Title: HIV PROTEASE INHIBITORS

Abstract: Compounds of Formula (I) are disclosed; wherein $X^A, k, A, B, R^{1A}, R^{1B}, R^4$ and $R^3$ are defined herein. The compounds of Formula (I) are HIV protease inhibitors. The compounds and their pharmaceutically acceptable salts are useful for the prophylaxis or treatment of infection by HIV and the prophylaxis, treatment, or delay in the onset of AIDS. The compounds and their salts can be employed as ingredients in pharmaceutical compositions, optionally in combination with other antivirals, immunomodulators, antibiotics or vaccines.
HIV PROTEASE INHIBITORS

FIELD OF THE INVENTION

The present invention is directed to certain 3,4-disubstituted pyrrolidine compounds and their pharmaceutically acceptable salts. The compounds are HTV protease inhibitors and are useful for the prophylaxis of HIV infection and HIV replication, the treatment of HIV infection and HTV replication, the prophylaxis of AIDS, the treatment of AIDS, and the delay in the onset and/or progression of AIDS.

BACKGROUND OF THE INVENTION

A retrovirus designated human immunodeficiency virus (HIV), particularly the strains known as HIV type-1 (HIV-1) virus and type-2 (HIV-2) virus, is the etiological agent of acquired immunodeficiency syndrome (AIDS), a disease characterized by the destruction of the immune system, particularly of CD4 T-cells, with attendant susceptibility to opportunistic infections, and its precursor AIDS-related complex ("ARC"), a syndrome characterized by symptoms such as persistent generalized lymphadenopathy, fever and weight loss. This virus was previously known as LAV, HTLV-III, or ARV. A common feature of retrovirus replication is the extensive post-translational processing of precursor polyproteins by a virally encoded protease to generate mature viral proteins required for virus assembly and function. Inhibition of this processing prevents the production of normally infectious virus. For example, Kohl et al., Proc. Nat'l Acad. Sci. 1988, 85: 4686, demonstrated that genetic inactivation of the HIV encoded protease resulted in the production of immature, non-infectious virus particles. These results indicated that inhibition of the HIV protease represents a viable method for the treatment of AIDS and the prevention or treatment of infection by HTV.

Nucleotide sequencing of HIV shows the presence of apol gene in one open reading frame [Ratner et al., Nature 1985, 313: 277]. Amino acid sequence homology provides evidence that ibepol sequence encodes reverse transcriptase, an endonuclease, HIV protease and gag, which encodes the core proteins of the virion (Toh et al., EMBOJ. 1985, 4: 1267; Power et al., Science 1986, 231.: 1567; Pearl et al., Nature 1987, 329: 351].

Several HTV protease inhibitors are presently approved for clinical use in the treatment of AIDS and HIV infection, including indinavir (see US 5413999), amprenavir (US 5585397), saquinavir (US 5196438), ritonavir (US 5484801), nelfinavir (US 5484926), and atazanavir (US 584991 I and US6087383). Each of these protease inhibitors is a peptide-derived peptidomimetic, competitive inhibitor of the viral protease which prevents cleavage of the HTV gag-pol polyprotein precursor. Tipranavir (US 5852195) is a non-peptide peptidomimetic protease inhibitors also approved for use in treating HIV infection. The protease inhibitors are administered in combination with at least one and typically at least two other HIV antiviral
agents, particularly nucleoside reverse transcriptase inhibitors such as zidovudine (AZT) and lamivudine (3TC) and/or non-nucleoside reverse transcriptase inhibitors such as efavirenz and nevirapine. Indinavir, for example, has been found to be highly effective in reducing HIV viral loads and increasing CD4 cell counts in HIV-infected patients, when used in combination with nucleoside reverse transcriptase inhibitors. See, for example, Hammer et al., New England J. Med 1997, 337: 725-733 and Gulick et al., New England J. Med 1997, 337: 734-739.

The established therapies employing a protease inhibitor are not suitable for use in all HIV-infected subjects. Some subjects, for example, cannot tolerate these therapies due to adverse effects. Many HIV-infected subjects often develop resistance to particular protease inhibitors. Accordingly, there is a continuing need for new compounds which are capable of inhibiting HFV protease and suitable for use in the treatment or prophylaxis of infection by HIV and/or for the treatment or prophylaxis or delay in the onset or progression of AIDS.


Also of interest is WO 2009/042093 which discloses certain lysine sulfonamide derivatives some of which are HIV protease inhibitors and others of which can be metabolized in vivo to HIV protease inhibitors. Many of the derivatives are characterized by the inclusion of branching on the lysine side chain.

SUMMARY OF THE INVENTION

The present invention is directed to certain 3,4-disubstituted pyrrolidine compounds and their use in the inhibition of HIV protease, the prophylaxis of infection by HTV, the treatment of infection by HIV, and the prophylaxis, treatment, and delay in the onset or progression of AIDS. More particularly, the present invention includes compounds of Formula I:

![Chemical Structure]

and pharmaceutically acceptable salts thereof, wherein:

A is N-R1 or CH-R1;
B is N-R2 or CH-R2;
R1 is H, Ci-6 alkyl, C-β fluoroalkyl, C3-6 cycloalkyl, Ci-6 alkyl substituted with C3-6 cycloalkyl, or Ci-6 alkyl substituted with AryA;
R2 is H, C1-6 alkyl, C1-6 fluoroalkyl, C3-6 cycloalkyl, C1-6 alkyl substituted with C3-6 cycloalkyl, C1-6 alkyl substituted with AryB, C(O)-Ci-6 alkyl, or SO2-Ci-6 alkyl;
R3A is H, C1-6 alkyl, C1-6 fluoroalkyl, C3.5 cycloalkyl, or C1-6 alkyl substituted with C3-5 cycloalkyl;
R3B is H or C1-6 alkyl;
each XA is independently:
(1) C1-6 alkyl,
(2) C3-6 cycloalkyl,
(3) C1-6 haloalkyl,
(4) OH,
(5) O-C1-6 alkyl,
(6) O-C1-6 haloalkyl,
(7) O-C3-6 cycloalkyl,
(8) SH,
(9) S-C1-6 alkyl,
(10) S-C1-6 haloalkyl,
(H) S-C3-6 cycloalkyl,
(12) halo,
(13) CN,
(14) NO2,
(15) NH2,
(16) N(H)-C1-6 alkyl,
(17) N(-C1-6 alkyl)2,
(18) N(H)C(O)-C1-6 alkyl,
(19) N(H)CH(O),
(20) CH(O),
(21) C(O)-C1-6 alkyl,
(22) C(O)OH,
(23) C(O)O-C1-6 alkyl,
(24) SO2H,
(25) SO2-C1-6 alkyl, or
(26) C1-6 alkyl substituted with:
(a) C3-6 cycloalkyl,
(b) C1-6 haloalkyl,
(c) OH,
(d) O-C1-6 alkyl,
(e) O-C1-6 haloalkyl,
(f) O-C3-6 cycloalkyl,
(g) SH,
(h) S-Ci-6 alkyl,
(i) S-Ci-6 haloalkyl,
(j) S-C3-6 cycloalkyl,
(k) halo,
(l) CN,
(m) NO₂,
(n) NH₂,
(o) N(H)-Ci-6 alkyl,
(p) N(-Ci-6 alkyl)₂,
(q) N(H)C(O)-C1-6 alkyl,
(r) N(H)CH(O),
(s) CH(O),
(t) C(O)-Ci-6 alkyl,
(u) C(O)OH,
(v) C(O)O-Ci-6 alkyl,
(w) SO₂H, or
(x) SO₂-C1-6 alkyl;

or, alternatively, when two or more XA substituents are present on the phenyl ring and two of the

XA are attached to adjacent carbon atoms of the phenyl ring, the two XA are optionally taken together with the carbon atoms to which they are attached to form a 5- or 6-membered, saturated or unsaturated heterocycle fused to the phenyl ring, wherein the heterocycle contains from 1 to 2 heteroatoms independently selected from N, O and S;

k is an integer equal to 0, 1, 2, or 3;

R⁴ is:

wherein the asterisk (*) denotes the point of attachment to the rest of the compound;

each XB and each XC are independently selected from the group consisting of:

(1) Ci-6 alkyl,
(2) C3-6 cycloalkyl,
(3) C1-6 haloalkyl,
(4) OH,
(5) O-Ci-6 alkyl,
(6) O-C 1-6 haloalkyl,
(7) O-C3-6 cycloalkyl,
(8) SH,
(9) S-Ci-6 alkyl,
(10) S-C 1-6 haloalkyl,
(11) S-C3-6 cycloalkyl,
(12) halo,
(13) CN,
(14) NO2,
(15) NH2,
(16) N(H)-C 1-6 alkyl,
(17) N(-Ci-6 alkyl)2,
(18) N(H)(O)-Ci -6 alkyl,
(19) N(H)CH(O),
(20) CH(O),
(21) C(O)-Ci -6 alkyl,
(22) C(O)OH,
(23) C(O)O-C 1-6 alkyl,
(24) SO2H,
(25) SO2-C 1-6 alkyl; and
(26) C1-6 alkyl substituted with:
   (a) C 1-6 haloalkyl,
   (b) OH
   (c) O-C 1-6 alkyl,
   (d) O-C 1-6 haloalkyl,
   (e) O-C3-6 cycloalkyl,
   (f) SH,
   (g) S-Ci-6 alkyl,
   (h) halo,
   (i) CN,
   (j) NO2,
   (k) NH2,
   (l) N(H)-Ci-6 alkyl,
   (m) N(-Ci_6 alkyl)2.
(n) C(O)-C 1-6 alkyl,
(o) C(O)OH,
(p) C(O)O-C i-6 alkyl, or
(q) SO2-C1-6 alkyl;
m is an integer equal to 0, 1, 2, or 3;
n is an integer equal to 0, 1, 2, or 3;
R5 is H, C1-6 alkyl, C3-6 cycloalkyl, C1-6 alkyl substituted with C3.6 cycloalkyl, or C(O)-RK;
RK is:
  (I) C6- alkyl,
  (2) C3-6 cycloalkyl,
  (3) C1-6 alkyl substituted with C3-6 cycloalkyl,
  (4) O-Ci-6 alkyl,
  (5) O-Ci-6 alkyl substituted with O-Ci-6 alkyl,
  (6) O-Ci-6 fluoroalkyl,
  (7) C(0)0-Ci-6 alkyl,
  (8) C1-6 alkyl substituted with C(O)O-C1-6 alkyl,
  (9) C1-6 alkyl substituted with C(O)OH,
  (10) C1-6 alkyl substituted with C(O)-C1-6 alkyl,
  (11) N(H)-C] -6 alkyl,
  (12) N(-Cl-6 alkyl)2,
  (13) C1-6 alkyl substituted with NH2, N(H)-C1-6 alkyl, or N(-C1-6 alkyl)2,
  (14) AryC,
  (15) C1-6 alkyl substituted with AryC,
  (16) O-C 1-6 alkyl substituted with AryC,
  (17) HetA,
  (18) C1-6 alkyl substituted with HetA,
  (19) O-C 1-6 alkyl substituted with HetA,
  (20) HetB, or
  (21) O-HetB;
AryA is an aryl which is independently phenyl or naphthyl, wherein the phenyl or naphthyl is
optionally substituted with from 1 to 4 YA wherein each YA independently has the same
definition as XB;
AryB is an aryl which is independently phenyl or naphthyl, wherein the phenyl or naphthyl is
optionally substituted with from 1 to 4 YA wherein each YA independently has the same
definition as XB;
AryC is an aryl which is independently phenyl or naphthyl, wherein the phenyl or naphthyl is
optionally substituted with from 1 to 4 YB wherein each YB independently has the same
definition as XB;
HetA is a heteroaryl which is independently (i) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, or (ii) is a heterobicyclic ring selected from quinolinyl, isoquinolinyl, and quinoxaliny1; wherein the heteroaromatic ring (i) or the bicyclic ring (ii) is optionally substituted with from 1 to 4 YC wherein each YC independently has the same definition as XB; and

HetB is independently a 4- to 7-membered, saturated or unsaturated, non-aromatic heterocyclic ring containing at least one carbon atom and from 1 to 4 heteroatoms independently selected from N, O and S, where each S is optionally oxidized to S(O) or S(O)2, and wherein the saturated or unsaturated heterocyclic ring is optionally substituted with from 1 to 4 substituents each of which is independently halogen, CN, C1-6 alkyl, OH, oxo, O-Ci-6 alkyl, Ci-6 haloalkyl, O-Cj-6 haloalkyl, C(O)NH2, C(O)N(H)-Ci-6 alkyl, C(0)N(-Ci-6 alkyl)2, C(0)H, C(O)-Ci-6 alkyl, CO2H, CO2-C1-6 alkyl, SO2H, or SO2-C 1-6 alkyl.

The present invention also includes pharmaceutical compositions containing a compound of Formula I or a pharmaceutically acceptable salt thereof. The present invention further includes methods involving compounds of Formula I for the treatment of AIDS, the delay in the onset or progression of AIDS, the prophylaxis of AIDS, the prophylaxis of infection by HIV, and the treatment of infection by HIV.

Other embodiments, sub-embodiments, aspects, classes, sub-classes and features of the present invention are either further described in or will be apparent from the ensuing description, examples and appended claims.

DETAILED DESCRIPTION OF THE INVENTION

The present invention includes compounds of Formula I above and pharmaceutically acceptable salts thereof. The compounds encompassed by Formula I are HIV protease inhibitors.

A first embodiment of the present invention (alternatively referred to herein as "Embodiment E1") is a compound of Formula I (alternatively and more simply referred to as "Compound I"), or a pharmaceutically acceptable salt thereof, wherein R1 is Ci-6 alkyl or Ci-6 alkyl substituted with AryA; and all other variables are as originally defined (i.e., as defined for Compound I in the Summary of the Invention).

A second embodiment of the present invention (Embodiment E2) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R1 is C3-6 branched alkyl or CH2-AryA; and all other variables are as originally defined.

A third embodiment of the present invention (Embodiment E3) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R1 is CH(CH3)2, CH2CH(CH3)2, CH2CH2CH(CH3)2, CH2CH2CH2CH(CH3)2, or benzyl; and all other variables are as originally defined.
A fourth embodiment of the present invention (Embodiment E4) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R1 is C1-6 alkyl; and all other variables are as originally defined.

A fifth embodiment of the present invention (Embodiment E5) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R1 is CH3, CH2CH3, CH(CH3)2, CH2CH2CH3, CH2CH(CH3)2, CH2CH2CH(CH3)2, or CH2CH2CH2CH(CH3)2; and all other variables are as originally defined.

A sixth embodiment of the present invention (Embodiment E6) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R1 is C3-6 branched alkyl; and all other variables are as originally defined.

A seventh embodiment of the present invention (Embodiment E7) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R1 is CH(CH3)2, CH2CH(CH3)2, CH2CH2CH(CH3)2, or CH2CH2CH2CH(CH3)2; and all other variables are as originally defined.

An eighth embodiment of the present invention (Embodiment E8) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R2 is H, C1-6 alkyl, C1-6 alkyl substituted with AryB, C(O)-C1-6 alkyl, or SO2-C1-6 alkyl; and all other variables are as originally defined or as defined in any of the preceding embodiments.

A ninth embodiment of the present invention (Embodiment E9) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R2 is H, C1-4 alkyl, CH2-AryB, C(O)-CM alkyl, or SO2-C1.4 alkyl; and all other variables are as originally defined or as defined in any of the preceding embodiments.

A tenth embodiment of the present invention (Embodiment E10) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R2 is H or C1-6 alkyl; and all other variables are as originally defined or as defined in any of the preceding embodiments.

An eleventh embodiment of the present invention (Embodiment E11) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R2 is H or C1-4 alkyl; and all other variables are as originally defined or as defined in any of the preceding embodiments.

