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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 July 2012 (05.07.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/092188 A1

(51) International Patent Classification:
A01N 43/02 (2006.01) *A61K 31/335* (2006.01)

(21) International Application Number:
PCT/US2011/067160

(22) International Filing Date:
23 December 2011 (23.12.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/427,295 27 December 2010 (27.12.2010) US

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(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, QA, RO, RS, RU, RW, 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, RW, 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, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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))*

WO 2012/092188 A1

(54) Title: HYDROGEN BOND FORMING P1 LIGANDS AND METHODS FOR TREATING HIV

(57) Abstract: Inhibitors of HIV-1 protease and compositions containing them are described. Use of the inhibitors and compositions containing them to treat HIV, AIDS, and AIDS-related diseases is described.

HYDROGEN BOND FORMING P1 LIGANDS AND METHODS FOR TREATING HIV

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority under 35 U.S.C. § 119 of U.S. Provisional Application Serial No. 61/427,295 filed on December 27, 2010, the entirety of which is incorporated by reference herein.

TECHNICAL FIELD

The invention described herein pertains to compounds, to compositions and formulations comprising the compounds, and to methods of use of the compounds and their compositions and formulations for the treatment of diseases, including diseases such as HIV, AIDS, and AIDS-related diseases.

BACKGROUND AND SUMMARY OF THE INVENTION

The AIDS epidemic is one of the most challenging problems in medicine in the 21st century (United Nations. 2004 Report on the global HIV/AIDS Epidemic: 4th global report. New York, U.S.A., 2004). The disclosure of the foregoing is incorporated herein in its entirety by reference. In addition, the entirety of the disclosures of each of the publications cited herein are also incorporated herein by reference. Among many strategies to combat this disease, highly active antiretroviral therapy (HAART) with HIV protease inhibitors (PIs) in combination with reverse transcriptase inhibitors (RTIs) continues to be the first line treatment for control of HIV infection (Sepkowitz, K.A. AIDS – the first 20 years. N. Engl. J. Med. 2001, 344, 1764-1772). This treatment regimen has definitely improved quality of life, enhanced HIV management, and halted the progression of the disease. However, despite these impressive successes, there remain many challenges to treating this devastating disease, including decreasing both the toxicity of and complexity of these treatment regimens. In addition, there is a growing population of patients that are developing multi-drug resistant strains of HIV, and there is ample evidence that these strains can be further transmitted (Staszewski et al., Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. N. Engl. J. Med. 1999, 341, 1865-1873; Wainberg et al., Public health implications of antiretroviral therapy and HIV drug resistance. J. Am. Med. Assoc. 1998, 279, 1977-1983).

HAART has had a major impact on the AIDS epidemic in industrially advanced nations; however, eradication of human immunodeficiency virus type 1 (HIV 1) appears to be currently unachieved, in part due to the viral reservoirs remaining in blood and infected tissues.

The limitation of antiviral therapy of AIDS is also exacerbated by complicated regimens, the development of drug-resistant HIV-1 variants, and a number of inherent adverse effects.

However, a number of challenges have nonetheless been encountered in bringing about the optimal benefits of the currently available therapeutics of AIDS and HIV-1 infection to individuals receiving HAART (De Clercq 2002. Strategies in the design of antiviral drugs. Nat Rev Drug Discov 1:13-25; Siliciano et al. 2004. A long-term latent reservoir for HIV-1: discovery and clinical implications. J Antimicrob Chemother 54:6-9; Simon, et al. 2003. HIV-1 dynamics in vivo: implications for therapy. Nat Rev Microbiol 1:181-90). They include (i) drug-related toxicities; (ii) partial restoration of immunologic functions once individuals developed AIDS; (iii) development of various cancers as a consequence of survival prolongation; (iv) flame-up of inflammation in individuals receiving HAART or immune re-construction syndrome (IRS); and (v) increased cost of antiviral therapy. Such limitations of HAART are exacerbated by the development of drug-resistant HIV-1 variants (Carr 2003. Toxicity of antiretroviral therapy and implications for drug development. Nat Rev Drug Discov 2:624-34; Fumero et al. 2003. New patterns of HIV-1 resistance during HAART. Clin Microbiol Infect 9:1077-84; Grabar et al. 2006. HIV infection in older patients in the HAART era. J Antimicrob Chemother 57:4-7; Hirsch et al. 2004. Immune reconstitution in HIV-infected patients. Clin Infect Dis 38:1159-66; Little et al. 2002. Antiretroviral-drug resistance among patients recently infected with HIV. N Engl J Med 347:385-94.

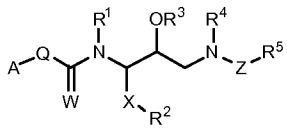
Successful antiviral drugs, in theory, exert their virus-specific effects by interacting with viral receptors, virally encoded enzymes, viral structural components, viral genes, or their transcripts without disturbing cellular metabolism or function. However, at present, no antiretroviral drugs or agents are likely to be completely specific for HIV-1 or to be devoid of toxicity or side effects in the therapy of AIDS, which has been an issue because patients with AIDS and its related diseases will have to receive antiretroviral therapy for a long period of time, perhaps for the rest of their lives.

In one embodiment, described herein are novel non-peptidyl compounds and compositions for treating patients in need of relief from HIV, AIDS, and AIDS-related diseases. Also described herein are methods for treating such diseases. In one embodiment, it has been discovered that the non-peptidyl compounds described herein are potent inhibitors of HIV-1 protease. It has also been discovered that those compounds may offer therapeutic benefits to patients suffering from or in need of relief from HIV-1/AIDS.

In another embodiment, described herein is structure-based design of novel HIV-1 protease inhibitors (PI) incorporating hydrogen bonding residues as the P_1 ligand. In one aspect, the inhibitors herein are designed to make extensive interactions including hydrogen

bonding with the protein backbone of the HIV-1 protease active site. In another embodiment, the inhibitors described herein appear to show excellent enzyme inhibitory activity and antiviral potency. In one aspect, this antiviral potency may be comparable to that of approved protease inhibitors. In another embodiment, the inhibitors described herein may show excellent activity against multi-PI-resistant variants.

In one illustrative embodiment of the invention, compounds of formula (I)



(I)

and pharmaceutically acceptable salts thereof are described herein, wherein

A is cycloheteroalkyl or cycloheteroalkyl-alkyl, each of which is optionally substituted;

Q is oxygen, sulfur, nitrogen, or $C(R^aR^b)$ where each of R^a and R^b is independently selected in each instance from the group consisting of hydrogen, alkyl, and alkoxy;

W is oxygen or sulfur;

R^1 is hydrogen, a nitrogen protecting group, or a pro-drug substituent;

X is $C(R^aR^b)_n$, where n is 1, 2, or 3, and each of R^a and R^b is defined as above;

R^2 is alkyl, heteroalkyl, cycloalkyl, cycloheteroalkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, each of which is substituted, where at least one substituent is a hydrogen bond forming group;

R^3 is hydrogen, an oxygen protecting group, or a pro-drug substituent;

R^4 is alkyl, heteroalkyl, cycloalkyl, cycloheteroalkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, each of which is optionally substituted;

Z is C(O), $S(O)_2$, NH, NHC(O), or $NHS(O)_2$; and

R^5 is alkyl, heteroalkyl, cycloalkyl, cycloheteroalkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, each of which is optionally substituted.

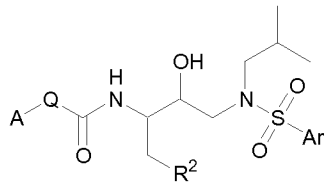
In another embodiment, compositions containing one or more of the compounds are also described herein. In one aspect, the compositions include a therapeutically effective amount of the one or more compounds for treating a patient with HIV-1/AIDS. In another embodiment, methods for using the compounds and compositions for treating patients with HIV-1/AIDS are also described herein. In one aspect, the methods include the step of administering one or more of the compounds and/or compositions containing them to a patient with HIV-1/AIDS. In another aspect, the methods include administering a therapeutically effective amount of the one or more compounds and/or compositions for treating patients with

HIV-1/AIDS. In another embodiment, uses of the compounds and compositions in the manufacture of a medicament for treating patients with HIV-1/AIDS are also described herein. In one aspect, the medicaments include a therapeutically effective amount of the one or more compounds and/or compositions for treating a patient with HIV-1/AIDS.

It is appreciated herein that the compounds described herein may be used alone or in combination with other compounds useful for treating HIV/AIDS, including those compounds that may operate by the same or different modes of action. In addition, it is appreciated herein that the compounds described herein may be used in combination with other compounds that are administered to treat other symptoms of HIV/AIDS.

DETAILED DESCRIPTION

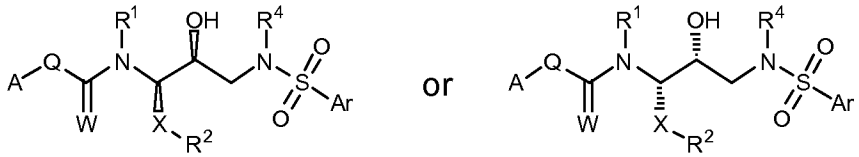
In another embodiment, compounds of the following formula are described herein:



wherein A, Q, R^2 and Ar are as described in the various embodiments and aspects disclosed herein.

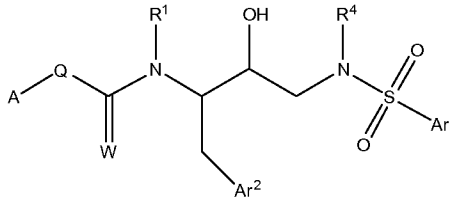
In one embodiment, Ar is aryl or heteroaryl as defined herein. In another embodiment, Ar is selected from the group consisting of 4-methoxyphenyl, 4-(hydroxymethyl)phenyl, a 3-substituted phenyl, a 4-substituted phenyl, an optionally substituted benzisoxazole, an optionally substituted benzoxazole; an optionally substituted benzodioxane or an optionally substituted benzodioxolane, and the like.

In another embodiment, compounds having the following relative and/or absolute stereochemistry are described herein:



wherein A, Q, W, R^1, X, R^2, R^4 and Ar are as described in the various descriptions herein. In one embodiment, Ar is optionally substituted aryl or heteroaryl. In another embodiment, Ar is optionally substituted aryl.

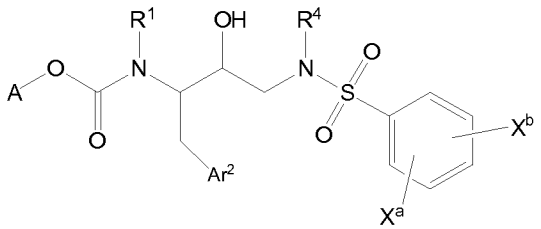
In another embodiment compounds of the following formula are described herein:



where Ar^2 is substituted aryl or substituted heteroaryl having one or more of the following illustrative substituents: halo, amino, hydroxy, alkyl, alkenyl, alkoxy, arylalkyl, arylalkyloxy, hydroxyalkyl, hydroxyalkenyl, alkylene dioxy, aminoalkyl, where the amino group may also be substituted with one or two alkyl groups, arylalkylgroups, and/or acylgroups, nitro, acyl and derivatives thereof such as oximes, hydrazones, and the like, cyano, alkylsulfonyl, alkylsulfonylamino, and the like, where at least one substituent is a hydrogen bond forming group, and

A, Q, W, R^1, R^4 and Ar have the meanings described above.

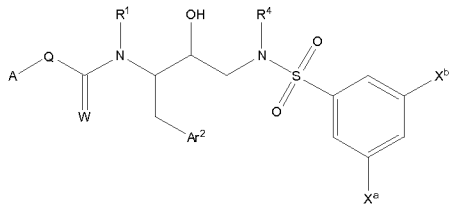
In another embodiment compounds of the following formula are described herein:



where X^a and X^b are each independently selected from hydrogen, halo, amino, hydroxy, alkyl, alkenyl, alkoxy, arylalkyl, arylalkyloxy, hydroxyalkyl, hydroxyalkenyl, aminoalkyl, where the amino group may also be substituted with one or two alkyl groups, arylalkylgroups, and/or acylgroups, nitro, acyl and derivatives thereof such as oximes, hydrazones, and the like, cyano, alkylsulfonyl, alkylsulfonylamino, and the like, or X^a and X^b together form alkylene dioxy; and

A, R^1, Ar^2, and R^4 have the meanings described above.

In another embodiment, compounds of the formula:

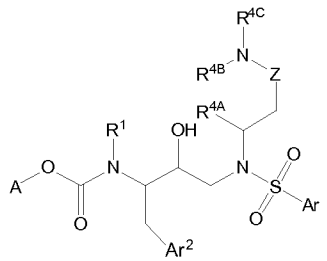


and pharmaceutically acceptable salts thereof are described herein wherein

X^a and X^b are independently selected from hydrogen, OH or OR^{5A}, where R^{5A} is alkyl, alkylaryl, an oxygen protecting group or a pro-drug substituent; and A, Q, W, R^1, Ar^2 and R^4 have the meanings described above.

In another embodiment of the compounds described herein, R^4 is alkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, hydroxy, alkoxy, cycloalkoxy, heterocyclyloxy, heterocyclylalkoxy, amino, mono or dialkylamino, cycloalkylamino, heterocyclylamino, or heterocyclylalkylamino, each of which is optionally substituted. In one aspect, R^4 is amino substituted alkyl or heterocycyl, or heterocyclylalkyl. In one variation of this aspect, the nitrogen atom of the amino group is mono or disubstituted with alkyl, cycloalkyl, or acyl, or is included in another heterocyclic group such as a pyrrolidinyl, piperidinyl, or piperazinyl group. In another variation of this aspect, the nitrogen atom of the hetetocylclyl group is substituted with alkyl, cycloalkyl, or acyl. In another aspect, R^4 is optionally substituted alkyl or cycloalkyl, including both linear and branched variations thereof, such as methyl, ethyl, butyl, isobutyl, and the like, and cyclobutyl, cyclopentyl, 3-methylcyclopentyl, and the like. In another aspect, R^4 is optionally substituted heterocyclyl or heterocyclylalkyl, where the heterocyclic portions includes, but is not limited to, tetrahydrofuranyl, azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, and the like.

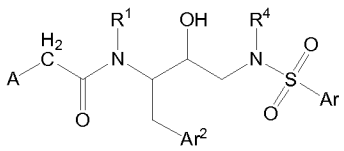
In another illustrative embodiment, compounds of formula



and pharmaceutically acceptable salts thereof are described, wherein

Z is $C(R^cR^d)$ where each of R^c and R^d is independently selected in each instance from the group consisting of hydrogen, alkyl, and arylalkyl; R^{4A}, R^{4B} and R^{4C} are independently selected in each instance from the group consisting of hydrogen, alkyl, and arylalkyl, each of which may be optionally substituted, or R^{4A}, R^{4B} and the atoms to which they are attached form a ring, and R^{4C} is selected from the group consisting of hydrogen, alkyl, and arylalkyl, each of which may be optionally substituted; and A, R^1 and Ar^2 have the meanings disclosed above.

In another embodiment, compounds of the formula:

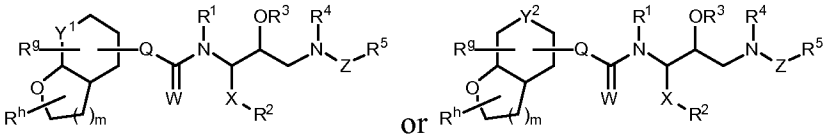


and pharmaceutically acceptable salts thereof are described herein wherein A, R^1, Ar^2, R^4 and Ar have the meanings described above.

In another embodiment, compounds are described where in of each of the foregoing formulae and embodiments, A is cycloheteroalkyl, which includes monocyclic and

polycyclic rings that have at least one nitrogen, oxygen, or sulfur atom, where it is to be understood that the polycyclic rings may be fused and/or spiro ring systems. Illustratively, monocyclic cycloheteroalkyls include, but are not limited to 5-, 6-, and 7-membered cyclic ethers and diethers, such as tetrahydrofurans, pyrans, 1,3-dioxolanes, 1,3-dixoxanes, 1,4-dioxanes, 1,3-dioxepanes, and the like; pyrrolidines, piperidines, piperazines, and the like; and tetrahydrothiophenes, thiopyrans, including oxidized variations thereof, and the like. Illustratively, polycyclic cycloheteroalkyls include, but are not limited to, the foregoing monocyclic rings fused to each other, or to cycloalkyls, and alternatively the spiro variations thereof. As indicated herein, it is also to be understood that where such fused or spiro ring systems include chiral centers, any and all possible stereoisomers are contemplated to be included herein. In addition, both the pure enantiomers and diastereomers, as well as various mixtures of pure enantiomers and diastereomers are contemplated to be included herein. It is also to be understood that the point of attachment of the cycloheteroalkyl groups described herein may be at any locus of the ring system.

