceptable derivatives thereof, may be employed alone or in combination with other therapeutic agents. The compounds of the present invention and the other pharmaceutically active agent(s) may be administered together or separately and, when administered separately, administration may occur simultaneously or sequentially, in any order. The amounts of the compound of the present invention and the other pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect. The administration in combination of a compound of the present invention and any pharmaceutically acceptable derivatives thereof with other treatment agents may be in combination by administration concomitantly in: (1) a unitary pharmaceutical composition including both compounds; or (2) separate pharmaceutical compositions each including one of the compounds. Alternatively, the combination may be administered separately in a sequential manner wherein one treatment agent is administered first and the other second or vice versa. Such sequential administration may be close in time or remote in time.

The compounds of the present invention may be used in the treatment of a variety of disorders and conditions and, as such, the compounds of the present invention may be used in combination with a variety of other suitable therapeutic agents useful in the treatment or prophylaxis of those disorders or conditions. The compounds may be used in combination with any other pharmaceutical composition where such combined therapy may be useful to modulate chemokine receptor activity and thereby prevent and treat inflammatory and/or immunoregulatory diseases.

The present invention may be used in combination with one or more agents useful in the prevention or treatment of HIV. Examples of such agents include:

Nucleoside reverse transcriptase inhibitors such as zidovudine, didanosine, lamivudine, zalcitabine, abacavir, stavidine, adefovir, adefovir dipivoxil, fozivudine, todoxil, emtricitabine, alovudine, amdoxovir, elvucitabine, and similar agents;

Non-nucleoside reverse transcriptase inhibitors (including an agent having anti-oxidation activity such as immunocal, oltipraz, etc.) such as nevirapine, delavirdine, efavirenz, loviride, immunocal, oltipraz, capravirine, TMC-278, TMC-125, etravirine, and similar agents;

Protease inhibitors such as saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, fosamprenavir, brecanavir, atazanavir, tipranavir, palinavir, lasinavir, and similar agents;

Entry inhibitors such as enfuvirtide (T-20), T-1249, PRO-542, PRO-140, TNX-355, BMS-806, 5-Helix and similar agents;

Integrase inhibitors such as L-870,180 and similar agents;

Budding inhibitors such as PA-344 and PA-457, and similar agents; and

CXCR4 and/or CCR5 inhibitors such as vicriviroc (Sch-C), Sch-D, TAK779, maraviroc (UK 427,857), TAK449, as well as those disclosed in WO 02/74769, PCT/US03/39644, PCT/US03/39975, PCT/US03/39619, PCT/US03/39618, PCT/US03/39740, and PCT/US03/39732, and similar agents.

The scope of combinations of the compounds of this invention with HIV agents is not limited to those mentioned above, but includes in principle any combination with any pharmaceutical composition useful for the treatment of HIV. As noted, in such combinations the compounds of the present invention and other HIV agents may be administered separately or in conjunction. In addition, one agent may be prior to, concurrent to, or subsequent to the administration of other agent(s).

The compounds of this invention may be made by a variety of methods, including well-known standard synthetic methods. Illustrative general synthetic methods are set out below and then the specific compounds of the invention are prepared in the working Examples.

In all of the schemes described below, protecting groups for sensitive or reactive groups are employed where necessary in accordance with general principles of synthetic chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T. W. Green and P. G. M. Wuts (1991) *Protecting Groups in Organic Synthesis*, John Wiley & Sons, incorporated by reference with regard to protecting groups). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art. The selection of processes as

well as the reaction conditions and order of their execution shall be consistent with the preparation of compounds of the present invention.

Those skilled in the art will recognize if a stereocenter exists in compounds of the present invention. Accordingly, the present invention includes all possible stereoisomers and includes not only racemic compounds but the individual enantiomers as well. When a compound is desired as a single enantiomer, such may be obtained by stereospecific synthesis or by resolution of the final product or any convenient intermediate. Resolution of the final product, an intermediate, or a starting material may be effected by any suitable method known in the art. See, for example, *Stereochemistry of Organic Compounds* by E. L. Eliel, S. H. Wilen, and L. N. Mander (Wiley-Interscience, 1994), incorporated by reference with regard to stereochemistry.

ABBREVIATIONS

As used herein the symbols and conventions used in these processes, schemes and examples are consistent with those used in the contemporary scientific literature, for example, the *Journal of the American Chemical Society* or the *Journal of Biological Chemistry*. Specifically, the following abbreviations may be used in the examples and throughout the specification:

g (grams);	mg (milligrams);
L (liters);	mL (milliliters);
μL (microliters);	psi (pounds per square inch);
M (molar);	mM (millimolar);
Hz (Hertz);	MHz (megahertz);
mol (moles);	mmol (millimoles);
rt (room temperature);	min (minute);
h (hour);	mp (melting point);
TLC (thin layer chromatography);	CH_2Cl_2 (methylene chloride);
TEA (triethylamine);	TFA (trifluoroacetic acid);
TFAA (trifluoroacetic anhydride);	THF (tetrahydrofuran);
$CDCl_3$ (deuterated chloroform);	CD_3OD (deuterated methanol);
SiO_2 (silica);	DMSO (dimethylsulfoxide);
EtOAc (ethyl acetate);	atm (atmosphere);

HCl (hydrochloric acid); $CHCl_3$ (chloroform);
DMF (*N*,*N*-dimethylformamide); Ac (acetyl);
Cs_2CO_3 (cesium carbonate); Me (methyl);
Et (ethyl); EtOH (ethanol);
MeOH (methanol); t-Bu (tert-butyl);
Et_2O (diethyl ether); N_2 (nitrogen);
MsCl (methanesulphonyl chloride); sat'd (saturated);
K_2CO_3 (potassium carbonate); DMAP (4-(dimethylamino)pyridine);
DCE (1,2-dichloroethane); Ps (polymer supported);
EDCI (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride);
P-BEMP (polymer-supported 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diaza-phosphorine); TsCl (tosyl chloride);
TES (triethylsilane); TBAF (tetrabutylammonium fluoride);
CSA (camphor sulfonic acid); n-BuLi (n-butyllithium);
TBDPSCl (tert-butyldiphenyl silylchloride);
HOAc (acetic acid); AcCl (acetyl chloride);
DIBAL-H (diisobutyl aluminium hydride);
DBU (1,8-diazabicyclo[5.4.0]undec-7-ene);
$MgSO_4$ (magnesium sulfate);
$NaHCO_3$ (sodium bicarbonate);
Pd/C (palladium on carbon);
DCM (dichloromethane);
Eq (equivalents);
IPA (isopropyl alcohol);
Rt (retention time);
SFC (supercritical fluid chromatography);
N (normal);
mCPBA (meta-chloroperoxybenzoic acid);
ACN (acetonitrile);
DBU (1,8-diazabicyclo[5.4.0]undec-7-ene);
$MgSO_4$ (magnesium sulfate);
$NaHCO_3$ (sodium bicarbonate);
Pd/C (palladium on carbon);