A twelfth embodiment of the present invention (Embodiment E12) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R2 is H or CH3; and all other variables are as originally defined or as defined in any of the preceding embodiments.

A thirteenth embodiment of the present invention (Embodiment E13) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein A is N-R1; B is N-R2; and all other variables are as originally defined or as defined in any of the preceding embodiments.

A fourteenth embodiment of the present invention (Embodiment E14) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein A is N-R1; B is
CH-R.2; and all other variables are as originally defined or as defined in any of the preceding embodiments.

A fifteenth embodiment of the present invention (Embodiment E15) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein A is CH-R1; B is N-R.2; and all other variables are as originally defined or as defined in any of the preceding embodiments.

A sixteenth embodiment of the present invention (Embodiment E16) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R3A is H or C1-6 alkyl; and all other variables are as originally defined or as defined in any of the preceding embodiments.

A seventeenth embodiment of the present invention (Embodiment E17) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R3A is H or C1.4 alkyl; R3B is H or C1-4 alkyl; and all other variables are as originally defined or as defined in any of the preceding embodiments.

An eighteenth embodiment of the present invention (Embodiment E18) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R3A i, H, CH3, CH2CH3, CH(CH3)2, CH2CH2CH3, CH2CH(CH3)2, C(CH3)3, CH2CH2CH(CH3)2, or CH2CH2CH2CH(CH3)2; R3A is H or CH3; and all other variables are as originally defined or as defined in any of the preceding embodiments.

A nineteenth embodiment of the present invention (Embodiment E19) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein either (i) R3A i, H, CH3, CH2CH3, CH(CH3)2, CH2CH2CH3, CH2CH(CH3)2, C(CH3)3, CH2CH2CH(CH3)2, or CH2CH2CH2CH(CH3)2, and R3B i; H; or (ii) R3A and R3B are both CH3; and all other variables are as originally defined or as defined in any of the preceding embodiments.

A twentieth embodiment of the present invention (Embodiment E20) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R4 is:

\[
\begin{align*}
(X^B)_m \quad (X^C)_n \quad (X^B)_m \quad (X^C)_n
\end{align*}
\]

and all other variables are as originally defined or as defined in any of the preceding embodiments.

A twenty-first embodiment of the present invention (Embodiment E21) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R4 is:
A twenty-second embodiment of the present invention (Embodiment E22) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R\textsuperscript{4} is:

\[ \text{Formula I} \]

![Diagram](image)

; and all other variables are as originally defined or as defined in any of the preceding embodiments.

A twenty-third embodiment of the present invention (Embodiment E23) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R\textsuperscript{4} is:

\[ \text{Formula I} \]

![Diagram](image)

; and all other variables are as originally defined or as defined in any of the preceding embodiments.

A twenty-fourth embodiment of the present invention (Embodiment E24) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R\textsuperscript{5} is H, C\textsubscript{1}-6 alkyl, C(O)-Ci-6 alkyl, C(O)O-Ci-6 alkyl, C(O)N(-Ci-6 alkyl)\textsubscript{2}, C(O)-HetA, C(O)OCH\textsubscript{2}-HetA, C(O)-HetB, or C(O)O-HetB; and all other variables are as originally defined or as defined in any of the preceding embodiments.

A twenty-fifth embodiment of the present invention (Embodiment E25) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R\textsuperscript{5} is H, CH\textsubscript{3}, C(O)CH\textsubscript{3}, C(O)OCH\textsubscript{3}, C(O)OC(CH\textsubscript{3})\textsubscript{3}, C(O)N(CH\textsubscript{3})\textsubscript{2}, C(O)-morpholinyl, C(O)-pyridyl, or...
C(O)O-CH2-pyridyl; and all other variables are as originally defined or as defined in any of the preceding embodiments.

A twenty-sixth embodiment of the present invention (Embodiment E26) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R.5 is H, CH3, C(O)OCH3, C(O)OC(CH3)3, or C(0)0-CH2- pyridyl; and all other variables are as originally defined or as defined in any of the preceding embodiments.

A twenty-seventh embodiment of the present invention (Embodiment E27) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R.5 is C(O)O-Ci-6 alkyl; and all other variables are as originally defined or as defined in any of the preceding embodiments.

A twenty-eighth embodiment of the present invention (Embodiment E28) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R.5 is C(O)OCH3 or C(O)OC(CH3)3; and all other variables are as originally defined or as defined in any of the preceding embodiments.

A twenty-ninth embodiment of the present invention (Embodiment E29) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R.5 is C(O)OCH3; and all other variables are as originally defined or as defined in any of the preceding embodiments.

A thirtieth embodiment of the present invention (Embodiment E30) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein each XA is independently:

1. Cl-3 alkyl,
2. cyclopropyl,
3. CF3,
4. OH,
5. O-Ci-3 alkyl,
6. OCF3,
7. Cl,
8. Br,
9. F,
10. CN,
11. NO2,
12. NH2,
13. N(H)-C1-3 alkyl,
14. N(-Ci-3 alkyl)2,
15. C(O)-C1-3 alkyl,
16. CO2H,
17. C(O)O-Ci-3 alkyl, or
(18) Ci-3 alkyl substituted with
   (a) cyclopropyl,
   (b) CF₃,
   (c) OH,
   (d) O-Ci-3 alkyl,
   (e) OCF₃,
   (f) Cl,
   (g) Br,
   (h) F,
   (i) CN,
   (j) NO₂,
   (k) NH₂,
   (l) N(H)-C₁₃ alkyl,
   (m) N(-Ci-3 alkyl)₂,
   (n) C(O)-Ci₃ alkyl,
   (o) CO₂H, or
   (p) C(O)O-C₁-3 alkyl;

or, alternatively, when two XA substituents are present on the phenyl ring and the two XA are attached to adjacent carbon atoms of the phenyl ring, the two XA are optionally taken together with the carbon atoms to which they are attached to form a 5- or 6-membered, saturated or unsaturated heterocycle fused to the phenyl ring, wherein the heterocycle contains from 1 to 2 heteroatoms independently selected from N, O and S (e.g., the two XA are optionally taken together with the carbon atoms to which they are attached to form -OCH₂O- or -OCH₂CH₂O-);

k is an integer equal to 0, 1 or 2; and all other variables are as originally defined or as defined in any of the preceding embodiments.

A thirty-first embodiment of the present invention (Embodiment E31) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein each XA is independently:

(D) CH₃,
(2) CH₂CH₃,
(3) CF₃,
(4) OH,
(5) OCH₃,
(6) OCF₃,
(7) Cl,
(8) Br,
(9) F,
(10) CN,
(H) NH₂,
(12) N(H)CH₃,
(13) N(CH₃)₂,
(14) C(O)CH₃,
(15) C(O)OCH₃,
(16) CH₂OH,
(17) CH₂OCH₃,
(18) CH₂NH₂,
(19) CH₃N(H)CH₃,
(20) CH₂N(CH₃)₂,
(21) CH(CH₃)OH,
(22) CH(CH₃)OCH₃,
(23) CH(CH₃)NH₂,
(24) CH(CH₃)N(H)CH₃, or
(25) CH(CH₃)₂N(CH₃)₂;

or, alternatively, when two XA substituents are present on the phenyl ring and the two XA are attached to adjacent carbon atoms of the phenyl ring, the two XA are optionally taken together with the carbon atoms to which they are attached to form a 5- or 6-membered, saturated or unsaturated heterocycle fused to the phenyl ring, wherein the heterocycle contains from 1 to 2 heteroatoms independently selected from N, O and S (e.g., the two XA are optionally taken together with the carbon atoms to which they are attached to form -OCH₂O- or -OCH₂CH₂O-); k is an integer equal to 0, 1, or 2; and all other variables are as originally defined or as defined in any of the preceding embodiments.

A thirty-second embodiment of the present invention (Embodiment E32) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein there are 1 or 2 XA groups on the phenylsulfonyl moiety (i.e., k is 1 or 2) wherein one XA is in the para position on the phenyl ring and is CH₃, Cl, Br, F, NH₂, CH₂NH₂, C(O)CH₃, CH₂OH, or CH(CH₃)OH; and the other, optional XA is in the meta position on the phenyl ring and is Cl, Br, or F; or, alternatively, when two XA substituents are present on the phenyl ring (i.e., k is 2) and the two XA are attached to adjacent carbon atoms, the two XA are optionally taken together with the carbon atoms to which they are attached to form -OCH₂O- or -OCH₂CH₂O-; and all other variables are as originally defined or as defined in any of the preceding embodiments.

A thirty-third embodiment of the present invention (Embodiment E33) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein there is one XA group which is NH₂ in the para position of the phenyl ring; and all other variables are as originally defined or as defined in any of the preceding embodiments.
A thirty-fourth embodiment of the present invention (Embodiment E34) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein each XB and each XC are independently selected from the group consisting of:

(I) Ci-3 alkyl,
(2) cyclopropyl,
(3) CF₃,
(4) OH,
(5) O-Ci-3 alkyl,
(6) OCF₃,
(7) Cl,
(8) Br,
(9) F,
(10) CN,
(11) NO₂,
(12) NH₂,
(13) N(H)-Ci-3 alkyl,
(14) N(-Ci-3 alkyl)₂,
(15) C(O)-C₁-₃ alkyl,
(16) CO₂H,
(17) C(O)O-Ci-3 alkyl,
(18) CH₂OH, and
(19) CH₂O-C₁-₃ alkyl;

m is an integer equal to 0, 1, or 2; n is an integer equal to 0, 1, or 2; and all other variables are as originally defined or as defined in any of the preceding embodiments.

A thirty-fifth embodiment of the present invention (Embodiment E35) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein each XB and each XC are independently selected from the group consisting of:

(1) CH₃,
(2) CH₂CH₃,
(3) CF₃,
(4) OH,
(5) OCH₃,
(6) OCF₃,
(7) Cl,
(8) Br,
(9) F,
(10) CN,
(H) NH₂,
(12) N(H)CH₃,
(13) N(CH₃)₂,
(14) C(O)CH₃,
(15) C(O)OCH₃,
(16) CH₂OH, and
(17) CH₂OCH₃;

m is an integer equal to 0, 1, or 2; n is an integer equal to 0, 1, or 2; and all other variables are as originally defined or as defined in any of the preceding embodiments.

A thirty-sixth embodiment of the present invention (Embodiment E36) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein AryA is phenyl which is optionally substituted with from 1 to 3 substituents each of which is independently C1-3 alkyl, CF₃, OH, O-Ci-3 alkyl, OCF₃, Cl, Br, F, CN, NH₂, N(H)-Ci-3 alkyl, N(-Ci-3 alkyl)₂, C(O)-Ci-3 alkyl, CO₂H, C(O)O-Ci-3 alkyl, CH₂OH, CH₂O-Ci-3 alkyl, C(O)-Ci-3 alkyl, or SO₂-Ci-3 alkyl; and all other variables are as originally defined or as defined in any of the preceding embodiments.

A thirty-seventh embodiment of the present invention (Embodiment E37) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein AryA is phenyl which is optionally substituted with from 1 to 3 substituents each of which is independently CH₃, CF₃, OH, OCH₃, OCF₃, Cl, Br, F, CN, NH₂, N(H)CH₃, N(CH₃)₂.

A thirty-eighth embodiment of the present invention (Embodiment E38) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein AryB is phenyl which is optionally substituted with from 1 to 3 substituents each of which is independently Ci-3 alkyl, CF₃, OH, O-Ci-3 alkyl, OCF₃, Cl, Br, F, CN, NH₂, N(H)-Ci-3 alkyl, N(-Ci-3 alkyl)₂, C(O)-Ci-3 alkyl, CO₂H, C(O)O-Ci-3 alkyl, CH₂OH, CH₂O-Ci-3 alkyl, C(O)-Ci-3 alkyl, or SO₂-Ci-3 alkyl; and all other variables are as originally defined or as defined in any of the preceding embodiments.

A thirty-ninth embodiment of the present invention (Embodiment E39) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein AryB is phenyl which is optionally substituted with from 1 to 3 substituents each of which is independently CH₃, CF₃, OH, OCH₃, OCF₃, Cl, Br, F, CN, NH₂, N(H)CH₃, N(CH₃)₂, C(O)CH₃, CO₂H, C(O)OCH₃, CH₂OH, CH₂OCH₃, C(O)CH₃, or S₈ 2CH₃; and all other variables are as originally defined or as defined in any of the preceding embodiments.

A fortieth embodiment of the present invention (Embodiment E40) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein AryC is phenyl which is optionally substituted with from 1 to 3 substituents each of which is independently C1-3 alkyl, CF₃, OH, O-Ci-3 alkyl, OCF₃, Cl, Br, F, CN, NH₂, N(H)-Ci-3 alkyl, N(-Ci-3 alkyl)₂,
C(O)-Ci-3 alkyl, CO2H, C(O)O-Ci.3 alkyl, CH2OH, CH2O-C1-3 alkyl, C(O)-Ci-3 alkyl, or SO2-C1.3 alkyl; and all other variables are as originally defined or as defined in any of the preceding embodiments.

A forty-first embodiment of the present invention (Embodiment E41) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein

AryC is phenyl which is optionally substituted with from 1 to 3 substituents each of which is independently CH3, CF3, OH, OCH3, OCF3, Cl, Br, F, CN, NH2, N(H)CH3, N(CH3)2, C(O)CH3, CO2H, C(O)OCH3, CH2OH, CH2OCH3, C(O)CH3, or SO2CH3; and all other variables are as originally defined or as defined in any of the preceding embodiments.

A forty-second embodiment of the present invention (Embodiment E42) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein HetA is a heteroaryl selected from the group consisting of pyrrolyl, imidazolyl, pyridyl, pyrazinyl, quinolyl, isoquinolyl, and quinoxalinyl, wherein the heteroaryl is optionally substituted with from 1 to 3 substituents each of which is independently Cj-3 alkyl, CF3, OH, O-Cj-3 alkyl, OCF3, Cl, Br, F, CN, NH2, N(H)-Ci-3 alkyl, N(Ci-3 alkyl)2, C(0)-Ci-3 alkyl, CO2-C1-3 alkyl, or SO2-C1-3 alkyl; and all other variables are as originally defined or as defined in any of the preceding embodiments.

A forty-third embodiment of the present invention (Embodiment E43) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein HetA is a heteroaryl selected from the group consisting of pyrrolyl, imidazolyl, pyridyl, pyrazinyl, quinolyl, isoquinolyl, and quinoxalinyl, wherein the heteroaryl is optionally substituted with from 1 to 3 substituents each of which is independently CH3, CF3, OH, OCH3, OCF3, Cl, Br, F, CN, NH2, N(H)CH3, N(CH3)2, C(0)CH3, CO2CH3, or SO2CH3; and all other variables are as originally defined or as defined in any of the preceding embodiments.

A forty-fourth embodiment of the present invention (Embodiment E44) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein HetA is pyridyl; and all other variables are as originally defined or as defined in any of the preceding embodiments. In an aspect of this embodiment, HetA is 2-pyridyl. In another aspect of this embodiment, HetA is 3-pyridyl. In still another aspect of this embodiment, HetA is 4-pyridyl.

A forty-fifth embodiment of the present invention (Embodiment E45) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein HetB is a saturated heterocyclic ring selected from the group consisting of tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, and thiomorpholinyl in which the S is optionally oxidized to S(O) or S(O)2, and wherein the ring is optionally substituted with 1 or 2 substituents each of which is independently Cj.3 alkyl, oxo, C(O)N(Cj.3 alkyl)2, C(O)-Ci-3 alkyl, CO2-Q-3 alkyl, or S(O)2-Ci-3 alkyl; and all other variables are as originally defined or as defined in any of the preceding embodiments.
A forty-sixth embodiment of the present invention (Embodiment E46) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein HetB is a saturated heterocyclic ring selected from the group consisting of tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, and thiomorpholinyl in which the S is optionally oxidized to S(O) or S(O)2, and wherein the ring is optionally substituted with 1 or 2 substituents each of which is independently CH3, o xo, C(O)N(CH3)2, C(O)CH3, CO2CH3, or S(O)2CH3; and all other variables are as originally defined or as defined in any of the preceding embodiments.