In another illustrative embodiment, compounds of formulae

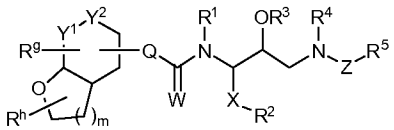


and pharmaceutically acceptable salts thereof are described herein, wherein

Y^1 is $C(R^eR^f)$ or oxygen; Y^2 is $C(R^eR^f)$, $CHNR^e$, oxygen, or SO_2, where R^e and R^f are independently selected in each instance from hydrogen, alkyl, and alkoxy; m is an integer selected from 0, 1, 2, or 3; and R^g and R^h each represent one or more optional substituents, each of which is independently selected in each instance from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, alkoxy, alkenyloxy, alkynyloxy, cycloalkoxy, cycloalkylalkoxy, aryl, arylalkoxy, heterocyclyloxy, heterocyclylalkoxy, heteroaryloxy, and heteroarylalkoxy, each of which is itself optionally substituted; and

Q, W, R^1, X, R^2, R^3, R^4, Z and R^5 have the meanings described above.

In another illustrative embodiment, compounds of the formula



and pharmaceutically acceptable salts thereof are described herein, wherein

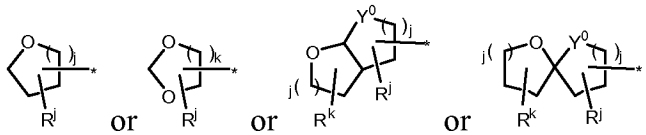
one of Y^1 and Y^2 is methylene, and the other of Y^1 and Y^2 is defined as follows:

Y^1 is $C(R^eR^f)$ or oxygen; Y^2 is $C(R^eR^f)$, $CHNR^e$, oxygen, or SO_2, where R^e and R^f are independently selected in each instance from hydrogen, alkyl, and alkoxy; m is an integer selected from 0, 1, 2, or 3; and R^g and R^h each represent one or more optional substituents, each of which is independently selected in each instance from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, alkoxy, alkenyloxy, alkynyloxy, cycloalkoxy, cycloalkylalkoxy, aryl, arylalkoxy, heterocyclyloxy, heterocyclylalkoxy, heteroaryloxy, and heteroarylalkoxy, each of which is itself optionally substituted; and

Q, W, R^1, X, R^2, R^3, R^4, Z and R^5 have the meanings described above.

In another embodiment, compounds are described where in of each of the foregoing formulae and embodiments, Y^1 is oxygen; or Y^1 is $C(R^eR^f)$, where R^e is hydrogen, and R^f is hydrogen or alkoxy, such as methoxy; or Y^2 is oxygen; or Y^2 is $C(R^eR^f)$, where R^e is hydrogen, and R^f is hydrogen, such as methoxy.

In another embodiment, A is a mono or polycyclic ether. In another embodiment, A is a radical having one of the following structures

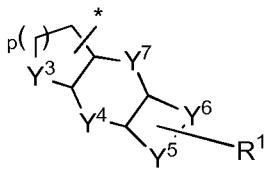


where (*) indicates the point of attachment of the group A; j is an integer that is independently selected in each instance from 0, 1, 2, or 3; k is an integer from 1 to 5; Y^0 is $C(R^aR^b)$ or oxygen; each of R^a and R^b is independently selected in each instance from the group consisting of hydrogen, alkyl, and alkoxy; and R^j and R^k each represent one or more optional substituents, each of which is independently selected in each instance from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl ,aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, alkoxy, alkenyloxy, alkynyloxy, cycloalkoxy, cycloalkylalkoxy ,aryl, arylalkoxy, heterocyclyloxy, heterocyclylalkoxy, heteroaryloxy, and heteroarylalkoxy, each of which is itself optionally substituted In one aspect, R^a and R^b are both hydrogen. In another aspect, R^j and R^k are both hydrogen. In another aspect, R^a, R^b, R^j and R^k are each hydrogen. In another aspect, one or more of R^j and R^k is alkoxy.

It is appreciated that when the integer j is in each case 0 or 1, the ring fusion is syn, whereas when in one instance the integer j is 2 and in the other instance the integer j is 1 or 2, the ring fusion may be syn or anti. It is further appreciated that in each of these relative stereochemical configurations, there are potentially two absolute stereochemical configurations. Unless otherwise indicated by specific reference to a relative or absolute stereochemical configuration, the structures described herein refer both individually to each enantiomer, as well

as collectively to all possible mixtures of such enantiomers. It is appreciated that the foregoing cyclic ethers may be optionally substituted with one or more groups R^a and/or R^b, each of which is independently selected, and is as described in the various embodiments and aspects disclosed herein.

In another illustrative embodiment, compounds, and pharmaceutically acceptable salts thereof are described herein, wherein A is of the formula



wherein (*) indicates the point of attachment;

p is 1, 2, or 3;

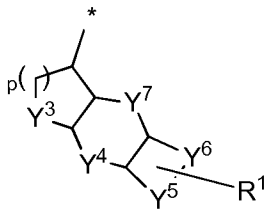
Y^3 and Y^4 are in each instance independently selected from the group consisting of optionally substituted methylene, oxygen, and amino;

Y^5 and Y^6 are in each instance independently selected from the group consisting of amino, oxygen, alkylene, and heteroalkylene, providing that at least one of Y^3 and Y^4 is oxygen, and wherein when one of Y^3 and Y^4 is optionally substituted methylene, at least one of Y^5 and Y^6 is oxygen, and A does not include a peroxide bond, a sulfenate bond, or a sulfenamide bond;

Y^7 is a bond or optionally substituted methylene; and

R^i is hydrogen, hydroxyl, carboxylate or derivative thereof, amino or derivative thereof, acyl, sulfonyl or derivative thereof, alkyl, or heteroalkyl.

In another illustrative embodiment, compounds, and pharmaceutically acceptable salts thereof are described herein, wherein A as described above is of the formula

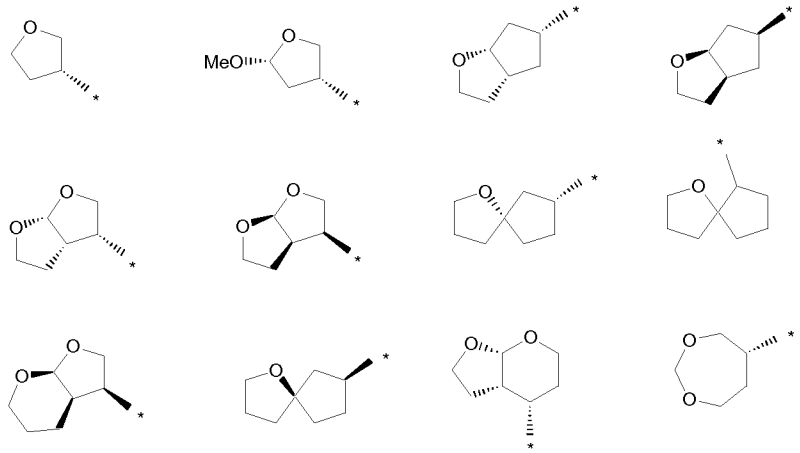


wherein (*) indicates the point of attachment; and p, Y^3, Y^4, Y^5, Y^6, Y^7, and R^1 are each defined as above.

In one embodiment for any of the above descriptions of A, Y^4 is oxygen. In one embodiment for any of the above descriptions of A, Y^7 is a bond. In one embodiment for any of the above descriptions of A, p is 1 or 2. In one embodiment for any of the above descriptions of A, p is 1. In one embodiment for any of the above descriptions of A, R^1 is hydrogen. In one embodiment for any of the above descriptions of A, Y^4 is oxygen. In one embodiment for any

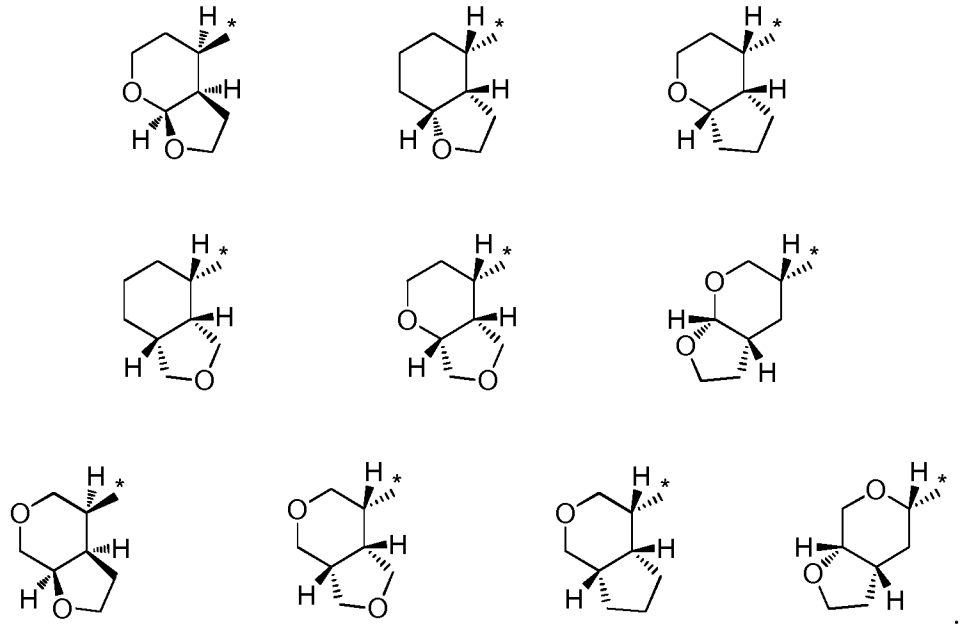
of the above descriptions of A, Y^5 or Y^6 is oxygen. In one embodiment for any of the above descriptions of A, Y^4 and one of Y^5 and Y^6 are oxygen. In one embodiment for any of the above descriptions of A, Y^4 and Y^5 are oxygen. In one embodiment for any of the above descriptions of A, each of Y^3, Y^4 and Y^5 is oxygen. In one embodiment for any of the above descriptions of A, Y^3 is optionally substituted methylene.

In another embodiment, A is a radical having one of the following structures



and stereoisomers thereof and mixtures thereof, where (*) indicates the point of attachment of A. It is therefore appreciated that such groups are attached to the group Q, which is oxygen, sulfur, nitrogen, or $C(R^aR^b)$; where each of R^a and R^b is independently selected in each instance, as defined in the various embodiments and aspects disclosed herein.

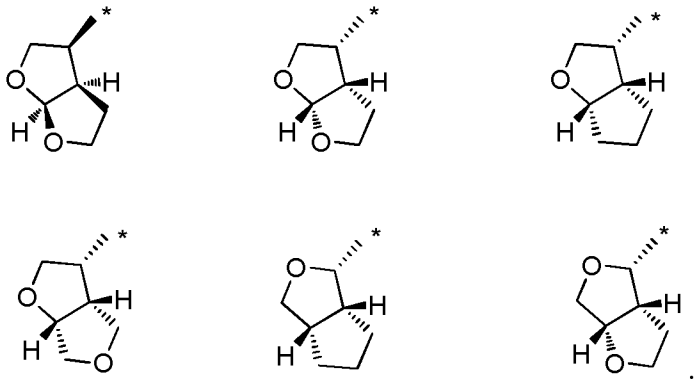
In another embodiment, A is a radical having one of the following structures



and stereoisomers thereof and mixtures thereof. where (*) indicates the point of attachment of A. It is therefore appreciated that such groups are attached to the group Q, which is oxygen,

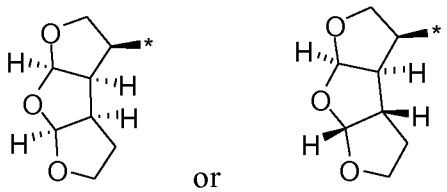
sulfur, nitrogen, or $C(R^aR^b)$; where each of R^a and R^b is independently selected in each instance, as defined in the various embodiments and aspects disclosed herein.

In another embodiment, A is a radical having one of the following structures



and stereoisomers thereof and mixtures thereof, where (*) indicates the point of attachment of A. It is therefore appreciated that such groups are attached to the group Q, which is oxygen, sulfur, nitrogen, or $C(R^aR^b)$; where each of R^a and R^b is independently selected in each instance, as defined in the various embodiments and aspects disclosed herein.

In another illustrative embodiment, compounds, and pharmaceutically acceptable salts thereof are described herein, wherein A is of the formula



wherein (*) indicates the point of attachment.

In another embodiment, the group A is cycloheteroalkyl-alkyl of the formula Het-$(CH_2)_q$-; where q is an integer selected from 1, 2, or 3; and Het is optionally substituted cycloheteroalkyl. In another embodiment, Het is oxazolidine, thiazolidine, pyrollidine, piperidine, piperazine, and the like, each of which is optionally substituted, including oxo substituents that form the corresponding oxazolidinones, thiazolidinones, pyrollidinones, piperidinones, piperazinones, and the like.

In any of the foregoing formulae and embodiments, the following compounds are described wherein:

Q is oxygen; and/or

W is oxygen; and/or

R^1 is hydrogen; and/or

R^3 is hydrogen; and/or

R^4 is a group CH_2-K-R^{4D}, where K is a bond or $NHCH_2$, and R^{4D} is alkyl, cycloalkyl, cycloheteroalkyl, aryl, or heteroaryl, each of which is optionally substituted; or R^{4D}

is isopropyl, furanyl, tetrahydrofuranyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyrrolidinonyl, oxazolidinonyl, thiazolidinonyl, isoxazolidionyl, or isothiazolidinonyl, each of which is optionally substituted; or R^4 is branched alkyl; or R^4 is isobutyl; or R^4 is lactamylalkyl; or R^4 is pyrrolidin-4-on-2-ylalkyl; or R^4 is pyrrolidin-4-on-2-ylmethyl; and/or

Z is SO_2; or Z is CO; or Z is NH; and/or

R^5 is aryl or heteroaryl, each of which is optionally substituted; or R^5 is substituted phenyl; or R^5 is substituted phenyl, where the substituent is hydroxy or a derivative thereof, amino or a derivative thereof, thio or a derivative thereof, or any of the foregoing where the substituent is covalently attached to the aryl through a group $C(R^xR^y)$; where each of R^x and R^y is independently selected in each instance from the group consisting of hydrogen and alkyl; or R^x and R^y are each hydrogen; and/or

R^5 is phenyl substituted with NH_2, OH, OMe, CH_2OH, and/or OCH_2O; or R^5 is optionally substituted benzofuran; or R^5 is optionally substituted dihydrobenzofuran; or R^5 is optionally substituted benzothiopene; or R^5 is optionally substituted benzoxazole; or R^5 is optionally substituted benzothiazole; or R^5 is optionally substituted benzisoxazole; or R^5 is optionally substituted benzoisothiazole; and/or

R^a and R^b are each hydrogen; and/or

n is 1.

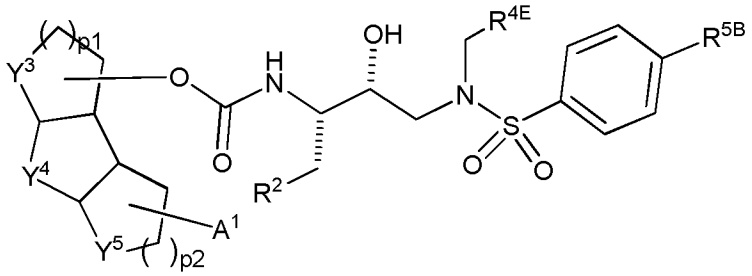
In another embodiment, compounds are described where in of each of the foregoing formulae and embodiments, R^2 or Ar^2 is substituted phenyl.

In another embodiment, compounds are described where in of each of the foregoing formulae and embodiments, R^2 or Ar^2 is phenyl substituted with hydroxy or a derivative thereof, amino or a derivative thereof, thio or a derivative thereof, or any of the foregoing where the substituent is covalently attached to the phenyl through a group $C(R^xR^y)$; where each of R^x and R^y is independently selected in each instance from the group consisting of hydrogen and alkyl; or both R^x and R^y are hydrogen.

