(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 November 2010 (18.11.2010)

PCT

(10) International Publication Number
WO 2010/132663 A1

(51) International Patent Classification:
C07D 213/42 (2006.01) *A61P 31/00* (2006.01)
A61K 31/4402 (2006.01) *C07B 59/00* (2006.01)

(21) International Application Number:
PCT/US2010/034710

(22) International Filing Date:
13 May 2010 (13.05.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/216,086 13 May 2009 (13.05.2009) US

(71) Applicant *(for all designated States except US)*: **CONCERT PHARMACEUTICALS, INC.** [US/US]; 99 Hayden Avenue, Suite 500, Lexington, MA 02421 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **HARBESON, Scott, L.** [US/US]; 203 Pemberton Street, Apt. 5, Cambridge, MA 02140 (US). **TUNG, Roger, D.** [US/US]; 3 Burnham Road, Lexington, MA 02420 (US).

(74) Agents: **ABELLEIRA, Susan, M.** et al.; Hamilton, Brook, Smith & Reynolds, P.C., 530 Virginia Rd, P.O. Box 9133, Condcord, MA 01742-9133 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

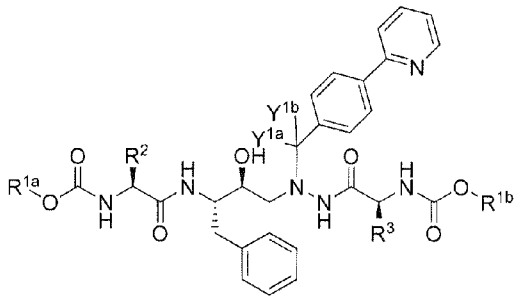
— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) Title: PEGYLATED AZAPEPTIDE DERIVATIVES AS HIV PROTEASE INHIBITORS



(I)

(57) Abstract: This invention relates to novel compounds that are pegylated forms of deuterium-substituted azapeptides, and pharmaceutically acceptable salts thereof. More specifically, the invention relates to novel pegylated forms of deuterium- substituted atazanavir sulfate. This invention also provides pyrogen-free compositions comprising one or more compounds of the invention and a carrier, and the use of the disclosed compounds and compositions in methods of treating diseases and conditions that are treated by administering HIV protease inhibitors.

WO 2010/132663 A1

PEGYLATED AZAPEPTIDE DERIVATIVES AS HIV PROTEASE INHIBITORS

RELATED APPLICATION

[1] This application claims the benefit of U.S. provisional patent application no. 61/216,086, filed May 13, 2009. The contents of this application are incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

[2] Many current medicines suffer from poor absorption, distribution, metabolism and/or excretion (ADME) properties that prevent their wider use or limit their use in certain indications. Poor ADME properties are also a major reason for the failure of drug candidates in clinical trials. While formulation technologies and prodrug strategies can be employed in some cases to improve certain ADME properties, these approaches often fail to address the underlying ADME problems that exist for many drugs and drug candidates. One such problem is rapid metabolism that causes a number of drugs, which otherwise would be highly effective in treating a disease, to be cleared too rapidly from the body. A possible solution to rapid drug clearance is frequent or high dosing to attain a sufficiently high plasma level of drug. This, however, introduces a number of potential treatment problems such as poor subject compliance with the dosing regimen, side effects that become more acute with higher doses, and increased cost of treatment. A rapidly metabolized drug may also expose subjects to undesirable toxic or reactive metabolites.

[3] Another ADME limitation that affects many medicines is the formation of toxic or biologically reactive metabolites. As a result, some subjects receiving the drug may experience toxicities, or the safe dosing of such drugs may be limited such that subjects receive a suboptimal amount of the active agent. In certain cases, modifying dosing intervals or formulation approaches can help to reduce clinical adverse effects, but often the formation of such undesirable metabolites is intrinsic to the metabolism of the compound.

[4] In some select cases, a metabolic inhibitor will be co-administered with a drug that is cleared too rapidly. Such is the case with the protease inhibitor class of drugs that are used to treat HIV infection. The FDA recommends that these drugs be co-dosed with ritonavir, an inhibitor of cytochrome P450 enzyme 3A4 (CYP3A4), the enzyme typically responsible for their metabolism (see Kempf, D.J. et al., Antimicrobial agents and chemotherapy, 1997, 41(3): 654-60). Ritonavir, however, causes adverse effects and adds to the pill burden for HIV subjects who must already take a combination of different drugs. Similarly, the CYP2D6 inhibitor quinidine has been added to dextromethorphan for the purpose of reducing rapid CYP2D6 metabolism of dextromethorphan in a treatment of pseudobulbar affect. Quinidine, however, has unwanted side effects that greatly limit its use in potential combination therapy (see Wang, L et al., Clinical Pharmacology and Therapeutics, 1994, 56(6 Pt 1): 659-67; and FDA label for quinidine at www.accessdata.fda.gov).

[5] In general, combining drugs with cytochrome P450 inhibitors is not a satisfactory strategy for decreasing drug clearance. The inhibition of a CYP enzyme's activity can affect the metabolism and clearance of other drugs metabolized by that same enzyme. CYP inhibition can cause other drugs to accumulate in the body to toxic levels.

[6] A potentially attractive strategy for improving a drug's metabolic properties is deuterium modification. In this approach, one attempts to slow the CYP-mediated metabolism of a drug or to reduce the formation of undesirable metabolites by replacing one or more hydrogen atoms with deuterium atoms. Deuterium is a safe, stable, non-radioactive isotope of hydrogen. Compared to hydrogen, deuterium forms stronger bonds with carbon. In select cases, the increased bond strength imparted by deuterium can positively impact the ADME properties of a drug, creating the potential for improved drug efficacy, safety, and/or tolerability. At the same time, because the size and shape of deuterium are essentially identical to those of hydrogen, replacement of hydrogen by deuterium would not be expected to affect the biochemical potency and selectivity of the drug as compared to the original chemical entity that contains only hydrogen.

[7] Over the past 35 years, the effects of deuterium substitution on the rate of metabolism have been reported for a very small percentage of approved drugs (see, e.g., Blake, MI et al, J Pharm Sci, 1975, 64:367-91; Foster, AB, Adv Drug Res

1985, 14:1-40 ("Foster"); Kushner, DJ et al, Can J Physiol Pharmacol 1999, 79-88; Fisher, MB et al, Curr Opin Drug Discov Devel, 2006, 9:101-09 ("Fisher")). The results have been variable and unpredictable. For some compounds deuteration caused decreased metabolic clearance *in vivo*. For others, there was no change in metabolism. Still others demonstrated increased metabolic clearance. The variability in deuterium effects has also led experts to question or dismiss deuterium modification as a viable drug design strategy for inhibiting adverse metabolism (see Foster at p. 35 and Fisher at p. 101).

[8] The effects of deuterium modification on a drug's metabolic properties are not predictable even when deuterium atoms are incorporated at known sites of metabolism. Only by actually preparing and testing a deuterated drug can one determine if and how the rate of metabolism will differ from that of its non-deuterated counterpart. *See,* for example, Fukuto et al. (J. Med. Chem. 1991, 34, 2871-76). Many drugs have multiple sites where metabolism is possible. The site(s) where deuterium substitution is required and the extent of deuteration necessary to see an effect on metabolism, if any, will be different for each drug.

[9] AIDS or autoimmune deficiency syndrome is caused by the HIV virus. HIV destroys CD4 positive (CD4+) T cells, which are white blood cells crucial to maintaining the function of the human immune system. As the virus attacks those cells, the person infected with HIV is less equipped to fight off infection and disease ultimately resulting in the development of AIDS. Despite the fact that newer treatments have cut the AIDS death rate significantly, it continues to be a serious disease. By the end of 2006, the Centers for Disease Control and Prevention (CDC) estimated that over 1.1 million people in the United States were infected with the HIV virus.

[10] When HIV infects a CD4 cell in a person's body, it copies its own genetic code into the cell's DNA. As a result, the CD4 cell becomes programmed to make new HIV genetic material and HIV proteins. These proteins are cleaved by an HIV protease to make functional new HIV particles. One important class of drugs that are used to treat HIV are protease inhibitors that inhibit the protease enzyme and thus prevent the cell from producing new viruses. It is recommended that a protease inhibitor be used in combination with at least two other HIV drugs to treat HIV infection.

[11] Atazanavir sulfate, also known as (3*S*,8*S*,9*S*,12*S*)-3,12-Bis(1,1-

dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6-[[4-(2-pyridinyl)phenyl] methyl]-2,5,6,10,13-pentaazatetradecanedioic acid dimethyl ester, sulfate, prevents the formation of mature HIV virions in HIV-1 infected cells by selectively inhibiting the virus-specific processing of certain polyproteins (viral Gag and Gag-Pol). Atazanavir sulfate is currently approved for the treatment of HIV infection.

[12] Atazanavir is metabolized by CYP3A4 which leads to sub-optimal serum concentrations and thus decreased antiviral efficacy. Typically atazanavir is co-dosed with a CYP3A4 inhibitor, such as ritonavir, to counteract its metabolism. This places an additional expense and pill burden on the subject. Additionally, ritonavir is known to significantly alter metabolism of many other drugs requiring dosing adjustments and is also known to cause undesirable side effects including nausea, vomiting, diarrhea, loss of appetite and elevated serum concentrations of triglycerides and LDL cholesterol leading to dyslipidemia.

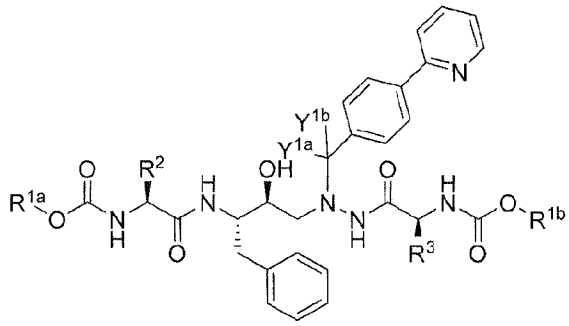
[13] Various strategies are being employed for overcoming the problems assoicated with ritonavir co-dosing. For example, deuterated forms of atazanavir are described in PCT publication WO 2008/156632. Pegylated forms of atazanavir are described in PCT Publication WO 2008/112289.

[14] Despite the beneficial activities of atazanavir, and the advent of modified forms of atazanavir, there is a continuing need for new compounds to treat HIV.

SUMMARY OF THE INVENTION

[15] This invention relates to novel compounds that are pegylated forms of deuterium-substituted azapeptides, and pharmaceutically acceptable salts thereof. More specifically, the invention relates to novel pegylated forms of deuterium-substituted atazanavir sulfate. This invention also provides pyrogen-free compositions comprising one or more compounds of the invention and a carrier, and the use of the disclosed compounds and compositions in methods of treating diseases and conditions that are treated by administering HIV protease inhibitors.

[16] The compounds of the invention are represented by Formula I:



(I), or a pharmaceutically acceptable salt thereof, wherein:

one of R^{1a} or R^{1b} is $(CH_2CH_2O)_m$-CH_3, and the other R^{1a} or R^{1b} is selected from $(CH_2CH_2O)_m$-CH_3 and -(C_1-C_3)-alkyl, wherein each of R^{1a} and R^{1b} is optionally and independently substituted with one or more deuterium;

m is an integer from 1 to 30;

each of R^2 and R^3 are independently selected from isopropyl, sec-butyl, and tert-butyl, wherein one of R^2 or R^3 is substituted with one or more deuterium and the other of R^2 and R^3 is optionally substituted with one or more deuterium; and

Y^{1a} and Y^{1b} are independently selected from hydrogen and deuterium.

[17] The compounds, pharmaceutically acceptable salts thereof and compositions of the invention are useful for treating diseases that are effectively treated by a compound that is an HIV protease inhibitor. As such, the present invention includes a method of treating HIV, comprising administering to a subject in need thereof an effective amount of: (i) a compound of Formula I or pharmaceutically acceptable salt thereof; or (ii) a pyrogen-free composition (e.g., a pharmaceutical composition) described herein.