A forty-seventh embodiment of the present invention (Embodiment E47) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein HetB is morpholinyl; and all other variables are as originally defined or as defined in any of the preceding embodiments. In an aspect of this embodiment, HetB is 4-morpholinyl.

A forty-eighth embodiment of the present invention (Embodiment E48) is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of Formula II:

![Chemical Structure](image)

or a pharmaceutically acceptable salt thereof, wherein all of the variables are as originally defined. Sub-embodiments include Compound II, or a pharmaceutically acceptable salt thereof, incorporating one, two, three or more of the definitions of the variables XA, k, A, B, Rl, R2, R3, Xb, Xc, m, R3A, R3B, R4, R5, AryA, AryB, AryC, HetA and HetB from the foregoing embodiments. Each such possible combination is a separate sub-embodiment. It is understood that certain combinations of the foregoing embodiments cannot be incorporated into the same sub-embodiment. For example, Embodiment E4 (i.e., R1 is C1-6 alkyl) cannot be combined with Embodiment E36 or Embodiment E37, both of which are directed to AryA, because AryA is a variable that appears in certain definitions of R1, but does not appear in the definition of R1 in Embodiment E4. As another example, Embodiments E22 and E23 defining R4 cannot be combined with Embodiments E34 and E35 directed to XB and XC, because XB and XC appear only in certain definitions of R4, but not in the definitions of R4 in Embodiments E22 and E23.

A first class of compounds of the present invention (alternatively referred to herein as Class CI) includes compounds of Formula I and pharmaceutically acceptable salts thereof, wherein:

A is N-R1 or CH-R1;
B is N-R2 or CH-R2;
R1 is C1-6 alkyl or C1-6 alkyl substituted with AryA;
R2 is H, Ci-6 alkyl, C-β alkyl substituted with AryB, C(O)-Ci-6 alkyl, or SO2-C1-6 alkyl;
R3A is H or Ci-6 alkyl;
R3B is H or C1-6 alkyl;
R4 is:

\[
\begin{align*}
(X^B)_m \text{, (X^C)_n } \text{ or } \text{or}
\end{align*}
\]

XB, χC, m and n are as defined in Embodiment E34;
XA and k are as defined in Embodiment E30;
R5 is H, C1-6 alkyl, C(O)-Ci, alkyl, C(O)O-Ci alkyl, C(O)N(-Ci alkyl)2, C(O)-HetA,
C(O)OCH2-HetA, C(O)-HetB, or C(O)O-HetB;
AryA is phenyl which is optionally substituted with from 1 to 3 substituents each of which is independently Ci-3 alkyl, CF3, OH, O-C1-3 alkyl, OCF3, Cl, Br, F, CN, NH2,
N(H)-Ci-3 alkyl, N(-Ci-3 alkyl)2, C(O)-Ci-3 alkyl, CO2H, C(O)O-Ci-3 alkyl, CH2OH,
CH2O-C1-3 alkyl, C(O)-Ci-3 alkyl, or SO2-Ci-3 alkyl;
HetA is a heteroaryl selected from the group consisting of pyrrolyl, imidazolyl, pyridyl,
pyrazinyl, quinolyl, isoquinolyl, and quinoxalinyl, wherein the heteroaryl is optionally substituted with from 1 to 3 substituents each of which is independently Ci-3 alkyl, CF3, OH, O-Ci-3 alkyl, OCF3, Cl, Br, F, CN, NH2, N(H)-Ci-3 alkyl, N(Ci-3 alkyl)2,
C(O)-C1-3 alkyl, CO2-C1-3 alkyl, or SO2-C1-3 alkyl; and
HetB is a saturated heterocyclic ring selected from the group consisting of tetrahydrofuranyl,
pyrrolidinyl, piperidinyl, pyrazinyl, morpholinyl, and thiomorpholinyl in which the S is optionally oxidized to S(O) or S(0)2, and wherein the ring is optionally substituted with 1 or 2 substituents each of which is independently Ci-3 alkyl, oxo, C(O)N(Ci-3 alkyl)2,
C(O)-C1-3 alkyl, CO2-C1-3 alkyl, or S(O)2-C1-3 alkyl.

A first sub-class of the first class (alternatively referred to herein as "Sub-class CI-SI") includes compounds of Formula I and pharmaceutically acceptable salts thereof,

wherein:
R1 is C3-6 branched alkyl or CH2-AryA;
R2 is H, Ci-4 alkyl, CH2-AryB, C(O)-Ci_4 alkyl, or SO2-C1-4 alkyl;
R3A is H or C1-4 alkyl;
R3B is H or C1-4 alkyl;
R4 is:
R5 is C(O)O-Ci-6 alkyl;
and all other variables are as originally defined in Class Cl.

A second sub-class of the first class (Sub-class C1-S2) includes compounds of

Formula I and pharmaceutically acceptable salts thereof, wherein R1 is C3-6 branched alkyl; and

all of the other variables are as defined in Sub-class Cl-S1.

A second class of compounds of the present invention (Class C2) includes

compounds of Formula I and pharmaceutically acceptable salts thereof, wherein:

A is N-R1;

B is N-R2;

R1 is C3-6 alkyl or CH2-AryA;

R2 is H or C1-6 alkyl;

R3A is H or Ci-6 alkyl;

R3B is H or Ci-6 alkyl;

R4 is:

each XB and each XC are independently selected from the group consisting of: (1) C1.3 alkyl,
(2) cyclopropyl, (3) CF3, (4) OH, (5) O-Ci-3 alkyl, (6) OCF3, (7) Cl, (8) Br, (9) F,
(10) CN, (11) NO2, (12) NH2, (13) N(H)-Ci -3 alkyl, (14) N(-Ci -3 alkyl)2,
(15) C(O)-Ci -3 alkyl, (16) CO2H, (17) C(O)O-Ci-3 alkyl, (18) CH2 OH, and
(19) CH2 O-Ci-3 alkyl;

m is an integer equal to 0, 1, or 2;

n is an integer equal to 0, 1, or 2;

eachXA is independently: (1) C1-3 alkyl, (2) cyclopropyl, (3) CF3, (4) OH, (5) O-C1.3 alkyl,
(6) OCF3, (7) Cl, (8) Br, (9) F, (10) CN, (11) NO2, (12) NH2, (13) N(H)-Ci -3 alkyl,
(14) N(-Ci -3 alkyl)2, (15) C(O)-Ci-3 alkyl, (16) CO2H, (17) C(O)O-Ci -3 alkyl, or
(18) C1-3 alkyl substituted with (a) cyclopropyl, (b) CF3, (c) OH, (d) O-Q-3 alkyl,
(e) OCF3, (f) Cl, (g) Br, (h) F, (i) CN, (j) NO2, (k) NH2, (l) N(H)-CL -3 alkyl,
(m) N(-Ci -3 alkyl)2, (n) C(O)-Cl -3 alkyl, (o) CO2H, or (p) C(O)O-CL -3 alkyl;

k is an integer equal to 0, 1, or 2;

or, alternatively, when twoXA substituents are present on the phenyl ring and the twoXA are
attached to adjacent carbon atoms of the phenyl ring, the twoXA are optionally taken
together with the carbon atoms to which they are attached to form a 5- or 6-membered,
saturated or unsaturated heterocycle fused to the phenyl ring, wherein the heterocycle contains from 1 to 2 heteroatoms independently selected from N, O and S; 
R5 is C(O)O-C 1-6 alkyl; and

AryA is phenyl which is optionally substituted with from 1 to 3 substituents each of which is independently Ci-3 alkyl, CF3, OH, O-C1-3 alkyl, 0CF3, Cl, Br, F, CN, NH2, N(H)-Ci-3 alkyl, N(-Ci-3 alkyl)2, C(0)-Ci-3 alkyl, CO2H, C(O)O-Ci-3 alkyl, CH2OH, CH2O-C1.3 alkyl, C(O)O-Ci-3 alkyl, or SO2-C1-3 alkyl.

A first sub-class of the first class (Sub-class C2-S1) includes compounds of Formula I and pharmaceutically acceptable salts thereof, wherein R¹ is C3-6 branched alkyl or CH2-AryA; and all of the other variables are as defined in Class C2.

A second sub-class of the second class (Sub-class C2-S2) includes compounds of Formula I and pharmaceutically acceptable salts thereof, wherein R¹ is C3-6 branched alkyl; and all of the other variables are as defined in Class C2.

A third sub-class of the second class (Sub-class C2-S3) includes compounds of Formula I and pharmaceutically acceptable salts thereof, wherein the compounds are of Formula III:

![Chemical Structure](image)

and all of the variables are as defined in Class C2. A subset of the sub-class includes compounds of Formula III and pharmaceutically acceptable salts thereof, wherein R¹ is C3.6 branched alkyl or CH2-AryA; and all of the other variables are as defined in Sub-class C2-S3. Another subset of the sub-class includes compounds of Formula III and pharmaceutically acceptable salts thereof, wherein R¹ is C3-6 branched alkyl; and all of the other variables are as defined in Sub-class C2-S3.

A third class of compounds of the present invention (Class C3) includes compounds of Formula I and pharmaceutically acceptable salts thereof, wherein:
A is N-R¹;
B is N-R²;
R¹ is CH(CH3)2, CH2CH2CH3, CH2CH(CH3)2, CH2CH2CH(CHR2)2, or benzyl;
R² is H or CH3;
R³A is H, CH3, CH2CH3, CH(CH3)2, CH2CH2CH3, CH2CH(CH3)2, C(CH3)3, CH2CH2CH(CH3)2, or CH2CH2CH2CH(CH3)2
R³B is H or CH3;

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R4 is:

$\left(\text{X}_B\right)_m - \text{phenyl} - \left(\text{X}_C\right)_n$

; each XB and each XC are independently selected from the group consisting of:

1. CH$_3$
2. CH$_2$CH$_3$
3. CF$_3$
4. OH
5. OCH$_3$
6. OCF$_3$
7. Cl
8. Br
9. F
10. CN
11. NH$_2$
12. N(H)CH$_3$
13. N(CH$_3$)$_2$
14. C(O)CH$_3$
15. C(O)OCH$_3$
16. CH$_2$OH
17. CH$_2$OCH$_3$
18. CH$_2$NH$_2$
19. CH$_2$N(H)CH$_3$
20. CH$_2$N(CH$_3$)$_2$
21. CH(CH$_3$)OH
22. CH(CH$_3$)OCH$_3$
23. CH(CH$_3$)NH$_2$
24. CH(CH$_3$)N(H)CH$_3$
25. CH(CH$_3$)N(CH$_3$)$_2$

m is an integer equal to 0, 1, or 2;

n is an integer equal to 0, 1, or 2;

eachXA is independently:

1. CH$_3$
2. CH$_2$CH$_3$
3. CF$_3$
4. OH
5. OCH$_3$
6. OCF$_3$
7. Cl
8. Br
9. F
10. CN
11. NH$_2$
12. N(H)CH$_3$
13. N(CH$_3$)$_2$
14. C(O)CH$_3$
15. C(O)OCH$_3$
16. CH$_2$OH
17. CH$_2$OCH$_3$
18. CH$_2$NH$_2$
19. CH$_2$N(H)CH$_3$
20. CH$_2$N(CH$_3$)$_2$
21. CH(CH$_3$)OH
22. CH(CH$_3$)OCH$_3$
23. CH(CH$_3$)NH$_2$
24. CH(CH$_3$)N(H)CH$_3$
25. CH(CH$_3$)N(CH$_3$)$_2$

k is an integer equal to 0, 1, or 2;

or, alternatively, when twoXA substituents are present on the phenyl ring and the twoXA are attached to adjacent carbon atoms of the phenyl ring, the twoXA are optionally taken together with the carbon atoms to which they are attached to form a 5- or 6-membered, saturated or unsaturated heterocycle fused to the phenyl ring, wherein the heterocycle contains from 1 to 2 heteroatoms independently selected from N, O and S; and

R5 is C(O)OCH$_3$ or C(O)OC(CH$_3$)$_3$.

A first sub-class of the third class (Sub-class C3-S1) includes compounds of Formula I and pharmaceutically acceptable salts thereof, wherein R1 is CH(CH$_3$)$_2$,

CH$_2$CH$_2$CH$_3$, CH$_2$CH(CH$_3$)$_2$, CH$_2$CH$_2$CH(CH$_3$)$_2$, or CH$_2$CH$_2$CH$_2$CH(CH$_3$)$_2$; and all of the other variables are as defined in Class C3.

A second sub-class of the third class (Sub-class C3-S2) includes compounds of Formula I and pharmaceutically acceptable salts thereof, wherein the compounds are of Formula III; and all of the variables are as defined in Class C3. A subset of the sub-class includes compounds of Formula III and pharmaceutically acceptable salts thereof, wherein R1 is CH(CH$_3$)$_2$, CH$_2$CH$_2$CH$_3$, CH$_2$CH(CH$_3$)$_2$, CH$_2$CH$_2$CH(CH$_3$)$_2$, CH$_2$CH$_2$CH$_2$CH(CH$_3$)$_2$; and all of the other variables are as defined in Sub-class C3-S1.

A fourth class of compounds of the present invention (Class C4) includes compounds of Formula I and pharmaceutically acceptable salts thereof, wherein:

A is N-R1;
B is N-R2;
R1 is CH(CH$_3$)$_2$, CH$_2$CH(CH$_3$)$_2$, CH$_2$CH$_2$CH(CH$_3$)$_2$, or CH$_2$CH$_2$CH$_2$CH(CH$_3$)$_2$;
R2 is H or CH$_3$. 

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either (i) \( R_3A, J, S, H, CH_3, CH_2CH_3, CH(CH_3)_2, CH_2CH_2CH_3, CH_2CH(CH_3)_2, C(CH_3)_3, \) 
\( \) 
\( CH_2CH_2CH(CH_3)_2, \) or \( CH_2CH_2CH_2CH(CH_3)_2, \) and \( R_3B, H; \) or (ii) \( R_3A \) and \( R_3B \) are both \( CH_3; \) 

\( R \) is: 

\( \) 

there are 1 or 2 \( XA \) groups on the phenylsulfonyl moiety wherein one \( XA \) is in the para position on the phenyl ring and is \( CH_3, Cl, Br, F, NH_2, CH_2NH_2, C(O)CH_3, CH_2OH, \) or \( CH(CH_3)OH; \) and the other, optional \( XA \) is in the meta position on the phenyl ring and is \( Cl, Br, \) or \( F; \) 

or, alternatively, when two \( XA \) substituents are present on the phenyl ring and the two \( XA \) are attached to adjacent carbon atoms, the two \( XA \) are optionally taken together with the carbon atoms to which they are attached to form \( -OCH_2O- \) or \( --OCH_2CH_2O--; \) and \( R_5 \) is \( C(O)OCH_3. \) 

A first sub-class of the fourth class (Sub-class C4-S1) includes compounds of 

\( \) 

Formula I and pharmaceutically acceptable salts thereof, wherein \( R_4 \) is; and all of the other variables are as defined in Class C4.

A second sub-class of the fourth class (Sub-class C4-S2) includes compounds of 

\( \) 

Formula I and pharmaceutically acceptable salts thereof, wherein \( XA \) is \( NH_2 \) in the para position on the phenyl; and all of the other variables are as defined in Class C4.

A third sub-class of the fourth class (Sub-class C4-S3) includes compounds of 

\( \) 

Formula I and pharmaceutically acceptable salts thereof, wherein \( R_4 \) is; \( XA \) is \( NH_2 \) in the para position on the phenyl; and all of the other variables are as defined in Class C4.