In another embodiment, compounds are described where in of each of the foregoing formulae and embodiments, R^2 or Ar^2 is phenyl substituted with a hydroxy derivative, a thio derivative, or an amino derivative, where in each of the foregoing, derivatives include those that include a phosphorus-containing group; or R^2 or Ar^2 is phenyl substituted with OH, alkoxy, SH, alkylthio, NH_2, alkylamino, or dialkylamino; or R^2 or Ar^2 is phenyl substituted with hydroxymethyl, alkoxymethyl, thiomethyl, alkylthiomethyl, H_2N-methyl, alkylaminomethyl, or dialkylaminomethyl; or R^2 or Ar^2 is phenyl substituted with heterocyclylalkyloxy, such as morpholin-1-ylalkyloxy, pyrrolidin-1-ylalkyloxy, or piperidin-1-ylalkyloxy.

In another embodiment, compounds are described where in of each of the foregoing formulae and embodiments, R^2 or Ar^2 is capable of forming a hydrogen bond with a group in the S2 site of an HIV protease. In one variation, the group in the S2 site is a glycine, such as Gly-48.

In another embodiment, a compound having the formula



or a pharmaceutically acceptable salt thereof, is described, wherein

each of Y^3, Y^4 and Y^5 is oxygen; or

Y^3 is methylene and each of Y^4 and Y^5 is oxygen; or

Y^4 is methylene and each of Y^3 and Y^5 is oxygen; or

Y^5 is methylene and each of Y^3 and Y^4 is oxygen;

each of p_1 and p_2 is independently 1, 2 or 3;

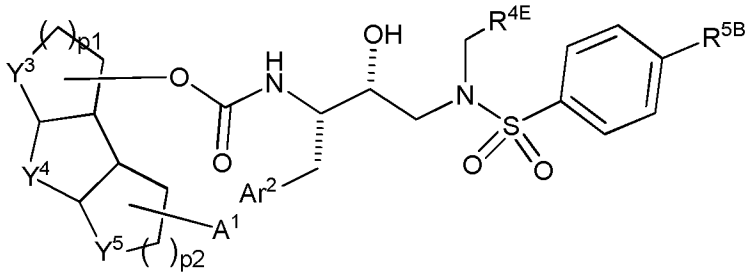
A^1 is selected from the group consisting of hydrogen, hydroxyl or derivative thereof, carboxylate or derivative thereof, amino or derivative thereof, or sulfonyl or derivative thereof, and the like;

R^2 has any of the values defined above for R^2;

R^{4E} is selected from the group consisting of isopropyl, alkyl, or heteroalkyl, and the like; and

R^{5B} is selected from the group consisting of methoxy, aminomethyl; amino, or heteroalkyl, and the like.

In another embodiment, a compound having the formula



or a pharmaceutically acceptable salt thereof, is described, wherein

each of Y^3, Y^4 and Y^5 is oxygen; or

Y^3 is methylene and each of Y^4 and Y^5 is oxygen; or

Y^4 is methylene and each of Y^3 and Y^5 is oxygen; or

Y^5 is methylene and each of Y^3 and Y^4 is oxygen;

each of p_1 and p_2 is independently 1, 2 or 3;

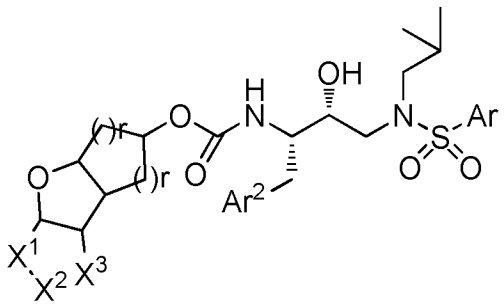
A^1 is selected from the group consisting of hydrogen, hydroxyl or derivative thereof, carboxylate or derivative thereof, amino or derivative thereof, or sulfonyl or derivative thereof, and the like;

Ar^2 has any of the values defined above for Ar^2;

R^{4E} is selected from the group consisting of isopropyl, alkyl, or heteroalkyl, and the like; and

R^{5B} is selected from the group consisting of methoxy, aminomethyl; amino, or heteroalkyl, and the like.

In another embodiment, a compound having the formula



or a pharmaceutically acceptable salt thereof, is described, wherein

each of X^1, X^2 and X^3 is methylene; or

X^1 is oxygen or NR^m and each of X^2 and X^3 is methylene; or

each of $X^1$and X^2 is methylene and X^3 is oxygen or NR^m; or

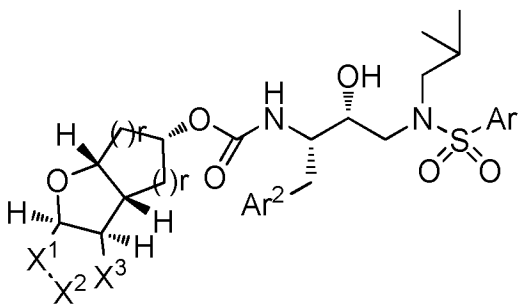
each of $X^1$and X^3 is methylene and X^2 is oxygen or NR^m;

R^m is selected from the group consisting of hydrogen, methyl, methylsulfonyl, acetyl or methoxycarbonyl, and the like;

Ar^2 has any of the values defined above for Ar^2; and

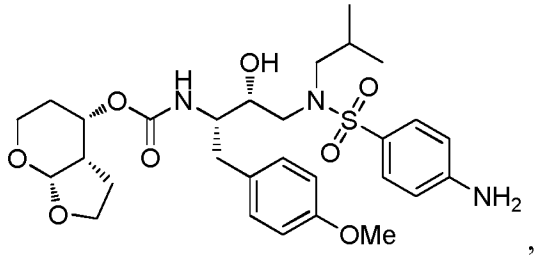
Ar has any of the values defined above for Ar.

In another embodiment, a compound having the formula



or a pharmaceutically acceptable salt thereof, is described, wherein X^1, X^2, X^3, R^m, Ar^2, and Ar are as defined above.

In another embodiment, there is provided a compound selected from the group consisting of



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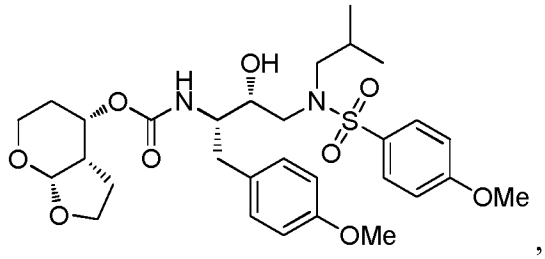

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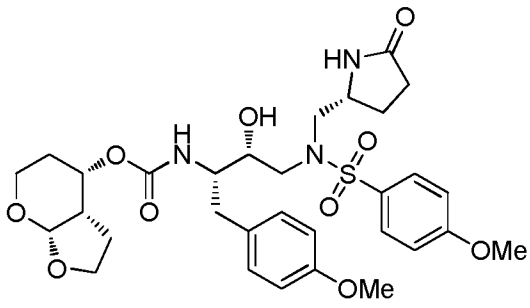
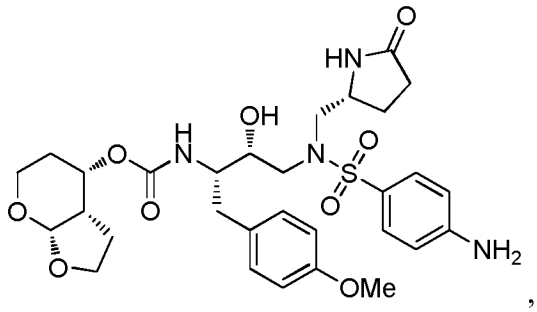


,and



,

or a pharmaceutically acceptable salt thereof.

In a further embodiment, there is provided a pharmaceutical composition comprising one or more compounds of any of the preceding descriptions and one or more carriers, diluents, or excipients, or a combination thereof.

In a further embodiment, there is provided a method for treating a patient in need of relieve from an HIV infection, the method comprising the step of administering to a patient in need of relief from the HIV infection a therapeutically effective amount of one or more compounds or compositions of any of the preceding descriptions.

In each of the foregoing and following embodiments, it is to be understood that the formulae include and represent not only all pharmaceutically acceptable salts of the compounds, but also include any and all hydrates and/or solvates of the compound formulae. It

is appreciated that certain functional groups, such as the hydroxy, amino, and like groups form complexes and/or coordination compounds with water and/or various solvents, in the various physical forms of the compounds. Accordingly, the above formulae are to be understood to include and represent those various hydrates and/or solvates. In each of the foregoing and following embodiments, it is also to be understood that the formulae include and represent each possible isomer, such as stereoisomers and geometric isomers, both individually and in any and all possible mixtures. In each of the foregoing and following embodiments, it is also to be understood that the formulae include and represent any and all crystalline forms, partially crystalline forms, and non crystalline and/or amorphous forms of the compounds.

Illustrative derivatives include, but are not limited to, both those compounds that may be synthetically prepared from the compounds described herein, as well as those compounds that may be prepared in a similar way as those described herein, but differing in the selection of starting materials. For example, described herein are compounds that include various functional groups, such as hydroxy groups, amino groups and carboxylate groups from which derivatives may formed by e.g. acylation and esterification.

It is to be understood that such derivatives may include prodrugs of the compounds described herein, compounds described herein that include one or more protection or protecting groups, including compounds that are used in the preparation of other compounds described herein.

The compounds described herein may contain one or more chiral centers, or may otherwise be capable of existing as multiple stereoisomers. It is to be understood that in one embodiment, the invention described herein is not limited to any particular sterochemical requirement, and that the compounds, and compositions, methods, uses, and medicaments that include them may be optically pure, or may be any of a variety of stereoisomeric mixtures, including racemic and other mixtures of enantiomers, other mixtures of diastereomers, and the like. It is also to be understood that such mixtures of stereoisomers may include a single stereochemical configuration at one or more chiral centers, while including mixtures of stereochemical configuration at one or more other chiral centers.

Similarly, the compounds described herein may be include geometric centers, such as cis, trans, E, and Z double bonds. It is to be understood that in another embodiment, the invention described herein is not limited to any particular geometric isomer requirement, and that the compounds, and compositions, methods, uses, and medicaments that include them may be pure, or may be any of a variety of geometric isomer mixtures. It is also to be understood that such mixtures of geometric isomers may include a single configuration at one or more double bonds, while including mixtures of geometry at one or more other double bonds.

As used herein, the term "alkyl" includes a chain of carbon atoms, which is optionally branched. As used herein, the term "alkenyl" and "alkynyl" includes a chain of carbon atoms, which is optionally branched, and includes at least one double bond or triple bond, respectively. It is to be understood that alkynyl may also include one or more double bonds. It is to be further understood that in certain embodiments, alkyl is advantageously of limited length, including C_1-C_{24}, C_1-C_{12}, C_1-C_8, C_1-C_6, and C_1-C_4. It is to be further understood that in certain embodiments alkenyl and/or alkynyl may each be advantageously of limited length, including C_2-C_{24}, C_2-C_{12}, C_2-C_8, C_2-C_6, and C_2-C_4. It is appreciated herein that shorter alkyl, alkenyl, and/or alkynyl groups may add less lipophilicity to the compound and accordingly will have different pharmacokinetic behavior. Illustrative alkyl groups are, but not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, 3-pentyl, neopentyl, hexyl, heptyl, octyl and the like.

As used herein, the term "cycloalkyl" includes a chain of carbon atoms, which is optionally branched, where at least a portion of the chain in cyclic. It is to be understood that cycloalkylalkyl is a subset of cycloalkyl. It is to be understood that cycloalkyl may be polycyclic. Illustrative cycloalkyl include, but are not limited to, cyclopropyl, cyclopentyl, cyclohexyl, 2-methylcyclopropyl, cyclopentyleth-2-yl, adamantyl, and the like. As used herein, the term "cycloalkenyl" includes a chain of carbon atoms, which is optionally branched, and includes at least one double bond, where at least a portion of the chain in cyclic. It is to be understood that the one or more double bonds may be in the cyclic portion of cycloalkenyl and/or the non-cyclic portion of cycloalkenyl. It is to be understood that cycloalkenylalkyl and cycloalkylalkenyl are each subsets of cycloalkenyl. It is to be understood that cycloalkyl may be polycyclic. Illustrative cycloalkenyl include, but are not limited to, cyclopentenyl, cyclohexylethen-2-yl, cycloheptenylpropenyl, and the like. It is to be further understood that chain forming cycloalkyl and/or cycloalkenyl is advantageously of limited length, including C_3-C_{24}, C_3-C_{12}, C_3-C_8, C_3-C_6, and C_5-C_6. It is appreciated herein that shorter alkyl and/or alkenyl chains forming cycloalkyl and/or cycloalkenyl, respectively, may add less lipophilicity to the compound and accordingly will have different pharmacokinetic behavior.

As used herein, the term "heteroalkyl" includes a chain of atoms that includes both carbon and at least one heteroatom, and is optionally branched. Illustrative heteroatoms include nitrogen, oxygen, and sulfur. In certain variations, illustrative heteroatoms also include phosphorus, and selenium. As used herein, the term "cycloheteroalkyl" including heterocyclyl and heterocycle, includes a chain of atoms that includes both carbon and at least one heteroatom, such as heteroalkyl, and is optionally branched, where at least a portion of the chain is cyclic. Illustrative heteroatoms include nitrogen, oxygen, and sulfur. In certain

variations, illustrative heteroatoms also include phosphorus, and selenium. Illustrative cycloheteroalkyl include, but are not limited to, tetrahydrofuryl, pyrrolidinyl, tetrahydropyranyl, piperidinyl, morpholinyl, piperazinyl, homopiperazinyl, quinuclidinyl, and the like.

As used herein, the term "aryl" includes monocyclic and polycyclic aromatic carbocyclic groups, each of which may be optionally substituted. Illustrative aromatic carbocyclic groups described herein include, but are not limited to, phenyl, naphthyl, and the like. As used herein, the term "heteroaryl" includes aromatic heterocyclic groups, each of which may be optionally substituted. Illustrative aromatic heterocyclic groups include, but are not limited to, pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, tetrazinyl, quinolinyl, quinazolinyl, quinoxalinyl, thienyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, benzisoxazolyl, benzisothiazolyl, and the like.

As used herein, the term "amino" includes the group NH_2, alkylamino, and dialkylamino, where the two alkyl groups in dialkylamino may be the same or different, i.e. alkylalkylamino. Illustratively, amino includes methylamino, ethylamino, dimethylamino, methylethylamino, and the like. In addition, it is to be understood that when amino modifies or is modified by another term, such as aminoalkyl, or acylamino, the above variations of the term amino are included therein. Illustratively, aminoalkyl includes H_2N-alkyl, methylaminoalkyl, ethylaminoalkyl, dimethylaminoalkyl, methylethylaminoalkyl, and the like. Illustratively, acylamino includes acylmethylamino, acylethylamino, and the like.

As used herein, the term "amino and derivatives thereof" includes amino as described herein, and alkylamino, alkenylamino, alkynylamino, heteroalkylamino, heteroalkenylamino, heteroalkynylamino, cycloalkylamino, cycloalkenylamino, cycloheteroalkylamino, cycloheteroalkenylamino, arylamino, arylalkylamino, arylalkenylamino, arylalkynylamino, heteroarylamino, heteroarylalkylamino, heteroarylalkenylamino, heteroarylalkynylamino, acylamino, and the like, each of which is optionally substituted. The term "amino derivative" also includes urea, carbamate, and the like.

As used herein, the term "hydroxy and derivatives thereof" includes OH, and alkyloxy, alkenyloxy, alkynyloxy, heteroalkyloxy, heteroalkenyloxy, heteroalkynyloxy, cycloalkyloxy, cycloalkenyloxy, cycloheteroalkyloxy, cycloheteroalkenyloxy, aryloxy, arylalkyloxy, arylalkenyloxy, arylalkynyloxy, heteroaryloxy, heteroarylalkyloxy, heteroarylalkenyloxy, heteroarylalkynyloxy, acyloxy, and the like, each of which is optionally substituted. The term "hydroxy derivative" also includes carbamate, and the like.

As used herein, the term "thio and derivatives thereof" includes SH, and alkylthio, alkenylthio, alkynylthio, heteroalkylthio, heteroalkenylthio, heteroalkynylthio,

cycloalkylthio, cycloalkenylthio, cycloheteroalkylthio, cycloheteroalkenylthio, arylthio, arylalkylthio, arylalkenylthio, arylalkynylthio, heteroarylthio, heteroarylalkylthio, heteroarylalkenylthio, heteroarylalkynylthio, acylthio, and the like, each of which is optionally substituted. The term "thio derivative" also includes thiocarbamate, and the like.