DETAILED DESCRIPTION OF THE INVENTION

[18] The term "treat" as used herein means decrease, suppress, attenuate, diminish, arrest, or stabilize the development or progression of a disease (e.g., a disease or disorder delineated herein), lessen the severity of the disease or improve the symptoms associated with the disease.

[19] "Disease" means any condition or disorder that damages or interferes with the normal function of a cell, tissue, or organ.

[20] It will be recognized that some variation of natural isotopic abundance

occurs in a synthesized compound depending upon the origin of chemical materials used in the synthesis. Thus, a preparation of atazanavir will inherently contain small amounts of deuterated isotopologues. The concentration of naturally abundant stable hydrogen isotopes, notwithstanding this variation, is small and immaterial as compared to the degree of stable isotopic substitution of compounds of this invention. See, for instance, Wada, E et al., Seikagaku, 1994, 66:15; Gannes, LZ et al., Comp Biochem Physiol Mol Integr Physiol, 1998, 119:725.

[21] Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition. Also unless otherwise stated, when a position is designated specifically as "D" or "deuterium", the position is understood to have deuterium at an abundance that is at least 3500 times greater than the natural abundance of deuterium, which is 0.015% (i.e., at least 52.5% incorporation of deuterium).

[22] The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance of D at a specified position in a compound of this invention and the naturally occurring abundance of that isotope. The natural abundance of deuterium is 0.015%.

[23] In other embodiments, a compound of this invention has an isotopic enrichment factor for each deuterium present at a site designated as a potential site of deuteration on the compound of at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation). It is understood that the isotopic enrichment factor of each deuterium present at a site designated as a site of deuteration is independent of other deuterated sites. For example, if there are two sites of deuteration on a compound one site could be deuterated at 52.5% while the other could be deuterated at 75%. The resulting compound would be considered to be a compound wherein the isotopic enrichment factor is at least 3500 (52.5%).

[24] The term "isotopologue" refers to a species in which the chemical stucture differs from a specific compound of this invention only in the isotopic composition thereof. Isotopologues can differ in the level of isotopic enrichment at one or more positions and/or in the positions(s) of isotopic enrichment.

[25] It will be understood that the term "compound," when referring to the compounds of the invention, refers to a collection of molecules having an identical chemical structure, except that there may be isotopic variation among the constituent atoms of the molecules. Thus, it will be clear to those of skill in the art that a compound represented by a particular chemical structure containing indicated deuterium atoms, will also contain lesser amounts of isotopologues having hydrogen atoms at one or more of the designated deuterium positions in that structure. The relative amount of such isotopologues in a compound of this invention will depend upon a number of factors including the isotopic purity of deuterated reagents used to make the compound and the efficiency of incorporation of deuterium in the various synthesis steps used to prepare the compound. However, as set forth above the relative amount of such isotopologues will be less than 47.5% of the compound. In other embodiments, the relative amount of such isotopologues *in toto* will be less than 45%, less than 40%, less than 35%, less than 30%, less than 25%, less than 17.5%, less than 10%, less than 5%, less than 3%, less than 1%, or less than 0.5% of the compound.

[26] The invention also provides salts of the compounds of the invention.

[27] A salt of a compound of this invention is formed between an acid and a basic group of the compound, such as an amino functional group, or a base and an acidic group of the compound, such as a carboxyl functional group. According to another embodiment, the compound is a pharmaceutically acceptable acid addition salt.

[28] The term "pharmaceutically acceptable," as used herein, refers to a component that is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and other mammals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A "pharmaceutically acceptable salt" means any non-toxic salt that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention. A "pharmaceutically acceptable counterion" is an ionic portion of a salt that is not toxic when released from the salt upon administration to a recipient.

[29] Acids commonly employed to form pharmaceutically acceptable salts include inorganic acids such as hydrogen bisulfide, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and phosphoric acid, as well as organic acids such as para-toluenesulfonic acid, salicylic acid, tartaric acid, bitartaric acid,

ascorbic acid, maleic acid, besylic acid, fumaric acid, gluconic acid, glucuronic acid, formic acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, lactic acid, oxalic acid, para-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid and acetic acid, as well as related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-l,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, terephthalate, sulfonate, xylene sulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β-hydroxybutyrate, glycolate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2- sulfonate, mandelate and other salts. In one embodiment, pharmaceutically acceptable acid addition salts include those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and especially those formed with organic acids such as maleic acid.

[30] The pharmaceutically acceptable salt may also be a salt of a compound of the present invention having an acidic functional group, such as a carboxylic acid functional group, and a base. Exemplary bases include, but are not limited to, hydroxide of alkali metals including sodium, potassium, and lithium; hydroxides of alkaline earth metals such as calcium and magnesium; hydroxides of other metals, such as aluminum and zinc; ammonia, organic amines such as unsubstituted or hydroxyl-substituted mono-, di-, or tri-alkylamines, dicyclohexylamine; tributyl amine; pyridine; N-methyl, N-ethylamine; diethylamine; triethylamine; mono-, bis-, or tris-(2-OH-(C_1-C_6)-alkylamine), such as N,N-dimethyl-N-(2-hydroxyethyl)amine or tri-(2-hydroxyethyl)amine; N-methyl-D-glucamine; morpholine; thiomorpholine; piperidine; pyrrolidine; and amino acids such as arginine, lysine, and the like.

[31] The disclosed compounds may exist in various stereoisomeric forms. Stereoisomers are compounds which differ only in their spatial arrangement. Enantiomers are pairs of stereoisomers whose mirror images are not superimposable, most commonly because they contain an asymmetrically substituted carbon atom that acts as a chiral center. "Enantiomer" means one of a pair of molecules that are

mirror images of each other and are not superimposable. Diastereomers are stereoisomers that are not related as mirror images, most commonly because they contain two or more asymmetrically substituted carbon atoms. "R" and "S" represent the configuration of substituents around one or more chiral carbon atoms.

[32] When the stereochemistry of the disclosed compounds is named or depicted by structure, the named or depicted stereoisomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight pure relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% optically pure. Percent optical purity by weight is the ratio of the weight of the enantiomer over the weight of the enantiomer plus the weight of its optical isomer.

[33] When a disclosed compound is named or depicted by structure without indicating the stereochemistry, and has at least one chiral center, it is to be understood that the name or structure encompasses one enantiomer of the compound free from the corresponding optical isomer, a racemic mixture of the compound and mixtures enriched in one enantiomer relative to its corresponding optical isomer ("scalemic mixtures").

[34] When a disclosed compound is named or depicted by structure without indicating the stereochemistry and has at least two chiral centers, it is to be understood that the name or structure encompasses a diastereomer free of other diastereomers, a pair of diastereomers free from other diastereomeric pairs, mixtures of diastereomers, mixtures of diastereomeric pairs, mixtures of diastereomers in which one diastereomer is enriched relative to the other diastereomer(s) and mixtures of diastereomeric pairs in which one diastereomeric pair is enriched relative to the other diastereomeric pair(s).

[35] The term "substantially free of other stereoisomers" as used herein means less than 25% of other stereoisomers, preferably less than 10% of other stereoisomers, more preferably less than 5% of other stereoisomers and most preferably less than 2% of other stereoisomers are present. Methods of obtaining or synthesizing an individual enantiomer for a given compound are known in the art and may be applied as practicable to final compounds or to starting material or intermediates.

[36] Unless otherwise indicated, when a disclosed compound is named or depicted by a structure without specifying the stereochemistry and has one or more

chiral centers, it is understood to represent all possible stereoisomers of the compound.

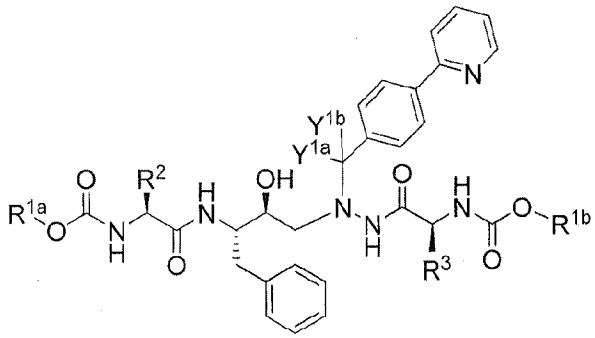
[37] The term "stable compounds," as used herein, refers to compounds which possess stability sufficient to allow for their manufacture and which maintain the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., formulation into therapeutic products, intermediates for use in production of therapeutic compounds, isolatable or storable intermediate compounds, treating a disease or condition responsive to therapeutic agents).

[38] "D" refers to deuterium. "Stereoisomer" refers to both enantiomers and diastereomers. "Tert", " ^{t} ", and "t-" each refer to tertiary.

[39] The term "substituted" refers to the replacement of one or more hydogen atoms with another moiety. The phrase "[optionally] substituted with deuterium" refers to the replacement of one or more hydogen atoms with an equal number of deuterium atoms. Unless otherwise specified, any hydrogen atom including terminal hydrogen atoms, can be replaced.

[40] Throughout this specification, a variable may be referred to generally (e.g.,"each R") or may be referred to specifically (e.g., R^1, R^2, R^3, etc.). Unless otherwise indicated, when a variable is referred to generally, it is meant to include all specific embodiments of that particular variable.

[41] The compounds of the invention are represented by Formula I:



(I), or a pharmaceutically acceptable salt thereof, wherein:

one of R^{1a} or R^{1b} is $-(CH_2CH_2O)_m-CH_3$, and the other R^{1a} or R^{1b} is selected from $-(CH_2CH_2O)_m-CH_3$, and $-(C_1-C_3)$-alkyl, wherein each of R^{1a} and R^{1b} is optionally and independently substituted with one or more deuterium;

m is an integer from 1 to 30;

each of R^2 and R^3 are independently selected from isopropyl, sec-butyl, and tert-butyl, wherein one of R^2 or R^3 is substituted with one or more deuterium and the other of R^2 and R^3 is optionally substituted with one or more deuterium; and

Y^{1a} and Y^{1b} are independently selected from hydrogen and deuterium.

[42] In one embodiment, Y^{1a} and Y^{1b} are preferably the same.

[43] In one embodiment of Formula I, one of R^2 or R^3 is $-C(CD_3)_3$ and the other of R^2 or R^3 is $-C(CH_3)_3$ or $-C(CD_3)_3$; m is an integer from 1 to 15; and Y^{1a} and Y^{1b} are the same. In one aspect of this embodiment, R^2 is $-C(CD_3)_3$. In another aspect of this embodiment, one of R^{1a} or R^{1b} is $-(CH_2CH_2O)_m-CH_3$ or $-(CD_2CD_2O)_m-CD_3$, and the other R^{1a} or R^{1b} is $(CH_2CH_2O)_m-CH_3$, $(CD_2CD_2O)_m-CD_3$, $-CH_3$, or $-CD_3$. In a more specific aspect of this embodiment Y^{1a} and Y^{1b} are both hydrogen. In an alternate aspect, Y^{1a} and Y^{1b} are both deuterium.

[44] In another embodiment of Formula I, one of R^{1a} or R^{1b} is $-(CH_2CH_2O)_m-CH_3$ and the other R^{1a} or R^{1b} is $(CH_2CH_2O)_m-CH_3$, $-CH_3$, or $-CD_3$; one of R^2 or R^3 is $-C(CD_3)_3$ and the other of R^2 or R^3 is $-C(CH_3)_3$ or $-C(CD_3)_3$; Y^{1a} and Y^{1b} are the same and each m is 1, 2, 3, 4 or 5. In one aspect of this embodiment, R^2 is $-C(CD_3)_3$. In a more specific aspect of this embodiment Y^{1a} and Y^{1b} are both hydrogen and each m is 3 or 5. In an alternate aspect, Y^{1a} and Y^{1b} are both deuterium; and each m is 3 or 5.