A fourth sub-class of the fourth class (Sub-class C4-S4) includes compounds of 

\( \) 

Formula I and pharmaceutically acceptable salts thereof, wherein the compounds are of Formula
III; and all of the variables are as defined in Class C4. A subset of the sub-class includes compounds of Formula III and pharmaceutically acceptable salts thereof, wherein

\[ \text{Formula III} \]

\[ \text{R}^4 \text{ is } \]

; and all of the other variables are as defined in Sub-class C4-S4. Another subset of the sub-class includes compounds of Formula III and pharmaceutically acceptable salts thereof, wherein \( X^4 \) is NH2 in the para position on the phenyl; and all of the other variables are as defined in Sub-class C4-S4. Another subset of the sub-class includes compounds of Formula III and pharmaceutically acceptable salts thereof, wherein \( R^4 \) is

\[ \text{Formula III} \]

; \( X^4 \) is NH2 in the para position on the phenyl; and all of the other variables are as defined in Sub-class C4-S4.

Another embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of the title compounds set forth in Examples 1 to 12 and pharmaceutically acceptable salts thereof.

Another embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, as originally defined or as defined in any of the foregoing embodiments, sub-embodiments, aspects, classes, sub-classes or subsets, wherein the compound or its salt is in a substantially pure form. As used herein "substantially pure" means suitably at least about 60 wt.%, typically at least about 70 wt.%, preferably at least about 80 wt.%, more preferably at least about 90 wt.% (e.g., from about 90 wt.% to about 99 wt.%), even more preferably at least about 95 wt.% (e.g., from about 95 wt.% to about 99 wt.%), or from about 98 wt.% to 100 wt.%, and most preferably at least about 99 wt.% (e.g., 100 wt.%) of a product containing a compound of Formula I or its salt (e.g., the product isolated from a reaction mixture affording the compound or salt) consists of the compound or salt. The level of purity of the compounds and salts can be determined using a standard method of analysis such as thin layer chromatography, gel electrophoresis, high performance liquid chromatography, and/or mass spectrometry. If more than one method of analysis is employed and the methods provide experimentally significant differences in the level of purity determined, then the method providing the highest level of purity governs. A compound or salt of 100% purity is one which is free of detectable impurities as determined by a standard method of analysis. The compounds of the invention have two or more asymmetric centers and can occur as mixtures of stereoisomers. It is understood that a substantially pure compound can be either a substantially pure mixture of stereoisomers or a substantially pure individual diastereomer or enantiomer.

Other embodiments of the present invention include the following:
(a) A pharmaceutical composition comprising an effective amount of a compound of Formula I as defined above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

(b) A pharmaceutical composition which comprises the product prepared by combining (e.g., mixing) an effective amount of a compound of Formula I as defined above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

(c) The pharmaceutical composition of (a) or (b), further comprising an effective amount of an anti-HTV agent selected from the group consisting of HFV antiviral agents, immunomodulators, and anti-infective agents.

(d) The pharmaceutical composition of (c), wherein the anti-HIV agent is an antiviral selected from the group consisting of HIV protease inhibitors, HIV reverse transcriptase inhibitors, HIV integrase inhibitors, HIV fusion inhibitors, HIV entry inhibitors, and HIV maturation inhibitors.

(e) The pharmaceutical composition of (d), wherein the antiviral is selected from the group consisting of HIV reverse transcriptase inhibitors and HTV integrase inhibitors.

(f) A combination which is (i) a compound of Formula I as defined above, or a pharmaceutically acceptable salt thereof, and (ii) an anti-HIV agent selected from the group consisting of HIV antiviral agents, immunomodulators, and anti-infective agents; wherein Compound I and the anti-HTV agent are each employed in an amount that renders the combination effective for inhibition of HIV protease, for treatment or prophylaxis of infection by HIV, or for treatment, prophylaxis of, or delay in the onset or progression of AIDS.

(g) The combination of (f), wherein the anti-HIV agent is an antiviral selected from the group consisting of HIV protease inhibitors, HIV reverse transcriptase inhibitors, HIV integrase inhibitors, HIV fusion inhibitors, HIV entry inhibitors, and HIV maturation inhibitors.

(h) The combination of (g), wherein the antiviral is selected from the group consisting of HIV reverse transcriptase inhibitors and HIV integrase inhibitors.

(i) A method for the inhibition of HIV protease in a subject in need thereof which comprises administering to the subject an effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof.

(j) A method for the prophylaxis or treatment of infection by HTV (e.g., HIV-I) in a subject in need thereof which comprises administering to the subject an effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof.

(k) The method of (j), wherein the compound of Formula I is administered in combination with an effective amount of at least one other HIV antiviral selected from the group consisting of HTV protease inhibitors, HFV reverse transcriptase inhibitors, HIV integrase inhibitors, HIV fusion inhibitors, HIV entry inhibitors, and HIV maturation inhibitors.

(l) The method of (k), wherein at least one other HIV antiviral is selected from the group consisting of HTV reverse transcriptase inhibitors and HTV integrase inhibitors.
(m) A method for the prophylaxis, treatment or delay in the onset or progression of AIDS in a subject in need thereof which comprises administering to the subject an effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof.

(n) The method of (m), wherein the compound is administered in combination with an effective amount of at least one other HIV antiviral, selected from the group consisting of HFV protease inhibitors, HTV reverse transcriptase inhibitors, HIV integrase inhibitors, HIV fusion inhibitors, HIV entry inhibitors, and HIV maturation inhibitors.

(o) The method of (n), wherein the at least one other HIV antiviral is selected from the group consisting of HTV reverse transcriptase inhibitors and HIV integrase inhibitors.

(p) A method for the inhibition of HTV protease in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), (c), (d), or (e) or the combination of (e), (f), or (g).

(q) A method for the prophylaxis or treatment of infection by HIV (e.g., HIV-1) in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), (c), (d), or (e) or the combination of (e), (f), or (g).

(r) A method for the prophylaxis, treatment, or delay in the onset or progression of AIDS in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), (c), (d), or (e) or the combination of (e), (f), or (g).

The present invention also includes a compound of Formula I, or a pharmaceutically acceptable salt thereof, (i) for use in, (ii) for use as a medicament for, or (iii) for use in the manufacture/preparation of a medicament for: (a) therapy (e.g., of the human body), (b) medicine, (c) inhibition of HIV protease, (d) treatment or prophylaxis of infection by HIV, or (e) treatment, prophylaxis of, or delay in the onset or progression of AIDS. In these uses, the compounds of the present invention can optionally be employed in combination with one or more other anti-HIV agents selected from HIV antiviral agents, anti-infective agents, and immunomodulators.

Additional embodiments of the invention include the pharmaceutical compositions, combinations and methods set forth in (a)-(r) above and the uses (i)(a)-(e) through (iii)(a)-(e) set forth in the preceding paragraph, wherein the compound of the present invention employed therein is a compound of one of the embodiments, sub-embodiments, aspects, classes, sub-classes, subsets or features described above. In all of these embodiments etc., the compound can optionally be used in the form of a pharmaceutically acceptable salt.

Additional embodiments of the present invention include each of the pharmaceutical compositions, combinations, methods and uses set forth in the preceding paragraphs, wherein the compound of the present invention or its salt employed therein is substantially pure. With respect to a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable carrier and optionally one or more excipients, it is
understood that the term "substantially pure" is in reference to a compound of Formula I or its salt per se.

As used herein, the term "alkyl" refers to a monovalent straight or branched chain, saturated aliphatic hydrocarbon radical having a number of carbon atoms in the specified range. Thus, for example, "C1-6 alkyl" (or "Ci-C6 alkyl") refers to any of the hexyl alkyl and pentyl alkyl isomers as well as n-, iso-, sec- and t-butyl, n- and iso-propyl, ethyl and methyl. As another example, "Ci -4 alkyl" refers to n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl. As another example, "C1-3 alkyl" refers to n-propyl, isopropyl, ethyl and methyl.

The term "branched alkyl" refers to an alkyl group as defined above except that straight chain alkyl groups in the specified range are excluded. As defined herein, branched alkyl includes alkyl groups in which the alkyl is attached to the rest of the compound via a secondary or tertiary carbon; e.g., isopropyl is a branched alkyl group.

The term "cycloalkyl" refers to any monocyclic ring of an alkane having a number of carbon atoms in the specified range. Thus, for example, "C3-6 cycloalkyl" (or "C3-C6 cycloalkyl") refers to cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl, and "C3.5 cycloalkyl" refers to cyclopentyl, cyclobutyl, and cyclohexyl.

The term "halogen" (or "halo") refers to fluorine, chlorine, bromine and iodine (alternatively referred to as fluoro, chloro, bromo, and iodo).

The term "haloalkyl" refers to an alkyl group as defined above in which one or more of the hydrogen atoms have been replaced with a halogen (i.e., F, Cl, Br and/or I). Thus, for example, "C1-6 haloalkyl" (or "C1-C6 haloalkyl") refers to a C1 to C6 linear or branched alkyl group as defined above with one or more halogen substituents. The term "fluoroalkyl" has an analogous meaning except that the halogen substituents are restricted to fluoro. Suitable fluoroalkyls include the series (CH2)0-4CF3 (i.e., trifluoromethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoro-n-propyl, etc.). A fluoroalkyl of particular interest is CF3.

The term "C(O)" refers to carbonyl. The terms "S(O)2" and "SO2" each refer to sulfonyl. The term "S(O)" refers to sulfinyl.

An asterisk ("*"), as the end of an open bond in a chemical group denotes the point of attachment of the group to the rest of the compound.

The term "aryl" refers to phenyl and naphthyl. The aryl of particular interest is phenyl.

The term "heteroaryl" refers to (i) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, or (ii) a heterobicyclic ring selected from quinolinyl, isoquinolinyl, and quinoxalinyl. Suitable 5- and 6-membered heteroaromatic rings include, for example, pyridyl (also referred to as pyridinyl), pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, thienyl, furanyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isooxazolyl, oxadiazolyl, oxatriazolyl, thiazolyl, isothiazolyl, and thiadiazolyl. A class of heteroaryls of interest consists of (i) 5- and 6-membered heteroaromatic
rings containing from 1 to 3 heteroatoms independently selected from N, O and S, and (ii) heterobicyclic rings selected from quinolinyl, isoquinolinyl, and quinoxalinyl. Heteroaryls of particular interest are pyrrolyl, imidazolyl, pyridyl, pyrazinyl, quinolinyl (or quinolyl), isoquinolinyl (or isoquinolyl), and quinoxalinyl.

Examples of 4- to 7-membered, saturated heterocyclic rings within the scope of this invention include, for example, azetidinyl, piperidinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, isothiazolidinyl, oxazolidinyl, isoaxazolidinyl, pyrrolidinyl, imidazolidinyl, pyrazinyl, tetrahydrofuranyl, tetrahydrothienyl, pyrazolidinyl, hexahydropyrimidinyl, thiazinanoyl, thiazepanyl, azepanyl, diazepanyl, tetrahydropyranoyl, tetrahydrothiopyranoyl, and dioxanyl. Examples of 4- to 7-membered, unsaturated heterocyclic rings within the scope of this invention (see HetB) include mono-unsaturated heterocyclic rings corresponding to the saturated heterocyclic rings listed in the preceding sentence in which a single bond is replaced with a double bond (e.g., a carbon-carbon single bond is replaced with a carbon-carbon double bond).

It is understood that the specific rings listed above are not a limitation on the rings which can be used in the present invention. These rings are merely representative.

Unless expressly stated to the contrary in a particular context, any of the various cyclic rings and ring systems described herein may be attached to the rest of the compound at any ring atom (i.e., any carbon atom or any heteroatom) provided that a stable compound results.

Unless expressly stated to the contrary, all ranges cited herein are inclusive. For example, a heteroaromatic ring described as containing from "1 to 4 heteroatoms" means the ring can contain 1, 2, 3 or 4 heteroatoms. It is also understood that any range cited herein includes within its scope all of the sub-ranges within that range. Thus, for example, a heterocyclic ring described as containing from "1 to 4 heteroatoms" is intended to include as aspects thereof, heterocyclic rings containing 2 to 4 heteroatoms, 3 or 4 heteroatoms, 1 to 3 heteroatoms, 2 or 3 heteroatoms, 1 or 2 heteroatoms, 1 heteroatom, 2 heteroatoms, 3 heteroatoms, and 4 heteroatoms.

As another example, an aryl or heteroaryl described as optionally substituted with "from 1 to 4 substituents" is intended to include as aspects thereof, an aryl or heteroaryl substituted with 1 to 4 substituents, 2 to 4 substituents, 3 to 4 substituents, 4 substituents, 1 to 3 substituents, 2 to 3 substituents, 3 substituents, 1 to 2 substituents, 2 substituents, and 1 substituent.

When any variable (e.g., XA or XB) occurs more than one time in any constituent or in Formula I or in any other formula depicting and describing compounds of the present invention, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

Unless expressly stated to the contrary, substitution by a named substituent is permitted on any atom in a ring (e.g., cycloalkyl, aryl, or heteroaryl) provided such ring substitution is chemically allowed and results in a stable compound.
The compounds of the invention contain chiral centers and, as a result of the selection of substituents and substituent patterns, can contain additional chiral centers, and thus can occur as mixtures of stereoisomers, or as individual diastereomers, or enantiomers. All isomeric forms of these compounds, whether individually or in mixtures, are within the scope of the present invention.

To the extent substituents and substituent patterns provide for the existence of tautomers (e.g., keto-enol tautomers) in the compounds of the invention, all tautomeric forms of these compounds, whether present individually or in mixtures, are within the scope of the present invention. Compounds of the present invention having a hydroxy substituent on a carbon atom of a heteroaromatic ring are understood to include compounds in which only the hydroxy is present, compounds in which only the tautomeric keto form (i.e., an oxo substituent) is present, and compounds in which the keto and enol forms are both present.

A "stable" compound is a compound which can be prepared and isolated and whose structure and properties remain or can be caused to remain essentially unchanged for a period of time sufficient to allow use of the compound for the purposes described herein (e.g., therapeutic or prophylactic administration to a subject). The compounds of the present invention are limited to stable compounds embraced by Formula I.

The methods of the present invention involve the use of compounds of the present invention in the inhibition of HIV protease (e.g., wild type HIV-I and/or mutant strains thereof), the prophylaxis or treatment of infection by human immunodeficiency virus and the prophylaxis, treatment or delay in the onset or progression of consequent pathological conditions such as AIDS. Prophylaxis of AIDS, treating AIDS, delaying the onset or progression of AIDS, or treating or prophylaxis of infection by HTV is defined as including, but not limited to, treatment of a wide range of states of HIV infection: AIDS, ARC (AIDS related complex), both symptomatic and asymptomatic, and actual or potential exposure to HIV. For example, the present invention can be employed to treat infection by HIV after suspected past exposure to HIV by such means as blood transfusion, exchange of body fluids, bites, accidental needle stick, or exposure to patient blood during surgery.

The compounds can be administered in the form of pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt" refers to a salt which possesses the effectiveness of the parent compound and which is not biologically or otherwise undesirable (e.g., is neither toxic nor otherwise deleterious to the recipient thereof). Suitable salts include acid addition salts which may, for example, be formed by mixing a solution of the compound of the present invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, acetic acid, or benzoic acid. When compounds employed in the present invention carry an acidic moiety (e.g., -COOH or a phenolic group), suitable pharmaceutically acceptable salts thereof can include alkali metal salts (e.g., sodium or potassium salts), alkaline
earth metal salts (e.g., calcium or magnesium salts), and salts formed with suitable organic ligands such as quaternary ammonium salts.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of Formula I mean providing the compound to the individual in need of treatment or prophylaxis. When a compound is provided in combination with one or more other active agents (e.g., antiviral agents useful for treating or prophylaxis of HIV infection or AIDS), "administration" and its variants are each understood to include provision of the compound and other agents at the same time or at different times. When the agents of a combination are administered at the same time, they can be administered together in a single composition or they can be administered separately.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients, as well as any product which results, directly or indirectly, from combining the specified ingredients.