DCM (dichloromethane);

Eq (equivalents);

IPA (isopropyl alcohol);

Rt (retention time);

SFC (supercritical fluid chromatography;

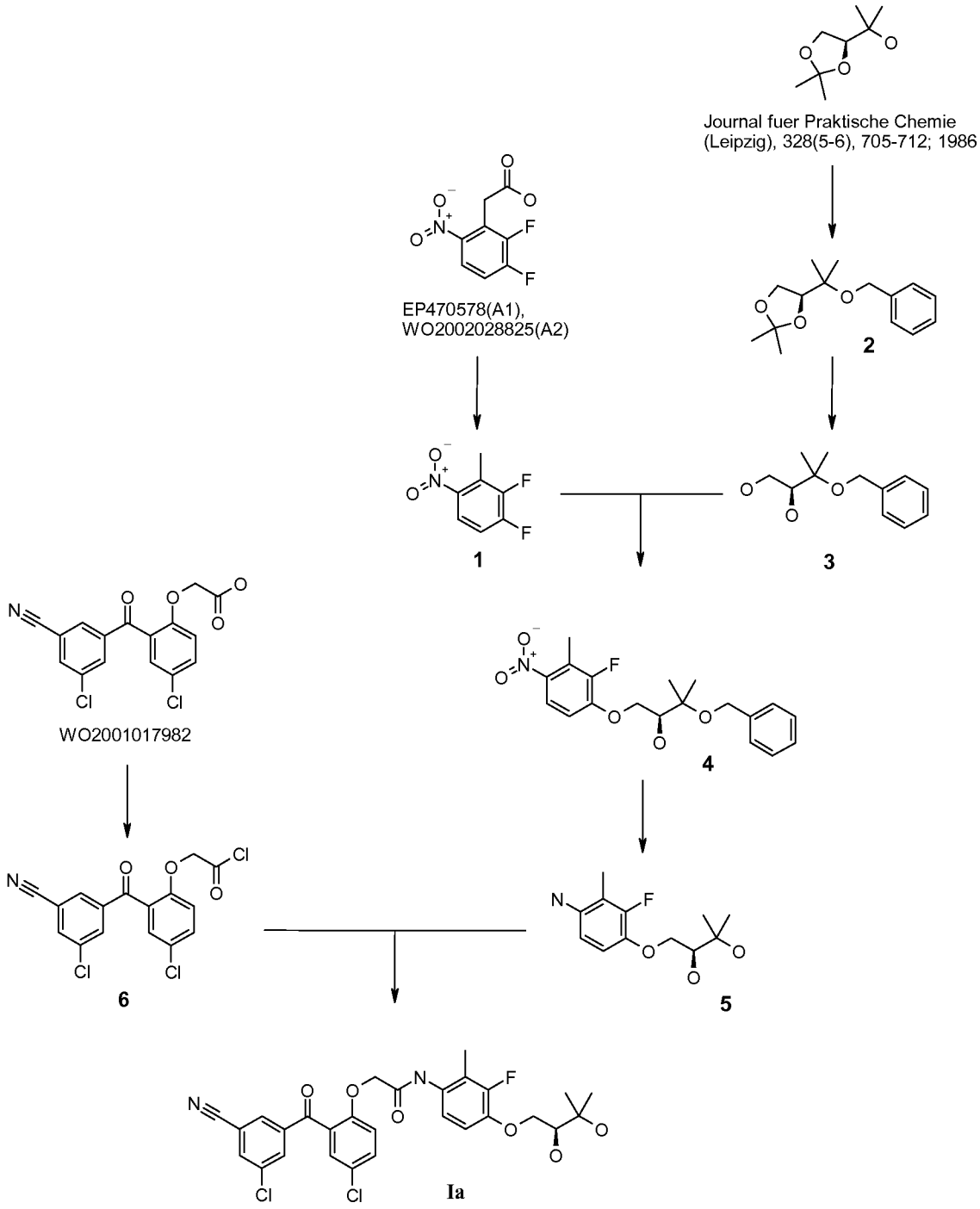
N (normal);

mCPBA (meta-chloroperoxybenzoic acid).

Unless otherwise indicated, all temperatures are expressed in °C (degrees Centigrade). All reactions conducted under an inert atmosphere at room temperature unless otherwise noted. Reagents employed without synthetic details are commercially available or made according to literature procedures.

Compounds of the present invention may be prepared by processes described hereinbelow.

Scheme 1:


Journal fuer Praktische Chemie
(Leipzig), 328(5-6), 705-712; 1986
EP470578(A1),
WO2002028825(A2)
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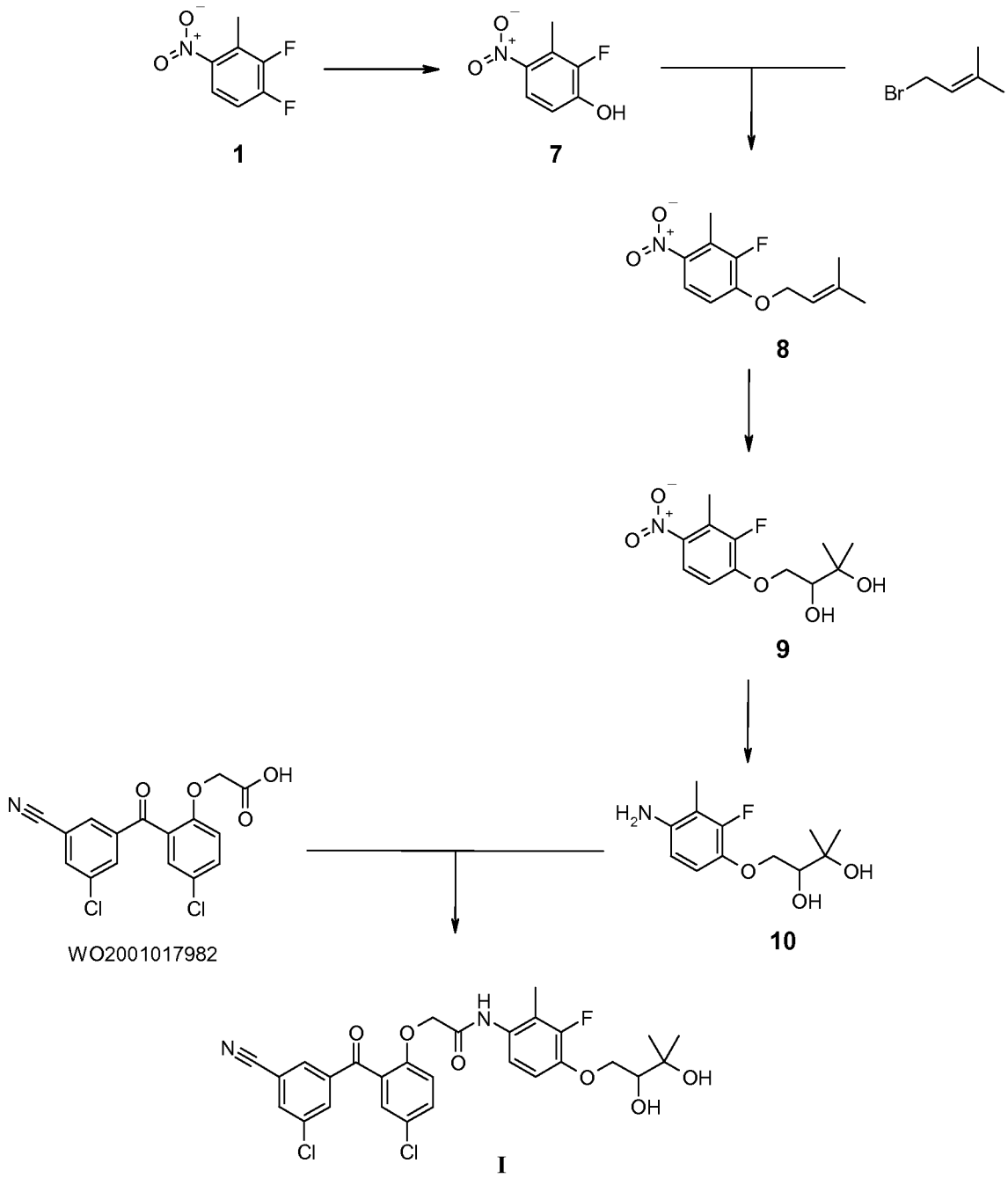
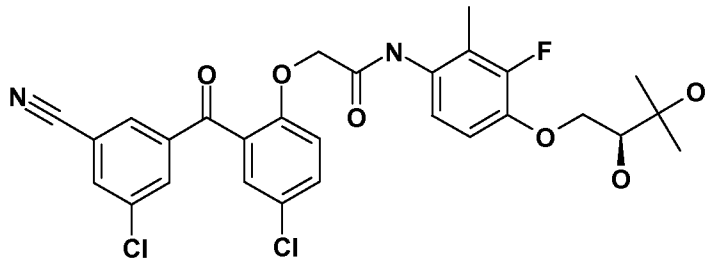
Scheme 2:

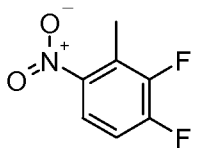


Example 1: 2-({4-chloro-2-[(3-chloro-5-cyanophenyl)carbonyl]phenyl}oxy)-*N*-(4-{[(2*S*)-2,3-dihydroxy-3-methylbutyl]oxy}-3-fluoro-2-methylphenyl)acetamide



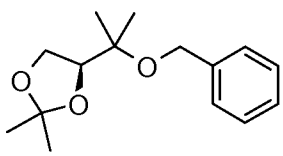
Procedure 1

Step A: 1,2-difluoro-3-methyl-4-nitrobenzene (intermediate **1**)



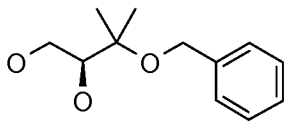
(2,3-difluoro-6-nitrophenyl)acetic acid (34.78g, 160mmol, EP470578(A1), WO2002028825(A2)) was combined with copper(I) oxide (4.58g, 32mmol, 0.2eq) in 500mL acetonitrile and heated at reflux 1h. The reaction mixture was filtered through celite and the filtrate was concentrated to a green oil. This residue was dissolved in diethyl ether and filtered through celite a second time. The filtrate was concentrated to dryness and the crude product purified by vacuum distillation (79-90°C, 2-5mm Hg) to give the title compound (28.0g) as a light yellow oil which crystallized on standing. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.44 (d, *J*=2.7 Hz, 3 H), 7.57 (m, 1 H), 7.95 (ddd, *J*=9.3, 4.7, 2.1 Hz, 1 H).

Step B: (4*S*)-2,2-dimethyl-4-{1-methyl-1-[(phenylmethyl)oxy]ethyl}-1,3-dioxolane (intermediate **2**)



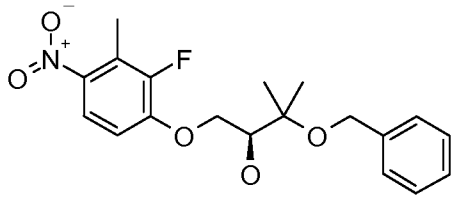
To a stirred slurry of sodium hydride (60% in mineral oil, 13.5g, 336mmol, 1.2 eq) in 400mL dry THF was added 2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-propanol (44.89g, 280mmol, *Journal fuer Praktische Chemie* (Leipzig), 328(5-6), 705-712; 1986) in 200mL dry THF dropwise at ambient temperature. The reaction mixture was stirred 30min post-addition at ambient temperature. To this mixture was added tetrabutylammonium iodide (5.18g, 14mmol, 0.05eq) followed by dropwise addition of benzyl bromide (47.9g, 280mmol, 1eq) in 300mL dry THF at ambient temperature. The reaction mixture was stirred at ambient temperature for 16h, quenched by addition of 1L water, and extracted twice with EtOAc. The organic phases were combined, dried over $MgSO_4$, filtered, and the filtrate concentrated to dryness to give the title compound (70.1g) as a golden oil which was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.16 (s, 3 H), 1.20 (s, 3 H), 1.26 (s, 3 H), 1.33 (s, 3 H), 3.81 (m, 1 H), 3.93 (m, 1 H), 4.05 (m, 1 H), 4.47 (m, 2 H), 7.21-7.33 (m, 5 H).

Step C: (2*S*)-3-methyl-3-[(phenylmethyl)oxy]-1,2-butanediol (intermediate **3**)



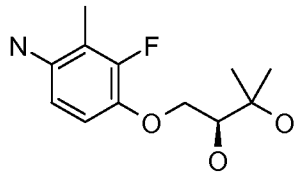
A solution of (4*S*)-2,2-dimethyl-4-{1-methyl-1-[(phenylmethyl)oxy]ethyl}-1,3-dioxolane (70.1g crude, intermediate **2**) in 560mL THF was treated with 560mL 1N HCl at ambient temperature for 4h. The reaction mixture was concentrated to remove most of the THF, diluted with water, and extracted four times with diethyl ether. The organic phases were combined, dried over $MgSO_4$, filtered, and the filtrate concentrated to dryness to give crude title compound (58.9g) as an amber oil which was used without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.11 (s, 3 H), 1.19 (s, 3 H), 3.29 (m, 1 H), 3.42 (m, 1 H), 3.65 (m, 1 H), 4.30 (dd, *J*=6.0, 5.4 Hz, 1 H), 4.4 (m, 2 H), 4.7 (d, *J*=4.9 Hz, 1 H), 7.20-7.34 (m, 5 H).