[45] In another embodiment of Formula I, one of R^{1a} or R^{1b} is $-(CD_2CD_2O)_m-CD_3$ and the other R^{1a} or R^{1b} is $-(CH_2CH_2O)_m-CH_3$, $-(CD_2CD_2O)_m-CD_3$, $-CH_3$, or $-CD_3$; one of R^2 or R^3 is $-C(CD_3)_3$ and the other of R^2 or R^3 is selected from $-C(CH_3)_3$ and $-C(CD_3)_3$; Y^{1a} and Y^{1b} are the same; and each m is 1, 2, 3, 4 or 5. In one aspect of this embodiment, R^2 is $-C(CD_3)_3$. In a more specific aspect of this embodiment Y^{1a} and Y^{1b} are both hydrogen and each m is 3 or 5. In an alternate aspect, Y^{1a} and Y^{1b} are both deuterium; and each m is 3 or 5.

[46] Specific examples of compounds of Formula I where each Y is hydrogen are shown in Table 1a, below.

Table 1a. Exemplary Compounds of Formula I, wherein Y^{1a} and Y^{1b} are hydrogen.

Compound	R^{1a}	R^{1b}	R^2	R^3
105	$(CH_2CH_2O)_3-CH_3$	CH_3	$C(CD_3)_3$	$C(CH_3)_3$
106	$(CH_2CH_2O)_5-CH_3$	CH_3	$C(CD_3)_3$	$C(CH_3)_3$

Compound	R^{1a}	R^{1b}	R^2	R^3
107	CH_3	$(CH_2CH_2O)_3$-CH_3	$C(CD_3)_3$	$C(CH_3)_3$
108	CH_3	$(CH_2CH_2O)_5$-CH_3	$C(CD_3)_3$	$C(CH_3)_3$
109	$(CH_2CH_2O)_3$-CH_3	CH_3	$C(CH_3)_3$	$C(CD_3)_3$
110	$(CH_2CH_2O)_5$-CH_3	CH_3	$C(CH_3)_3$	$C(CD_3)_3$
111	CH_3	$(CH_2CH_2O)_3$-CH_3	$C(CH_3)_3$	$C(CD_3)_3$
112	CH_3	$(CH_2CH_2O)_5$-CH_3	$C(CH_3)_3$	$C(CD_3)_3$
113	$(CH_2CH_2O)_3$-CH_3	CD_3	$C(CH_3)_3$	$C(CD_3)_3$
114	$(CH_2CH_2O)_5$-CH_3	CD_3	$C(CH_3)_3$	$C(CD_3)_3$
115	CD_3	$(CH_2CH_2O)_3$-CH_3	$C(CH_3)_3$	$C(CD_3)_3$
116	CD_3	$(CH_2CH_2O)_5$-CH_3	$C(CH_3)_3$	$C(CD_3)_3$
117	$(CH_2CH_2O)_3$-CH_3	CD_3	$C(CD_3)_3$	$C(CH_3)_3$
118	$(CH_2CH_2O)_5$-CH_3	CD_3	$C(CD_3)_3$	$C(CH_3)_3$
119	CD_3	$(CH_2CH_2O)_3$-CH_3	$C(CD_3)_3$	$C(CH_3)_3$
120	CD_3	$(CH_2CH_2O)_5$-CH_3	$C(CD_3)_3$	$C(CH_3)_3$
121	$(CH_2CH_2O)_3$-CH_3	CH_3	$C(CD_3)_3$	$C(CD_3)_3$
122	$(CH_2CH_2O)_5$-CH_3	CH_3	$C(CD_3)_3$	$C(CD_3)_3$
123	CH_3	$(CH_2CH_2O)_3$-CH_3	$C(CD_3)_3$	$C(CD_3)_3$
124	CH_3	$(CH_2CH_2O)_5$-CH_3	$C(CD_3)_3$	$C(CD_3)_3$
125	$(CH_2CH_2O)_3$-CH_3	CD_3	$C(CD_3)_3$	$C(CD_3)_3$
126	$(CH_2CH_2O)_5$-CH_3	CD_3	$C(CD_3)_3$	$C(CD_3)_3$
127	CD_3	$(CH_2CH_2O)_3$-CH_3	$C(CD_3)_3$	$C(CD_3)_3$
128	CD_3	$(CH_2CH_2O)_5$-CH_3	$C(CD_3)_3$	$C(CD_3)_3$
129	$(CH_2CH_2O)_3$-CH_3	$(CH_2CH_2O)_3$-CH_3	$C(CD_3)_3$	$C(CH_3)_3$
130	$(CH_2CH_2O)_5$-CH_3	$(CH_2CH_2O)_5$-CH_3	$C(CD_3)_3$	$C(CH_3)_3$
131	$(CH_2CH_2O)_3$-CH_3	$(CH_2CH_2O)_3$-CH_3	$C(CH_3)_3$	$C(CD_3)_3$
132	$(CH_2CH_2O)_5$-CH_3	$(CH_2CH_2O)_5$-CH_3	$C(CH_3)_3$	$C(CD_3)_3$
133	$(CH_2CH_2O)_3$-CH_3	$(CH_2CH_2O)_3$-CH_3	$C(CD_3)_3$	$C(CD_3)_3$
and 134	$(CH_2CH_2O)_5$-CH_3	$(CH_2CH_2O)_5$-CH_3	$C(CD_3)_3$	$C(CD_3)_3$

or a pharmaceutically acceptable salt of any of the foregoing.

[47] Additional specific examples of compounds of Formula I where each Y is hydrogen are shown in Table 1b, below.

Table 1b. Exemplary Compounds of Formula I, wherein Y^{1a} and Y^{1b} are hydrogen.

Compound	R^{1a}	R^{1b}	R^2	R^3
205	$(CH_2CH_2O)_3$-CH_3	CD_3	$C(CH_3)_3$	$C(CH_3)_3$
206	CD_3	$(CH_2CH_2O)_3$-CH_3	$C(CH_3)_3$	$C(CH_3)_3$

or a pharmaceutically acceptable salt of any of the foregoing.

[48] Specific examples of compounds of Formula I where each Y is deuterium are shown in Table 2, below.

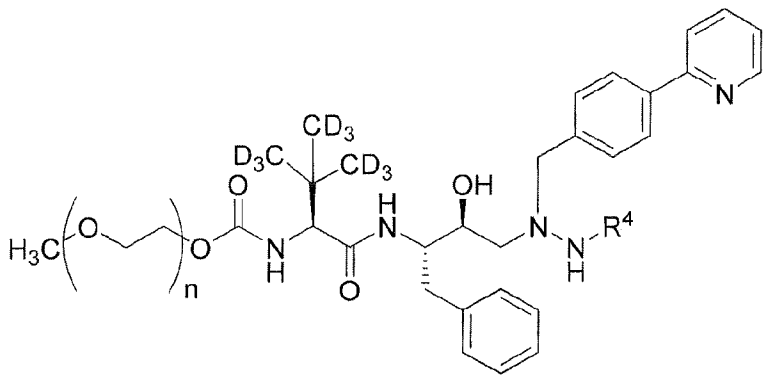
Table 2. Exemplary Compounds of Formula I, wherein Y^{1a} and Y^{1b} are deuterium.

Compound	R^{1a}	R^{1b}	R^2	R^3
135	$(CH_2CH_2O)_3$-CH_3	CH_3	$C(CD_3)_3$	$C(CH_3)_3$
136	$(CH_2CH_2O)_5$-CH_3	CH_3	$C(CD_3)_3$	$C(CH_3)_3$
137	CH_3	$(CH_2CH_2O)_3$-CH_3	$C(CD_3)_3$	$C(CH_3)_3$
138	CH_3	$(CH_2CH_2O)_5$-CH_3	$C(CD_3)_3$	$C(CH_3)_3$
139	$(CH_2CH_2O)_3$-CH_3	CH_3	$C(CH_3)_3$	$C(CD_3)_3$
140	$(CH_2CH_2O)_5$-CH3	CH_3	$C(CH_3)_3$	$C(CD_3)_3$
141	CH_3	$(CH_2CH_2O)_3$-CH_3	$C(CH_3)_3$	$C(CD_3)_3$
142	CH_3	$(CH_2CH_2O)_5$-CH_3	$C(CH_3)_3$	$C(CD_3)_3$
143	$(CH_2CH_2O)_3$-CH_3	CD_3	$C(CH_3)_3$	$C(CD_3)_3$
144	$(CH_2CH_2O)_5$-CH_3	CD_3	$C(CH_3)_3$	$C(CD_3)_3$
145	CD_3	$(CH_2CH_2O)_3$-CH_3	$C(CH_3)_3$	$C(CD_3)_3$
146	CD_3	$(CH_2CH_2O)_5$-CH_3	$C(CH_3)_3$	$C(CD_3)_3$
147	$(CH_2CH_2O)_3$-CH_3	CD_3	$C(CD_3)_3$	$C(CH_3)_3$
148	$(CH_2CH_2O)_5$-CH_3	CD_3	$C(CD_3)_3$	$C(CH_3)_3$
149	CD_3	$(CH_2CH_2O)_3$-CH_3	$C(CD_3)_3$	$C(CH_3)_3$
150	CD_3	$(CH_2CH_2O)_5$-CH_3	$C(CD_3)_3$	$C(CH_3)_3$
151	$(CH_2CH_2O)_3$-CH_3	CH_3	$C(CD_3)_3$	$C(CD_3)_3$
152	$(CH_2CH_2O)_5$-CH_3	CH_3	$C(CD_3)_3$	$C(CD_3)_3$
153	CH_3	$(CH_2CH_2O)_3$-CH_3	$C(CD_3)_3$	$C(CD_3)_3$

Compound	R^{1a}	R^{1b}	R^2	R^3
154	CH_3	$(CH_2CH_2O)_5$-CH_3	$C(CD_3)_3$	$C(CD_3)_3$
155	$(CH_2CH_2O)_3$-CH_3	CD_3	$C(CD_3)_3$	$C(CD_3)_3$
156	$(CH_2CH_2O)_5$-CH_3	CD_3	$C(CD_3)_3$	$C(CD_3)_3$
157	CD_3	$(CH_2CH_2O)_3$-CH_3	$C(CD_3)_3$	$C(CD_3)_3$
158	CD_3	$(CH_2CH_2O)_5$-CH_3	$C(CD_3)_3$	$C(CD_3)_3$
159	$(CH_2CH_2O)_3$-CH_3	$(CH_2CH_2O)_3$-CH_3	$C(CD_3)_3$	$C(CH_3)_3$
160	$(CH_2CH_2O)_5$-CH_3	$(CH_2CH_2O)_5$-CH_3	$C(CD_3)_3$	$C(CH_3)_3$
161	$(CH_2CH_2O)_3$-CH_3	$(CH_2CH_2O)_3$-CH_3	$C(CH_3)_3$	$C(CD_3)_3$
162	$(CH_2CH_2O)_5$-CH_3	$(CH_2CH_2O)_5$-CH_3	$C(CH_3)_3$	$C(CD_3)_3$
163	$(CH_2CH_2O)_3$-CH_3	$(CH_2CH_2O)_3$-CH_3	$C(CD_3)_3$	$C(CD_3)_3$
and 164	$(CH_2CH_2O)_5$-CH_3	$(CH_2CH_2O)_5$-CH_3	$C(CD_3)_3$	$C(CD_3)_3$

or a pharmaceutically acceptable salt of any of the foregoing.

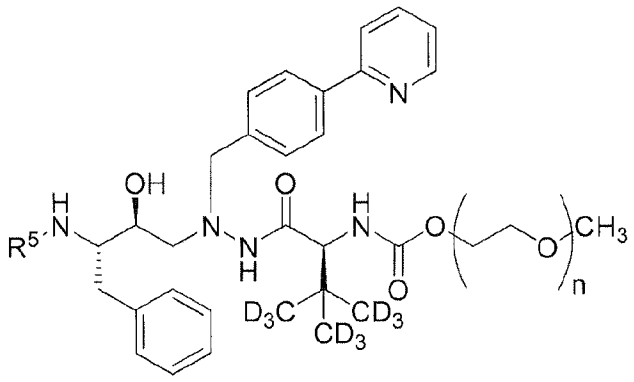
[49] In still another embodiment, the invention provides a compound of Formula II:



(II), or a pharmaceutically acceptable salt thereof wherein:

R^4 is selected from hydrogen and benzyloxycarbonyl; and n is 1, 2, 3, 4, or 5. Compounds of Formula II are useful intermediates for preparing certain compounds of this invention.