By "pharmaceutically acceptable" is meant that the ingredients of the pharmaceutical composition must be compatible with each other and not deleterious to the recipient thereof.

The term "subject" as used herein refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

The term "effective amount" as used herein means 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. In one embodiment, the effective amount is a "therapeutically effective amount" for the alleviation of the symptoms of the disease or condition being treated. In another embodiment, the effective amount is a "prophylactically effective amount" for prophylaxis of the symptoms of the disease or condition being prevented. The term also includes herein the amount of active compound sufficient to inhibit HFV protease (wild type and/or mutant strains thereof) and thereby elicit the response being sought (i.e., an "inhibition effective amount"). When the active compound (i.e., active ingredient) is administered as the salt, references to the amount of active ingredient are to the free form (i.e., the non-salt form) of the compound.

In the methods of the present invention (i.e., inhibiting HTV protease, treating or prophylaxis of HFV infection or treating, prophylaxis of, or delaying the onset or progression of AIDS), the compounds of Formula I, optionally in the form of a salt, can be administered by any means that produces contact of the active agent with the agent's site of action. They can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but typically are administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice. The compounds of the invention can, for example, be administered orally, parenterally (including
subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, in the form of a unit dosage of a pharmaceutical composition containing an effective amount of the compound and conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. Liquid preparations suitable for oral administration (e.g., suspensions, syrups, elixirs and the like) can be prepared according to techniques known in the art and can employ any of the usual media such as water, glycols, oils, alcohols and the like. Solid preparations suitable for oral administration (e.g., powders, pills, capsules and tablets) can be prepared according to techniques known in the art and can employ such solid excipients as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like. Parenteral compositions can be prepared according to techniques known in the art and typically employ sterile water as a carrier and optionally other ingredients, such as a solubility aid. Injectable solutions can be prepared according to methods known in the art wherein the carrier comprises a saline solution, a glucose solution or a solution containing a mixture of saline and glucose. Further description of methods suitable for use in preparing pharmaceutical compositions for use in the present invention and of ingredients suitable for use in said compositions is provided in Remington's Pharmaceutical Sciences, 18th edition, edited by A. R. Gennaro, Mack Publishing Co., 1990 and in Remington - The Science and Practice of Pharmacy, 21st edition, Lippincott Williams & Wilkins, 2005.

The compounds of Formula I can be administered orally in a dosage range of 0.001 to 1000 mg/kg of mammal (e.g., human) body weight per day in a single dose or in divided doses. One preferred dosage range is 0.01 to 500 mg/kg body weight per day orally in a single dose or in divided doses. Another preferred dosage range is 0.1 to 100 mg/kg body weight per day orally in single or divided doses. For oral administration, the compositions can be provided in the form of tablets or capsules containing 1.0 to 500 milligrams of the active ingredient, particularly 1, 5, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

As noted above, the present invention is also directed to use of a compound of Formula I with one or more anti-HTV agents. An "anti-HIV agent" is any agent which is directly or indirectly effective in the inhibition of HIV reverse transcriptase, protease, or another enzyme required for HIV replication or infection, the treatment or prophylaxis of HTV infection, and/or the treatment, prophylaxis or delay in the onset or progression of AIDS. It is understood that an anti-HTV agent is effective in treating, preventing, or delaying the onset or progression of HIV infection or AIDS and/or diseases or conditions arising therefrom or associated therewith. For
example, the compounds of this invention may be effectively administered, whether at periods of
pre-exposure and/or post-exposure, in combination with effective amounts of one or more anti-
HIV agents selected from HIV antiviral agents, imunomodulators, antibacterials, or vaccines
useful for treating HIV infection or AIDS, such as those disclosed in Table 1 of WO 01/38332 or
in the Table in WO 02/30930. Suitable HIV antivirals for use in combination with the
compounds of the present invention include, for example, those listed in Table A as follows:

<table>
<thead>
<tr>
<th>Name</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>abacavir, ABC, Ziacon®</td>
<td>nRTI</td>
</tr>
<tr>
<td>abacavir +lamivudine, Epzicom®</td>
<td>nRTI</td>
</tr>
<tr>
<td>abacavir +lamivudine + zidovudine, Trizivir®</td>
<td>nRTI</td>
</tr>
<tr>
<td>amphotericin, Agenerative®</td>
<td>PI</td>
</tr>
<tr>
<td>atazanavir, Reyataz®</td>
<td>PI</td>
</tr>
<tr>
<td>AZT, zidovudine, azidothymidine, Retrovir®</td>
<td>nRTI</td>
</tr>
<tr>
<td>capravirine</td>
<td>nnRTI</td>
</tr>
<tr>
<td>darunavir, Prezista®</td>
<td>PI</td>
</tr>
<tr>
<td>ddC, zalcitabine, deoxycytidine, Hivid®</td>
<td>nRTI</td>
</tr>
<tr>
<td>ddI, didanosine, deoxyxynosine, Videx®</td>
<td>nRTI</td>
</tr>
<tr>
<td>ddI (enteric coated), Videx EC®</td>
<td>nRTI</td>
</tr>
<tr>
<td>delavirdine, DLV, Rescriptor®</td>
<td>nnRTI</td>
</tr>
<tr>
<td>efavirenz, EFV, Sustiva®, Stocrin®</td>
<td>nnRTI</td>
</tr>
<tr>
<td>efavirenz + emtricitabine + tenofovir DF, Atripla®</td>
<td>nnRTI + nRTI</td>
</tr>
<tr>
<td>emtricitabine, FTC, Emtriva®</td>
<td>nRTI</td>
</tr>
<tr>
<td>emtricitabine + tenofovir DF, Truvada®</td>
<td>nRTI</td>
</tr>
<tr>
<td>emvirine, Coactinon®</td>
<td>nnRTI</td>
</tr>
<tr>
<td>enfuvirtide, Fuzeon®</td>
<td>PI</td>
</tr>
<tr>
<td>enteric coated didanosine, Videx EC®</td>
<td>nRTI</td>
</tr>
<tr>
<td>etravirine, TMC-125</td>
<td>nRTI</td>
</tr>
<tr>
<td>fosamprenavir calcium, Lexiva®</td>
<td>PI</td>
</tr>
<tr>
<td>indinavir, Crixivan®</td>
<td>PI</td>
</tr>
<tr>
<td>lamivudine, 3TC, Epivir®</td>
<td>nRTI</td>
</tr>
<tr>
<td>lamivudine + zidovudine, Combivir®</td>
<td>nRTI</td>
</tr>
<tr>
<td>lopinavir</td>
<td>PI</td>
</tr>
<tr>
<td>lopinavir + ritonavir, Kaletra®</td>
<td>PI</td>
</tr>
<tr>
<td>maraviroc, Selzentry®</td>
<td>EI</td>
</tr>
<tr>
<td>nelfinavir, Viracept®</td>
<td>PI</td>
</tr>
<tr>
<td>nevirapine, NVP, Viramune®</td>
<td>nnRTI</td>
</tr>
<tr>
<td>PPL-100 (also known as PL-462) (Ambril)</td>
<td>PI</td>
</tr>
<tr>
<td>raltegravir, MK-0518, Isentress™</td>
<td>InI</td>
</tr>
<tr>
<td>ritonavir, Norvir®</td>
<td>PI</td>
</tr>
<tr>
<td>saquinavir, Indinase®, Fortovase®</td>
<td>PI</td>
</tr>
<tr>
<td>stavudine, d4T,didehydrodeoxythymidine, Zerit®</td>
<td>nRTI</td>
</tr>
<tr>
<td>tenofovir DF (DF = disoproxyl fumarate), TDF, Viread®</td>
<td>nRTI</td>
</tr>
<tr>
<td>tipranavir, Aptivus®</td>
<td>PI</td>
</tr>
</tbody>
</table>

EI = entry inhibitor; FI = fusion inhibitor; InI = integrase inhibitor; PI = protease
inhibitor; nRTI = nucleoside reverse transcriptase inhibitor; nnRTI = non-nucleoside
reverse transcriptase inhibitor. Some of the drugs listed in the table are used in a salt form; e.g., abacavir sulfate, indinavir sulfate, atazanavir sulfate, nelfinavir mesylate.

It is understood that the scope of combinations of the compounds of this invention with anti-HTV agents is not limited to the HIV antivirals listed in Table A and/or listed in the above-referenced Tables in WO 01/38332 and WO 02/30930, but includes in principle any combination with any pharmaceutical composition useful for the treatment or prophylaxis of AIDS. The HIV antiviral agents and other agents will typically be employed in these combinations in their conventional dosage ranges and regimens as reported in the art, including, for example, the dosages described in the Physicians’ Desk Reference, Thomson PDR, Thomson PDR, 57th edition (2003), the 58th edition (2004), or the 59th edition (2005). The dosage ranges for a compound of the invention in these combinations are the same as those set forth above.

The compounds of this invention are also useful in the preparation and execution of screening assays for antiviral compounds. For example, the compounds of this invention are useful for isolating enzyme mutants, which are excellent screening tools for more powerful antiviral compounds. Furthermore, the compounds of this invention are useful in establishing or determining the binding site of other antivirals to HFV protease, e.g., by competitive inhibition.

Thus the compounds of this invention are commercial products to be sold for these purposes.

Abbreviations employed herein include the following: APCI = atmospheric pressure chemical ionization (mass spectroscopy); Bn = benzyl; Boc = t-butyloxycarbonyl; Boc-ON = 2-(tert-butyloxycarboxyloxyamino)-2-phenyl acetonitrile; Boc2θ = di-t-butyl carbonate; BSA = bovine serum albumin; Cbz = benzoxycarbonyl; DBU = 1.8-diazabicyclo[5.4.0]undec-7-one; DIPEA = diisopropylethylamine (or Hunig's base); DMF = dimethylformamide; DMSO = dimethyl sulfoxide; DPPA = diphenylphosphoryl azide; Et = ethyl; EtOAc = ethyl acetate; EtOH = ethanol; FBS = fetal bovine serum; Fmoc = 9-fluorenlymethoxy carbonyl; HPLC = high performance liquid chromatography; HSu = hydroxy succinimide; LC-MS = liquid chromatography-mass spectroscopy; m-CPBA = meta-chloroperbenzoic acid; Me = methyl; MeOH = methanol; Moc = methoxycarbonyl; Ms = mesyl or methanesulfonyl; i-Am = isoamyl; i-Bu = isobutyl; n-Bu = n-butyl; NMR = nuclear magnetic resonance; n-Pr = n-propyl; Ph = phenyl; RP-HPLC = reverse phase HPLC; STAB = sodium triacetoxycarbonyl; TEA = triethylamine; TFA = trifluoroacetic acid; THF = tetrahydrofuran.

The compounds of the present invention can be readily prepared according to the following reaction schemes and examples, or modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail. Furthermore, other methods for preparing compounds of the invention will be readily apparent to the person of ordinary skill in the art in light of the following reaction schemes and examples. Unless otherwise indicated, all variables are as defined above. The term "Ar" appears in several of the schemes and refers to phenyl optionally substituted with one or more XA.
Scheme 1 below depicts a method for preparing trans 3,4-diaminopyrrolidine compounds of the present invention, wherein L-tartaric acid 1-1 is treated with benzylamine to afford (3R,4R)-1-benzy1-3,4-dihydroxypyrrolidine-2,5-dione 1-2, which can then be treated with an appropriate reducing agent such as UAIH₄ to obtain (3S,4S)-1-benzypyrrolidine-3,4-diol 1-3. Diol 1-3 can then be converted to (3R,4R)-3,4-diazido-1-benzy1pyrrolidine 1-4 by mesylation and treatment with sodium azide. Diazide 1-4 can then be treated with triphenylphosphine as described in J. Am. Chem. Soc. 1998, vol. 120, p. 9112 to give (3R,4R)-4-azido-1-benzylpyrrolidin-3-amine 1-5, which can then be protected with a suitable protecting group such as Boc using di-t-butylcarbonate or Boc-ON or the like to afford 1-6. Further azide reduction using a reagent such as triphenylphosphine can afford the mono protected diamine 1-7, which can then be sulfonlated using an arylsulfonyl chloride and an acid scavenger to afford arylsulfonylated amine 1-8, which can then be N-alkylated using an appropriately substituted alkyl halide, or alkyl alcohol under Mitsunobu conditions. Alkylated amine 1-9 can then be deprotected (e.g., cleavage of Boc by treatment with acid) and the resulting amine 1-10 can then be reductively aminated using an appropriately substituted N-protected amino aldehyde to give product 1-11, which can in turn be deprotected (e.g., Boc removal by treatment with acid) to afford amine 1-12. Amine 1-12 can then be coupled with a suitably protected amino acid derivative to give coupled product (amide) 1-13. The secondary amine can then be functionalized to add R₂ (e.g., alkylated), the benzyl group protecting the pyrrolidinyl nitrogen can be removed (e.g., by treatment with 1-chloroethyl chloroformate), and the aryl sulfonamide can optionally be further functionalized (i.e., adding and/or changing substituents on the phenyl ring to give Arorphotin the like) such as reducing Ar = p-nitrophenyl to Ar' = p-aminophenyl by treatment with SnCl₂ to give the final targets 1-14.
Scheme 2 depicts a method for preparing trans 3-amino-4-alkyl pyrrolidine compounds of the invention, wherein monoethyl fumarate 2-1 can be benzylated (e.g., by treatment with BnBr in the presence of DBU) to compound 2-2, and then cyclized into pyrrolidine derivative 2-3 (e.g., by treatment of 2-2 with PhCH2NHCH2SiMe3 as described in Chem. Lett. 1996, p. 747 (see Scheme 14). The O- and N-benzyl groups can then be removed and a carbamate (e.g., Boc) formed at the pyrrolidinyl N by hydrogenation in the presence of a carbamate-forming reagent (e.g., Boc20). The resulting acid 2-4 can then be reacted under conditions known to effect a Curtius rearrangement (e.g., treatment with BnOH and DPPA) to afford 2-5. The ester functional group in 2-5 can then be converted to the aldehyde 2-6 in a two-step procedure by, for example, treating with a reducing agent (e.g., LiBH-J) then oxidizing the formed alcohol with a reagent such as manganese(IV)oxide and the aldehyde can then be olefinated (e.g., by coupling with methyl (triphenylphosphoranilydene) acetate) to give the unsaturated ester 2-7. The ester 2-7 can then be reduced (e.g., by treatment with LiAlH4) to the saturated alcohol 2-8. The Cbz protecting group can then be removed via hydrogenolysis and the
resulting amine 2-9 sulfonylated with an arylsulfonyl chloride such as p-nitrobenzenesulfonyl chloride to provide 2-10. Arylsulfonamide 2-10 can then be alkylated (e.g., with an alkyl halide and base) to introduce R\(^1\) and thereby afford intermediate compound 2-11. The hydroxy group in 2-11 can be converted to azide using standard methodology (e.g., by treatment with mesyl chloride and then with NaN\(_3\)) to obtain 2-12, which can be reduced (e.g., by treatment with PPI13) to amine 2-13. Amine 2-13 can then be coupled with a suitably protected amino acid derivative to give coupled product (amide) 2-14. The Boc group protecting the pyrrolidinyl nitrogen can be removed (e.g., by treatment with acid), and the aryl sulfonamide can optionally be further functionalized (i.e., adding and/or changing substituents on the phenyl ring to give Ar', such as reducing Ar = p-nitrophenyl to Ar'\(=\) p-aminophenyl by treatment with SnCl\(_2\)) to give the final targets 2-15.

Scheme 2
The following examples serve only to illustrate the invention and its practice. The examples are not to be construed as limitations on the scope or spirit of the invention.