Step D: (2*S*)-1-[(2-fluoro-3-methyl-4-nitrophenyl)oxy]-3-methyl-3-[(phenylmethyl)oxy]-2-butanol (intermediate **4**)



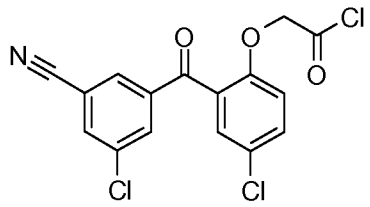
(2*S*)-3-methyl-3-[(phenylmethyl)oxy]-1,2-butanediol (58.9g crude, intermediate **3**) and 1,2-difluoro-3-methyl-4-nitrobenzene (42.6g, 219mmol, intermediate **1**) were combined in 730mL benzene and treated with 730mL 6N NaOH and benzyltriethylammonium chloride (2.50g, 11mmol, 0.05eq) with vigorous mechanical stirring at 60°C for 16h. The phases were separated and the aqueous phase extracted twice with EtOAc. The organic phases were combined, dried over $MgSO_4$, filtered, and the filtrate concentrated to dryness. The crude material was purified by flash chromatography on silica eluted with 0 → 40% EtOAc in hexanes. Appropriate fractions were combined and concentrated to give the title compound (33.9g, 93.2mmol, 33% over 3 steps) as an amber oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.22 (s, 3 H), 1.28 (s, 3 H), 2.42 (d, *J*=2.6 Hz, 3 H), 3.79 (t, *J*=5.9 Hz, 1 H), 4.10 (dd, *J*=10.3, 8.1 Hz, 1 H), 4.41 (dd, *J*=10.3, 2.0 Hz, 1 H), 4.49 (m, 2 H), 5.38 (d, *J*=6.0 Hz, 1 H), 7.20-7.33 (m, 6 H), 7.88 (dd, *J*=9.2, 1.7 Hz, 1 H).

Step E: (2*S*)-1-[(4-amino-2-fluoro-3-methylphenyl)oxy]-3-methyl-2,3-butanediol (intermediate **5**)



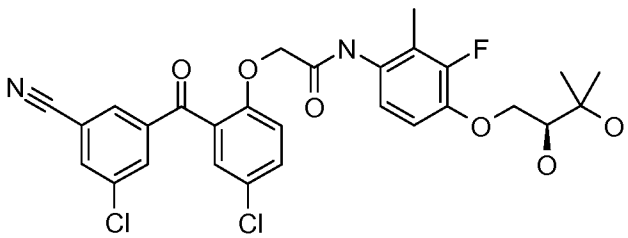
(2*S*)-1-[(2-fluoro-3-methyl-4-nitrophenyl)oxy]-3-methyl-3-[(phenylmethyl)oxy]-2-butanol (33.87g, 93.2mmol, intermediate **4**) dissolved in 200mL EtOH was treated with palladium hydroxide (3g, 20% on carbon) under an atmosphere of 60psi hydrogen gas with vigorous stirring for 3 days. The catalyst was filtered off through celite and the filtrate concentrated to dryness to give the title compound (20.39g, 83.8mmol, 90%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.02 (s, 3 H), 1.10 (s, 3 H), 1.94 (d, *J*=2.0 Hz, 3 H), 3.48 (ddd, *J*=8.0, 5.7, 2.3 Hz, 1 H), 3.70 (dd, *J*=10.1, 8.1 Hz, 1 H), 4.07 (dd, *J*=10.0, 2.3 Hz, 1 H), 4.31 (s, 1 H), 4.67 (s, 2 H), 4.90 (d, *J*=5.7 Hz, 1 H), 6.33 (dd, *J*=8.7, 1.6 Hz, 1 H), 6.70 (t, *J*=9.1 Hz, 1 H).

Step F: ({4-chloro-2-[(3-chloro-5-cyanophenyl)carbonyl]phenyl}oxy)acetyl chloride (intermediate **6**)



To a suspension of ({4-chloro-2-[(3-chloro-5-cyanophenyl)carbonyl]phenyl}oxy)acetic acid (74.85g, 213.8mmol, WO2001017982) in 1L DCM was added a catalytic amount of DMF (1mL) followed by dropwise addition of 2M oxalyl chloride in DCM (214mL, 428mmol, 2eq) at ambient temperature with stirring. The reaction mixture was stirred 1h post-addition at ambient temperature at which time no further carbon dioxide evolution was noted. The reaction mixture was concentrated to dryness and pumped under high vacuum to give the title compound as a yellow solid (78.8g, 213.8mmol) which was used without further purification or characterization.

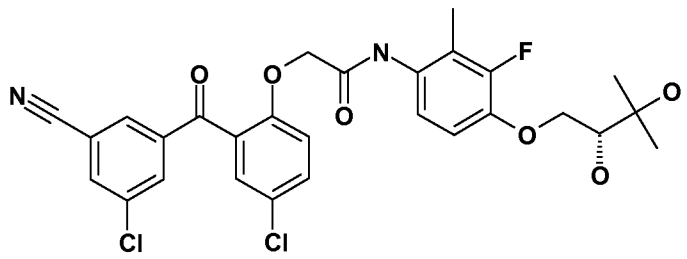
Step G: **2**-({4-chloro-2-[(3-chloro-5-cyanophenyl)carbonyl]phenyl}oxy)-*N*-(4-{[(2*S*)-2,3-dihydroxy-3-methylbutyl]oxy}-3-fluoro-2-methylphenyl)acetamide



(2*S*)-1-[(4-amino-2-fluoro-3-methylphenyl)oxy]-3-methyl-2,3-butanediol (29.9g, 81.1mmol, intermediate **5**) and ({4-chloro-2-[(3-chloro-5-cyanophenyl)carbonyl]phenyl}oxy)acetyl chloride (19.73g, 81.1mmol, 1eq, intermediate **6**) were combined in 300mL acetone with sodium bicarbonate (34.06g, 405mmol, 5eq) and stirred 2h at ambient temperature. The reaction mixture was concentrated, partitioned between EtOAc and water, and the phases separated. The aqueous phase was extracted twice with EtOAc. The organic phases were combined, dried over $MgSO_4$, filtered, and the filtrate concentrated to a white solid. The crude product was recrystallized from

900mL boiling ethyl alcohol, cooled in an ice-acetone bath, filtered and the filter cake washed three times with 200mL cold EtOH. The precipitate was air dried to give the title compound (35.83g, 62.3mmol, 77%) as a white crystalline solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.05 (s, 3 H), 1.12 (s, 3 H), 1.95 (d, *J*=2.4 Hz, 3 H), 3.53 (ddd, *J*=8.0, 5.9, 2.1 Hz, 1 H), 3.85 (dd, *J*=10.1, 8.1 Hz, 1 H), 4.23 (dd, *J*=10.1, 2.0 Hz, 1 H), 4.41 (s, 1 H), 4.73 (s, 2 H), 5.03 (d, *J*=5.7 Hz, 1 H), 6.98 (m, 2 H), 7.22 (d, *J*=9.2 Hz, 1 H), 7.53 (d, *J*=2.6 Hz, 1 H), 7.68 (dd, *J*=9.0, 2.7 Hz, 1 H), 8.06 (m, 1 H), 8.13 (t, *J*=1.5 Hz, 1 H), 8.30 (m, 1 H), 9.29 (s, 1 H). LCMS (ES$^-$) *m/z* 573.06, 575.01 (M-H), LCMS (ES$^+$) *m/z* 597.07, 599.07 (M+Na). ee = 96.4% (chiral SFC, 25% CH_3OH in CO_2, 2000psi, 30°C, 2mL/min on a 4.6 x 250mm Diacel OJ-H column; Rt = 6.3min, first eluting peak of racemic mixture).