As used herein, the term "acyl" includes formyl, and alkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, heteroalkylcarbonyl, heteroalkenylcarbonyl, heteroalkynylcarbonyl, cycloalkylcarbonyl, cycloalkenylcarbonyl, cycloheteroalkylcarbonyl, cycloheteroalkenylcarbonyl, arylcarbonyl, arylalkylcarbonyl, arylalkenylcarbonyl, arylalkynylcarbonyl, heteroarylcarbonyl, heteroarylalkylcarbonyl, heteroarylalkenylcarbonyl, heteroarylalkynylcarbonyl, acylcarbonyl, and the like, each of which is optionally substituted.

As used herein, the term "carbonyl and derivatives thereof" includes the group C(O), C(S), C(NH) and substituted amino derivatives thereof.

As used herein, the term "carboxylate and derivatives thereof" includes the group CO_2H and salts thereof, and esters and amides thereof, and CN.

As used herein, the term "sulfinyl or a derivative thereof" includes SO_2H and salts thereof, and esters and amides thereof.

As used herein, the term "sulfonyl or a derivative thereof" includes SO_3H and salts thereof, and esters and amides thereof.

As used herein, the term "phosphinyl or a derivative thereof" includes $P(R)O_2H$ and salts thereof, and esters and amides thereof, where R is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, cycloheteroalkyl, cycloheteroalkenyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, each of which is optionally substituted.

As used herein, the term "phosphonyl or a derivative thereof" includes PO_3H_2 and salts thereof, and esters and amides thereof.

"Phosphorous-containing group" includes phosphinyl or a derivative thereof and phosphonyl or a derivative thereof.

As used herein, the term "hydroxylamino and derivatives thereof" includes NHOH, and alkyloxylNH alkenyloxylNH alkynyloxylNH heteroalkyloxylNH heteroalkenyloxylNH heteroalkynyloxylNH cycloalkyloxylNH cycloalkenyloxylNH cycloheteroalkyloxylNH cycloheteroalkenyloxylNH aryloxylNH arylalkyloxylNH arylalkenyloxylNH arylalkynyloxylNH heteroaryloxylNH heteroarylalkyloxylNH heteroarylalkenyloxylNH heteroarylalkynyloxylNH acyloxy, and the like, each of which is optionally substituted.

As used herein, the term "hydrazino and derivatives thereof" includes alkylNHNH, alkenylNHNH, alkynylNHNH, heteroalkylNHNH, heteroalkenylNHNH,

heteroalkynylNHNH, cycloalkylNHNH, cycloalkenylNHNH, cycloheteroalkylNHNH, cycloheteroalkenylNHNH, arylNHNH, arylalkylNHNH, arylalkenylNHNH, arylalkynylNHNH, heteroarylNHNH, heteroarylalkylNHNH, heteroarylalkenylNHNH, heteroarylalkynylNHNH, acylNHNH, and the like, each of which is optionally substituted.

The term "optionally substituted" as used herein includes the replacement of hydrogen atoms with other functional groups on the radical that is optionally substituted. Such other functional groups illustratively include, but are not limited to, amino, hydroxyl, halo, thiol, alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, arylheteroalkyl, heteroaryl, heteroarylalkyl, heteroarylheteroalkyl, nitro, sulfonic acids and derivatives thereof, carboxylic acids and derivatives thereof, and the like. Illustratively, any of amino, hydroxyl, thiol, alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, arylheteroalkyl, heteroaryl, heteroarylalkyl, heteroarylheteroalkyl, and/or sulfonic acid is optionally substituted.

As used herein, the terms "optionally substituted aryl" and "optionally substituted heteroaryl" include the replacement of hydrogen atoms with other functional groups on the aryl or heteroaryl that is optionally substituted. Such other functional groups illustratively include, but are not limited to, amino, hydroxy, halo, thio, alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, arylheteroalkyl, heteroaryl, heteroarylalkyl, heteroarylheteroalkyl, nitro, sulfonic acids and derivatives thereof, carboxylic acids and derivatives thereof, and the like. Illustratively, any of amino, hydroxy, thio, alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, arylheteroalkyl, heteroaryl, heteroarylalkyl, heteroarylheteroalkyl, and/or sulfonic acid is optionally substituted.

Illustrative substituents include, but are not limited to, a radical $-(CH_2)_xZ^X$, where x is an integer from 0-6 and Z^X is selected from halogen, hydroxy, alkanoyloxy, including C_1-C_6 alkanoyloxy, optionally substituted aroyloxy, alkyl, including C_1-C_6 alkyl, alkoxy, including C_1-C_6 alkoxy, cycloalkyl, including C_3-C_8 cycloalkyl, cycloalkoxy, including C_3-C_8 cycloalkoxy, alkenyl, including C_2-C_6 alkenyl, alkynyl, including C_2-C_6 alkynyl, haloalkyl, including C_1-C_6 haloalkyl, haloalkoxy, including C_1-C_6 haloalkoxy, halocycloalkyl, including C_3-C_8 halocycloalkyl, halocycloalkoxy, including C_3-C_8 halocycloalkoxy, amino, C_1-C_6 alkylamino, (C_1-C_6 alkyl)(C_1-C_6 alkyl)amino, alkylcarbonylamino, N-(C_1-C_6 alkyl)alkylcarbonylamino, aminoalkyl, C_1-C_6 alkylaminoalkyl, (C_1-C_6 alkyl)(C_1-C_6 alkyl)aminoalkyl, alkylcarbonylaminoalkyl, N-(C_1-C_6 alkyl)alkylcarbonylaminoalkyl, cyano, and nitro; or Z^X is selected from $-CO_2R^4$ and $-CONR^5R^6$, where R^4, R^5, and R^6 are each independently selected in each occurrence from hydrogen, C_1-C_6 alkyl, aryl-C_1-C_6 alkyl, and heteroaryl-C_1-C_6 alkyl.

The term "prodrug" as used herein generally refers to any compound that when administered to a biological system generates a biologically active compound as a result of one or more spontaneous chemical reaction(s), enzyme-catalyzed chemical reaction(s), and/or metabolic chemical reaction(s), or a combination thereof. In vivo, the prodrug is typically acted upon by an enzyme (such as esterases, amidases, phosphatases, and the like), simple biological chemistry, or other process in vivo to liberate or regenerate the more pharmacologically active drug. This activation may occur through the action of an endogenous host enzyme or a non-endogenous enzyme that is administered to the host preceding, following, or during administration of the prodrug. Additional details of prodrug use are described in U.S. Pat. No. 5,627,165; and Pathalk et al., Enzymic protecting group techniques in organic synthesis, Stereosel. Biocatal. 775-797 (2000). It is appreciated that the prodrug is advantageously converted to the original drug as soon as the goal, such as targeted delivery, safety, stability, and the like is achieved, followed by the subsequent rapid elimination of the released remains of the group forming the prodrug.

Prodrugs may be prepared from the compounds described herein by attaching groups that ultimately cleave in vivo to one or more functional groups present on the compound, such as -OH-, -SH, $-CO_2H$, $-NR_2$. Illustrative prodrugs include but are not limited to carboxylate esters where the group is alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl as well as esters of hydroxyl, thiol and amines where the group attached is an acyl group, an alkoxycarbonyl, aminocarbonyl, phosphate or sulfate. Illustrative esters, also referred to as active esters, include but are not limited to 1-indanyl, N-oxysuccinimide; acyloxyalkyl groups such as acetoxymethyl, pivaloyloxymethyl, β-acetoxyethyl, β-pivaloyloxyethyl, 1-(cyclohexylcarbonyloxy)prop-1-yl, (1 -aminoethyl)carbonyloxymethyl, and the like; alkoxycarbonyloxyalkyl groups, such as ethoxycarbonyloxymethyl, α-ethoxycarbonyloxyethyl, β-ethoxycarbonyloxyethyl, and the like; dialkylaminoalkyl groups, including di-lower alkylamino alkyl groups, such as dimethylaminomethyl, dimethylaminoethyl, diethylaminomethyl, diethylaminoethyl, and the like; 2-(alkoxycarbonyl)-2-alkenyl groups such as 2-(isobutoxycarbonyl) pent-2-enyl, 2-(ethoxycarbonyl)but-2-enyl, and the like; and lactone groups such as phthalidyl, dimethoxyphthalidyl, and the like.

Further illustrative prodrugs contain a chemical moiety, such as an amide or phosphorus group functioning to increase solubility and/or stability of the compounds described herein. Further illustrative prodrugs for amino groups include, but are not limited to, (C_3-C_{20})alkanoyl; halo-(C_3-C_{20})alkanoyl; (C_3-C_{20})alkenoyl; (C_4-C_7)cycloalkanoyl; (C_3-C_6)-cycloalkyl(C_2-C_{16})alkanoyl; optionally substituted aroyl, such as unsubstituted aroyl or aroyl

substituted by 1 to 3 substituents selected from the group consisting of halogen, cyano, trifluoromethanesulphonyloxy, (C_1-C_3)alkyl and (C_1-C_3)alkoxy, each of which is optionally further substituted with one or more of 1 to 3 halogen atoms; optionally substituted aryl(C_2-C_{16})alkanoyl and optionally substituted heteroaryl(C_2-C_{16})alkanoyl, such as the aryl or heteroaryl radical being unsubstituted or substituted by 1 to 3 substituents selected from the group consisting of halogen, (C_1-C_3)alkyl and (C_1-C_3)alkoxy, each of which is optionally further substituted with 1 to 3 halogen atoms; and optionally substituted heteroarylalkanoyl having one to three heteroatoms selected from O, S and N in the heteroaryl moiety and 2 to 10 carbon atoms in the alkanoyl moiety, such as the heteroaryl radical being unsubstituted or substituted by 1 to 3 substituents selected from the group consisting of halogen, cyano, trifluoromethanesulphonyloxy, (C_1-C_3)alkyl, and (C_1-C_3)alkoxy, each of which is optionally further substituted with 1 to 3 halogen atoms. The groups illustrated are exemplary, not exhaustive, and may be prepared by conventional processes.

It is understood that the prodrugs themselves may not possess significant biological activity, but instead undergo one or more spontaneous chemical reaction(s), enzyme-catalyzed chemical reaction(s), and/or metabolic chemical reaction(s), or a combination thereof after administration in vivo to produce the compound described herein that is biologically active or is a precursor of the biologically active compound. However, it is appreciated that in some cases, the prodrug is biologically active. It is also appreciated that prodrugs may often serves to improve drug efficacy or safety through improved oral bioavailability, pharmacodynamic half-life, and the like. Prodrugs also refer to derivatives of the compounds described herein that include groups that simply mask undesirable drug properties or improve drug delivery. For example, one or more compounds described herein may exhibit an undesirable property that is advantageously blocked or minimized may become pharmacological, pharmaceutical, or pharmacokinetic barriers in clinical drug application, such as low oral drug absorption, lack of site specificity, chemical instability, toxicity, and poor patient acceptance (bad taste, odor, pain at injection site, and the like), and others. It is appreciated herein that a prodrug, or other strategy using reversible derivatives, can be useful in the optimization of the clinical application of a drug.

The term "therapeutically effective amount" as used herein, refers to that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated. In one aspect, the therapeutically effective amount is that which may treat or alleviate the disease or symptoms of the disease at a reasonable benefit/risk ratio applicable to

any medical treatment. However, it is to be understood that the total daily usage of the compounds and compositions described herein may be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically-effective dose level for any particular patient will depend upon a variety of factors, including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, gender and diet of the patient: the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidentally with the specific compound employed; and like factors well known to the researcher, veterinarian, medical doctor or other clinician of ordinary skill.

It is also appreciated that the therapeutically effective amount, whether referring to monotherapy or combination therapy, is advantageously selected with reference to any toxicity, or other undesirable side effect, that might occur during administration of one or more of the compounds described herein. Further, it is appreciated that the co-therapies described herein may allow for the administration of lower doses of compounds that show such toxicity, or other undesirable side effect, where those lower doses are below thresholds of toxicity or lower in the therapeutic window than would otherwise be administered in the absence of a cotherapy.

As used herein, the term "composition" generally refers to any product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts. It is to be understood that the compositions described herein may be prepared from isolated compounds described herein or from salts, solutions, hydrates, solvates, and other forms of the compounds described herein. It is also to be understood that the compositions may be prepared from various amorphous, non-amorphous, partially crystalline, crystalline, and/or other morphological forms of the compounds described herein. It is also to be understood that the compositions may be prepared from various hydrates and/or solvates of the compounds described herein. Accordingly, such pharmaceutical compositions that recite compounds described herein are to be understood to include each of, or any combination of, the various morphological forms and/or solvate or hydrate forms of the compounds described herein. Illustratively, compositions may include one or more carriers, diluents, and/or excipients. The compounds described herein, or compositions containing them, may be formulated in a therapeutically effective amount in any conventional dosage forms appropriate for the methods described herein. The compounds described herein, or compositions containing them, including such formulations, may be administered by a wide variety of conventional routes for the

methods described herein, and in a wide variety of dosage formats, utilizing known procedures (see generally, Remington: The Science and Practice of Pharmacy, (21st ed., 2005)).

The term "administering" as used herein includes all means of introducing the compounds and compositions described herein to the patient, including, but are not limited to, oral (po), intravenous (iv), intramuscular (im), subcutaneous (sc), transdermal, inhalation, buccal, ocular, sublingual, vaginal, rectal, and the like. The compounds and compositions described herein may be administered in unit dosage forms and/or formulations containing conventional nontoxic pharmaceutically-acceptable carriers, adjuvants, and vehicles.

It is to be understood that in the methods described herein, the individual components of a co-administration, or combination can be administered by any suitable means, contemporaneously, simultaneously, sequentially, separately or in a single pharmaceutical formulation. Where the co-administered compounds or compositions are administered in separate dosage forms, the number of dosages administered per day for each compound may be the same or different. The compounds or compositions may be administered via the same or different routes of administration. The compounds or compositions may be administered according to simultaneous or alternating regimens, at the same or different times during the course of the therapy, concurrently in divided or single forms.

Illustrative routes of oral administration include tablets, capsules, elixirs, syrups, and the like.

Illustrative routes for parenteral administration include intravenous, intraarterial, intraperitoneal, epidurial, intraurethral, intrasternal, intramuscular and subcutaneous, as well as any other art recognized route of parenteral administration. Illustrative means of parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques, as well as any other means of parenteral administration recognized in the art. Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably at a pH in the range from about 3 to about 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water. The preparation of parenteral formulations under sterile conditions, for example, by lyophilization, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art. Parenteral administration of a compound is illustratively performed in the form of saline solutions or with the compound incorporated into liposomes. In cases where the compound in itself is not sufficiently soluble to be dissolved, a solubilizer such as ethanol can be applied.

The dosage of each compound of the claimed combinations depends on several factors, including: the administration method, the condition to be treated, the severity of the condition, whether the condition is to be treated or prevented, and the age, weight, and health of the person to be treated. Additionally, pharmacogenomic (the effect of genotype on the pharmacokinetic, pharmacodynamic or efficacy profile of a therapeutic) information about a particular patient may affect the dosage used.

In making the pharmaceutical compositions of the compounds described herein, a therapeutically effective amount of one or more compounds in any of the various forms described herein may be mixed with one or more excipients, diluted by one or more excipients, or enclosed within such a carrier which can be in the form of a capsule, sachet, paper, or other container. Excipients may serve as a diluent, and can be solid, semi-solid, or liquid materials, which act as a vehicle, carrier or medium for the active ingredient. Thus, the formulation compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders. The compositions may contain anywhere from about 0.1% to about 99.9% active ingredients, depending upon the selected dose and dosage form.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxybenzoates; sweetening agents; and flavoring agents. The compositions can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art. It is appreciated that the carriers, diluents, and excipients used to prepare the compositions described herein are advantageously GRAS (generally regarded as safe) compounds.