The term "room temperature" in the examples refers to the ambient temperature which was typically in the range of about 19°C to 26°C.

EXAMPLE 1

\[ N-(2-\{(3i?,4/f)-4-\{[(4-aminophenyI)sulfonyl](3-methylbutyl)amino\} pyrrolidin-3-yl\}amino\} ethyl)-N\alpha-(methoxycarbonyl)-\beta\text{-phenyl-L-phenylalaninamide} \]

Step 1 (3R,4R)- 1-Benzyl-3,4-dihydroxypyrrolidine-2,5-dione

L-Tartaric acid (90 g, 600 mmol) and benzylamine (64.3 g, 600 mmol) were mixed in 400 mL of o-xylene and the mixture was refluxed 14 hours with a Dean-Stark trap. The pellet was filtered off and the compound was crystallized from hot EtOH (1600 mL). The formed crystals were washed with cold hexane to afford the title compound.
Step 2 (3S,4S)-1-Benzylpyrrolidine-3,4-diol

To a suspension of UAIH₄ (18.33 g, 219.2 mmol) in 200 mL THF, (3R,4R)-1-benzyl-3,4-dihydroxypyrrolidine-2,5-dione (23.1 g, 104.4 mmol) was added and the mixture was refluxed for 12 hours. The mixture was cooled down to room temperature and carefully quenched with 3 mL EtOAc and 3 mL MeOH. Wet silica gel was added to the mixture following by addition of MeOH-CHCl₃, 1:1, and the mixture was filtered. The filtrate was evaporated giving the title compound that was used for the next step without additional purification.

Step 3 (3R,4R)-3,4-Diazido-1-benzylpyrrolidine

To a mixture of (3S,4S)-1-benzylpyrrolidine-3,4-diol (14.8 g, 76.6 mmol) and Et₃N (23.3 g, 229.8 mmol) in 300 mL CH₂Cl₂, MsCl (26.3 g, 229.8 mmol) was added dropwise at 0°C. The mixture was stirred at room temperature for 1 hour, water was added following by addition of IN HCl. The aqueous acidic layer was washed with CH₂Cl₂ and basified with 50% aqueous NaOH. The mixture was extracted with CH₂Cl₂, the combined organic extracts were dried with Na₂SO₄ and evaporated. The residue was dissolved in 300 mL DMSO, and sodium azide (16.9 g, 260 mmol) was added. The mixture was stirred at 90°C for 24 hours, cooled down to room temperature, diluted with 1200 mL of water, and extracted with Et₂O. The combined organic extracts were dried with Na₂SO₄ and evaporated. The residue was purified by column chromatography on silica gel eluting with 2 -> 5% Et₂O in hexane giving the desired diazide.

Step 4 (3R,4R)-4-Azido-1-benzylpyrrolidine 3-amine

-37-
To a solution of diazide prepared as described in Step 3 (8.9 g, 36.5 mmol) in 350 mL PhMe, PPh3 9.6 g, 36.5 mmol) was added and the mixture was refluxed for 1 hour. The mixture was cooled down to room temperature, diluted with 350 mL THF, water (1.31 g, 73.0 mmol) was added and the mixture was refluxed for additional 1 hour. 4N HCl was added, the aqueous acidic layer was separated, washed with CHCl3 and basified with aqueous NH3 to pH 9-10. The product was extracted with CHCl3, the combined organic extracts were dried with Na2SO4 and evaporated giving the title compound.

Step 5  tert-Butyl (3R,4R)-4-azido-l-benzylpyrrolidin-3-ylcarbamate

\[
\begin{align*}
\text{N}_3 & \quad \text{NH}_2 \\
& \quad \text{Boc}_2O \\
\text{N}_3 & \quad \text{NHBOc}
\end{align*}
\]

To a solution of (3R,4R)-4-azido-l-benzylpyrrolidin-3-amine (6.5 g, 22.3 mmol) in 100 mL THF, Boc2O (4.9 g, 22.3 mmol) was added and the mixture was stirred at reflux for 0.5 hour. The mixture was taken to dryness giving the desired compound (7.15 g). 1H NMR (400 MHz, OMSO-d6): 1.38 (9H, s), 2.21 (IH, dd, J1=7.1 Hz, J2=9.3 Hz), 2.58 (IH, dd, J1=3.4 Hz, J2=10.0 Hz), 2.67 (IH, dd, J1=6.8 Hz, J2=10.3 Hz), 2.96 (IH, dd, J1=1.5 Hz, J2=8.3 Hz), 3.50 (IH, d, J=13.2 Hz), 3.60 (IH, d, J=13.2 Hz), 3.75-3.87 (2 x m, 2 x IH), 7.22-7.33 (5H, m). LC-MS APCI: m/z 318.1 [M + H]+.

Step 6  /erf-Butyl (SR^N^-amino-l-benzylpyrrolidin-S-ylcarbamate

\[
\begin{align*}
\text{N}_3 & \quad \text{JMHBOc} \\
& \quad \text{H}_2\text{N} \\
& \quad \text{NHBOc}
\end{align*}
\]

To a solution of /erf-butyl (3R,4R)-4-azido-l-benzylpyrrolidin-3-ylcarbamate (7.0 g, 22.0 mmol) in 250 mL toluene, PPH3 6.0 g, 23.0 mmol) was added and the mixture was refluxed for 1 hour. The mixture was cooled down to room temperature, diluted with 250 mL THF, water (0.54 g, 30.0 mmol) was added and the mixture was refluxed for an additional 1 hour. 4N HCl was added, the aqueous acidic layer was separated, washed with CHCl3 and basified with aqueous NH3 to pH 9-10. The product was extracted with CHCl3, the combined organic extracts were dried with Na2SO4 and evaporated. The residue was purified by column chromatography on silica gel eluting with 10% MeOH in CHCl3 giving the title mono-Boc protected diamine.
Step 7  

**tert-Butyl (3S,4R)-1-benzyl-4-[[4-(nitrophenyl)sulfonyl]amino]pyrrolidin-3-yl]carbamate**

To a solution of **tert-butyl (3R,4R)-4-amino-1-benzylpyrrolidin-3-yl]carbamate** (5.8 g, 20 mmol) in 100 mL of CH2Cl2, triethylamine (4.04 g, 40 mmol) was added following by addition of 4-nitrobenzenesulfonyl chloride (1.1 eq) and the mixture was stirred at room temperature overnight. The reaction was quenched with saturated aqueous NH4Cl, extracted with CH2Cl2, the combined organic extracts were dried with Na2SO4 and evaporated. The residue was purified by column chromatography on silica gel eluting with 1-2% MeOH in CHCl3 to give the title product.

Step 8  

**tert-Butyl [(3S,4R)-1-benzyl-4-((3-methylbutyl)[(4-nitrophenyl)sulfonyl] amino]pyrrolidin-3-yl]carbamate**

A mixture of **tert-butyl (3S,4R)-1-benzyl-4-[[4-(nitrophenyl)sulfonyl]amino]pyrrolidin-3-yl]carbamate** (4.76 g, 10 mmol), isoamyl bromide (1.2 eq), and K2CO3 (2.76 g, 20 mmol) in 50 mL of DMF was stirred overnight at 50°C. The mixture was diluted with H2O, extracted with EtOAc, the combined organic extracts were dried with Na2SO4 and evaporated. The residue was purified by column chromatography on silica gel eluting with 5 - » 20% EtOAc in hexane to give the title product.

Step 9  

**N-[(3S,4R)-4-Amino-1-benzylpyrrolidin-3-yl]-N-methyl-4-nitrobenzenesulfonamide**
A solution of tert-butyl $[(3R,4R)$-1-benzyl-4-{$(3$-methylbutyl)[$(4$-nitrophenyl)sulfonyl] amino} pyrrolidin-3-yl]carbamate in 2N HCl dioxane was stirred overnight at room temperature. The solvent was evaporated to a minimal volume, diethyl ether was added, and the formed pellet was filtered off and washed with diethyl ether giving the crude title product which was used in the next step without purification.

Step 10 tert-Butyl $2-[(3R,4R)$-1-benzyl-4-{$(3$-methylbutyl)[$(4$-nitrophenyl)sulfonyl] amino} pyrrolidin-3-yl]aminoethyl)carbamate

To a solution of $N$-$(3R,4R)$-4-amino-$l$-benzylpyrrolidin-3-yl]- $N$-methyl-4-nitrobenzenesulfonamide (692 mg, 1.5 mmol) in MeOH was added K2CO3 (405 mg, 3 mmol) and the mixture was stirred for 0.5 hour at room temperature. To this mixture, Boc-amino glycinal (1.8 mmol) was added following by addition of a solution of NaBH3CN (111 mg, 1.8 mmol) and ZnCl2 (0.6 eq) in MeOH at room temperature. The reaction mixture was stirred at room temperature overnight, quenched with IN aqueous NaOH, extracted with CHCl3, the combined organic extracts were dried with Na2SO4 and evaporated. The residue was purified by column chromatography on silica gel eluting with 2-5% MeOH in CHCl3 giving the desired product.

Step 11 $N$-$(3R,4R)$-4-{$(2$-Aminoethyl)amino}$l$-benzylpyrrolidin-3-yl]- $N$-$(3$-methylbutyl)-4-nitrobenzenesulfonamide
A solution of tert-butyl (2-[(3,4#)-1-benzyl-4-{(3-methylbutyl)[(4-nitrophenyl)sulfonyl]amino} pyrrolidin-3-yl]amino)ethyl)carbamate in 2N HCl dioxane was stirred overnight at room temperature before the solvent was evaporated to dryness. The resulting tris HCl salt was used directly in the next reaction.

**Step 12**

\[ N-(2-[(3R,4#)-1-Benzyl-4-{(3-methylbutyl)[(4-nitrophenyl)sulfonyl]amino} pyrrolidin-3-yJaminOJethyO-NG-Cmethoxycarbonylβ-phenyl-L-phenylalaninamide \]

A mixture of an amine salt prepared as described in Step 11 (437 mg, 1 mmol), saturated aqueous NaHCO₃, and methoxycarbonyl-L-di-Phe-Hsu ester (322 mg, 1 mmol) in acetone-THF, 1:1, was stirred 2 hours at room temperature. To the mixture H₂O was added, and the product was extracted with CHCl₃. The combined organic extracts were dried with Na₂SO₄ and evaporated giving the crude product that was used for the next step without additional purification. LC-MS APCI: \( \text{mfz} 111.3 \ [\text{M} + \text{H}]^+ \).
Step 13  
\[ N\alpha-(\text{Methoxycarbonyl})-N-(2-[[3R,4R]-4-((3-\text{methylbutyl})\text{[(4-nitrophenyl)sulfonyl] amino} \text{pyrrolidin-3-yl} \text{amino}] \text{ethyl})-\beta-\text{phenyl-L-phenylalaninamide} \]

A mixture of the product prepared as described in Step 12 (1 eq), 1-chloroethyl chloroformate (3 eq) in 1,2-dichloroethane was stirred overnight at reflux. The solvent was evaporated, the residue was re-dissolved in MeOH and the mixture was refluxed for 1 hour. MeOH was evaporated and the residue containing compound the deprotected pyrrolidine was used for the next step without additional purification. LC-MS APCI: m/z 681.3 [M + H]+.

Step 14  
\[ N-(2-[[3\text{J},4\text{R}]-4-[[4-\text{Aminophenyl}sulfonyl]3-\text{methylbutyl}])\text{amino} \text{pyrrolidin-3-yl} \text{amino}] \text{ethyl})-N\alpha-(\text{methoxycarbonyl})-\beta-\text{phenyl-L-phenylalaninamide} \]

To a mixture of \(N\alpha-(\text{methoxycarbonyl})-N-(2-[[3\text{R},4\text{R}]-4-((3-\text{methylbutyl})\text{[(4-nitrophenyl)sulfonyl] amino} \text{pyrrolidin-3-yl} \text{amino}] \text{ethyl})-\beta-\text{phenyl-L-phenylalaninamide} \) (340 mg, 0.5 mmol), anhydrous SnCl2 (564 mg, 2.5 mmol) in EtOAc, H2O (10 eq) was added and the mixture was stirred at reflux for 2 hours. Saturated aqueous NaHC03 was added following by addition of water, the mixture was extracted with EtOAc, the combined organic extracts were dried with Na2SO4 and evaporated. The residue was purified by preparative RP-HPLC. The collected fractions were partially evaporated, basified with 1M K2CO3, and extracted with CH2Cl2. The combined organic extracts were dried with Na2SO4 and evaporated. The residue was re-dissolved in 0.5 mL CH2Cl2 and 1-2 mL of 2N HCl in Et2O was added. The mixture was diluted with Et2O, the pellet was filtered off, washed with Et2O and dried in vacuo at 50-60°C giving target compounds as tris-hydrochloride salts. 1H NMR (400 MHz, CD3OD): 0.91 and 0.92 (6H, two d, J=6.5 Hz), 1.45-1.65 (3H, m), 2.90-3.01 (2H, br. m), 3.1 1-3.30 (4H, m), 3.34-3.41 (IH, m), 3.45-3.55 (2H, m), 3.57 (3H, s), 3.87 (IH, dd, J=13.0 Hz, J=8.0 Hz), 4.17-4.26 (IH, m), 4.355 (IH, d, J=1 1.0 Hz), 4.68-4.78 (IH, m), 4.92 (IH, d, J=1 1.0 Hz), 6.83-6.88
EXAMPLES 2-9

The compounds in the following table were prepared in a manner similar to Example 1 by substituting the appropriately substituted alkyl group in Step 8 or amino acid aldehyde in Step 10.