Example 2: 2-({4-chloro-2-[(3-chloro-5-cyanophenyl)carbonyl]phenyl}oxy)-*N*-(4-{[(2*R*)-2,3-dihydroxy-3-methylbutyl]oxy}-3-fluoro-2-methylphenyl)acetamide

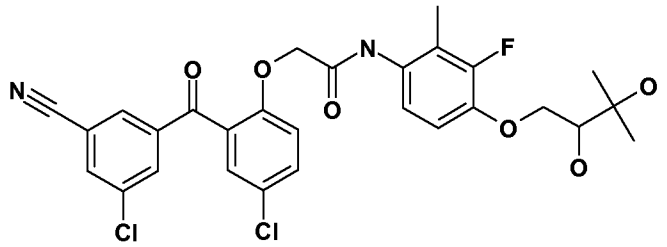


Procedure 2:

Example **2** was prepared via the method of Procedure 1 with the following exception: 2-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-propanol was used in place of 2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-propanol in step B. 2-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-propanol was in turn prepared according to the method of Schrotter *et. al.* (*Journal fuer Praktische Chemie* (Leipzig), 328(5-6), 705-712; 1986) from methyl (4*R*)-2,2-dimethyl-1,3-dioxolane-4-carboxylate instead of methyl (4*S*)-2,2-dimethyl-1,3-dioxolane-4-carboxylate. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.05 (s, 3 H), 1.12 (s, 3 H), 1.95 (d, *J*=2.4 Hz, 3 H), 3.53 (ddd, *J*=8.0, 5.9, 2.1 Hz, 1 H), 3.85 (dd, *J*=10.1, 8.1 Hz, 1 H), 4.23 (dd, *J*=10.1, 2.0 Hz, 1 H), 4.41 (s, 1 H), 4.73 (s, 2 H), 5.03 (d, *J*=5.7 Hz, 1 H), 6.98 (m, 2 H), 7.22 (d, *J*=9.2 Hz, 1 H), 7.53 (d, *J*=2.6 Hz, 1 H), 7.68 (dd, *J*=9.0, 2.7 Hz, 1 H), 8.06

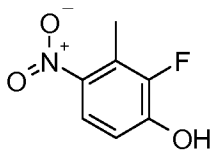
(m, 1 H), 8.13 (t, *J*=1.5 Hz, 1 H), 8.30 (m, 1 H), 9.29 (s, 1 H). LCMS (ES^-) *m/z* 573.26 (M-H), LCMS (ES^+) *m/z* 597.28 (M+Na). ee = 97.4% (chiral SFC, 25% CH_3OH in CO_2, 2000psi, 30°C, 2mL/min on a 4.6 x 250mm Diacel OJ-H column; Rt = 7.4min, second eluting peak of racemic mixture).

Example 3: 2-({4-chloro-2-[(3-chloro-5-cyanophenyl)carbonyl]phenyl}oxy)-*N*-{4-[(2,3-dihydroxy-3-methylbutyl)oxy]-3-fluoro-2-methylphenyl}acetamide



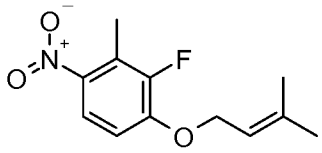
Procedure 3:

Step A: 2-fluoro-3-methyl-4-nitrophenol (intermediate **7**)



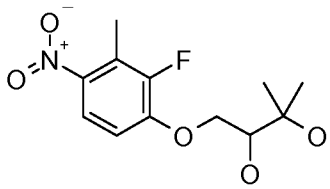
To a solution of 1,2-difluoro-3-methyl-4-nitrobenzene (1.0 g, 5.7 mmol, intermediate **1**) in anhydrous DMF (15 mL) was added sodium acetate (2.4 g, 28.9 mmol) and the solution heated to 120°C for 24 h. The reaction was diluted with ethyl acetate and washed with water, followed by brine and dried over $MgSO_4$ and chromatographed on silica gel eluted with 0 to 30% EtOAc in hexanes. Appropriate fractions were combined and concentrated to give the title compound (311 mg, 1.8 mmol, 32%) as an orange solid. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.40 (d, J = 2.6 Hz, 3 H), 6.93 (t, J = 9.1 Hz, 1 H), 7.81 (d, J = 9.2 Hz, 1 H), 11.26 (br s, 1 H). LCMS (ES-) *m/z* 170.12 (M-H).

Step B: 2-fluoro-3-methyl-1-[(3-methyl-2-buten-1-yl)oxy]-4-nitrobenzene (intermediate **8**)



To a solution of 2-fluoro-3-methyl-4-nitrophenol (311 mg, 1.8 mmol, intermediate **7**) and potassium carbonate (500 mg, 3.6 mmol) in anhydrous DMF (5 mL) was added 1-bromo-3-methyl-2-butene (315 μL, 2.7 mmol) and the solution stirred 2h at ambient temperature. The reaction was partitioned between equal volumes of EtOAc and water. The organic layer was washed with brine and dried over $MgSO_4$ and concentrated. The crude product was chromatographed on silica gel eluting with 0 to 40% EtOAc in hexanes. Appropriate fractions were combined and concentrated to give the title compound (400 mg, 1.7 mmol, 93%) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.73 (d, J = 11.0 Hz, 6 H), 2.41 (d, J = 2.6 Hz, 3 H), 4.72 (d, J = 6.6 Hz, 2 H), 5.44 (t, J = 6.6 Hz, 1 H), 7.23 (t, J = 8.8 Hz, 1 H), 7.93 (d, J = 9.2 Hz, 1H).

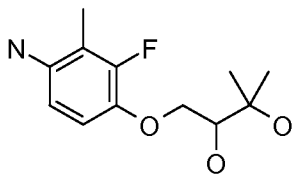
Step C: 1-[(2-fluoro-3-methyl-4-nitrophenyl)oxy]-3-methyl-2,3-butanediol (intermediate **9**)



To a solution of 2-fluoro-3-methyl-1-[(3-methyl-2-buten-1-yl)oxy]-4-nitrobenzene (400 mg, 1.7 mmol, intermediate **8**) in anhydrous dichloromethane (20 mL) was added mCPBA (750 mg, 3.4 mmol, 77%) and the reaction stirred for 2h at ambient temperature. The reaction was diluted with dichloromethane and washed with equal portions of aqueous sodium thiosulfate, saturated sodium bicarbonate (2X) and brine, dried over $MgSO_4$ and concentrated to afford a white solid which was used without further purification. The residue was dissolved in THF (12 mL) and diluted with water (6 mL) and to the solution was added methanesulfonic acid (0.6 mL) and the solution heated to 80^0 C in a sealed tube for 45 min. The solution was partitioned between EtOAc and water.