Examples of emulsifying agents are naturally occurring gums (e.g., gum acacia or gum tragacanth) and naturally occurring phosphatides (e.g., soybean lecithin and sorbitan monooleate derivatives). Examples of antioxidants are butylated hydroxy anisole (BHA), ascorbic acid and derivatives thereof, tocopherol and derivatives thereof, butylated hydroxy anisole, and cysteine. Examples of preservatives are parabens, such as methyl or propyl p-hydroxybenzoate, and benzalkonium chloride. Examples of humectants are glycerin, propylene glycol, sorbitol, and urea. Examples of penetration enhancers are propylene glycol, DMSO,

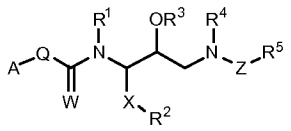
triethanolamine, N,N-dimethylacetamide, N,N-dimethylformamide, 2-pyrrolidone and derivatives thereof, tetrahydrofurfuryl alcohol, and AZONE. Examples of chelating agents are sodium EDTA, citric acid, and phosphoric acid. Examples of gel forming agents are CARBOPOL, cellulose derivatives, bentonite, alginates, gelatin and polyvinylpyrrolidone. Examples of ointment bases are beeswax, paraffin, cetyl palmitate, vegetable oils, sorbitan esters of fatty acids (Span), polyethylene glycols, and condensation products between sorbitan esters of fatty acids and ethylene oxide (e.g., polyoxyethylene sorbitan monooleate (TWEEN)).

A compound of the invention disclosed herein may be prepared by a route analogous to one previously disclosed for the preparation of protease inhibitors with a similar backbone structure, such as for example WO 2008/133734. In general, the compound may be prepared by acylating the corresponding amine with an acylating agent of formula A-Q-C(W)-L in which L denotes a leaving group. When Q represents NH, the acylating agent may be an isocyanate or isothiocyanate of formula A-N=C=W. Alternatively, a compound of formula A-Q-H is acylated by a compound of formula L-C(W)-NH-R or W=C=N-R in which R represents the remainder of the compound of the invention disclosed herein.

Further preparation and additional illustrative examples are described in copending US provisional application no. 61/379,414, filed September 2, 2010, the disclosure of which is incorporated herein by reference in its entirety.

Embodiments of the invention include those described by the following emumerated clauses:

1. A compound of the formula



(I)

and pharmaceutically acceptable salts thereof, wherein

A is cycloheteroalkyl or cycloheteroalkyl-alkyl, each of which is optionally substituted;

Q is oxygen, sulfur, nitrogen, or $C(R^aR^b)$ where each of R^a and R^b is independently selected in each instance from the group consisting of hydrogen, alkyl, and alkoxy;

W is oxygen or sulfur;

R^1 is hydrogen, a nitrogen protecting group, or a pro-drug substituent;

X is $C(R^aR^b)_n$, where n is 1, 2, or 3, and each of R^a and R^b is defined as above;

R^2 is alkyl, heteroalkyl, cycloalkyl, cycloheteroalkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, each of which is substituted, where at least one substituent is a hydrogen bond forming group;

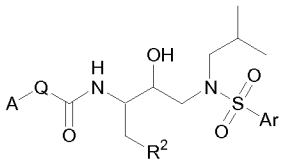
R^3 is hydrogen, an oxygen protecting group, or a pro-drug substituent;

R^4 is alkyl, heteroalkyl, cycloalkyl, cycloheteroalkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, each of which is optionally substituted;

Z is C(O), $S(O)_2$, NH, NHC(O), or $NHS(O)_2$; and

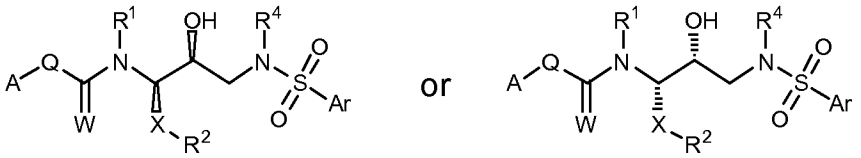
R^5 is alkyl, heteroalkyl, cycloalkyl, cycloheteroalkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, each of which is optionally substituted.

2. The compound or salt of clause 1 which is a compound of formula



wherein Ar is aryl or heteroaryl, each of which is optionally substituted.

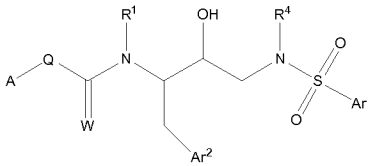
3. The compound or salt of clause 1 or 2 which is a compound having the relative and/or absolute stereochemistry of formula



wherein A, Q, W, R^1, X, R^2, and R^4 have any of the values of Clause 1 or Clause 2; and Ar is an optionally substituted aryl or heteroaryl.

4. The compound or salt of any of the preceding clauses wherein Ar is 4-methoxyphenyl, 4-(hydroxymethyl)phenyl, a 3-substituted phenyl, a 4-substituted phenyl, an optionally substituted benzisoxazole, an optionally substituted benzoxazole; an optionally substituted benzodioxane or an optionally substituted benzodioxolane.

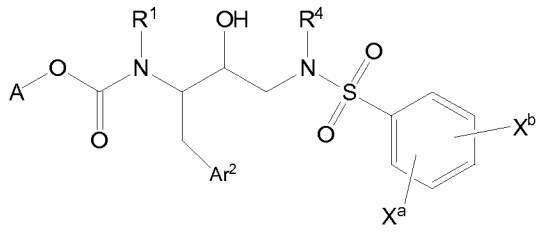
5. The compound or salt of any of the preceding clauses which is a compound having the formula



where Ar is aryl or heteroaryl, each of which is optionally substituted; and Ar^2 is substituted aryl or substituted heteroaryl having one or more of the following illustrative substituents: halo, amino, hydroxy, alkyl, alkenyl, alkoxy, arylalkyl, arylalkyloxy, hydroxyalkyl, hydroxyalkenyl, alkylene dioxy, aminoalkyl, where the amino group may also be substituted with one or two

alkyl groups, arylalkylgroups, and/or acylgroups, nitro, acyl and oxime or hydrazone derivatives thereof, cyano, alkylsulfonyl, and alkylsulfonylamino, where at least one substituent is a hydrogen bond forming group.

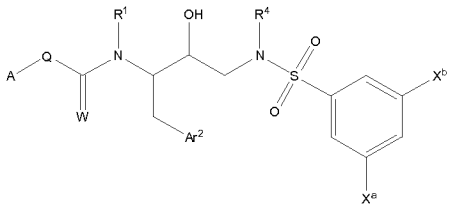
6. A compound of any of the preceding clauses of the following formula:



or a pharmaceutically acceptable salt thereof,

where X^a and X^b are each independently selected from halo, amino, hydroxy, alkyl, alkenyl, alkoxy, arylalkyl, arylalkyloxy, hydroxyalkyl, hydroxyalkenyl, aminoalkyl, where the amino group may also be substituted with one or two alkyl groups, arylalkylgroups, and/or acylgroups, nitro, acyl and derivatives thereof such as oximes, hydrazones, and the like, cyano, alkylsulfonyl, alkylsulfonylamino; or X^a and X^b together form alkylenedioxy.

7. A compound of any of the preceding clauses of the following formula:



and pharmaceutically acceptable salts thereof, wherein

X^a and X^b are independently selected from OH or OR^{5A}, where R^{5A} is alkyl, alkylaryl, an oxygen protecting group or a pro-drug substituent; and A, Q, W, R^1, Ar^2 and R^4 have the meanings described in any of the preceding clauses.

8. The compound or salt of any of the preceding clauses wherein R^4 is alkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, hydroxy, alkoxy, cycloalkoxy, heterocyclyloxy, heterocyclylalkoxy, amino, mono or dialkylamino, cycloalkylamino, heterocyclylamino, or heterocyclylalkylamino, each of which is optionally substituted.

9. The compound or salt of any of the preceding clauses wherein R^4 is amino substituted alkyl or heterocycyl, or heterocyclylalkyl.

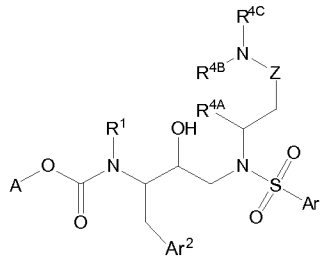
10. The compound or salt of the preceding clause wherein the nitrogen atom of the amino group is mono or disubstituted with alkyl, cycloalkyl, or acyl, or is included in another heterocyclic group such as a pyrrolidinyl, piperidinyl, or piperazinyl group or the nitrogen atom of the hetetocylclyl group is substituted with alkyl, cycloalkyl, or acyl.

11. The compound or salt of any of the preceding clauses wherein R^4 is optionally substituted alkyl or cycloalkyl, including both linear and branched variations thereof.

12. The compound or salt of the preceding clause wherein, R^4 is methyl, ethyl, butyl, isobutyl, cyclobutyl, cyclopentyl, or 3-methylcyclopentyl.

13. The compound or salt of any of the preceding clauses wherein R^4 is optionally substituted heterocyclyl or heterocyclylalkyl, where the heterocyclic portions includes, but is not limited to, tetrahydrofuranyl, azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, or piperazinyl.

14. A compound of any of the preceding clauses of the following formula

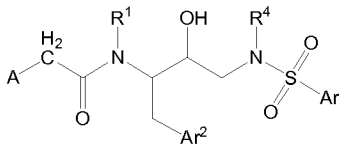


and pharmaceutically acceptable salts thereof, wherein

Z is $C(R^cR^d)$ where each of R^c and R^d is independently selected in each instance from the group consisting of hydrogen, alkyl, and arylalkyl;

R^{4A}, R^{4B} and R^{4C} are independently selected in each instance from the group consisting of hydrogen, alkyl, and arylalkyl, each of which may be optionally substituted, or R^{4A}, R^{4B} and the atoms to which they are attached form a ring, and R^{4C} is selected from the group consisting of hydrogen, alkyl, and arylalkyl, each of which may be optionally substituted.

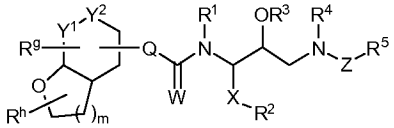
15. A compound of any of the preceding clauses of the following formula:



and pharmaceutically acceptable salts thereof.

16. The compound, or pharmaceutically acceptable salt thereof, of any of the preceding clauses wherein A is a mono or polycyclic ether.

17. A compound of any of the preceding clauses of the following formula:



and pharmaceutically acceptable salts thereof, wherein

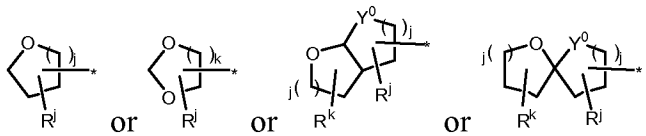
one of Y^1 and Y^2 is methylene, and the other of Y^1 and Y^2 is defined as follows:

Y^1 is $C(R^eR^f)$ or oxygen; Y^2 is $C(R^eR^f)$, $CHNR^e$, oxygen, or SO_2, where R^e and R^f are independently selected in each instance from hydrogen, alkyl, and alkoxy; m is an integer selected from 0, 1, 2, or 3; and R^g and R^h each represent one or more optional substituents, each of which is independently selected in each instance from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, alkoxy, alkenyloxy, alkynyloxy, cycloalkoxy, cycloalkylalkoxy, aryl, arylalkoxy, heterocyclyloxy, heterocyclylalkoxy, heteroaryloxy, and heteroarylalkoxy, each of which is itself optionally substituted.

18. The compound, or pharmaceutically acceptable salt thereof, of the preceding clause wherein Y^1 is oxygen; or Y^1 is $C(R^eR^f)$, where R^e is hydrogen, and R^f is hydrogen or alkoxy; or Y^2 is oxygen; or Y^2 is $C(R^eR^f)$, where R^e is hydrogen, and R^f is hydrogen or alkoxy.

19. The compound, or pharmaceutically acceptable salt thereof, of the preceding clause wherein alkoxy is methoxy.

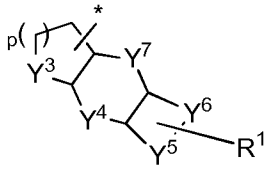
20. The compound, or pharmaceutically acceptable salt thereof, of any of the preceding clauses wherein A is a radical having one of the following structures



where (*) indicates the point of attachment of the group A; j is an integer that is independently selected in each instance from 0, 1, 2, or 3; k is an integer from 1 to 5; Y^0 is $C(R^aR^b)$ or oxygen; each of R^a and R^b is independently selected in each instance from the group consisting of hydrogen, alkyl, and alkoxy; and R^j and R^k each represent one or more optional substituents, each of which is independently selected in each instance from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl ,aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, alkoxy, alkenyloxy, alkynyloxy, cycloalkoxy, cycloalkylalkoxy ,aryl, arylalkoxy, heterocyclyloxy, heterocyclylalkoxy, heteroaryloxy, and heteroarylalkoxy, each of which is itself optionally substituted

21. The compound, or pharmaceutically acceptable salt thereof, of the preceding clause wherein R^a and R^b are both hydrogen; and/or R^j and R^k are both hydrogen; and/or R^a, R^b, R^j and R^k are each hydrogen; one or more of R^j and R^k is alkoxy.

22. The compound, or pharmaceutically acceptable salt thereof, of any of the preceding clauses wherein A is of the formula



wherein (*) indicates the point of attachment;

p is 1, 2, or 3;

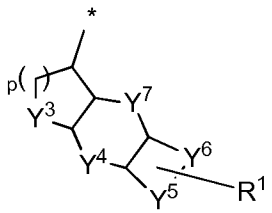
Y^3 and Y^4 are in each instance independently selected from the group consisting of optionally substituted methylene, oxygen, and amino;

Y^5 and Y^6 are in each instance independently selected from the group consisting of amino, oxygen, alkylene, and heteroalkylene, providing that at least one of Y^3 and Y^4 is oxygen, and wherein when one of Y^3 and Y^4 is optionally substituted methylene, at least one of Y^5 and Y^6 is oxygen, and A does not include a peroxide bond, a sulfenate bond, or a sulfenamide bond;

Y^7 is a bond or optionally substituted methylene; and

R^1 is hydrogen, hydroxyl, carboxylate or derivative thereof, amino or derivative thereof, acyl, sulfonyl or derivative thereof, alkyl, or heteroalkyl.

23. The compound, or pharmaceutically acceptable salt thereof, of the preceding clause wherein A is of the formula



wherein (*) indicates the point of attachment.

24. The compound, or pharmaceutically acceptable salt thereof, of any of the preceding clauses wherein Y^4 is oxygen.

25. The compound, or pharmaceutically acceptable salt thereof, of any of the preceding clauses wherein Y^7 is a bond.

26. The compound, or pharmaceutically acceptable salt thereof, of any of the preceding clauses wherein, p is 1 or 2.

27. The compound, or pharmaceutically acceptable salt thereof, of the preceding clause wherein p is 1.

28. The compound, or pharmaceutically acceptable salt thereof, of any of the preceding clauses wherein R^1 is hydrogen.

29. The compound, or pharmaceutically acceptable salt thereof, of any of the preceding clauses wherein Y^5 or Y^6 is oxygen.

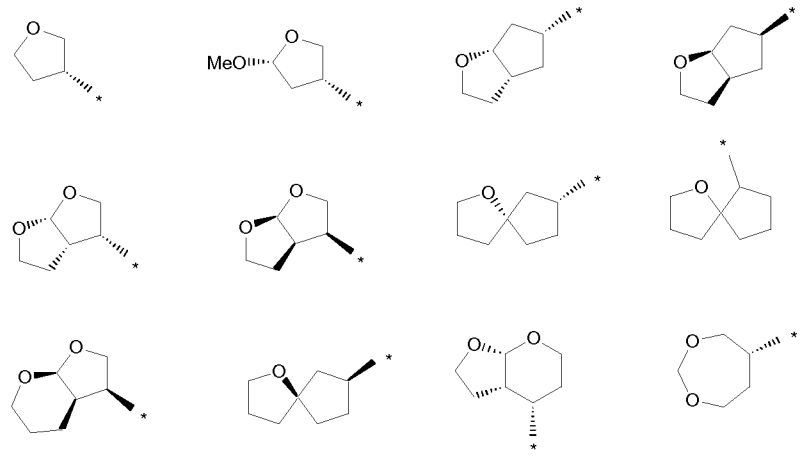
30. The compound, or pharmaceutically acceptable salt thereof, of any of the preceding clauses wherein Y^4 and one of Y^5 and Y^6 are oxygen.

31. The compound, or pharmaceutically acceptable salt thereof, of any of the preceding clauses wherein Y^4 and Y^5 are oxygen.

32. The compound, or pharmaceutically acceptable salt thereof, of any of the preceding clauses wherein each of Y^3, Y^4 and Y^5 is oxygen.