[50] In still another embodiment, the invention provides a compound of Formula III:



(III),

wherein:

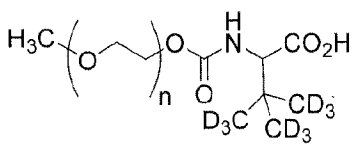
R^5 is selected from hydrogen and t-butoxycarbonyl; and n is 1, 2, 3, 4, or 5. Compounds of Formula III are useful intermediates for preparing certain compounds of this invention.

[51] In another set of embodiments, any atom not designated as deuterium in any of the embodiments of Formulae I, II or III set forth above is present at its natural isotopic abundance.

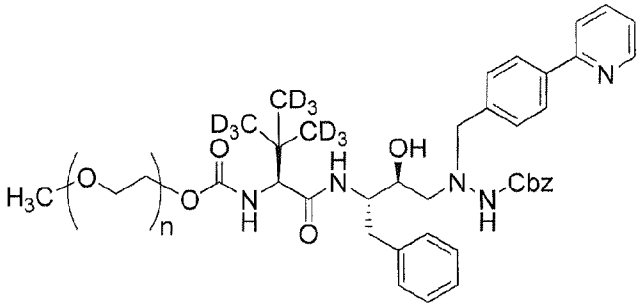
[52] The synthesis of compounds of Formula I can be readily achieved by synthetic chemists of ordinary skill. Relevant procedures and intermediates are disclosed, for instance, in United States Patent 5,849,911; PCT Intl Publication WO 97/46514; Bold, G et al., J Med Chem, 1998, 41:3387; Xu, Z et al., Org Process Res Dev, 2002, 6:323; and PCT Intl Publication WO 2006/014282.

[53] Such methods can be carried out utilizing corresponding deuterated and optionally, other isotope-containing reagents and/or intermediates to synthesize the compounds delineated herein, or invoking standard synthetic protocols known in the art for introducing isotopic atoms to a chemical structure. Certain intermediates can be used with or without purification (e.g., filtration, distillation, sublimation, crystallization, trituration, solid phase extraction, and chromatography).

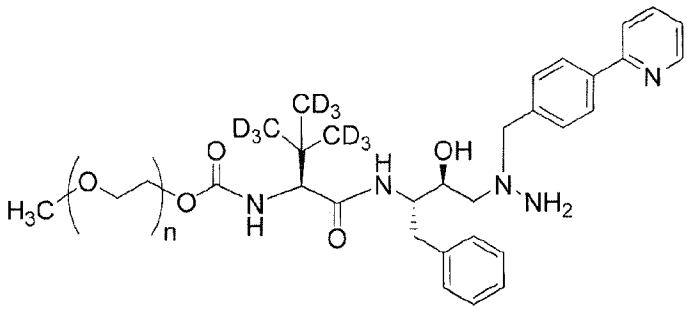
[54] The following compounds are also useful for preparing various compounds of Formula I:



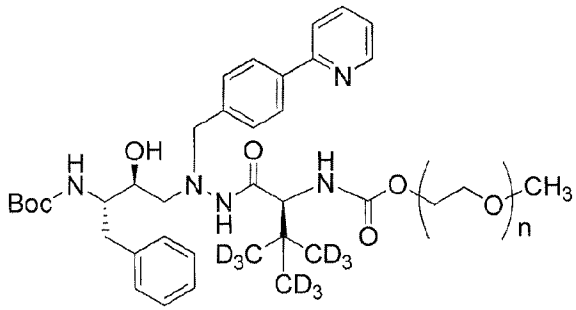
(IVa),



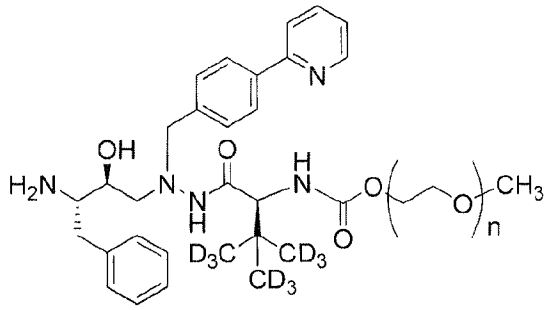
(IVb)



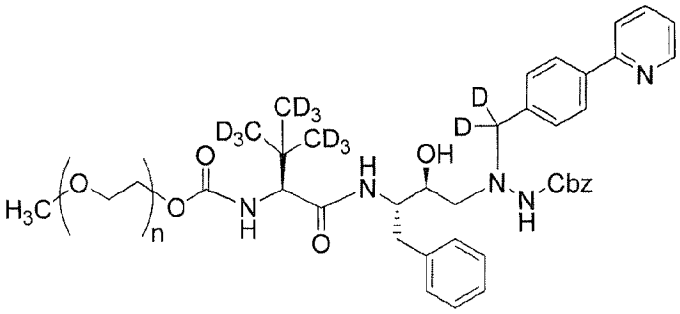
(IVc),



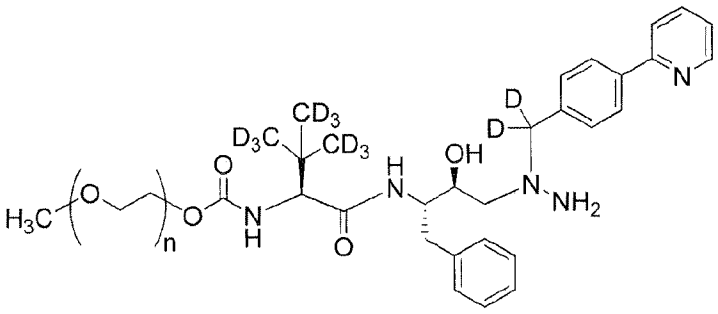
(IVd)



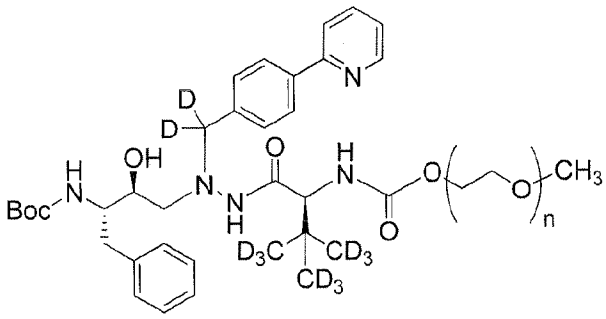
(IVe),



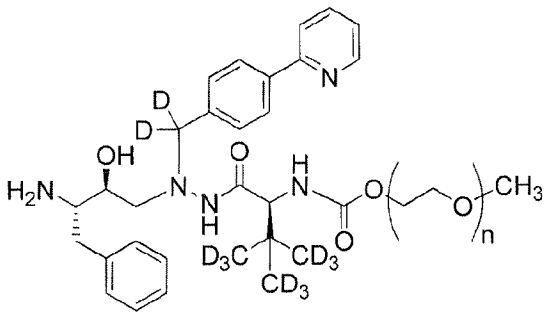
(IVf),



(IVg),



(IVh), and

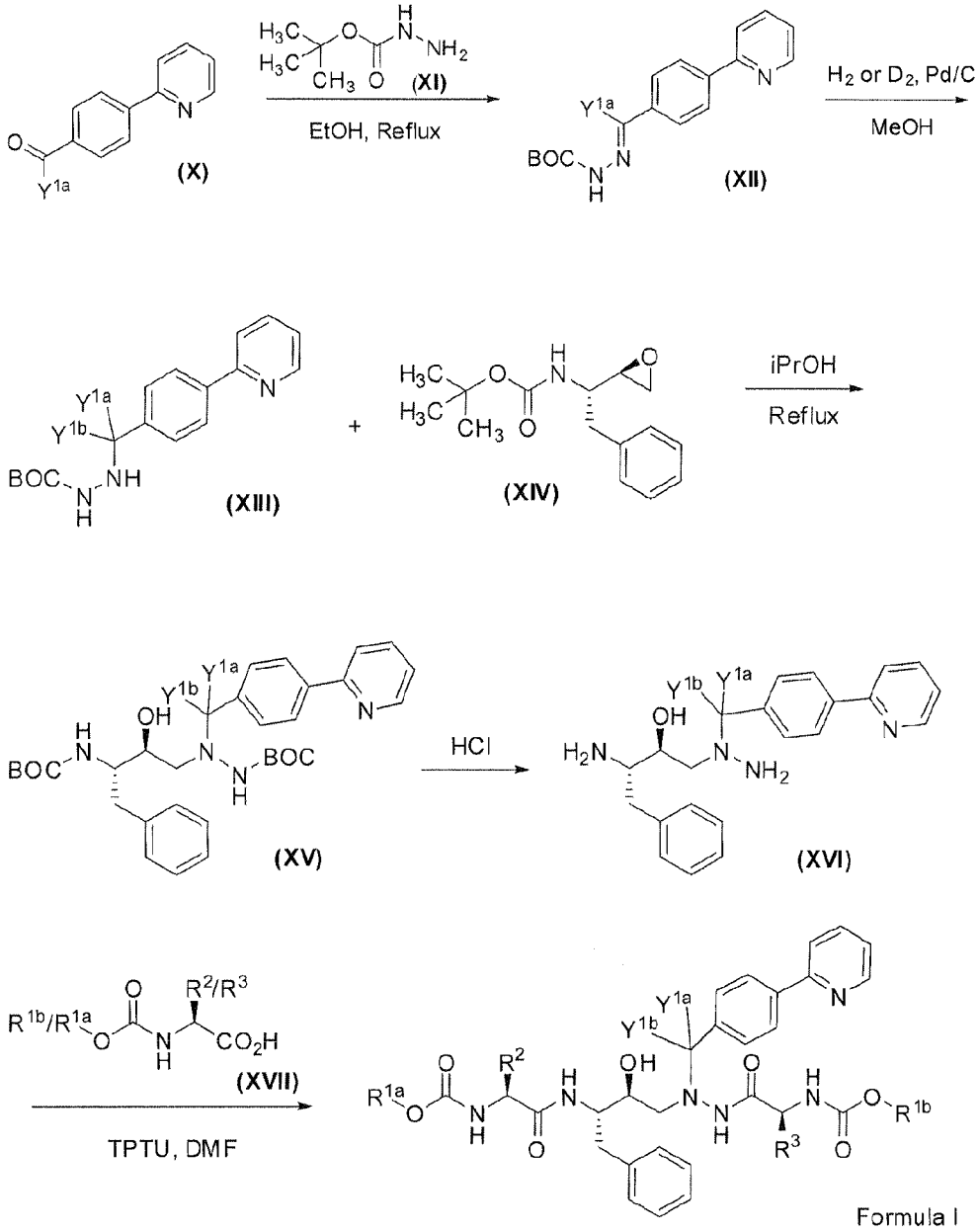


(IVi),

wherein n is selected from 1, 2, 3, 4 or 5.

EXEMPLARY SYNTHESIS

[55] Scheme 1. Synthesis of Compounds of Formula I.