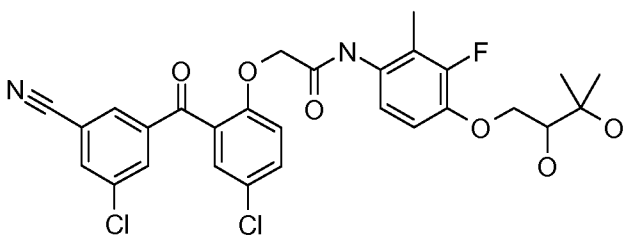
The organic layer was washed with saturated sodium bicarbonate solution followed by brine and dried over $MgSO_4$ and concentrated. The crude product was purified on silica gel eluting with 20-75% EtOAc in hexanes to give the title compound (369 mg, 1.4 mmol, 79%) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.22 (s, 3 H), 1.28 (s, 3 H), 2.43 (d, J = 2.6 Hz, 3 H), 3.54-3.59 (m, 1 H), 3.99-4.04 (m, 1 H), 4.39 (d, J = 10.3 Hz, 1 H), 4.49 (s, 1 H), 5.15 (d, J = 5.9 Hz, 1 H), 7.26 (t, J = 8.8 Hz, 1 H), 7.92 (d, J = 9.1 Hz, 1 H).

Step D: 1-[(4-amino-2-fluoro-3-methylphenyl)oxy]-3-methyl-2,3-butanediol (intermediate **10**)



To a solution of 1-[(2-fluoro-3-methyl-4-nitrophenyl)oxy]-3-methyl-2,3-butanediol (369 mg, 1.4 mmol, intermediate **9**) in ethanol (10 mL) was added 10% palladium on carbon (40 mg) and stirred under an atmosphere of 60 psi hydrogen gas with stirring for 2h at ambient temperature whereupon the catalyst was filtered through celite and the filtrate concentrated to dryness to give the title compound (296 mg, 1.2 mmol, 90%) as a white solid. . ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.02 (s, 3 H), 1.10 (s, 3 H), 1.94 (d, *J*=2.0 Hz, 3 H), 3.48 (ddd, *J*=8.0, 5.7, 2.3 Hz, 1 H), 3.70 (dd, *J*=10.1, 8.1 Hz, 1 H), 4.07 (dd, *J*=10.0, 2.3 Hz, 1 H), 4.31 (s, 1 H), 4.67 (s, 2 H), 4.90 (d, *J*=5.7 Hz, 1 H), 6.33 (dd, *J*=8.7, 1.6 Hz, 1 H), 6.70 (t, *J*=9.1 Hz, 1 H).

Step E: 2-({4-chloro-2-[(3-chloro-5-cyanophenyl)carbonyl]phenyl}oxy)-*N*-{4-[(2,3-dihydroxy-3-methylbutyl)oxy]-3-fluoro-2-methylphenyl}acetamide

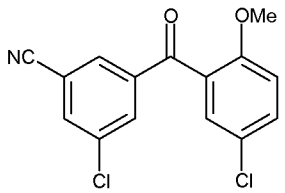


({4-chloro-2-[(3-chloro-5-cyanophenyl)carbonyl]phenyl}oxy)acetic acid (60 mg, 0.17 mmol, WO2001017982), 1-[(4-amino-2-fluoro-3-methylphenyl)oxy]-3-methyl-2,3-butanediol (50 mg, 0.2mmol, intermediate **10**), 1-hydroxybenzotriazole hydrate (6 mg) and 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (38 mg, 0.2 mmol) were combined with anhydrous dichloromethane (1.5 mL) and stirred for 1h at ambient temperature. The reaction mixture was purified on silica gel eluting with 50 to 100% EtOAc in hexanes. Appropriate fractions were collected and concentrated and the residue dissolved in EtOAc and washed with equal portions of 0.1 N HCl, water and brine. The organic layer was dried over $MgSO_4$ and concentrated to give the title compound (77 mg, 0.13 mmol, 79%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.05 (s, 3 H), 1.12 (s, 3 H), 1.95 (d, *J*=2.4 Hz, 3 H), 3.53 (ddd, *J*=8.0, 5.9, 2.1 Hz, 1 H), 3.85 (dd, *J*=10.1, 8.1 Hz, 1 H), 4.23 (dd, *J*=10.1, 2.0 Hz, 1 H), 4.41 (s, 1 H), 4.73 (s, 2 H), 5.03 (d, *J*=5.7 Hz, 1 H), 6.98 (m, 2 H), 7.22 (d, *J*=9.2 Hz, 1 H), 7.53 (d, *J*=2.6 Hz, 1 H), 7.68 (dd, *J*=9.0, 2.7 Hz, 1 H), 8.06 (m, 1 H), 8.13 (t, *J*=1.5 Hz, 1 H), 8.30 (m, 1 H), 9.29 (s, 1 H). LCMS (ES-) *m/z* 573.09 (M–H).

Example 4: 2-({4-chloro-2-[(3-chloro-5-cyanophenyl)carbonyl]phenyl}oxy)-*N*-(4-{[(2*S*)-2,3-dihydroxy-3-methylbutyl]oxy}-3-fluoro-2-methylphenyl)acetamide, Form 2

27.0g 2-({4-chloro-2-[(3-chloro-5-cyanophenyl)carbonyl]phenyl}oxy)-*N*-(4-{[(2*S*)-2,3-dihydroxy-3-methylbutyl]oxy}-3-fluoro-2-methylphenyl)acetamide made according to Example 1 was added to approximately 600mL of refluxing ethanol and stirred at this temperature until complete solution was obtained. The solution was allowed to cool slowly to ambient temperature then stirred for 2h at which time crystallization was noted. The mixture was cooled in an ice bath and stirred an additional 30min. The reaction mixture was filtered and the filter cake washed with cold ethanol and air dried. The resultant solid was further dried under high vacuum to give 24.6g of the title compound as a white crystalline powder. Characterization of this material by ^{1}H NMR and LC-MS gave results consistent with those obtained for the material in Example 1. Melting point was determined by differential scanning calorimetry using a non-hermetically crimped aluminum pan at a heating rate of 10 °C/min. Melting point onset was approximately 160° C.