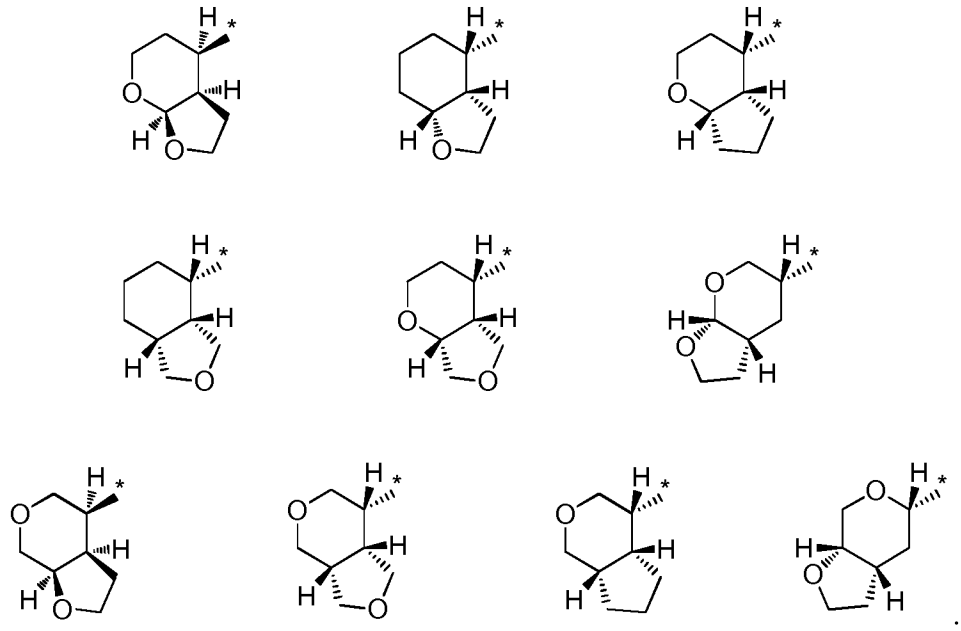
33. The compound, or pharmaceutically acceptable salt thereof, of any of the preceding clauses wherein Y^3 is optionally substituted methylene.

34. The compound, or pharmaceutically acceptable salt thereof, of any of the preceding clauses wherein A is a radical having one of the following structures



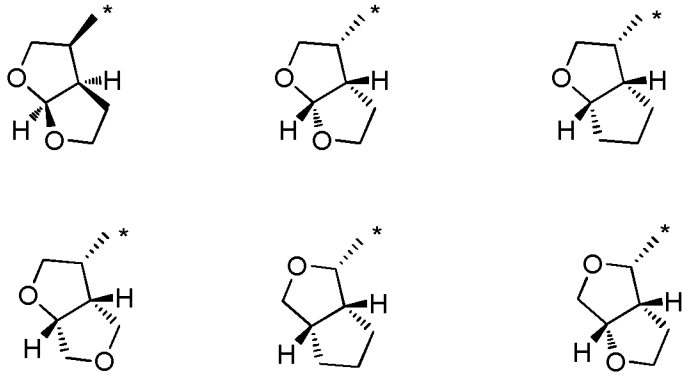
and stereoisomers thereof and mixtures thereof, where (*) indicates the point of attachment.

35. The compound, or pharmaceutically acceptable salt thereof, of any of the preceding clauses wherein A is a radical having one of the following structures



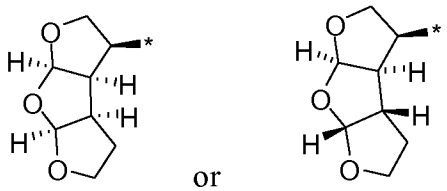
and stereoisomers thereof and mixtures thereof, where (*) indicates the point of attachment.

36. The compound, or pharmaceutically acceptable salt thereof, of any of the preceding clauses wherein A is a radical having one of the following structures



and stereoisomers thereof and mixtures thereof, where (*) indicates the point of attachment.

37. The compound, or pharmaceutically acceptable salt thereof, of any of the preceding clauses wherein A is of the formula



wherein (*) indicates the point of attachment.

38. The compound, or pharmaceutically acceptable salt thereof, of any of the preceding clauses wherein the group A is cycloheteroalkyl-alkyl of the formula Het-$(CH_2)_q$-; where q is an integer selected from 1, 2, or 3; and Het is optionally substituted cycloheteroalkyl.

39. The compound, or pharmaceutically acceptable salt thereof, of the preceding clause wherein Het is oxazolidine, thiazolidine, pyrollidine, piperidine, or piperazine, each of which is optionally substituted, including oxo substituents that form the corresponding oxazolidinones, thiazolidinones, pyrollidinones, piperidinones, and piperazinones.

40. The compound, or pharmaceutically acceptable salt thereof, of any of the preceding clauses wherein:

Q is oxygen; and/or

W is oxygen; and/or

R^1 is hydrogen; and/or

R^3 is hydrogen; and/or

R^4 is a group CH_2-K-R^{4D}, where K is a bond or $NHCH_2$, and R^{4D} is alkyl, cycloalkyl, cycloheteroalkyl, aryl, or heteroaryl, each of which is optionally substituted; or R^{4D} is isopropyl, furanyl, tetrahydrofuranyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyrrolidinonyl, oxazolidinonyl, thiazolidinonyl, isoxazolidionyl, or isothiazolidinonyl, each of

which is optionally substituted; or R^4 is branched alkyl; or R^4 is isobutyl; or R^4 is lactamylalkyl; or R^4 is pyrrolidin-4-on-2-ylalkyl; or R^4 is pyrrolidin-4-on-2-ylmethyl; and/or

Z is SO_2; or Z is CO; or Z is NH; and/or

R^5 is aryl or heteroaryl, each of which is optionally substituted; or R^5 is substituted phenyl; or R^5 is substituted phenyl, where the substituent is hydroxy or a derivative thereof, amino or a derivative thereof, thio or a derivative thereof, or any of the foregoing where the substituent is covalently attached to the aryl through a group $C(R^xR^y)$; where each of R^x and R^y is independently selected in each instance from the group consisting of hydrogen and alkyl; or R^x and R^y are each hydrogen; and/or

R^5 is phenyl substituted with NH_2, OH, OMe, CH_2OH, and/or OCH_2O; or R^5 is optionally substituted benzofuran; or R^5 is optionally substituted dihydrobenzofuran; or R^5 is optionally substituted benzothiopene; or R^5 is optionally substituted benzoxazole; or R^5 is optionally substituted benzothiazole; or R^5 is optionally substituted benzisoxazole; or R^5 is optionally substituted benzoisothiazole; and/or

R^a and R^b are each hydrogen; and/or

n is 1.

41. The compound, or pharmaceutically acceptable salt thereof, of any of the preceding clauses wherein R^2 or Ar^2 is substituted phenyl.

42. The compound, or pharmaceutically acceptable salt thereof, of any of the preceding clauses wherein R^2 or Ar^2 is phenyl substituted with hydroxy or a derivative thereof, amino or a derivative thereof, thio or a derivative thereof, or any of the foregoing where the substituent is covalently attached to the phenyl through a group $C(R^xR^y)$; where each of R^x and R^y is independently selected in each instance from the group consisting of hydrogen and alkyl; or both R^x and R^y are hydrogen.

43. The compound, or pharmaceutically acceptable salt thereof, of any of the preceding clauses wherein R^2 or Ar^2 is phenyl substituted with a hydroxy derivative, a thio derivative, or an amino derivative, where in each of the foregoing, derivatives include those that include a phosphorus-containing group; or R^2 or Ar^2 is phenyl substituted with OH, alkoxy, SH, alkylthio, NH_2, alkylamino, or dialkylamino; or R^2 or Ar^2 is phenyl substituted with hydroxymethyl, alkoxymethyl, thiomethyl, alkylthiomethyl, H_2N-methyl, alkylaminomethyl, or dialkylaminomethyl; or R^2 or Ar^2 is phenyl substituted with heterocyclylalkyloxy.

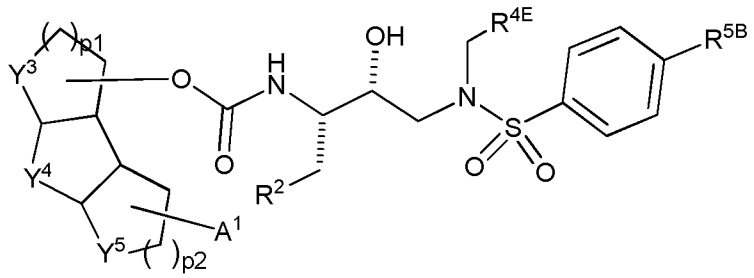
44. The compound, or pharmaceutically acceptable salt thereof, of the preceding clause wherein heterocyclylalkyloxy is morpholin-1-ylalkyloxy, pyrrolidin-1-ylalkyloxy, or piperidin-1-ylalkyloxy.

45. The compound, or pharmaceutically acceptable salt thereof, of any of the preceding clauses wherein R^2 or Ar^2 is capable of forming a hydrogen bond with a group in the S2 site of an HIV protease.

46. The compound, or pharmaceutically acceptable salt thereof, of the preceding clause wherein the group in the S2 site is a glycine.

47. The compound, or pharmaceutically acceptable salt thereof, of the preceding clause wherein the group in the S2 site is Gly-48.

48. The compound of any of the preceding clauses of the following formula:



or a pharmaceutically acceptable salt thereof, wherein

each of Y^3, Y^4 and Y^5 is oxygen; or

Y^3 is methylene and each of Y^4 and Y^5 is oxygen; or

Y^4 is methylene and each of Y^3 and Y^5 is oxygen; or

Y^5 is methylene and each of Y^3 and Y^4 is oxygen;

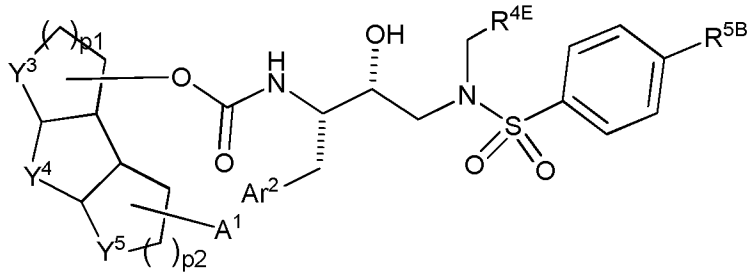
each of p_1 and p_2 is independently 1, 2 or 3;

A^1 is hydrogen, hydroxyl or derivative thereof, carboxylate or derivative thereof, amino or derivative thereof, or sulfonyl or derivative thereof;

R^{4E} is selected from the group consisting of isopropyl, alkyl, or heteroalkyl, and the like; and

R^{5B} is methoxy, aminomethyl; amino, or heteroalkyl.

49. A compound of any of the preceding clauses of the following formula:



or a pharmaceutically acceptable salt thereof, wherein

each of Y^3, Y^4 and Y^5 is oxygen; or

Y^3 is methylene and each of Y^4 and Y^5 is oxygen; or

Y^4 is methylene and each of Y^3 and Y^5 is oxygen; or

Y^5 is methylene and each of Y^3 and Y^4 is oxygen;

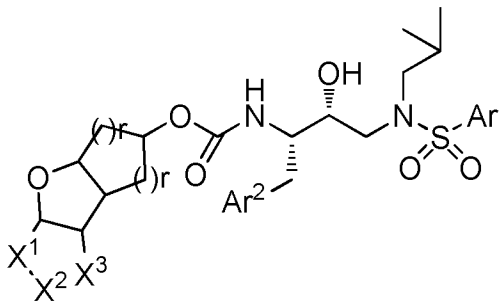
each of p_1 and p_2 is independently 1, 2 or 3;

R^i is hydrogen, hydroxyl or derivative thereof, carboxylate or derivative thereof, amino or derivative thereof, or sulfonyl or derivative thereof;

R^{4E} is selected from the group consisting of isopropyl, alkyl, or heteroalkyl, and the like; and

R^{5B} is methoxy, aminomethyl; amino, or heteroalkyl.

50. The compound of any of the preceding clauses having the formula



or a pharmaceutically acceptable salt thereof, wherein

each of X^1, X^2 and X^3 is methylene; or

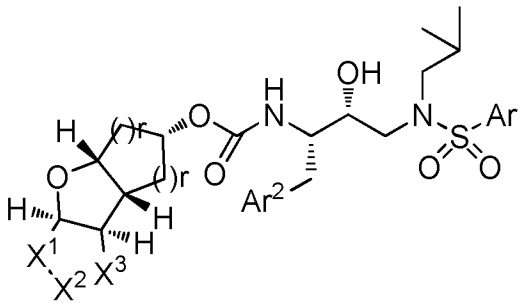
X^1 is oxygen or NR^m and each of X^2 and X^3 is methylene; or

each of $X^1$and X^2 is methylene and X^3 is oxygen or NR^m; or

each of $X^1$and X^3 is methylene and X^2 is oxygen or NR^m;

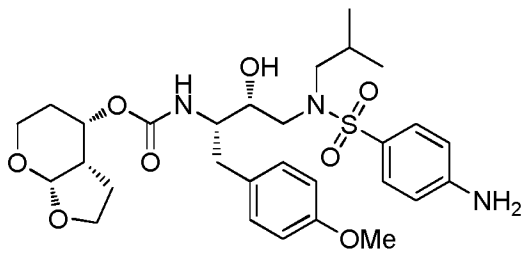
R^m is selected from the group consisting of hydrogen, methyl, methylsulfonyl, acetyl or methoxycarbonyl, and the like.

51. The compound of the preceding clause having the formula

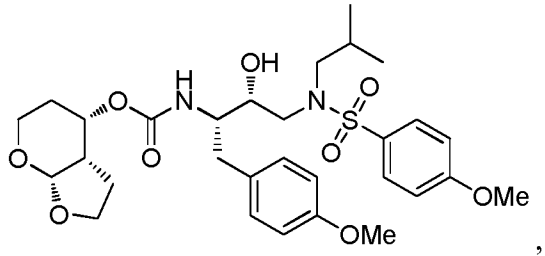


or a pharmaceutically acceptable salt thereof.

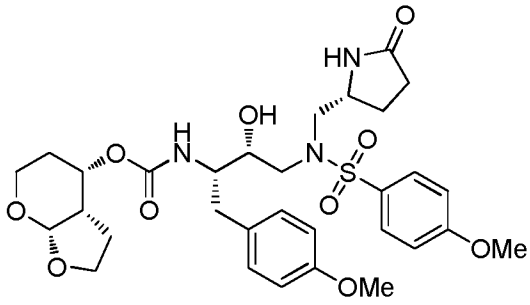
52. The compound of clause 1 selected from the group consisting of



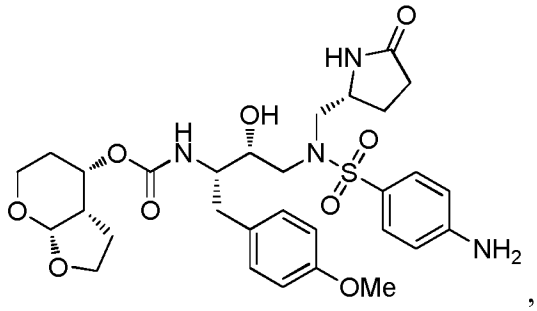
,



,



,and



,

or a pharmaceutically acceptable salt thereof.

53. A pharmaceutical composition comprising one or more compounds of any of the preceding clauses and one or more carriers, diluents, or excipients, or a combination thereof.

54. A method for treating a patient in need of relieve from an HIV infection, the method comprising the step of administering to a patient in need of relief from the HIV infection a therapeutically effective amount of one or more compounds or compositions of any of the preceding clauses.

The following examples further illustrate specific embodiments of the invention; however, the following illustrative examples should not be interpreted in any way to limit the invention.