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<thead>
<tr>
<th>Ex. No.</th>
<th>R^1</th>
<th>R^3A, R^3B</th>
<th>Name</th>
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<td>i-Am</td>
<td>Me, H</td>
<td>N-[(2S)-1-[[3(R),4'R)-4-[[4-aminophenyl]sulfonyl][3-methylbutyl]amino]pyrroline n-3-yl]amino]propan-2-yl]-Na-(methoxy carbonyl)-β-phenyl-L-phenylalaninamide</td>
<td>(400 MHz, CD3OD): 0.91 and 0.915 (6H, two d, J=6.5 Hz), 1.105 (3H, d, J=7.0 Hz), 1.43-1.65 (3H, m), 2.48-2.58 (1H, br. m), 2.82-2.92 (1H, br. m), 3.15-3.28 (2H, m), 3.40-3.53 (2H, m), 3.57 (3H, s), 3.57-3.66 (1H, m), 3.77-3.89 (2H, m), 4.15-4.25 (1H, m), 4.35 (1H, d, J=11.0 Hz), 4.65-4.74 (1H, m), 4.98 (1H, d, J=11.0 Hz), 6.83-6.88 (2H, m), 7.18-7.41 (10H, m), 7.64-7.70 (2H, m).</td>
</tr>
<tr>
<td>3</td>
<td>i-Am</td>
<td>Et, H</td>
<td>N-[(2S)-1-[[3(R),4'R)-4-[[4-aminophenyl]sulfonyl][3-methylbutyl]amino]pyrroline n-3-yl]amino]butan-2-yl]-Na-(methoxy carbonyl)-β-phenyl-L-phenylalaninamide</td>
<td>(400 MHz, CD3OD): 0.43 and 0.81 (3H, two d, J=7.0 Hz), 0.90-0.96 and 1.03-1.14 (7H, two m), 1.40-1.67 (4H, m), 2.55-2.65 and 2.95-3.30 (3H, two m), 3.35-4.05 (6H, m), 3.57 and 3.60 (3H, two s), 4.10-4.43 (2H, m), 4.85-5.05 (2H, m), 7.05-7.13 (2H, m), 7.15-7.44 (10H, m), 7.75-7.85 (2H, m).</td>
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<td>n-Bu, H</td>
<td>N-[(1-[[3(R),4'R)-4-[[4-aminophenyl]sulfonyl][3-methylbutyl]amino]pyrroline n-3-yl]amino]hexan-2-yl]-Na-(methoxy carbonyl)-β-phenyl-L-phenylalaninamide</td>
<td>(400 MHz, CD3OD): 0.60-0.80 (1H, br. m), 0.83 and 0.92 (3H, two d, J=7.0 Hz), 0.88-0.94 (6H, m), 0.94-1.20 (4H, m), 1.40-1.70 (4H, m), 2.62-2.72 and 2.98-3.28 (3H, two m), 3.35-3.70 (4H, m), 3.59 and 3.60 (3H, two s), 3.74-4.02 (2H, m), 4.20-4.42 (2H, m), 4.80-4.87 (1H, overlapping m), 4.91 and 5.00 (1H, d, J=11.5 Hz), 6.81-6.87 (2H, m), 7.16-7.43 (10H, m), 7.60-7.69 (2H, m).</td>
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<tr>
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<td>i-Bu, H</td>
<td>N-[(2S)-1-[[3(R),4'R)-4-[[4-aminophenyl]sulfonyl][3-methylbutyl]amino]pyrroline n-3-yl]amino]4-methylpentan-2-yl]-Na-</td>
<td>(400 MHz, CD3OD): 0.79 and 0.87 (6H, two d, J=6.0 Hz), 0.90 (6H, d, J=6.5 Hz), 1.18-1.65 (6H, m), 2.72-2.74 (1H, m), 2.98-3.27 (3H, m), 3.33-3.42 (1H, m), 3.47-3.66 (2H, m), 3.59 (3H, s), 3.81 (1H, dd, J=13.0 Hz).</td>
</tr>
</tbody>
</table>
EXAMPLE 1

\[
N\cdot\{1-\{(3R,4R)-4-\{(4-aminophenyl)sulfonyl\}[3-methylbutyl]amino\}pyrrolidin-3-yl\}-(methyl)amino\}ethyl\}-N-alpha-^ethoxycarbony0-beta-phenyl-L-phenylalaninamide
\]

\(J=8.5\) Hz, 3.87–3.97 (1H, m), 4.22–4.32 (1H, m), 4.38 (1H, d, \(J=11.0\) Hz), 4.80–4.87 (1H, m), 4.98 (1H, d, \(J=11.0\) Hz), 6.85–6.91 (2H, m), 7.18–7.26 (2H, m), 7.27–7.34 (4H, m), 7.34–7.43 (4H, m), 7.64–7.70 (2H, m).

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<tr>
<th>6</th>
<th>i-Am</th>
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<td>(N\cdot{1-{(3R,4R)-4-{(4-aminophenyl)sulfonyl}[3-methylbutyl]amino}pyrrolidin-3-yl}-(methyl)amino}ethyl}-N-alpha-^ethoxycarbony0-beta-phenyl-L-phenylalaninamide) (400 MHz, CD3OD): 0.89–0.95 (6H, m), 0.915 (3H, s), 1.23 (3H, s), 1.42–1.64 (3H, m), 2.83 (1H, br. d, (J=13.0) Hz), 3.09 (1H, d, (J=13.0) Hz), 3.24–3.30 (1H, m), 3.45–3.53 (1H, m), 3.56 (3H, s), 3.55–3.65 (3H, m), 3.855 (1H, dd, (J=13.0) Hz, (J=8.5) Hz), 4.16 (1H, dt, (J=7.5) Hz, (J=7.5) Hz), 4.28 (1H, d, (J=11.5) Hz), 4.725 (1H, dt, (J=7.5) Hz, (J=7.5) Hz), 5.02 (1H, d, (J=11.5) Hz), 6.81–6.86 (2H, m), 7.18–7.27 (2H, m), 7.28–7.36 (4H, m), 7.36–7.42 (4H, m), 7.64–7.70 (2H, m).</td>
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<td>(N\cdot{2-{(3R,4R)-4-{(4-aminophenyl)sulfonyl}[2-methylpropyl]amino}pyrrolidin-3-yl}amino}ethyl}-N-alpha-^ethoxycarbony0-beta-phenyl-L-phenylalaninamide) (400 MHz, DMSO-d6): 0.84 and 0.935 (6H, two d, (J=6.5) Hz), 1.92–2.08 (1H, m), 2.70–2.85 (2H, m), 2.86 (2H, d, (J=7.5) Hz), 2.98–3.35 (4H, m), 3.43 (3H, s), 3.55–3.80 (3H, overlapping m), 4.31 (1H, d, (J=11.5) Hz), 4.76–4.93 (2H, m), 6.68 (2H, d, (J=9.0) Hz), 7.12–7.20 (2H, m), 7.21–7.35 (8H, m), 7.47 (2H, d, (J=9.0) Hz), 8.32 (1H, br. t, (J=5.0) Hz), 9.51 (1H, br. s), 9.88 (1H, br. s), 10.00 (2H, br. s).</td>
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<td>(N\cdot{2-(3R,4R)-4-{(4-aminophenyl)sulfonyl}[isopropyl]amino}pyrrolidin-3-yl}amino}ethyl}-N-alpha-^ethoxycarbony0-beta-phenyl-L-phenylalaninamide) (400 MHz, CD3OD): 1.12 and 1.25 (6H, two d, (J=6.5) Hz), 2.64–2.74 (1H, m), 3.02–3.11 (1H, m), 3.22–3.28 (2H, m), 3.57 (3H, s), 3.56–3.62 (1H, m), 3.71–3.83 (3H, m), 3.96 (1H, dd, (J=12.5) Hz, (J=8.0) Hz), 4.35 (1H, d, (J=11.5) Hz), 4.49–4.60 (2H, m), 4.945 (1H, d, (J=11.5) Hz), 6.90–6.96 (2H, m), 7.17–7.24 (2H, m), 7.26–7.40 (8H, m), 7.72–7.78 (2H, m).</td>
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<td>(N\cdot{2-(3R,4R)-4-{(4-aminophenyl)sulfonyl}[benzyl]amino}pyrrolidin-3-yl}amino}ethyl}-N-alpha-^ethoxycarbony0-beta-phenyl-L-phenylalaninamide) (400 MHz, CD3OD): 2.51–2.87 (2H, m), 2.85–2.95 (1H, m), 3.01–3.11 (1H, m), 3.40–3.50 (3H, m), 3.56 (3H, s), 3.77 (1H, dd, (J=13.0) Hz, (J=8.5) Hz), 4.00–4.10 (1H, m), 4.27 (1H, d, (J=15.5) Hz), 4.35 (1H, d, (J=11.0) Hz), 4.57 (1H, d, (J=15.5) Hz), 4.67–4.77 (1H, m), 4.91 (1H, d, (J=11.0) Hz), 6.81–6.87 (2H, m), 7.17–7.24 (2H, m), 7.25–7.39 (8H, m), 7.66–7.71 (2H, m).</td>
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</table>

EXAMPLE 10

\(N\cdot\{2-\{(3R,4R)-4-\{(4-aminophenyl)sulfonyl\}[3-methylbutyl]amino\}pyrrolidin-3-yl\}amino\}ethyl\}-N-alpha-^ethoxycarbony0-beta-phenyl-L-phenylalaninamide\)
Step 1

^-(2-\{[(3\text{R},4\text{R})-1-Benzyl-4-{(3-methylbutyl)\{(4-nitrophenyl)sulfonyl\}amino} pyrrolidin-3-yl\}amino}ethyl\)-N\alpha-(methoxycarbonyl)-\beta-phenyl-L-phenylalaninamide

Step 2

N\alpha-(Methoxycarbonyl)-N-(2-\{methyl\[(3\text{R},4\text{R})-4-{(3-methylbutyl)\{(4-nitrophenyl)sulfonyl\}amino}pyrrolidin-3-yl\}amino\}ethyl\)-\beta-phenyl-L-phenylalaninamide
A mixture of \(N\)-(2-{[(3R,4R)-1-benzyl-4-{(3-methylbutyl)\[(4-nitrophenyl)sulfonyl\]amino}pyrrolidin-3-yl\}methyl]amino}ethyl) -N\(\alpha\)-(methoxycarbonyl)-\(\beta\)-phenyl-L-phenylalaninamide (168 mg, 0.15 mmol), 1-chloroethyl chlorofoimate (72 mg, 0.5 mmol) in 1.5 mL of 1,2-dichloroethane was stirred overnight at reflux. The solvent was evaporated, the residue was re-dissolved in MeOH and the mixture was refluxed for 1 hour. MeOH was evaporated and the residue containing compound the deprotected pyrrolidine was used for the next step without additional purification. LC-MS APCI: \(m/z\) 695.3 [M + H]+.

**EXAMPLE 1**

\(N\)-\{2-\{[(3R,4R)-4-{(4-aminophenyl)sulfonyl\}(3-methylbutyl)amino\]pyrrolidin-3-yl\}amino\}ethyl\} -N\(\alpha\)-(methoxycarbonyl)-\(\beta\)-phenyl-L-phenylalaninamide

To a mixture of \(N\\alpha\)-(methoxycarbonyl)-\(N\)-\{2-\{methyl[(3S,4R)-4-{(4-nitrophenyl)sulfonyl\}amino\}pyrrolidin-3-yl\}amino\}ethyl\} -\(\beta\)-phenyl-L-phenylalaninamide (69.5 mg, 0.1 mmol), anhydrous SnCl2 (95 mg, 0.5 mmol) in EtOAc, 1 mL of H2O was added and the mixture was stirred at reflux for 3 hours. Saturated aqueous NaHCO3 was added, and the mixture was extracted with EtOAc. The combined organic extracts were dried with Na2SO4 and evaporated. The residue was purified by preparative RP-HPLC. The collected fractions were evaporated, basified and extracted with CH2Cl2. The combined organic extracts were dried with Na2SO4 and evaporated. The residue was re-dissolved in 0.5 mL CH2Cl2 and 1-2 mL of 2N HCl in Et2O was added. The mixture was diluted with Et2O, the pellet was filtered off, washed with Et2O and dried in vacuo. 1H NMR (400 MHz, CD3OD): 0.925 and 0.945 (6H, two d, J=6.0 Hz), 1.50-1.67 (3H, m), 2.91 (3H, s), 3.07-3.30 (5H, m), 3.30-3.50 (3H, m), 3.52-3.60 (IH, m), 3.57 (3H, s), 3.84 (IH, dd, J=13.0 Hz, J=8.5 Hz), 4.27-4.36 (IH, m), 4.36 (IH, d, J=1 LOHz), 4.98 (IH, d, J=1 1.0 Hz), 4.94-5.02 (IH, m), 6.93-6.98 (2H, m), 7.17-7.24 (2H, m), 7.26-7.39 (8H, m), 7.69-7.75 (2H, m). LC-MS APCI: \(m/z\) 665.3 [M + H]+.

**EXAMPLE 11**

\(N\)-\{2-\{[(3R,4R)-4-{[(4-(hydroxymethyl)phenyl)sulfonyl\}(3-methylbutyl)amino\]pyrrolidin-3-yl\}amino\}ethyl\} -N\(\alpha\)-(methoxycarbonyl)-\(\beta\)-phenyl-L-phenylalaninamide
A solution containing 69 mg (0.1 mmol) of the ester substrate shown above (prepared as described in Example 1, except methyl 4-chlorosulfonilbenzoate was employed in place of 4-nitrobenzenesulfonil chloride) dissolved in 1 mL of THF was treated with 2M LiBH4 (1 eq) at room temperature for 8 hours. The mixture was quenched with H2O, extracted with EtOAc, the combined extracts were dried with Na2SO4 and evaporated giving the crude alcohol which was purified by preparative RP-HPLC to afford the title compound. 1H NMR (400 MHz, CD3OD): 0.92 (2 x d, 2 x 3H, J=6.3 Hz), 1.48-1.61 (m, 3H), 2.06-2.09 (m, 2H), 3.16-3.20 (m, IH), 3.22-3.28 (m, 2H), 3.42-3.50 (m, 2H), 3.57 (s, 3H), 3.80-3.85 (m, IH), 4.11-4.14 (m, IH), 4.34 (d, IH, J=1.2 Hz), 4.73 (s, 3H), 4.91 (d, IH, J=1.2 Hz), 7.19-7.22 (m, 2H), 7.27-7.37 (m, 8H), 7.64 (d, 2H, J=8.3 Hz), 7.93 (d, 2H, J=8.3 Hz). LC-MS APCI: m/z 666.1 [M + H]+.

EXAMPLE 12

N-{3-[3*i*]-4*}-(4-[aminophenyl)sulfonyl][3-methylbutyl] amino) pyrrolidin-3-yl)propyl}-Nα-(methoxycarbonyl)-β-phenyl-L-phenylalaninamide

Step 1 Benzyl (3*S*,4R*)-1-(rer/-butoxycarbonyl)-4-(ethoxycarbonyl)pyrrolidin-3-ylcarbamate

A mixture of (3*S*,4S*)-1-(rer/-butoxycarbonyl)-4-(ethoxycarbonyl)pyrrolidine-3-carboxylic acid (see Example 12, Step 2) (7.01 g, 24.4 mmol), benzyl alcohol (3.16 g, 29.15 mmol), diphenylphosphoryl azide (8.06 g, 29.3 mmol) and DIPEA (3.76 g, 29.15 mmol) in
Toluene (320 mL) was stirred at 80°C for 15 hours. The toluene was partially evaporated, water was added and the mixture was extracted with CHCl₃. The combined organic extracts were dried with Na₂SO₄ and evaporated. The residue was purified by column chromatography on silica gel eluting with 5 → 15% MeOH in CHCl₃ giving the title product.

**Step 2** Benzyl (3S*,4R*)-1-(tert-butoxycarbonyl)-4-formylpyrrolidin-3-ylcarbamate

To a solution of benzyl (3S*,4R*)-1-(tert-butoxycarbonyl)-4-(ethoxycarbonyl)pyrrolidin-3-ylcarbamate (4.4 g, 11.2 mmol) in 150 mL THF, LJBH₄ (0.74 g, 33.6 mmol) was added and the mixture was stirred at 80°C for 1.5 hours. The mixture was quenched with H₂O, extracted with EtOAc, the combined organic extracts were dried with Na₂SO₄ and evaporated. The residue was re-dissolved in 300 mL CH₂Cl₂, activated Mnθ₂ (3.86 g, 56 mmol) was added and the mixture was stirred for 24 hours at room temperature. Mnθ₂ was filtered off through Celite, and the filtrate was evaporated giving the title aldehyde.

**Step 3** Benzyl (3S*,4R*)-1-(tert-butoxycarbonyl)-4-((E)-2-(methoxycarbonyl)vinyl)pyrrolidin-3-ylcarbamate

A mixture of benzyl (3S*,4R*)-1-(tert-butoxycarbonyl)-4-formylpyrrolidin-3-ylcarbamate (1.71 g, 4.9 mmol) and methyl (triphenylphosphoranylidene)acetate (1.97 g, 5.9 mmol) in 100 mL benzene was stirred at reflux for 1.5 hours. Benzene was partially evaporated and the residue was purified by column chromatography on silica gel eluting with 5 → 25% EtOAc in hexane to give the title compound.

**Step 4** Benzyl (3S*,4R*)-1-(tert-butoxycarbonyl)-4-(3-hydroxypropyl)pyrrolidin-3-ylcarbamate
To a solution of benzyl (3S*,4R*)-l-(/m-butoxycarbonyl)-4-((E)-2-(methoxycarbonyl)vinyl) pyrrolidin-3-ylcarbamate (1.0 g, 2.47 mmol) in 100 mL THF, LiBH4 was added (0.2 g, 9.0 mmol) and the mixture was stirred at reflux for 9 hours. The mixture was quenched with H2O, extracted with EtOAc, the combined organic extracts were dried with Na2SO4 and evaporated. The residue was purified by column chromatography on silica gel eluting with 10 → 50% EtOAc in hexane giving the title compound.