Example 5 3-chloro-5-{[5-chloro-2-(methyloxy)phenyl]carbonyl}benzonitrile (Intermediate)



Under a nitrogen atmosphere, a reactor was charged with (3-bromo-5-chlorophenyl)[5-chloro-2-(methyloxy)phenyl]methanone (1.0 wt, 1.0 eq) and zinc cyanide (0.20 wt, 0.60 equiv.), and 90% 1,2-dimethoxyethane/water (5 vol). The reactor contents were heated to approximately 80°C under nitrogen. A slurry of 1,1-bis(diphenylphosphino) ferrocene (DPPF, 0.01 wt, 0.0065 equiv) and palladium acetate (.0031 wt, .005 equiv.) in DME (0.15 vol) was added in a single portion and washed into reactor with additional DME (0.05 vol). PMHS (0.01wt, 0.06 equiv) in DME (0.1 vol) was added in a single portion. The reaction was stirred at approximately 80°C for 2 hours. The second half of the catalyst, ligand, and PMHS was charged by adding a slurry of 1,1-bis(diphenylphosphino)ferrocene (DPPF, 0.01 wt, 0.0065 equiv) and palladium acetate (.0031 wt, .005 equiv.) in DME (0.15 vol) and washed into reactor with additional DME (0.05 vol). PMHS (0.01wt, 0.06 equiv) in DME (0.1 vol) was added in a single portion. The reaction was allowed to heat at approximately 80°C for an additional two hours at which point remaining starting material is <1% by standard LC method. The mixture was cooled to 20°C and a prepared solution of concentrated NH_4OH (1 vol), saturated aqueous NH_4Cl (4 vol), and water (5 vol) was added at such a rate that internal temperature was maintained below 30°C. After stirring for 1 hour the reaction mixture was filtered through filter cloth and the reactor rinsed with water (2 vol) through the filter cake. The filter cake was then washed with additional water (4 X 2 vol) and suctioned dry. The resulting solid was placed back in the reactor and disolved in acetone (8 vol) with warming to 50° C. The contents were filtered through celite pad and washed with acetone (0.1 vol). The filtrate was maintained at 50° C and treated with water (0.9 vol) while maintaining solution. The reactor was cooled to 10°C over a one hour period and maintained at 10°C for 1 to 2 hours. The solids were then filtered through filter cloth and the cake rinsed with cold 9:1

acetone:water (2x1 vol). The solid was transferred to a drying oven and dried under vacuum at 50°C for 24 hours. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 (s, 1H) 8.02 (s, 1H) 7.94 (s, 1H) 7.63 (d, J=8.8Hz, 1H) 7.45 (s, 1H) 7.22 (d, J=9.0Hz, 1H) 3.65 (s, 3H).

Example 6: Biological Activity

Inhibition of Viral Replication

I. HeLa Cell Assay

The HeLa cell assay was performed according to a modifcation of Kimpton J. and Emerman M., Detection of replication-competent and pseudotyped human immunodeficiency virus with a sensitive cell line on the basis of activation of an integrated β-galactosidase gene, *J. Virol.* 66:2232-2239 (1992), in which HIV-1 infection is detected by the activation of an HIV-LTR driven β-galactosidase reporter that is integrated into the genome of a $CD4^+$ HeLa cell line. Quantitation of β -galactosidase is achieved by measuring the activation of a chemiluminescent substrate (Applied Biosystems). The concentration of each compound required to inhibit 50% (IC_{50}) of the HIV-1 induced β -galactosidase signal, relative to untreated controls, was determined for each isogenic, recombinant virus.

A. Materials

HeLa-CD4-LTR- β -gal cell line (AIDS Research and Reference Reagent Program, Division of AIDS, NIAID)

DMEM (GibcoBRL # 12430-047)

Trypsin-EDTA (GibcoBRL #25300-054)

Heat inactivated Fetal Bovine Serum (FBS) (Hyclone # SH30070.03)

Geneticin (GibcoBRL # 10131-035)

Hygromycin B (GibcoBRL #1687-010)

96-well, black, clear-bottom, tissue culture-treated plates (Costar # 3904)

Phosphate Buffered Saline (PBS) (GibcoBRL #14190-144)

Dimethyl Sulfoxide (DMSO) (ATCC # 741625)

Gal-Screen Reporter Gene Assay System (Applied Biosystems # T1030)

B. Growth and Maintenance of the CD4-HIV LTR- β -gal HeLa cell line.

HeLa-CD4-LTR- β -gal cells are propagated in DMEM containing 10% fetal bovine serum + 0.2 mg/ml geneticin + 0.1 mg/ml hygromycin B. Cells are split by standard trypsinization when confluency reaches 80% (roughly every 2 to 3 days).

C. Construction of HIV-1 reverse transcriptase (RT) mutants

DNA encoding the HIV-1 reverse transcriptase was subcloned from a M13 phage into a general shuttle vector, pBCSK+, as a ~1.65 kbp EcoRI/HindIII ended DNA fragment. The HIV DNA insert of the resulting plasmid, pRT2, was completely sequenced on both strands prior to use in site directed mutagenesis experiments. Specific amino acid replacements were made using Stratagene Quick Change reagents and mutagenic oligonucleotides from Oligos. Following mutagenesis, the entire mutant RT coding sequence was verified by sequencing both DNA strands.

D. Construction of isogenic HIV-1 RT mutant virus

Mutant HIV-1 strains were isolated by a modified Recombinant Virus Assay (Kellam P. and Larder B., Recombinant virus assay: a rapid, phenotypic assay for assessment of drug susceptibility of human immunodeficiency virus type 1 isolates, *Antimicrobial Agents and Chemotherapy,* 38:23-30, 1994). 1 X 10^7 MT4 T-cells (maintained in RPMI containing 10% fetal bovine serum, split 1:5 every 5 to 6 days) were co-transfected with EcoRI/HindIII digested mutant RT plasmid and Bst EII-digested HIV-$1_{HXB2\Delta RT}$ DNA in the presence of DMRIE-C transfection reagent (Gibco) according to supplier's recommended protocol. Each mutant RT coding sequence was crossed into the RT-deleted HIV-1 viral DNA backbone by in vivo homologous recombination. Transfected cell cultures were expanded and monitored until syncitia formation and CPE were extensive. Virus was harvested by clear spin of the culture supernatants and frozen at - 80^0C as primary stock. Recombinant progeny virus was sequenced in the RT region to confirm the mutant genotype. Virus stocks were further expanded by infection of MT4 cells, harvested and stored as frozen aliquots. Stocks were titered in HeLa MAGI cells for assay.

E. Titering of virus stocks.

HIV-1 virus stocks were titered in the HeLa-CD4-LTR- β-gal assay system to establish the appropriate infecting dose. The endpoint for this assay is relative light units (RLUs), and titer is recorded as RLUs/ml. Virus stocks are diluted (serial 1:2) into DMEM containing 10% FBS plus 25ug/ml DEAE-dextran and assayed as described in the "Experimental Protocol" section below without test compound.

A "multiplicity of infection" (MOI) defined as infectious units per cell is usually not calculated but is typically <<1.0. Relationship of RLUs/ml to other measures of infectivity such as HeLa PFU/ml or MT4 TCID50/ml may not be consistent from lot to lot or strain to strain and should be determined for each lot.

F. Experimental Protocol

Day 1

1. Seed 96-well plate(s) (Costar #3904) with HeLa-CD4-LTR- β-gal @ 3 X 103 cells per well in 100ul DMEM containing 10% FBS. Incubate @ 37^0C, 5% CO_2 overnight.