EXAMPLES

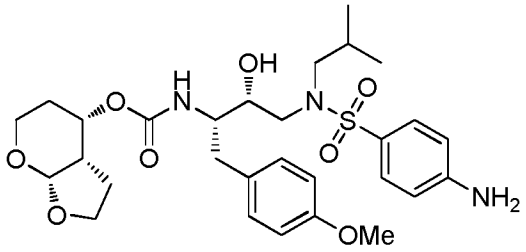
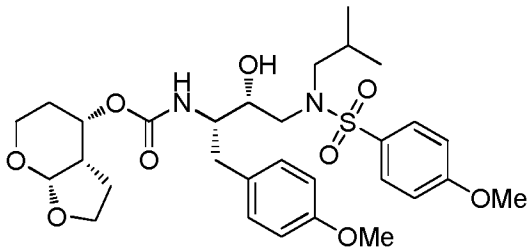
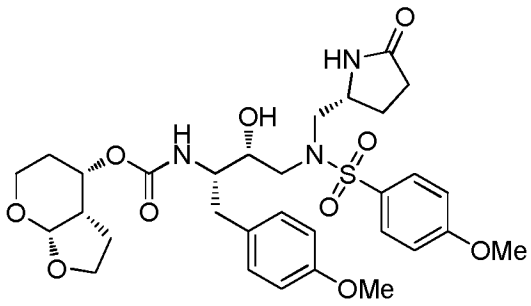
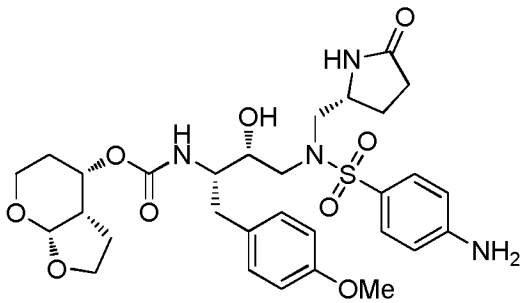
The scoring in the biological screens is as follows:

HIV-1 Inhibitory Potency

K_i:		IC_{50}:	
>10 nM	-	> 1000 nM	-

<10 nM	+	< 1000 nM	+
<1 nM	++	< 100 nM	++
<0.1 nM	+++	< 10 nM	+++
		< 1 nM	++++

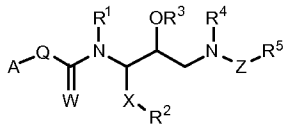
5

Ex. No.	Inhibitor	K_i	IC_{50} [a]
1		++	+++
2		+++	++++
3		+++	+
4		+	-

[a]Values are means of at least two experiments. The IC_{50} values of amprenavir (APV), saquinavir (SQV), and indinavir (IDV) were 0.03 μM, 0.015 μM, and 0.03 μM, respectively.

WHAT IS CLAIMED IS:

1. A compound of the formula



(I)

and pharmaceutically acceptable salts thereof, wherein

A is cycloheteroalkyl or cycloheteroalkyl-alkyl, each of which is optionally substituted;

Q is oxygen, sulfur, nitrogen, or $C(R^aR^b)$ where each of R^a and R^b is independently selected in each instance from the group consisting of hydrogen, alkyl, and alkoxy;

W is oxygen or sulfur;

R^1 is hydrogen, a nitrogen protecting group, or a pro-drug substituent;

X is $C(R^aR^b)_n$, where n is 1, 2, or 3, and each of R^a and R^b is defined as above;

R^2 is alkyl, heteroalkyl, cycloalkyl, cycloheteroalkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, each of which is substituted, where at least one substituent is a hydrogen bond forming group;

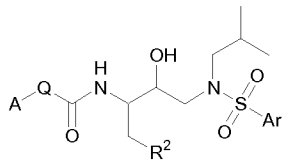
R^3 is hydrogen, an oxygen protecting group, or a pro-drug substituent;

R^4 is alkyl, heteroalkyl, cycloalkyl, cycloheteroalkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, each of which is optionally substituted;

Z is C(O), $S(O)_2$, NH, NHC(O), or $NHS(O)_2$; and

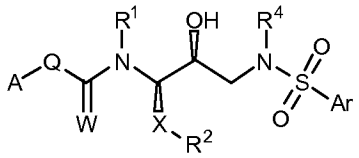
R^5 is alkyl, heteroalkyl, cycloalkyl, cycloheteroalkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, each of which is optionally substituted.

2. The compound or salt of claim 1 which is a compound of formula

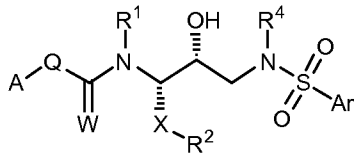


wherein Ar is aryl or heteroaryl, each of which is optionally substituted.

3. The compound or salt of claim 1 or 2 which is a compound having the relative and/or absolute stereochemistry of formula



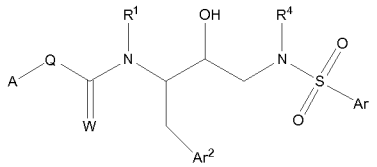
or



wherein A, Q, W, R^1, X, R^2, and R^4 have any of the values of Claim 1 or Claim 2; and Ar is an optionally substituted aryl or heteroaryl.

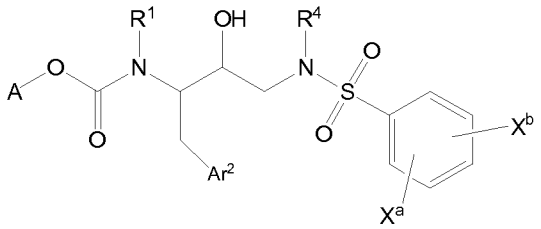
4. The compound or salt of claim 3 wherein Ar is 4-methoxyphenyl, 4-(hydroxymethyl)phenyl, a 3-substituted phenyl, a 4-substituted phenyl, an optionally substituted benzisoxazole, an optionally substituted benzoxazole; an optionally substituted benzodioxane or an optionally substituted benzodioxolane.

5. The compound or salt of claim 1 which is a compound having the formula



where Ar is aryl or heteroaryl, each of which is optionally substituted; and Ar^2 is substituted aryl or substituted heteroaryl having one or more of the following illustrative substituents: halo, amino, hydroxy, alkyl, alkenyl, alkoxy, arylalkyl, arylalkyloxy, hydroxyalkyl, hydroxyalkenyl, alkylene dioxy, aminoalkyl, where the amino group may also be substituted with one or two alkyl groups, arylalkylgroups, and/or acylgroups, nitro, acyl and oxime or hydrazone derivatives thereof, cyano, alkylsulfonyl, and alkylsulfonylamino, where at least one substituent is a hydrogen bond forming group.

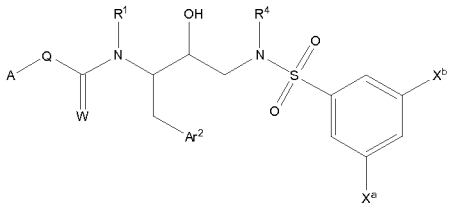
6. A compound of claim 5 of the following formula:



or a pharmaceutically acceptable salt thereof,

where X^a and X^b are each independently selected from halo, amino, hydroxy, alkyl, alkenyl, alkoxy, arylalkyl, arylalkyloxy, hydroxyalkyl, hydroxyalkenyl, aminoalkyl, where the amino group may also be substituted with one or two alkyl groups, arylalkylgroups, and/or acylgroups, nitro, acyl and derivatives thereof such as oximes, hydrazones, and the like, cyano, alkylsulfonyl, alkylsulfonylamino; or X^a and X^b together form alkylenedioxy.

7. A compound of claim 5 of the following formula:



and pharmaceutically acceptable salts thereof, wherein

X^a and X^b are independently selected from OH or OR^{5A}, where R^{5A} is alkyl, alkylaryl, an oxygen protecting group or a pro-drug substituent; and A, Q, W, R^1, Ar^2 and R^4 have the meanings described in any of the preceding claims.

8. The compound or salt of claim 1 wherein R^4 is alkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, hydroxy, alkoxy, cycloalkoxy, heterocyclyloxy, heterocyclylalkoxy, amino, mono or dialkylamino, cycloalkylamino, heterocyclylamino, or heterocyclylalkylamino, each of which is optionally substituted.

9. The compound or salt of claim 1 wherein R^4 is amino substituted alkyl or heterocycyl, or heterocyclylalkyl.

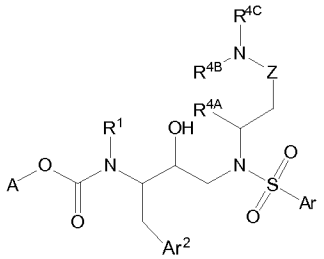
10. The compound or salt of claim 9 wherein the nitrogen atom of the amino group is mono or disubstituted with alkyl, cycloalkyl, or acyl, or is included in another heterocyclic group such as a pyrrolidinyl, piperidinyl, or piperazinyl group or the nitrogen atom of the hetetocylclyl group is substituted with alkyl, cycloalkyl, or acyl.

11. The compound or salt of claim 1 wherein R^4 is optionally substituted alkyl or cycloalkyl, including both linear and branched variations thereof.

12. The compound or salt of claim 11 wherein, R^4 is methyl, ethyl, butyl, isobutyl, cyclobutyl, cyclopentyl, or 3-methylcyclopentyl.

13. The compound or salt of claim 1 wherein R^4 is optionally substituted heterocyclyl or heterocyclylalkyl, where the heterocyclic portions includes, but is not limited to, tetrahydrofuranyl, azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, or piperazinyl.

14. A compound of claim 5 of the following formula

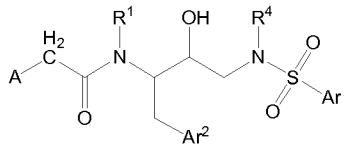


and pharmaceutically acceptable salts thereof, wherein

Z is $C(R^cR^d)$ where each of R^c and R^d is independently selected in each instance from the group consisting of hydrogen, alkyl, and arylalkyl;

R^{4A}, R^{4B} and R^{4C} are independently selected in each instance from the group consisting of hydrogen, alkyl, and arylalkyl, each of which may be optionally substituted, or R^{4A}, R^{4B} and the atoms to which they are attached form a ring, and R^{4C} is selected from the group consisting of hydrogen, alkyl, and arylalkyl, each of which may be optionally substituted.

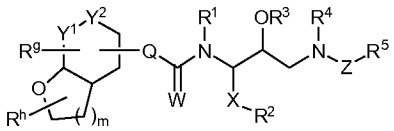
15. A compound of claim 5 of the following formula:



and pharmaceutically acceptable salts thereof.

16. The compound, or pharmaceutically acceptable salt thereof, of claim 1 wherein A is a mono or polycyclic ether.

17. A compound of claim 1 of the following formula:



and pharmaceutically acceptable salts thereof, wherein

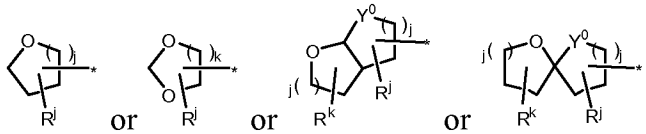
one of Y^1 and Y^2 is methylene, and the other of Y^1 and Y^2 is defined as follows:

Y^1 is $C(R^eR^f)$ or oxygen; Y^2 is $C(R^eR^f)$, $CHNR^e$, oxygen, or SO_2, where R^e and R^f are independently selected in each instance from hydrogen, alkyl, and alkoxy; m is an integer selected from 0, 1, 2, or 3; and R^g and R^h each represent one or more optional substituents, each of which is independently selected in each instance from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, alkoxy, alkenyloxy, alkynyloxy, cycloalkoxy, cycloalkylalkoxy, aryl, arylalkoxy, heterocyclyloxy, heterocyclylalkoxy, heteroaryloxy, and heteroarylalkoxy, each of which is itself optionally substituted.

18. The compound, or pharmaceutically acceptable salt thereof, of claim 17 wherein Y^1 is oxygen; or Y^1 is $C(R^eR^f)$, where R^e is hydrogen, and R^f is hydrogen or alkoxy; or Y^2 is oxygen; or Y^2 is $C(R^eR^f)$, where R^e is hydrogen, and R^f is hydrogen or alkoxy.

19. The compound, or pharmaceutically acceptable salt thereof, of claim 18 wherein alkoxy is methoxy.

20. The compound, or pharmaceutically acceptable salt thereof, of claim 1 wherein A is a radical having one of the following structures

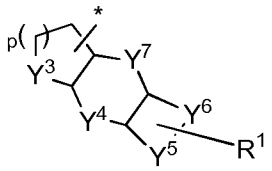


where (*) indicates the point of attachment of the group A; j is an integer that is independently selected in each instance from 0, 1, 2, or 3; k is an integer from 1 to 5; Y^0 is $C(R^aR^b)$ or oxygen; each of R^a and R^b is independently selected in each instance from the group consisting

of hydrogen, alkyl, and alkoxy; and R^j and R^k each represent one or more optional substituents, each of which is independently selected in each instance from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl ,aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, alkoxy, alkenyloxy, alkynyloxy, cycloalkoxy, cycloalkylalkoxy ,aryl, arylalkoxy, heterocyclyloxy, heterocyclylalkoxy, heteroaryloxy, and heteroarylalkoxy, each of which is itself optionally substituted

21. The compound, or pharmaceutically acceptable salt thereof, of claim 20 wherein R^a and R^b are both hydrogen; and/or R^j and R^k are both hydrogen; and/or R^a, R^b, R^j and R^k are each hydrogen; one or more of R^j and R^k is alkoxy.

22. The compound, or pharmaceutically acceptable salt thereof, of claim 1 wherein A is of the formula



wherein (*) indicates the point of attachment;

p is 1, 2, or 3;

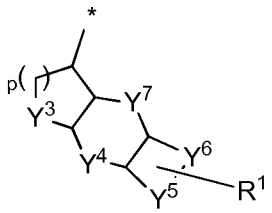
Y^3 and Y^4 are in each instance independently selected from the group consisting of optionally substituted methylene, oxygen, and amino;

Y^5 and Y^6 are in each instance independently selected from the group consisting of amino, oxygen, alkylene, and heteroalkylene, providing that at least one of Y^3 and Y^4 is oxygen, and wherein when one of Y^3 and Y^4 is optionally substituted methylene, at least one of Y^5 and Y^6 is oxygen, and A does not include a peroxide bond, a sulfenate bond, or a sulfenamide bond;

Y^7 is a bond or optionally substituted methylene; and

R^1 is hydrogen, hydroxyl, carboxylate or derivative thereof, amino or derivative thereof, acyl, sulfonyl or derivative thereof, alkyl, or heteroalkyl.

23. The compound, or pharmaceutically acceptable salt thereof, of claim 22 wherein A is of the formula



wherein (*) indicates the point of attachment.

24. The compound, or pharmaceutically acceptable salt thereof, of claim 22 or 23 wherein Y^4 is oxygen.

25. The compound, or pharmaceutically acceptable salt thereof, of claim 22 or 23 wherein Y^7 is a bond.

26. The compound, or pharmaceutically acceptable salt thereof, of claim 22 or 23 wherein, p is 1 or 2.

27. The compound, or pharmaceutically acceptable salt thereof, of claim 26 wherein p is 1.

28. The compound, or pharmaceutically acceptable salt thereof, of claim 22 or 23 wherein R^1 is hydrogen.

29. The compound, or pharmaceutically acceptable salt thereof, of claim 22 or 23 wherein Y^5 or Y^6 is oxygen.

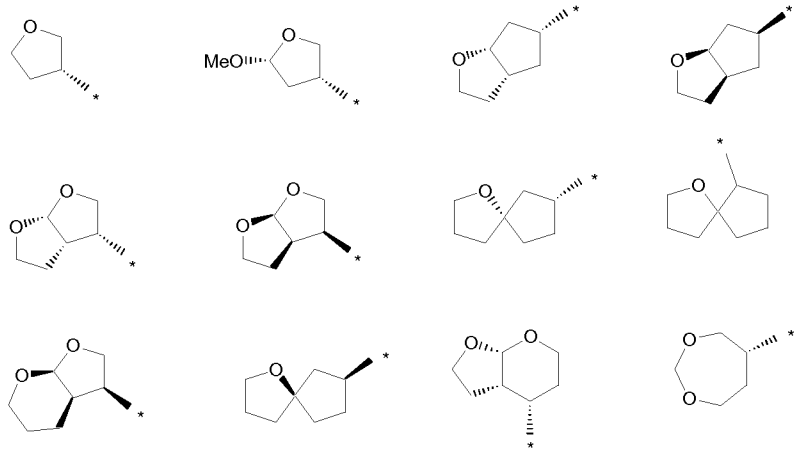
30. The compound, or pharmaceutically acceptable salt thereof, of claim 22 or 23 wherein Y^4 and one of Y^5 and Y^6 are oxygen.

31. The compound, or pharmaceutically acceptable salt thereof, of claim 22 or 23 wherein Y^4 and Y^5 are oxygen.

32. The compound, or pharmaceutically acceptable salt thereof, of claim 22 or 23 wherein each of Y^3, Y^4 and Y^5 is oxygen.