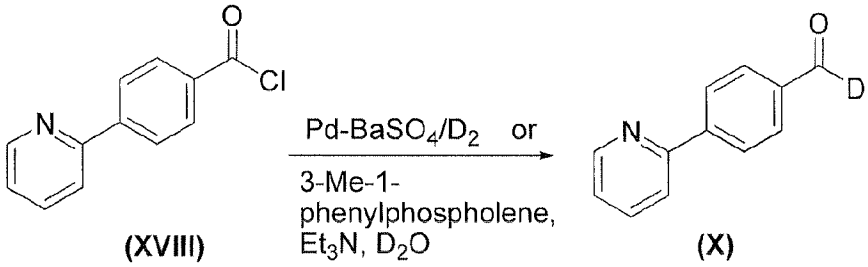


[56] A convenient method for synthesizing compounds of Formula I, wherein $R^{1a} = R^{1b}$; and $R^2 = R^3$ is depicted in Scheme 1. An appropriately deuterated aldehyde **X** is treated with the commercially available t-butoxycarbonylhydrazide (**XI**) to produce a BOC-protected hydrazide intermediate **XII**, which is then reduced using either hydrogen or deuterium gas to form the appropriate BOC-protected hydrazide **XIII**. The BOC-protected hydrazide **XIII** is then reacted with the commercially

available epoxide (**XIV**) to produce **XV**, which is then deprotected with hydrochloric acid to produce **XVI**. The appropriately deuterated carbamate derivative of tert-leucine **XVII** is reacted with **XVI** in the presence of O-(1,2-dihydro-2-oxo-1-pyridyl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TPTU) to produce a compound of Formula I.

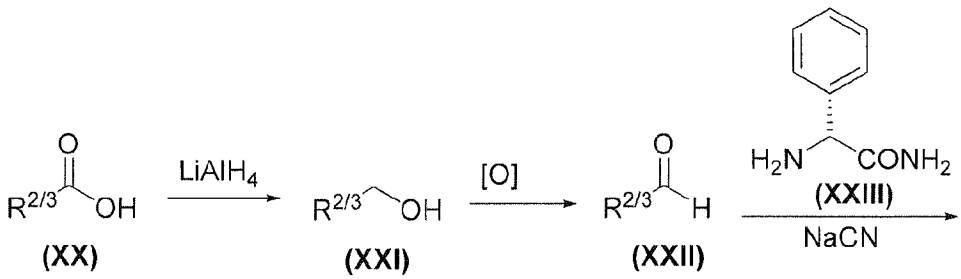
[57] In Scheme 1, intermediates may be used in place of **XI** or **XIV** that differ by having a protecting group other than BOC. Such intermediates would provide an intermediate that is the same as **XV**, except for the BOC protecting groups. This approach allows for different protecting groups that may be selectively removed. In this manner, different deuteration patterns for R^{1a} and R^{1b}; and/or R^2 and R^3 can be achieved. The choice of different protecting groups and differential deprotection is described in Zhang, H et al., J Label Comp Radiopharm, 2005, 48:1041-1047.

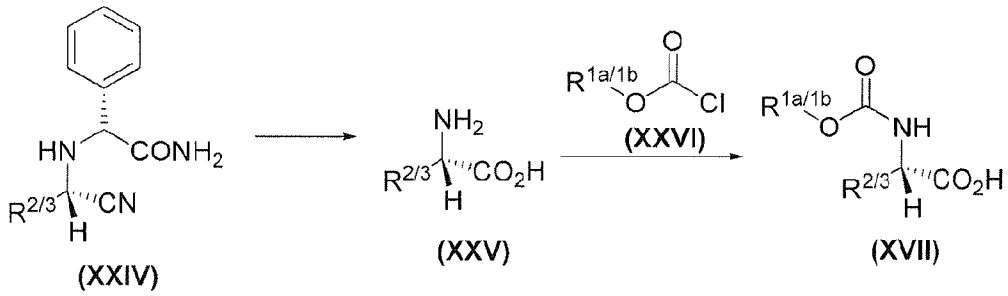
[58] Scheme 2. Synthesis of Appropriately Deuterated **X**.



[59] The deuterated aldehyde **X** may be synthesized as depicted above in Scheme 2 following the procedure described in Thompson, AF et al., JACS, 1939, 61:1374-1376 or in Scott, CA et al., Syn Comm, 1976, 6:135-139. 4-(Pyridin-2-yl)benzoyl chloride (**XVIII**) is commercially available.

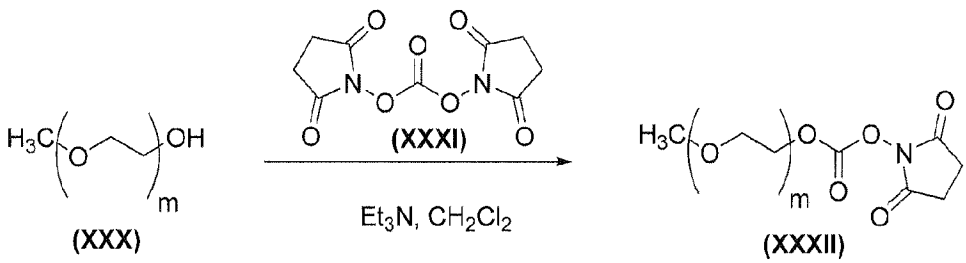
[60] Scheme 3. Synthesis of Appropriately Deuterated **XVII**.

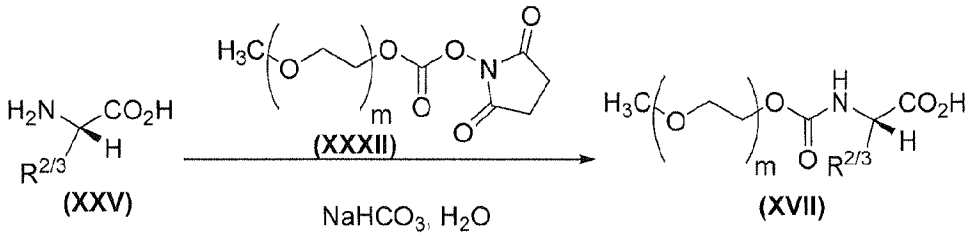




[61] Scheme 3 depicts a general route for the preparation of appropriately deuterated compounds of Formula XVII. To produce an appropriately deuterated carbamate derivative of tert-leucine an appropriately deuterated pivalic acid **XX**, such as commercially available d_9-pivalic acid, is reduced to the alcohol **XXI** with lithium aluminum hydride as described in Brainard, RL et al., Organometallics, 1986, 5:1481-1490. Alcohol **XXI** is oxidized to the aldehyde **XXII** by any one of a number of mild conditions (see, for example, Herrerias, CI et al., Tet Lett, 2005, 47:13-17). Aldehyde **XXII** is combined with (R)-2-amino-2-phenylacetamide (**XXIII**) and NaCN using an asymmetric Strecker synthesis as disclosed by Boesten, WHJ et al., Org Lett, 2001, 3:1121-1124 to form cyanophenylacetamide intermediate **XXIV** which spontaneously converts to an appropriately deuterated tert-leucine **XXV**. An alternate asymmetric Strecker synthesis is disclosed by Davis, FA et al., J Org Chem, 1996, 61:440-441 and can also be utilized in this step. The appropriately deuterated tert-leucine **XXV** is reacted with an appropriately deuterated chloromethylformate **XXVI** as described in United States Patent Application Publication 2005131017, to produce the desired carbamate derivative of tert-leucine **XVII**, which is utilized in Scheme 1.

[62] Scheme 4. Synthesis of Appropriately Deuterated **XVII** when R^{1a} or R^{1b} is $(CH_2CH_2O)_m$-CH_3, wherein m is 1, 2, 3, 4, or 5.





[63] Scheme 4 shows a general route for the preparation of appropriately deuterated **XVII** when R^{1a} or R^{1b} is $(CH_2CH_2O)_m$-CH_3, wherein m is 1, 2, 3, 4, or 5. The PEG alcohol **XXX**, where m is 1, 2, 3, 4 or 5, is dissolved in anhydrous dichloromethane. The solution is cooled to 0 °C and triethylamine is added. After stirring for 15 min at 0 °C, the solution is added to a suspension of disuccinimidocarbonate (**XXXI**) in dichloromethane. The reaction is allowed to warm to room temperature and then stirred for 18 hours. The desired product **XXXII** is obtained after an extractive work-up. An appropriately deuterated leucine **XXV** is dissolved in deionized water with 4.5 equivalents of sodium bicarbonate. To this is added a solution of **XXXII** and the reaction stirred for 20 hours at room temperature. The reaction is then cooled to 0 °C prior to acidification to pH 1 with 2N HCl. Extractive work-up with dichloromethane provides the desired tert-leu derivative **XVII**. This synthesis is disclosed in greater detail in PCT Publication No WO 2008112289.

[64] The specific approaches and compounds shown above are not intended to be limiting. The chemical structures in the schemes herein depict variables that are hereby defined commensurately with chemical group definitions (moieties, atoms, etc.) of the corresponding position in the compound formulae herein, whether identified by the same variable name (i.e., R^1, R^2, R^3, etc.) or not. The suitability of a chemical group in a compound structure for use in the synthesis of another compound is within the knowledge of one of ordinary skill in the art. Additional methods of synthesizing compounds of Formula I and their synthetic precursors, including those within routes not explicitly shown in schemes herein, are within the means of chemists of ordinary skill in the art. Methods for optimizing reaction conditions and, if necessary, minimizing competing by-products, are known in the art.

[65] Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the applicable compounds are

known in the art and include, for example, those described in Larock R, *Comprehensive Organic Transformations*, VCH Publishers (1989); Greene TW et al., *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley and Sons (1999); Fieser L et al., *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and Paquette L, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995) and subsequent editions thereof.

[66] Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds.

COMPOSITIONS

[67] The invention also provides pyrogen-free pharmaceutical compositions comprising an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt of said compound; and a pharmaceutically acceptable carrier. The carrier(s) are "pharmaceutically acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof in an amount used in the medicament.

[68] Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[69] If required, the solubility and bioavailability of the compounds of the present invention in pharmaceutical compositions may be enhanced by methods well-known in the art. One method includes the use of lipid excipients in the formulation. See "Oral Lipid-Based Formulations: Enhancing the Bioavailability of Poorly Water-Soluble Drugs (Drugs and the Pharmaceutical Sciences)," David J. Hauss, ed. Informa Healthcare, 2007; and "Role of Lipid Excipients in Modifying Oral and Parenteral Drug Delivery: Basic Principles and Biological Examples," Kishor M. Wasan, ed. Wiley-Interscience, 2006.

[70] Another known method of enhancing bioavailability is the use of an amorphous form of a compound of this invention optionally formulated with a poloxamer, such as LUTROL™ and PLURONIC™ (BASF Corporation), or block copolymers of ethylene oxide and propylene oxide. See United States patent 7,014,866; and United States patent publications 20060094744 and 20060079502.

[71] The pharmaceutical compositions of the invention include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), pulmonary, vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. In certain embodiments, the compound of the formulae herein is administered transdermally (e.g., using a transdermal patch or iontophoretic techniques). Other formulations may conveniently be presented in unit dosage form, e.g., tablets, sustained release capsules, and in liposomes, and may be prepared by any methods well known in the art of pharmacy. See, for example, Remington: The Science and Practice of Pharmacy, Lippincott Williams & Wilkins, Baltimore, MD (20th ed. 2000).

[72] Such preparative methods include the step of bringing into association with the molecule to be administered ingredients such as the carrier that constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers, liposomes or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[73] In certain embodiments, the compound is administered orally. Compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, sachets, or tablets each containing a predetermined amount of the active ingredient; a powder or granules; a solution or a suspension in an aqueous liquid or a non-aqueous liquid; an oil-in-water liquid emulsion; a water-in-oil liquid emulsion; packed in liposomes; or as a bolus, etc. Soft gelatin capsules can be useful for containing such suspensions, which may beneficially increase the rate of compound absorption.

[74] In the case of tablets for oral use, carriers that are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are administered orally,

the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

[75] Compositions suitable for oral administration include lozenges comprising the ingredients in a flavored basis, usually sucrose and acacia or tragacanth; and pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia.

[76] Compositions suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which 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 formulations 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.

[77] Such injection solutions may be in the form, for example, of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant.

[78] The pharmaceutical compositions of this invention may be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating

excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

[79] The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art. See, e.g.: Rabinowitz JD and Zaffaroni AC, US Patent 6,803,031, assigned to Alexza Molecular Delivery Corporation.