Day 2

1. Thaw virus stock in a water bath (room temperature) and dilute into DMEM +10% FBS + 25ug/ml DEAE-dextran to an infectious dose of approximately 10 million RLU/ml. The dilution of virus will vary depending on the titer of the stock (see "Titering of virus stocks" above).
2. Remove all of the media from every well with an 8 or 12-channel manifold aspirator. Work with one plate at a time to prevent drying of the HeLa-CD4-LTR-β-gal monolayer. Add 35ul (approximately 350,000 total RLUs) of diluted virus to each well. Incubate @ 37^0C, 5% CO_2 for 2 hours.
3. During the virus adsorption period prepare compound titration plates at 1.35X final concentration. In general, test compounds are titrated robotically in a four-fold stepwise manner from 2.7uM (2uM final) down to 0.01nM (0.008nM final). This scheme will allow for 8 test compounds per 96-well plate with 10 dilution points and 2 controls per compound (n=1). Test compounds are titrated into DMEM +

10% FBS + 0.135% DMSO (0.1% final). The final volume of titrated compound in each well should be at least 150ul and DMSO should be at 0.135% (0.1% final) including the no compound controls.

4. Remove 100ul of titrated compound from every well of the titration plate prepared in step 3 above and add to the virus adsorption plate (step 2 above).
5. Incubate @ 37^0C, 5% CO_2 for 72 hours.

Day 5

1. Reduce supernatants to 50uL and add 50uL of reconstituted Gal-Screen according to manufacturer's recommended protocol.
2. Mix plate(s) virgorously on a platform shaker.
3. Read plate(s) in a Topcount luminometer (Packard) at 1s/well.

G. Data Analysis

Raw data are transformed into percent of control by the following formula: (raw signal in each well / average raw signal for the two no compound controls in the same row)*100. Percent of control is plotted vs. compound concentration using either Robsage or Robofit programs (GSK). The default model is Y=Vmax*1-(x^n/(K^n+x^n)), however, any other model giving a reasonable estimation of the IC_{50} ("K" in formula) may be used.

Table 1. Antiviral activity against wild type and clinically relevant HIV. IC_{50} (nM)

Example No.	K103N	K103N/ G190A	V106A	V106I/Y181C	WTRVA	Y181C
1	a	a	a	b	a	a
2	a	b	a	b	a	a
3	a	ND	a	ND	a	a
10 +	a	b	b	b	a	a
251 *	b	ND	b	ND	a	b
105 *	b	c	c	c	b	b

106 *	b	c	c	c	b	b
252 *	b	b	b	b	b	b
1001**	b	ND	b	ND	a	b
1018**	c	ND	c	ND	b	c

a < 1nM

b 1 - 10 nM

c > 10 nM

[+] Compound 40, Example No. 10 from WO 02/070470

[*] Example No. from WO 01/17982

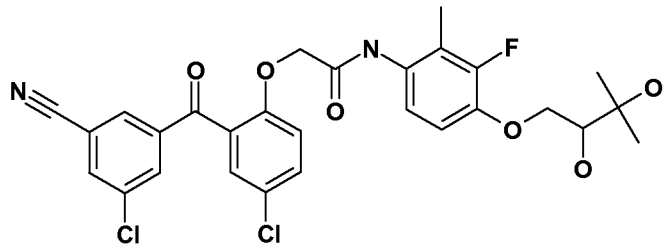
** Example No. from US 2006/0025480A1

ND = not determined

CLAIMS

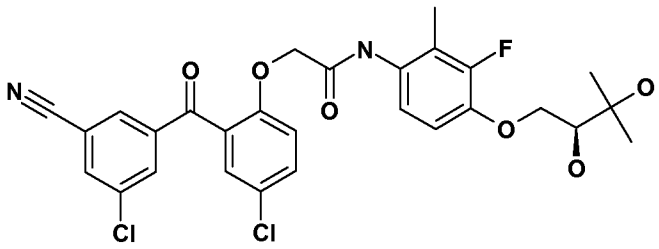
What is claimed is:

1. A compound of formula (I):



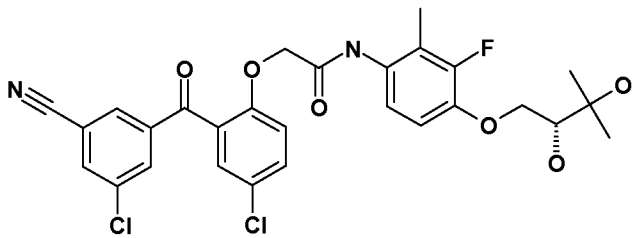
(I).

2. A compound of formula (IA):



(IA).

3. A compound of formula (IB):



(IB).

4. 2-({4-chloro-2-[(3-chloro-5-cyanophenyl)carbonyl]phenyl}oxy)-*N*-(4-{[(2*S*)-2,3-dihydroxy-3-methylbutyl]oxy}-3-fluoro-2-methylphenyl)acetamide.

5. 2-({4-chloro-2-[(3-chloro-5-cyanophenyl)carbonyl]phenyl}oxy)-*N*-(4-{[(2*S*)-2,3-dihydroxy-3-methylbutyl]oxy}-3-fluoro-2-methylphenyl)acetamide Form 2.

6. A pharmaceutical composition comprising a compound according to any of claims 1 to 5 and a pharmaceutically acceptable carrier.

7. A compound according to any of claims 1 to 5 for use in medical therapy.

8. A compound according to any of claims 1 to 5 for use in the treatment of viral infections and associated conditions.

9. A compound according to claim 8 wherein the viral infection is HIV infection.

10. The use of a compound according to any of claims 1 to 5 in the manufacture of a medicament for use in the treatment of viral infections and associated conditions.

11. The use of claim 10, wherein the viral infection is an HIV infection.

12. A method for the treatment of an HIV infection, comprising the administration of a compound according to any of claims 1 to 5.

13. A composition according to claim 6 wherein said composition comprises at least one additional therapeutic agent selected from the group consisting of nucleoside reverse transcriptase inhibitors such as zidovudine, didanosine, lamivudine, zalcitabine, abacavir, stavidine, adefovir, adefovir dipivoxil, fozivudine, todoxil, emtricitabine, alovudine, amdoxovir, elvucitabine, and similar agents; non-nucleoside reverse transcriptase inhibitors (including an agent having anti-oxidation activity such as immunocal, oltipraz, etc.) such as nevirapine, delavirdine, efavirenz, loviride, immunocal, oltipraz, capravirine, TMC-278, TMC-125, etravirine, and similar agents; Protease inhibitors such as saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, fosamprenavir, brecanavir, palinavir, lasinavir, atazanavir, tipranavir, and similar agents; Entry inhibitors such as enfuvirtide (T-20), T-1249, PRO-542, PRO-140, TNX-355, BMS-806, 5-Helix and similar agents; Integrase inhibitors such as L-870,180 and similar agents; Budding inhibitors such as PA-344 and PA-457, and similar agents; and CXCR4 and/or CCR5 inhibitors such as vicriviroc (Sch-C), Sch-D, TAK779, maraviroc (UK 427,857), TAK449; and similar agents.