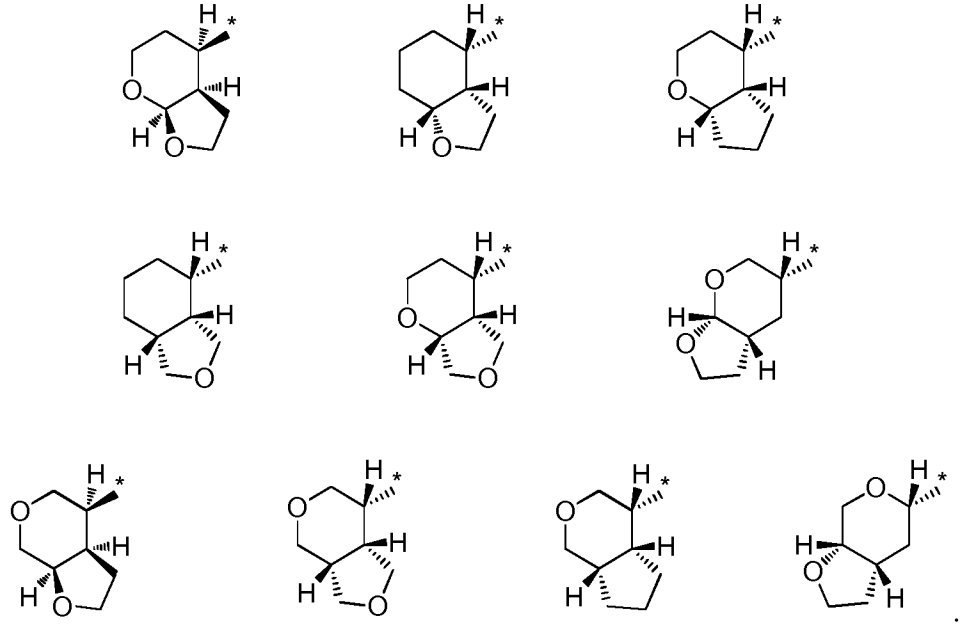
33. The compound, or pharmaceutically acceptable salt thereof, of claim 22 or 23 wherein Y^3 is optionally substituted methylene.

34. The compound, or pharmaceutically acceptable salt thereof, of claim 1 wherein A is a radical having one of the following structures



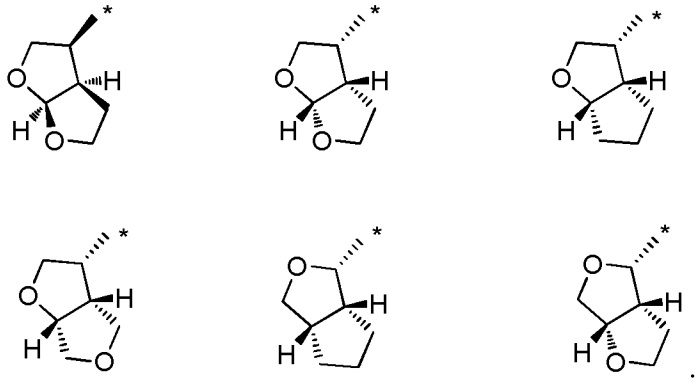
and stereoisomers thereof and mixtures thereof, where (*) indicates the point of attachment.

35. The compound, or pharmaceutically acceptable salt thereof, of claim 1 wherein A is a radical having one of the following structures



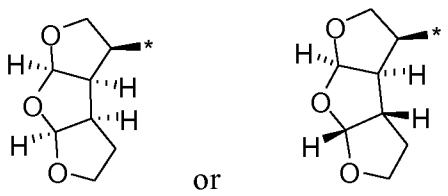
and stereoisomers thereof and mixtures thereof, where (*) indicates the point of attachment.

36. The compound, or pharmaceutically acceptable salt thereof, of claim 1 wherein A is a radical having one of the following structures



and stereoisomers thereof and mixtures thereof, where (*) indicates the point of attachment.

37. The compound, or pharmaceutically acceptable salt thereof, of claim 1 wherein A is of the formula



wherein (*) indicates the point of attachment.

38. The compound, or pharmaceutically acceptable salt thereof, of claim 1 wherein the group A is cycloheteroalkyl-alkyl of the formula Het-$(CH_2)_q$-; where q is an integer selected from 1, 2, or 3; and Het is optionally substituted cycloheteroalkyl.

39. The compound, or pharmaceutically acceptable salt thereof, of claim 38 wherein Het is oxazolidine, thiazolidine, pyrollidine, piperidine, or piperazine, each of which is

optionally substituted, including oxo substituents that form the corresponding oxazolidinones, thiazolidinones, pyrollidinones, piperidinones, and piperazinones.

40. The compound, or pharmaceutically acceptable salt thereof, of claim 1 wherein:

Q is oxygen; and/or

W is oxygen; and/or

R^1 is hydrogen; and/or

R^3 is hydrogen; and/or

R^4 is a group CH_2-K-R^{4D}, where K is a bond or $NHCH_2$, and R^{4D} is alkyl, cycloalkyl, cycloheteroalkyl, aryl, or heteroaryl, each of which is optionally substituted; or R^{4D} is isopropyl, furanyl, tetrahydrofuranyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyrrolidinonyl, oxazolidinonyl, thiazolidinonyl, isoxazolidionyl, or isothiazolidinonyl, each of which is optionally substituted; or R^4 is branched alkyl; or R^4 is isobutyl; or R^4 is lactamylalkyl; or R^4 is pyrrolidin-4-on-2-ylalkyl; or R^4 is pyrrolidin-4-on-2-ylmethyl; and/or

Z is SO_2; or Z is CO; or Z is NH; and/or

R^5 is aryl or heteroaryl, each of which is optionally substituted; or R^5 is substituted phenyl; or R^5 is substituted phenyl, where the substituent is hydroxy or a derivative thereof, amino or a derivative thereof, thio or a derivative thereof, or any of the foregoing where the substituent is covalently attached to the aryl through a group $C(R^xR^y)$; where each of R^x and R^y is independently selected in each instance from the group consisting of hydrogen and alkyl; or R^x and R^y are each hydrogen; and/or

R^5 is phenyl substituted with NH_2, OH, OMe, CH_2OH, and/or OCH_2O; or R^5 is optionally substituted benzofuran; or R^5 is optionally substituted dihydrobenzofuran; or R^5 is optionally substituted benzothiopene; or R^5 is optionally substituted benzoxazole; or R^5 is optionally substituted benzothiazole; or R^5 is optionally substituted benzisoxazole; or R^5 is optionally substituted benzoisothiazole; and/or

R^a and R^b are each hydrogen; and/or

n is 1.

41. The compound, or pharmaceutically acceptable salt thereof, of claim 1 or 5 wherein R^2 or Ar^2 is substituted phenyl.

42. The compound, or pharmaceutically acceptable salt thereof, of claim 41 wherein R^2 or Ar^2 is phenyl substituted with hydroxy or a derivative thereof, amino or a derivative thereof, thio or a derivative thereof, or any of the foregoing where the substituent is covalently attached to the phenyl through a group $C(R^xR^y)$; where each of R^x and R^y is

independently selected in each instance from the group consisting of hydrogen and alkyl; or both R^x and R^y are hydrogen.

43. The compound, or pharmaceutically acceptable salt thereof, of claim 41 wherein R^2 or Ar^2 is phenyl substituted with a hydroxy derivative, a thio derivative, or an amino derivative, where in each of the foregoing, derivatives include those that include a phosphorus-containing group; or R^2 or Ar^2 is phenyl substituted with OH, alkoxy, SH, alkylthio, NH_2, alkylamino, or dialkylamino; or R^2 or Ar^2 is phenyl substituted with hydroxymethyl, alkoxymethyl, thiomethyl, alkylthiomethyl, H_2N-methyl, alkylaminomethyl, or dialkylaminomethyl; or R^2 or Ar^2 is phenyl substituted with heterocyclylalkyloxy.

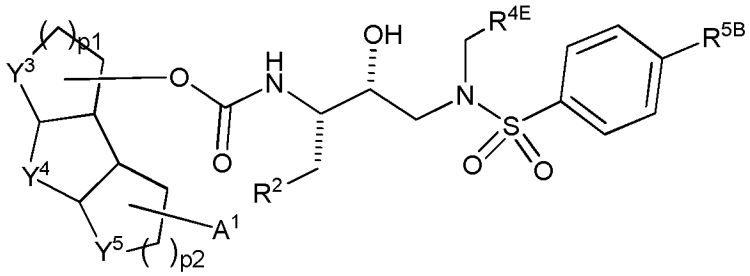
44. The compound, or pharmaceutically acceptable salt thereof, of claim 43 wherein heterocyclylalkyloxy is morpholin-1-ylalkyloxy, pyrrolidin-1-ylalkyloxy, or piperidin-1-ylalkyloxy.

45. The compound, or pharmaceutically acceptable salt thereof, of claim 1 or 5 wherein R^2 or Ar^2 is capable of forming a hydrogen bond with a group in the S2 site of an HIV protease.

46. The compound, or pharmaceutically acceptable salt thereof, of claim 45 wherein the group in the S2 site is a glycine.

47. The compound, or pharmaceutically acceptable salt thereof, of claim 46 wherein the group in the S2 site is Gly-48.

48. The compound of claim 1 of the following formula:



or a pharmaceutically acceptable salt thereof, wherein

each of Y^3, Y^4 and Y^5 is oxygen; or

Y^3 is methylene and each of Y^4 and Y^5 is oxygen; or

Y^4 is methylene and each of Y^3 and Y^5 is oxygen; or

Y^5 is methylene and each of Y^3 and Y^4 is oxygen;

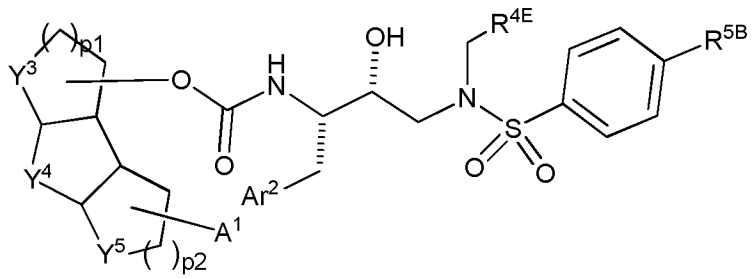
each of p_1 and p_2 is independently 1, 2 or 3;

A^1 is hydrogen, hydroxyl or derivative thereof, carboxylate or derivative thereof, amino or derivative thereof, or sulfonyl or derivative thereof;

R^{4E} is selected from the group consisting of isopropyl, alkyl, or heteroalkyl, and the like; and

R^{5B} is methoxy, aminomethyl; amino, or heteroalkyl.

49. The compound of claim 5 of the following formula:



or a pharmaceutically acceptable salt thereof, wherein

each of Y^3, Y^4 and Y^5 is oxygen; or

Y^3 is methylene and each of Y^4 and Y^5 is oxygen; or

Y^4 is methylene and each of Y^3 and Y^5 is oxygen; or

Y^5 is methylene and each of Y^3 and Y^4 is oxygen;

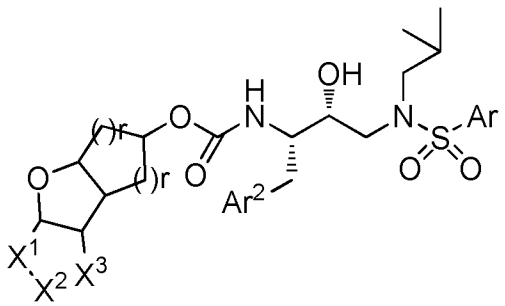
each of p_1 and p_2 is independently 1, 2 or 3;

A^1 is hydrogen, hydroxyl or derivative thereof, carboxylate or derivative thereof, amino or derivative thereof, or sulfonyl or derivative thereof;

R^{4E} is selected from the group consisting of isopropyl, alkyl, or heteroalkyl, and the like; and

R^{5B} is methoxy, aminomethyl; amino, or heteroalkyl.

50. The compound of claim 5 having the formula



or a pharmaceutically acceptable salt thereof, wherein

each of X^1, X^2 and X^3 is methylene; or

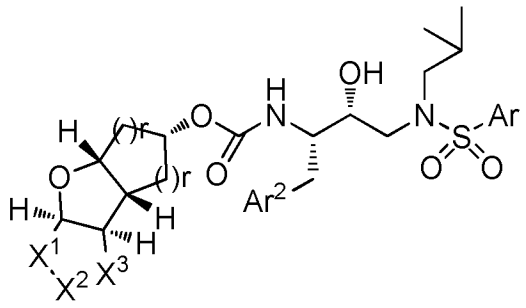
X^1 is oxygen or NR^m and each of X^2 and X^3 is methylene; or

each of $X^1$and X^2 is methylene and X^3 is oxygen or NR^m; or

each of $X^1$and X^3 is methylene and X^2 is oxygen or NR^m;

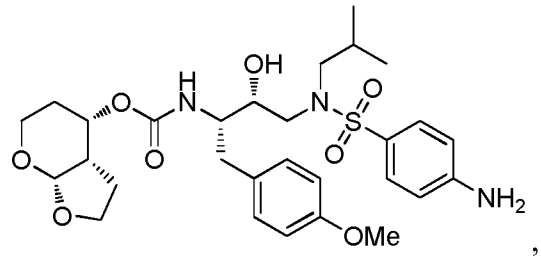
R^m is selected from the group consisting of hydrogen, methyl, methylsulfonyl, acetyl or methoxycarbonyl, and the like.

51. The compound of claim 50 having the formula



or a pharmaceutically acceptable salt thereof.

52. The compound of claim 1 selected from the group consisting of



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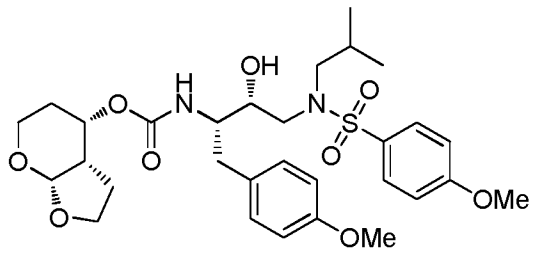

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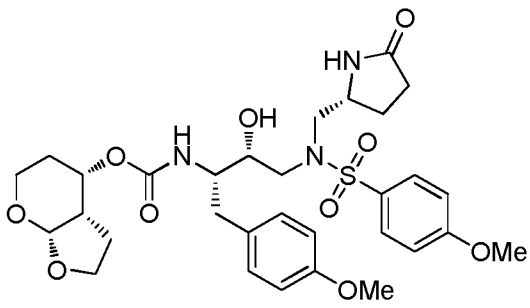
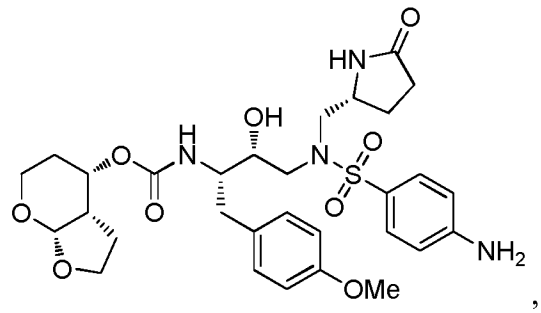


,and



,

or a pharmaceutically acceptable salt thereof.

53. A pharmaceutical composition comprising one or more compounds of claim 1 and one or more carriers, diluents, or excipients, or a combination thereof.

54. A method for treating a patient in need of relieve from an HIV infection, the method comprising the step of administering to a patient in need of relief from the HIV infection a therapeutically effective amount of one or more compounds of claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/67160

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/02; A61K 31/335 (2012.01)
USPC - 514/449
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)
USPC: 514/449

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/451-453, 456, 461, 464 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Electronic Database Searched: PUBWEST (PGPB,USPT,USOC,EPAB,JPAB). Search Terms Used dioxabicyclo$, oxindole sulfonamide, HIV-1 protease, treat$ HIV, gly-48, composition, formulation

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2004/0122000 A1 (Hale et al.) 24 June 2004 (24.06.2004) entire document, especially abstract; para [0135], [0140]-[0142], [0145]-[0146], [0233]; table 3, pg 42, compound of formula; pg 41, table 3, compound 348	1-46 and 48-54 ---------- 47
Y	US 2010/0113582 A1 (Ghosh et al.) 06 May 2010 (06.05.2010) especially para [0230]	47
Y	US 2003/0113748 A1 (Xie et al.) 19 July 2003 (19.07.2003) entire document, especially para [0065]	1-54
Y	US 2006/0058368 A1 (Tahri et al.) 16 March 2006 (16.03.2006) entire document, especially para [0011]-[0030]	1-54

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 April 2012 (13.04.2012)	27 APR 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774