[80] Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible by topical application. For topical application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax, and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol, and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches and iontophoretic administration are also included in this invention.

[81] Application of the subject therapeutics may be local, so as to be administered at the site of interest. Various techniques can be used for providing the subject compositions at the site of interest, such as injection, use of catheters, trocars, projectiles, pluronic gel, stents, sustained drug release polymers or other device which provides for internal access.

[82] Thus, according to yet another embodiment, the compounds of this invention may be incorporated into compositions for coating an implantable medical device,

such as prostheses, artificial valves, vascular grafts, stents, or catheters. Suitable coatings and the general preparation of coated implantable devices are known in the art and are exemplified in US Patents 6,099,562; 5,886,026; and 5,304,121. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polysaccharides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition. Coatings for invasive devices are to be included within the definition of pharmaceutically acceptable carrier, adjuvant or vehicle, as those terms are used herein.

[83] According to another embodiment, the invention provides a method of coating an implantable medical device comprising the step of contacting said device with the coating composition described above. It will be obvious to those skilled in the art that the coating of the device will occur prior to implantation into a mammal.

[84] According to another embodiment, the invention provides a method of impregnating an implantable drug release device comprising the step of contacting said drug release device with a compound or composition of this invention. Implantable drug release devices include, but are not limited to, biodegradable polymer capsules or bullets, non-degradable, diffusible polymer capsules and biodegradable polymer wafers.

[85] According to another embodiment, the invention provides an implantable medical device coated with a compound or a composition comprising a compound of this invention, such that said compound is therapeutically active.

[86] According to another embodiment, the invention provides an implantable drug release device impregnated with or containing a compound or a composition comprising a compound of this invention, such that said compound is released from said device and is therapeutically active.

[87] Where an organ or tissue is accessible because of removal from the subject, such organ or tissue may be bathed in a medium containing a composition of this invention, a composition of this invention may be painted onto the organ, or a composition of this invention may be applied in any other convenient way.

[88] In another embodiment, a composition of this invention further comprises a second therapeutic agent. In one embodiment, the second therapeutic agent is one or

more additional compounds of the invention. In a particular embodiment, each of the two or more compounds of the invention present in such compositions differs from all others in the positions of isotopic enrichment. Commonly, such a composition comprises three, four, five or more different compounds of this invention.

[89] In another embodiment, the second therapeutic agent may be selected from any compound or therapeutic agent known to have or that demonstrates advantageous properties when administered with a compound having the same mechanism of action as atazanavir. Such agents include those indicated as being useful in combination with atazanavir, including but not limited to, those described in PCT publications WO 2003020206, WO 2005058248, WO 2006060731 and WO 2005027855.

[90] Preferably, the second therapeutic agent is an agent useful in the treatment or prevention of HIV infection (i.e., an antiretroviral agent).

[91] In one embodiment, the second therapeutic agent is selected from other anti-retroviral agents or a pharmacokinetic enhancing agent including, but not limited to, a second HIV protease inhibitor (e.g., amprenavir, fosamprenavir, tipranavir, indinavir, saquinavir, lopinavir, ritonavir, darunavir, or nelfinavir), a non-nucleoside reverse transcriptase inhibitor ("NNRTI") (e.g., UK-453061, GSK2248761, etravirine, delavirdine, efavirenz, nevirapine, or rilpivirine), a nucleoside/nucleotide reverse transcriptase inhibitor ("NRTI") (e.g., zidovudine, lamivudine, emtricitabine, tenofovir disoproxil fumarate, didanosine, stavudine, abacavir, racivir, amdoxovir, apricitabine, entecavir, adefovir or elvucitabine) a viral entry inhibitor (e.g., enfuvirtide, maraviroc, vicriviroc, PF-232798, GSK 706769, PRO 140, or TNX-355), an integrase inhibitor (e.g., raltegravir, GSK 1349572 or elvitegravir), an immune based antiretroviral agent (e.g., immunitin, proleukin, remune, BAY 50-4798 or IR103) , a viral maturation inhibitor (e.g., bevirimat), a cellular inhibitor (e.g., droxia or hydroxyurea), a pharmacokinetic enhancing agent (e.g., GS 9350, ritonavir, or PF-3716539) or combinations of two or more of the above.

[92] In a more specific embodiment, the second therapeutic agent is selected from efavirenz, didanosine, tenofovir disoproxil, nelfinavir mesilate, amprenavir, raltegravir, saquinavir, lopinavir, nevirapine, emtricitabine, abacavir, lamivudine,

zidovudine, maraviroc, stavudine, darunavir, fosamprenavir, vicriviroc, pharmaceutically acceptable salts of any of the foregoing, and combinations thereof.

[93] In an even more specific embodiment, the second therapeutic agent is selected from efavirenz, didanosine, raltegravir, tenofovir disoproxil lamivudine, abacavir, zidovudine, emtricitabine, efavirenz, pharmaceutically acceptable salts of any of the foregoing, and combinations thereof. In another specific embodiment, the compositions of this invention comprise a compound of any one of Formulae I, and two to three of the second therapeutic agents set forth above in this paragraph. In an even more specific embodiment, the compositions of this invention comprise a compound of any one of Formulae I, and two of the second therapeutic agents set forth above in this paragraph.

[94] In another embodiment, the invention provides separate dosage forms of a compound of this invention and one or more of any of the above-described second therapeutic agents, wherein the compound and second therapeutic agent are associated with one another. The term "associated with one another" as used herein means that the separate dosage forms are packaged together or otherwise attached to one another such that it is readily apparent that the separate dosage forms are intended to be sold and administered together (within less than 24 hours of one another, consecutively or simultaneously).

[95] In the pharmaceutical compositions of the invention, the compound of the present invention is present in an effective amount. As used herein, the term "effective amount" refers to an amount which, when administered in a proper dosing regimen, is sufficient to treat the target disorder. Preferably, a compound of the present invention is present in the composition in an amount of from 0.1 to 50wt.%, more preferably from 1 to 30 wt.%, most preferably from 5 to 20wt.%.

[96] The interrelationship of dosages for animals and humans (based on milligrams per meter squared of body surface) is described in Freireich et al., (1966) Cancer Chemother. Rep 50: 219. Body surface area may be approximately determined from height and weight of the subject. See, e.g., Scientific Tables, Geigy Pharmaceuticals, Ardsley, N.Y., 1970, 537.

[97] In one embodiment, an effective amount of a compound of this invention can range from about 20 to about 2000 mg per treatment. In another embodiment, an effective amount of a compound of this invention can range from about 100 to about 1000 mg per treatment. Treatment is typically administered from one to two times

daily. Effective doses will also vary, as recognized by those skilled in the art, depending on the diseases treated, the severity of the disease, the route of administration, the sex, age and general health condition of the subject, excipient usage, the possibility of co-usage with other therapeutic treatments such as use of other agents and the judgment of the treating physician. For example, guidance for selecting an effective dose can be determined by reference to the prescribing information for atazanavir.

[98] For pharmaceutical compositions that comprise a second therapeutic agent, an effective amount of the second therapeutic agent is between about 20% and 100% of the dosage normally utilized in a monotherapy regime using just that agent. Preferably, an effective amount is between about 70% and 100% of the normal monotherapeutic dose. The normal monotherapeutic dosages of these second therapeutic agents are well known in the art. *See*, e.g., Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, Conn. (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, Calif. (2000), each of which references are incorporated herein by reference in their entirety.

[99] It is expected that some of the second therapeutic agents referenced above will act synergistically with the compounds of this invention. When this occurs, it will allow the effective dosage of the second therapeutic agent and/or the compound of this invention to be reduced from that required in a monotherapy. This has the advantage of minimizing toxic side effects of either the second therapeutic agent of a compound of this invention, synergistic improvements in efficacy, improved ease of administration or use and/or reduced overall expense of compound preparation or formulation.

METHODS OF TREATMENT

[100] In another embodiment, the invention provides a method of treating HIV infection in a subject in need thereof comprising the step of administering to the subject an effective amount of compound of any one of Formulae I, II or III or a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable composition comprising a compound of any one of Formulae I, II or III or a pharmaceutically acceptable salt thereof.

[101] Methods delineated herein also include those wherein the subject is

identified as in need of a particular stated treatment. Identifying a subject in need of such treatment can be in the judgment of a subject or a health care professional and can be subjective (e.g. opinion) or objective (e.g. measurable by a test or diagnostic method).

[102] In another embodiment, any of the above methods of treatment comprises the further step of co-administering to the subject one or more second therapeutic agents. The choice of second therapeutic agent may be made from any second therapeutic agent known to be useful for co-administration with atazanavir. The choice of second therapeutic agent is also dependent upon the particular disease or condition to be treated. Examples of second therapeutic agents that may be employed in the methods of this invention are those set forth above for use in combination compositions comprising a compound of this invention and a second therapeutic agent.

[103] In particular, the combination therapies of this invention include co-administering a compound of any one of Formulae I, II or III or a pharmaceutically acceptable salt thereof and a second HIV protease inhibitor (e.g., amprenavir, fosamprenavir, tipranavir, indinavir, saquinavir, lopinavir, ritonavir, darunavir, or nelfinavir), a non-nucleoside reverse transcriptase inhibitor ("NNRTI") (e.g., UK-453061, GSK2248761, etravirine, delavirdine, efavirenz, nevirapine, or rilpivirine), a nucleoside/nucleotide reverse transcriptase inhibitor ("NRTI") (e.g., zidovudine, lamivudine, emtricitabine, tenofovir disoproxil fumarate, didanosine, stavudine, abacavir, racivir, amdoxovir, apricitabine, entecavir, adefovir or elvucitabine) a viral entry inhibitor (e.g., enfuvirtide, maraviroc, vicriviroc, PF-232798, GSK 706769, PRO 140, or TNX-355), an integrase inhibitor (e.g., raltegravir, GSK 1349572 or elvitegravir), an immune based antiretroviral agent (e.g., immunitin, proleukin, remune, BAY 50-4798 or IR103) , a viral maturation inhibitor (e.g., bevirimat), a cellular inhibitor (e.g., droxia or hydroxyurea), a pharmacokinetic enhancing agent (e.g., GS 9350, ritonavir, or PF-3716539) or combinations of two or more of the above.

[104] In a more specific embodiment, the combination therapies of this invention include co-administering a compound of any one of Formulae I, II or III and a second therapeutic agent selected from efavirenz, didanosine, tenofovir disoproxil, nelfinavir mesilate, amprenavir, raltegravir, saquinavir, lopinavir, nevirapine, emtricitabine, abacavir, lamivudine, zidovudine, maraviroc, stavudine, darunavir,

fosamprenavir, vicriviroc, pharmaceutically acceptable salts of any of the foregoing, and combinations thereof to treat HIV infection in a subject in need thereof.

[105] In an even more specific embodiment, the second therapeutic agent is selected from efavirenz, didanosine, raltegravir, tenofovir disoproxil lamivudine, abacavir, zidovudine, emtricitabine, efavirenz, pharmaceutically acceptable salts of any of the foregoing, and combinations thereof. In another specific embodiment, the method comprises co-administering a compound of any one of Formulae I or a pharmaceutically acceptable salt thereof, and two to three of the second therapeutic agents set forth above in this paragraph. In an even more specific embodiment, the method comprises co-administering a compound of any one of Formulae I, and two of the second therapeutic agents set forth above in this paragraph.

[106] In another embodiment, the second therapeutic agent is an agent that does not inhibit CYP3A4. In a more specific embodiment, the second therapeutic agent is other than ritonavir.

[107] The term "co-administered" as used herein means that the second therapeutic agent may be administered together with a compound of this invention as part of a single dosage form (such as a composition of this invention comprising a compound of the invention and an second therapeutic agent as described above) or as separate, multiple dosage forms. Alternatively, the additional agent may be administered prior to, consecutively with, or following the administration of a compound of this invention. In such combination therapy treatment, both the compounds of this invention and the second therapeutic agent(s) are administered by conventional methods. The administration of a composition of this invention, comprising both a compound of the invention and a second therapeutic agent, to a subject does not preclude the separate administration of that same therapeutic agent, any other second therapeutic agent or any compound of this invention to said subject at another time during a course of treatment.

[108] Effective amounts of these second therapeutic agents are well known to those skilled in the art and guidance for dosing may be found in patents and published patent applications referenced herein, as well as in Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, Conn. (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, Calif. (2000), and other medical texts.

However, it is well within the skilled artisan's purview to determine the second therapeutic agent's optimal effective-amount range.

[109] In one embodiment of the invention, where a second therapeutic agent is administered to a subject, the effective amount of the compound of this invention is less than its effective amount would be where the second therapeutic agent is not administered. In another embodiment, the effective amount of the second therapeutic agent is less than its effective amount would be where the compound of this invention is not administered. In this way, undesired side effects associated with high doses of either agent may be minimized. Other potential advantages (including without limitation improved dosing regimens and/or reduced drug cost) will be apparent to those of skill in the art.

[110] In yet another aspect, the invention provides the use of a compound of Formula I alone or together with one or more of the above-described second therapeutic agents in the manufacture of a medicament, either as a single composition or as separate dosage forms, for treatment or prevention in a subject of a disease, disorder or symptom set forth above. Another aspect of the invention is a compound of any one of Formulae I, II or III or a pharmaceutically acceptable salt thereof for use in the treatment or prevention in a subject of a disease, disorder or symptom thereof delineated herein, more particularly a compound of Formula I or a pharmaceutically acceptable salt thereof for use in the treatment of an HIV infection. In a further aspect, the compounds of the invention may be used in medicine, such as in therapy. In any of these uses, the compound is preferably administered without co-administration of ritonavir.

Example 1. Evaluation of Metabolic Stability in Human Liver Microsomes. Human liver microsomes (20 mg/mL) are obtained from Xenotech, LLC (Lenexa, KS). β-nicotinamide adenine dinucleotide phosphate, reduced form (NADPH), magnesium chloride ($MgCl_2$), and dimethyl sulfoxide (DMSO) are purchased from Sigma-Aldrich.

[111] ***Determination of Metabolic Stability:*** 7.5 mM stock solutions of test compounds are prepared in DMSO. The 7.5 mM stock solutions are diluted to 12.5 μM in acetonitrile (ACN). The 20 mg/mL human liver microsomes are diluted to 0.625 mg/mL in 0.1 M potassium phosphate buffer, pH 7.4, containing 3 mM $MgCl_2$. The diluted microsomes (375 μL) are added to wells of a 96-well deep-well

polypropylene plate in triplicate. Ten to 40 μL of the 12.5 μM test compound is added to the microsomes and the mixture is pre-warmed for 10 minutes. Reactions are initiated by addition of 125 μL of pre-warmed NADPH solution. The final reaction volume is 0.5 mL and contains 0.5 mg/mL human liver microsomes, 0.25-1.0 μM test compound, and 2 mM NADPH in 0.1 M potassium phosphate buffer, pH 7.4, and 3 mM $MgCl_2$. The reaction mixtures are incubated at 37 °C, and 50 μL aliquots are removed at 0, 5, 10, 20, and 30 minutes and added to shallow-well 96-well plates which contain 50 μL of ice-cold ACN with internal standard to stop the reactions. The plates are stored at 4 °C for 20 minutes after which 100 μL of water is added to the wells of the plate before centrifugation to pellet precipitated proteins. Supernatants are transferred to another 96-well plate and analyzed for amounts of parent compound remaining by LC-MS/MS using an Applied Bio-systems API 4000 mass spectrometer. The same procedure is followed for the non-deuterated counterpart of the compound of Formula I and the positive control, 7-ethoxycoumarin (1 μM). Testing is done in triplicate..

[112] ***Data analysis:*** The *in vitro* half-lives ($t_{1/2}$s) for test compounds are calculated from the slopes of the linear regression of % parent remaining (ln) vs incubation time relationship using the following formula:

in vitro $t_{1/2} = 0.693/k$, where k = -[slope of linear regression of % parent remaining(ln) vs incubation time]

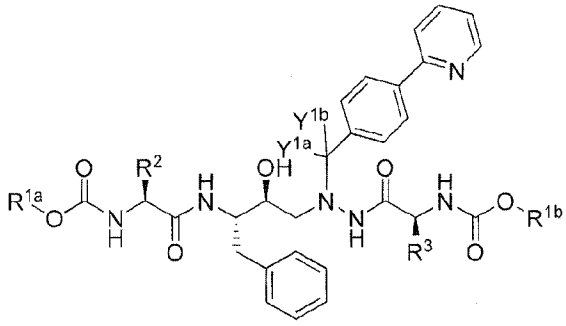
[113] Data analysis is performed using Microsoft Excel Software.

[114] Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods. It should be understood that the foregoing discussion and examples merely present a detailed description of certain preferred embodiments. It will be apparent to those of ordinary skill in the art that various modifications and equivalents can be made without departing from the spirit and scope of the invention.

CLAIMS

What is claimed is:

1. A compound represented by Formula I:



(I), or a pharmaceutically acceptable salt thereof, wherein:

one of R^{1a} or R^{1b} is $-(CH_2CH_2O)_m-CH_3$, and the other R^{1a} or R^{1b} is $(CH_2CH_2O)_m-CH_3$, or $-(C_1-C_3)$-alkyl, wherein each of R^{1a} and R^{1b} is optionally and independently substituted with one or more deuterium;

m is an integer from 1 to 30;

each of R^2 and R^3 is independently selected from isopropyl, sec-butyl, and tert-butyl, wherein one of R^2 or R^3 is substituted with one or more deuterium and the other of R^2 and R^3 is optionally substituted with one or more deuterium; and

Y^{1a} and Y^{1b} are independently selected from hydrogen and deuterium.

2. The compound of claim 1, wherein:

one of R^2 or R^3 is $-C(CD_3)_3$ and the other of R^2 or R^3 is $-C(CH_3)_3$ or $-C(CD_3)_3$;

m is an integer from 1 to 15; and

Y^{1a} and Y^{1b} are the same.

3. The compound of claim 2, wherein one of R^{1a} or R^{1b} is $-(CH_2CH_2O)_m-CH_3$ or $-(CD_2CD_2O)_m-CD_3$, and the other R^{1a} or R^{1b} is $(CH_2CH_2O)_m-CH_3$, $(CD_2CD_2O)_m-CD_3$, $-CH_3$, or $-CD_3$.

4. The compound of claim 3, wherein:

one of R^{1a} or R^{1b} is $(CH_2CH_2O)_m$-CH_3 and the other R^{1a} or R^{1b} is $(CH_2CH_2O)_m$-CH_3, -CH_3, or -CD_3; and

each m is 1, 2, 3, 4 or 5.

5. The compound of claim 3, wherein:

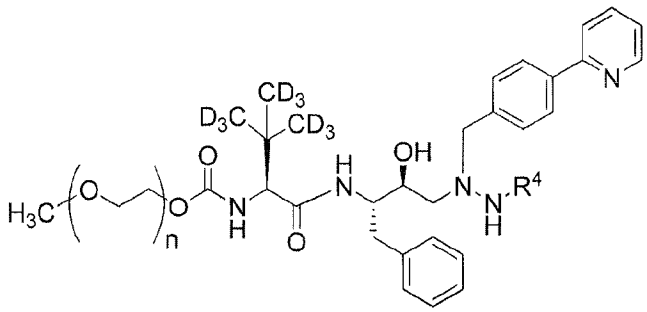
one of R^{1a} or R^{1b} is $(CD_2CD_2O)_m$-CD_3 and the other R^{1a} or R^{1b} is selected from $(CH_2CH_2O)_m$-CH_3, $(CD_2CD_2O)_m$-CD_3, -CH_3, or -CD_3; and

each m is 1, 2, 3, 4 or 5.

6. The compound of any one of claims 1 to 5, wherein Y^{1a} and Y^{1b} are both hydrogen.

7. The compound of any one of claims 1 to 5, wherein Y^{1a} and Y^{1b} are both deuterium.

8. A compound represented by Formula II:



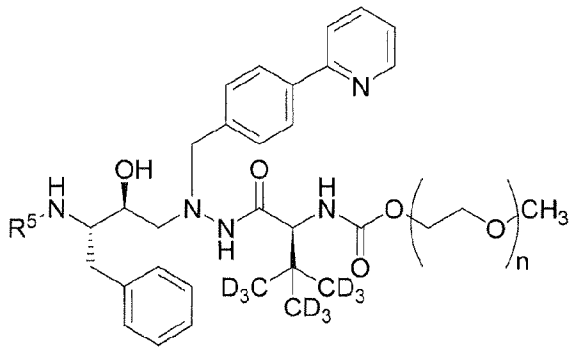
(II),

or a pharmaceutically acceptable salt thereof, wherein:

R^4 is selected from hydrogen and benzyloxycarbonyl; and

n is 1, 2, 3, 4 or 5.

9. A compound represented by Formula III:



(III),

or a pharmaceutically acceptable salt thereof, wherein:

R^5 is selected from hydrogen and t-butoxycarbonyl; and

n is 1, 2, 3, 4 or 5.

10. The compound of claim 6, selected from any one of the compounds set forth in the table below:

Compound	R^{1a}	R^{1b}	R^2	R^3
105	$(CH_2CH_2O)_3$-CH_3	CH_3	$C(CD_3)_3$	$C(CH_3)_3$
106	$(CH_2CH_2O)_5$-CH_3	CH_3	$C(CD_3)_3$	$C(CH_3)_3$
107	CH_3	$(CH_2CH_2O)_3$-CH_3	$C(CD_3)_3$	$C(CH_3)_3$
108	CH_3	$(CH_2CH_2O)_5$-CH_3	$C(CD_3)_3$	$C(CH_3)_3$
109	$(CH_2CH_2O)_3$-CH_3	CH_3	$C(CH_3)_3$	$C(CD_3)_3$
110	$(CH_2CH_2O)_5$-CH_3	CH_3	$C(CH_3)_3$	$C(CD_3)_3$
111	CH_3	$(CH_2CH_2O)_3$-CH_3	$C(CH_3)_3$	$C(CD_3)_3$
112	CH_3	$(CH_2CH_2O)_5$-CH_3	$C(CH_3)_3$	$C(CD_3)_3$
113	$(CH_2CH_2O)_3$-CH_3	CD_3	$C(CH_3)_3$	$C(CD_3)_3$
114	$(CH_2CH_2O)_5$-CH_3	CD_3	$C(CH_3)_3$	$C(CD_3)_3$
115	CD_3	$(CH_2CH_2O)_3$-CH_3	$C(CH_3)_3$	$C(CD_3)_3$
116	CD_3	$(CH_2CH_2O)_5$-CH_3	$C(CH_3)_3$	$C(CD_3)_3$
117	$(CH_2CH_2O)_3$-CH_3	CD_3	$C(CD_3)_3$	$C(CH_3)_3$
118	$(CH_2CH_2O)_5$-CH_3	CD_3	$C(CD_3)_3$	$C(CH_3)_3$
119	CD_3	$(CH_2CH_2O)_3$-CH_3	$C(CD_3)_3$	$C(CH_3)_3$
120	CD_3	$(CH_2CH_2O)_5$-CH_3	$C(CD_3)_3$	$C(CH_3)_3$
121	$(CH_2CH_2O)_3$-CH_3	CH_3	$C(CD_3)_3$	$C(CD_3)_3$

Compound	R^{1a}	R^{1b}	R^2	R^3
122	$(CH_2CH_2O)_5$-CH_3	CH_3	$C(CD_3)_3$	$C(CD_3)_3$
123	CH_3	$(CH_2CH_2O)_3$-CH_3	$C(CD_3)_3$	$C(CD_3)_3$
124	CH_3	$(CH_2CH_2O)_5$-CH_3	$C(CD_3)_3$	$C(CD_3)_3$
125	$(CH_2CH_2O)_3$-CH_3	CD_3	$C(CD_3)_3$	$C(CD_3)_3$
126	$(CH_2CH_2O)_5$-CH_3	CD_3	$C(CD_3)_3$	$C(CD_3)_3$
127	CD_3	$(CH_2CH_2O)_3$-CH_3	$C(CD_3)_3$	$C(CD_3)_3$
128	CD_3	$(CH_2CH_2O)_5$-CH_3	$C(CD_3)_3$	$C(CD_3)_3$
129	$(CH_2CH_2O)_3$-CH_3	$(CH_2CH_2O)_3$-CH_3	$C(CD_3)_3$	$C(CH_3)_3$
130	$(CH_2CH_2O)_5$-CH_3	$(CH_2CH_2O)_5$-CH_3	$C(CD_3)_3$	$C(CH_3)_3$
131	$(CH_2CH_2O)_3$-CH_3	$(CH_2CH_2O)_3$-CH_3	$C(CH_3)_3$	$C(CD_3)_3$
132	$(CH_2CH_2O)_5$-CH_3	$(CH_2CH_2O)_5$-CH_3	$C(CH_3)_3$	$C(CD_3)_3$
133	$(CH_2CH_2O)_3$-CH_3	$(CH_2CH_2O)_3$-CH_3	$C(CD_3)_3$	$C(CD_3)_3$
and 134	$(CH_2CH_2O)_5$-CH_3	$(CH_2CH_2O)_5$-CH_3	$C(CD_3)_3$	$C(CD_3)_3$

or a pharmaceutically acceptable salt of any of the foregoing.

11. The compound of claim 7, selected from any one of the compounds set forth in the table below:

Compound	R^{1a}	R^{1b}	R^2	R^3
135	$(CH_2CH_2O)_3$-CH_3	CH_3	$C(CD_3)_3$	$C(CH_3)_3$
136	$(CH_2CH_2O)_5$-CH_3	CH_3	$C(CD_3)_3$	$C(CH_3)_3$
137	CH_3	$(CH_2CH_2O)_3$-CH_3	$C(CD_3)_3$	$C(CH_3)_3$
138	CH_3	$(CH_2CH_2O)_5$-CH_3	$C(CD_3)_3$	$C(CH_3)_3$
139	$(CH_2CH_2O)_3$-CH_3	CH_3	$C(CH_3)_3$	$C(CD_3)_3$
140	$(CH_2CH_2O)_5$-CH3	CH_3	$C(CH_3)_3$	$C(CD_3)_3$
141	CH_3	$(CH_2CH_2O)_3$-CH_3	$C(CH_3)_3$	$C(CD_3)_3$
142	CH_3	$(CH_2CH_2O)_5$-CH_3	$C(CH_3)_3$	$C(CD_3)_3$
143	$(CH_2CH_2O)_3$-CH_3	CD_3	$C(CH_3)_3$	$C(CD_3)_3$
144	$(CH_2CH_2O)_5$-CH_3	CD_3	$C(CH_3)_3$	$C(CD_3)_3$
145	CD_3	$(CH_2CH_2O)_3$-CH_3	$C(CH_3)_3$	$C(CD_3)_3$
146	CD_3	$(CH_2CH_2O)_5$-CH_3	$C(CH_3)_3$	$C(CD_3)_3$
147	$(CH_2CH_2O)_3$-CH_3	CD_3	$C(CD_3)_3$	$C(CH_3)_3$

Compound	R^{1a}	R^{1b}	R^2	R^3
148	$(CH_2CH_2O)_5$-CH_3	CD_3	$C(CD_3)_3$	$C(CH_3)_3$
149	CD_3	$(CH_2CH_2O)_3$-CH_3	$C(CD_3)_3$	$C(CH_3)_3$
150	CD_3	$(CH_2CH_2O)_5$-CH_3	$C(CD_3)_3$	$C(CH_3)_3$
151	$(CH_2CH_2O)_3$-CH_3	CH_3	$C(CD_3)_3$	$C(CD_3)_3$
152	$(CH_2CH_2O)_5$-CH_3	CH_3	$C(CD_3)_3$	$C(CD_3)_3$
153	CH_3	$(CH_2CH_2O)_3$-CH_3	$C(CD_3)_3$	$C(CD_3)_3$
154	CH_3	$(CH_2CH_2O)_5$-CH_3	$C(CD_3)_3$	$C(CD_3)_3$
155	$(CH_2CH_2O)_3$-CH_3	CD_3	$C(CD_3)_3$	$C(CD_3)_3$
156	$(CH_2CH_2O)_5$-CH_3	CD_3	$C(CD_3)_3$	$C(CD_3)_3$
157	CD_3	$(CH_2CH_2O)_3$-CH_3	$C(CD_3)_3$	$C(CD_3)_3$
158	CD_3	$(CH_2CH_2O)_5$-CH_3	$C(CD_3)_3$	$C(CD_3)_3$
159	$(CH_2CH_2O)_3$-CH_3	$(CH_2CH_2O)_3$-CH_3	$C(CD_3)_3$	$C(CH_3)_3$
160	$(CH_2CH_2O)_5$-CH_3	$(CH_2CH_2O)_5$-CH_3	$C(CD_3)_3$	$C(CH_3)_3$
161	$(CH_2CH_2O)_3$-CH_3	$(CH_2CH_2O)_3$-CH_3	$C(CH_3)_3$	$C(CD_3)_3$
162	$(CH_2CH_2O)_5$-CH_3	$(CH_2CH_2O)_5$-CH_3	$C(CH_3)_3$	$C(CD_3)_3$
163	$(CH_2CH_2O)_3$-CH_3	$(CH_2CH_2O)_3$-CH_3	$C(CD_3)_3$	$C(CD_3)_3$
and 164	$(CH_2CH_2O)_5$-CH_3	$(CH_2CH_2O)_5$-CH_3	$C(CD_3)_3$	$C(CD_3)_3$

or a pharmaceutically acceptable salt of any of the foregoing.

12. The compound of any one of claims 1 to 11, wherein any atom not designated as deuterium is present at its natural isotopic abundance.

13. A pyrogen-free pharmaceutical composition comprising a compound of any one of Claims 1 to 12 or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

14. The composition of Claim 13, additionally comprising a second therapeutic agent selected from a second HIV protease inhibitor, a non-nucleoside reverse transcriptase inhibitor, a nucleoside/nucleotide reverse transcriptase inhibitor, a viral entry inhibitor, an integrase inhibitor, an immune based antiretroviral agent, a viral maturation inhibitor, a cellular inhibitor, a

pharmacokinetic enhancing agent or combinations of two or more of the above.

15. The composition of Claim 14, wherein the second therapeutic agent is selected from efavirenz, didanosine, tenofovir disoproxil, nelfinavir mesilate, amprenavir, raltegravir potassium, saquinavir, lopinavir, nevirapine, emtricitabine, abacavir, lamivudine, zidovudine, maraviroc, stavudine, darunavir, fosamprenavir, vicriviroc, a pharmaceutically acceptable salt of any of the foregoing, and combinations thereof.

16. The composition of Claim 15, wherein the second therapeutic agent is selected from efavirenz, didanosine, raltegravir, tenofovir disoproxil, lamivudine, abacavir, zidovudine, emtricitabine, efavirenz, a pharmaceutically acceptable salt of any of the foregoing, and combinations thereof.

17. The composition of Claim 13, comprising two to three additional second therapeutic agents independently selected from efavirenz, didanosine, raltegravir, tenofovir disoproxil, lamivudine, abacavir, zidovudine, emtricitabine, efavirenz, and a pharmaceutically acceptable salt of any of the foregoing.

18. The composition of Claim 17, comprising two additional second agents independently selected from efavirenz, didanosine, raltegravir, tenofovir disoproxil, lamivudine, abacavir, zidovudine, emtricitabine, efavirenz, and a pharmaceutically acceptable salt of any of the foregoing.

19. A method of treating HIV infection in a subject in need thereof comprising the step of administering to the subject an effective amount of a composition according to Claim 13.

20. The method of Claim 19, further comprising administering to the subject a second therapeutic agent selected from a second HIV protease inhibitor, a non-nucleoside reverse transcriptase inhibitor, a nucleoside/nucleotide

reverse transcriptase inhibitor, a viral entry inhibitor, an integrase inhibitor, an immune based antiretroviral agent, a viral maturation inhibitor, a cellular inhibitor, a pharmacokinetic enhancing agent and combinations of two or more of the above.

21. The method of Claim 20, wherein the second therapeutic agent is selected from efavirenz, didanosine, tenofovir disoproxil, nelfinavir, amprenavir, raltegravir, saquinavir, lopinavir, nevirapine, emtricitabine, abacavir, lamivudine, zidovudine, maraviroc, stavudine, darunavir, fosamprenavir, vicriviroc, a pharmaceutically acceptable salt of any of the foregoing, and combinations thereof.

22. The method of Claim 21, wherein the second therapeutic agent is selected from efavirenz, didanosine, raltegravir, tenofovir disoproxil, lamivudine, abacavir, zidovudine, emtricitabine, efavirenz, a pharmaceutically acceptable salt of any of the foregoing, and combinations thereof.

23. The method of Claim 19, further comprising administering to the subject two to three additional second therapeutic agents independently selected from efavirenz, didanosine, raltegravir, tenofovir disoproxil, lamivudine, abacavir, zidovudine, emtricitabine, efavirenz, and a pharmaceutically acceptable salt of any of the foregoing.

24. The method of Claim 23, further comprising administering to the subject two additional second therapeutic agents independently selected from efavirenz, didanosine, raltegravir, tenofovir disoproxil, lamivudine, abacavir, zidovudine, emtricitabine, efavirenz, and a pharmaceutically acceptable salt of any of the foregoing.

25. The method of claim 20, wherein the second therapeutic agent does not inhibit CYP3A4.

26. The method of claim 25, wherein the second agent is other than ritonavir.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/034710

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/42 A61K31/4402 A61P31/00 C07B59/00
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)
C07D A61K A61P C07B

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 practical, search terms used)
EPO-Internal, EMBASE, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2008/112289 A2 (NEKTAR THERAPEUTICS AL CORP [US]; RIGGS-SAUTHIER JENNIFER [US]; CHENG) 18 September 2008 (2008-09-18) cited in the application paragraph [0003], paragraphs [0129]-[0136]	1-26
Y	FOSTER A B: "Deuterium isotope effects in the metabolism of drugs and xenobiotics: implications for drug design" ADVANCES IN DRUG RESEARCH, ACADEMIC PRESS, LONDON, GB, vol. 14, 1 January 1985 (1985-01-01), pages 1-40, XP009086953 ISSN: 0065-2490 page 5	1-26

-/--

[X] Further documents are listed in the continuation of Box C.

[X] 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 document 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
21 October 2010	02/11/2010

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	Moriggi, J

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/034710

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 2 003 120 A1 (CONCERT PHARMACEUTICALS INC [US]) 17 December 2008 (2008-12-17) cited in the application claims 1, 2, 13	1-26

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2010/034710

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008112289 A2	18-09-2008	AU 2008226823 A1	18-09-2008
		CA 2679482 A1	18-09-2008
		CN 101631568 A	20-01-2010
		EP 2131865 A2	16-12-2009
		JP 2010522142 T	01-07-2010
		KR 20090118965 A	18-11-2009
EP 2003120 A1	17-12-2008	AR 066972 A1	23-09-2009
		AT 447554 T	15-11-2009
		AU 2008267048 A1	24-12-2008
		CA 2692028 A1	24-12-2008
		CN 101711237 A	19-05-2010
		DK 2003120 T3	15-03-2010
		EP 2116532 A1	11-11-2009
		HK 1127345 A1	20-05-2010
		HR 20100065 T1	31-03-2010
		JP 2010529196 T	26-08-2010
		KR 20100020033 A	19-02-2010
		PT 2003120 E	11-02-2010
		SI 2003120 T1	31-03-2010
		US 2009036357 A1	05-02-2009
		WO 2008156632 A1	24-12-2008