Step 5 (3S*,4R*)-tert-Butyl 3-amino-4-(3-hydroxypropyl)pyrrolidine-l-carboxylate

Benzyl (3S*,4R*)-l-(t-rr-butoxycarbonyl)-4-(3-hydroxypropyl)pyrrolidin-3-ylcarbamate (0.98 g, 2.59 mmol) was hydrogenated over 10% Pd/C (0.05 g) in MeOH for 3 hours at ambient pressure. The catalyst was filtered off and the solvent was evaporated giving the title compound.

Step 6 tert-Butyl (3R,4S)-3-(3-hydroxypropyl)-4-[[4-nitrophenyl)sulfonyl] amino] pyrrolidine-1-carboxylate

A mixture of (3S*,4R*)-tert-butyl 3-amino-4-(3-hydroxypropyl)pyrrolidine-l-carboxylate (0.55 g, 2.25 mmol) and p-nitrophenylsulfonyl chloride (0.50 g, 2.25 mmol) and Na2CO3 (0.29 g, 2.70 mmol) in 8 mL THF-water, 3:1, was stirred overnight at room temperature. THF was evaporated, the mixture was diluted with H2O, extracted with CH2Cl2, the combined organic extracts were dried with Na2SO4 and evaporated. The residue was
purified by column chromatography on silica gel eluting with 1 → 5% MeOH in CH2C12 giving the title compound.

Step 7  **tert-Butyl Q R**,4S**) -3-(3-hydroxypropyl)-4-{(3-methylbutyl)[(4-nitrophenyl)sulfonyl] amino}pyrrolidine-1-carboxylate

![Chemical Structure](image)

To a mixture of tert-butyl (3R*,4S*)-3-(3-hydroxypropyl)-4-{[(4-nitrophenyl)sulfonyl] amino} pyrrolidine-1-carboxylate (0.82 g, 1.91 mmol) and 1-bromo-3-methylbutane (0.30 g, 2.0 mmol) in 8 mL DMF, CS2CO3 (0.93 g, 2.86 mmol) was added and the mixture was stirred at 3.5 hours at 85°C. The mixture was diluted with H2O, extracted with CH2C12. The combined organic extracts were dried with Na2SO4 and evaporated. The residue was purified by column chromatography on silica gel eluting with 1 → 5% MeOH in CH2C12 giving the title compound.

Step 8  **tert-Butyl Q R**,4S**) -3-(3-azidopropyl)-4-{(3-methylbutyl)[(4-nitrophenyl)sulfonyl] amino}pyrrolidine-1-carboxylate

![Chemical Structure](image)

To a solution of tert-butyl (3R*,4S*)-3-(3-hydroxypropyl)-4-{[(3-methylbutyl)[(4-nitrophenyl)sulfonyl] amino} pyrrolidine-1-carboxylate (0.88 g, 1.76 mmol) and Et3N (0.27 g, 2.64 mmol) in 15 mL CH2C12, MsCl (0.24 g, 2.11 mmol) was added dropwise in 5 mL CH2C12 at room temperature. The mixture was stirred for 3 hours at room temperature and poured into saturated NH4Cl. The organic phase was separated and the aqueous phase was extracted with CH2C12. The combined organic extracts were dried with Na2SO4 and evaporated. The residue
was re-dissolved in 2 mL DMSO, sodium azide was added (180 mg, 2.76 mmol) and the mixture was stirred at room temperature for 1 hour. The mixture was diluted with H2O, extracted with CH2Cl2, the combined organic extracts were dried with Na2SO4 and evaporated. The residue was purified by column chromatography on silica gel eluting with 1 → 5% MeOH in CH2Cl2 giving the title compound.

Step 9  \( \text{}\text{L-Butyl (3}^R,4^S\text{)}\text{-3-(3-aminopropyl)}\text{-4-(3-methylbutyl)}\text{-[4-nitrophenyl)sulfonyl]}\text{-amino} \text{pyrrolidine-1-carboxylate} \)

To a solution of tert-butyl (3\(^R\),4\(^S\))-3-(3-azidopropyl)-4-(3-methylbutyl)[(4-nitrophenyl)sulfonyl] amino]pyrrolidine-1-carboxylate (0.55 g, 1.05 mmol) in toluene (50 mL), PPI13 (0.28 g, 1.05 mmol) was added and the mixture was heated at reflux for 1.5 hours. The mixture was diluted with 10 mL THF, H2O was added (28 mg, 1.57 mmol) and the reaction was heated at reflux for additional 1.5 hours. The solvents were evaporated and the residue was purified by column chromatography on silica gel eluting with 5 → 10% MeOH in CH2Cl2 giving the title compound.

Step 10  \( \text{N-alpha-(methoxycarbonyl) -beta-phenyl-L-phenylalaninamide} \)
A mixture of tert-buty\(3R^*,4S^*\)-3-(3-aminopropyl)-4-{(3-methylbutyl)[(4-nitrophenyl)sulfonyl]amino}pyrrolidine-1-carboxylate (390 mg, 0.78 mmol), saturated aqueous NaHCO\(3\) (0.5 mL), and Moc-diPhe-HSu (310 mg, 0.789 mmol) in acetone-THF, 1:1, was stirred 2 hours at room temperature. The mixture was quenched with water, and the product was extracted with CHCI\(_3\). The combined organic extracts were dried with Na\(_2\)SO\(_4\) and evaporated. The residue was re-dissolved in 5 mL EtOAc, anhydrous SnCl\(_2\) (321 mg, 1.70 mmol) and H\(_2\)O (61 \(\mu\)L, 3.40 mmol) were added and the mixture was stirred at reflux for 2 hours. Saturated aqueous NaHCO\(3\) was added following by addition of water, the mixture was extracted with EtOAc, the combined organic extracts were dried with Na\(_2\)SO\(_4\) and evaporated. The residue was purified by column chromatography on silica gel eluting with 10-15% MeOH in CHCI\(_3\).

**ASSAY EXAMPLE 1**

**Assay for Inhibition of Microbial Expressed HIV Protease**

Inhibition studies of the reaction of the protease (which was expressed in *Eschericia coli*) with a peptide substrate [Val-Ser-Gln-Asn-(betanaphthyl)Ala-Pro-Ile-Val] (SEQ ID NO: 1). The inhibitor is first preincubated with the enzyme in assay buffer (50mM sodium...
acetate, pH 5.5, 100mM NaCl, and 0.1% BSA) for 30 minutes at room temperature. Substrate is added to 440 micromolar in a total volume of 80 microliters containing 5 picomolar HIV-I protease, and the reaction is incubated for 1 hour at 30°C. The reaction is quenched by addition of 120 microliters of 10% phosphoric acid, and product formation is determined after separation of product and substrate on a Vydac C18 column connected to an Alliance high performance liquid chromatography system (Waters Corporation). The extent of inhibition of the reaction is determined from the peak area of the products. HPLC of the products, independently synthesized, proved quantitation standards and confirmation of the product composition. Representative compounds of the present invention exhibit inhibition of HTV-I protease in this assay. For example, as shown by their IC50 values in Table B below, the compounds set forth in the foregoing Examples exhibit inhibition against the wild-type HIV-I protease enzyme.

ASSAY EXAMPLE 2

Assay for inhibition of HIV replication

Assays for the inhibition of acute HFV infection of T-lymphoid cells were conducted in accordance with Vacca, J.P. et al., Proc. Natl Acad. Sci. USA 1994, 91: 4096. Representative compounds of the present invention exhibit inhibition of HIV replication in this assay (also referred to herein as the "Spread Assay"). For example, as shown by their IC95 values in Table B below, the compounds set forth in the foregoing Examples were tested in this assay and found to exhibit inhibition of HTV-I replication.

ASSAY EXAMPLE 3

Cytotoxicity

Cytotoxicity was determined by microscopic examination of the cells in each well in the spread assay, wherein a trained analyst observed each culture for any of the following morphological changes as compared to the control cultures: pH imbalance, cell abnormality, cytostatic, cytopathic, or crystallization (i.e., the compound is not soluble or forms crystals in the well). The toxicity value assigned to a given compound is the lowest concentration of the compound at which one of the above changes is observed. Representative compounds of the present invention do not exhibit cytotoxicity. For example, all of the exemplified compounds were tested in this assay and none was found to exhibit cytotoxicity.

Table B

<table>
<thead>
<tr>
<th>Example No.</th>
<th>Enzyme Inhibition -</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IC50 (nM)</td>
</tr>
<tr>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>2</td>
<td>0.055</td>
</tr>
<tr>
<td>3</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>IC95 (nM)</td>
</tr>
<tr>
<td></td>
<td>495</td>
</tr>
<tr>
<td></td>
<td>423</td>
</tr>
<tr>
<td></td>
<td>472</td>
</tr>
</tbody>
</table>
1. No cytotoxicity was observed for any of these compounds in the cytotoxicity assay set forth in Assay Example 3 up to a concentration of 10 µM.

2. Conducted using 10% FBS.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, the practice of the invention encompasses all of the usual variations, adaptations and/or modifications that come within the scope of the following claims. All publications, patents and patent applications cited herein are incorporated by reference in their entireties into the disclosure.
WHAT IS CLAIMED IS:

1. A compound of Formula I:

\[ \text{(I)} \]

or a pharmaceutically acceptable salt thereof, wherein:

A is N-R₁ or CH-R₁;

B is N-R₂ or CH-R₂;

R₁ is H, C₁-6 alkyl, C₁-6 fluoroalkyl, C₃-6 cycloalkyl, C₁-6 alkyl substituted with C₃-6 cycloalkyl, or C₁-6 alkyl substituted with AryA;

R₂ is H, C₁-6 alkyl, C₁-6 fluoroalkyl, C₃-6 cycloalkyl, C₁-6 alkyl substituted with C₃-6 cycloalkyl, C₁-6 alkyl substituted with AryB, C(O)-C₁-6 alkyl, or SO₂-C₁-6 alkyl;

R₃A is H, C₁-6 alkyl, C₁-6 fluoroalkyl, C₁-5 cycloalkyl, or C₁-6 alkyl substituted with C₁-5 cycloalkyl;

R₃B is H or C₁-6 alkyl;

each Xₐ is independently:

(1) C₁-6 alkyl,
(2) C₃-6 cycloalkyl,
(3) C₁-6 haloalkyl,
(4) OH,
(5) O-C₁-6 alkyl,
(6) O-C₁-6 haloalkyl,
(7) O-C₃-6 cycloalkyl,
(8) SH,
(9) S-C₁-6 alkyl,
(10) S-C₁-6 haloalkyl,
(11) S-C₃-6 cycloalkyl,
halo,
CN,
NO₂,
NH₂,
N(H)-C 1-6 alkyl,
N(-Ci-6 alkyl)₂,
N(H)C(O)-Cl-6 alkyl,
N(H)CH(O),
CH(O),
C(O)-C 1-6 alkyl,
C(O)OH,
C(O)O-C 1-6 alkyl,
SO₂H,
SO₂-C 1-6 alkyl, or
Ci-6 alkyl substituted with:
(a) Q3-6 cycloalkyl,
(b) Ci-6 haloalkyl,
(c) OH,
(d) O-Ci-6 alkyl,
(e) O-Ci-6 haloalkyl,
(f) O-C3-6 cycloalkyl,
(g) SH,
(h) S-C 1-6 alkyl,
(i) S-Ci-6 haloalkyl,
(j) S-C3-6 cycloalkyl,
(k) halo,
CN,
NO₂,
NH₂,
N(H)-C 1-6 alkyl,
N(-Cl-6 alkyl)₂,
N(H)C(O)-Cl-6 alkyl,
N(H)CH(O),
CH(O),
C(O)-C 1-6 alkyl,
C(O)OH,
C(O)O-C 1-6 alkyl,
SO₂H, or
(X) \( \text{SO}_2\text{-C} \ 1-6 \text{ alkyl}; \)

or, alternatively, when two or more XA substituents are present on the phenyl ring and two of the XA are attached to adjacent carbon atoms of the phenyl ring, the two XA are optionally taken together with the carbon atoms to which they are attached to form a 5- or 6-membered, saturated or unsaturated heterocycle fused to the phenyl ring, wherein the heterocycle contains from 1 to 2 heteroatoms independently selected from N, O and S;

\( k \) is an integer equal to 0, 1, 2, or 3;

\( R^4 \) js:

\[
\begin{align*}
(X^C)_n & \quad (X^B)_m \\
(X^C)_n & \quad (X^B)_m
\end{align*}
\]

\( \text{or} \)

\[
\begin{align*}
(X^C)_n & \quad (X^B)_m \\
(X^C)_n & \quad (X^B)_m
\end{align*}
\]

wherein the asterisk (*) denotes the point of attachment to the rest of the compound;

each XB and each XC are independently selected from the group consisting of:

(1) \( \text{C}i-6 \text{ alkyl}, \)
(2) \( \text{C}3-6 \text{ cycloalkyl}, \)
(3) \( \text{C}i-6 \text{ haloalkyl}, \)
(4) OH,
(5) O-C1-6 alkyl,
(6) O-C1-6 haloalkyl,
(7) O-C3-6 cycloalkyl,
(8) SH,
(9) S-C1-6 alkyl,
(10) S-C1-6 haloalkyl,
(H) S-C3-6 cycloalkyl,
(12) halo,
(13) CN,
(14) NO\(_2\).
(15) \( \text{NH}_2 \),
(16) \( \text{N(H-)} \text{C} \text{-6 alkyl} \),
(17) \( \text{N(-)} \text{C} \text{-6 alkyl} \),
(18) \( \text{N(H)} \text{C(O-)} \text{C} \text{-6 alkyl} \),
(19) \( \text{N(H)} \text{CH(O)} \),
(20) \( \text{CH(O)} \),
(21) \( \text{C(O-)} \text{C} \text{-6 alkyl} \),
(22) \( \text{C(O)} \text{OH} \),
(23) \( \text{C(O)} \text{O-C} \text{-6 alkyl} \),
(24) \( \text{SO}_2 \text{H} \),
(25) \( \text{SO}_2 \text{-C} \text{-6 alkyl} \); and
(26) \( \text{C} \text{l-6 alkyl substituted with:} \)
   (a) \( \text{C} \text{-6 haloalkyl} \),
   (b) \( \text{OH} \)
   (c) \( \text{O-C} \text{-6 alkyl} \),
   (d) \( \text{O-C} \text{-6 haloalkyl} \),
   (e) \( \text{O-C3.6 cycloalkyl} \),
   (f) \( \text{SH} \),
   (g) \( \text{S-C} \text{-6 alkyl} \),
   (h) \( \text{halo} \),
   (i) \( \text{CN} \),
   (j) \( \text{NO}_2 \),
   (k) \( \text{NH}_2 \),
   (l) \( \text{N(H-C} \text{-6 alkyl} \),
   (m) \( \text{N(-)} \text{C} \text{-6 alkyl} \),
   (n) \( \text{C(O-)} \text{C} \text{-6 alkyl} \),
   (o) \( \text{C(O)} \text{OH} \),
   (p) \( \text{C(O)} \text{O-C} \text{-6 alkyl} \), or
   (q) \( \text{SO}_2 \text{-C} \text{-6 alkyl} \);

\( m \) is an integer equal to 0, 1, 2, or 3;

\( n \) is an integer equal to 0, 1, 2, or 3;

\( R5 \) is \( \text{H, C} \text{-6 alkyl, C3-6 cycloalkyl, C} \text{-6 alkyl substituted with C3-6 cycloalkyl, or C(O)-RK;} \)

\( \text{RK is:} \)
   (1) \( \text{C} \text{-6 alkyl} \),
(2) C3-6 cycloalkyl,
(3) Ci-6 alkyl substituted with C3-6 cycloalkyl,
(4) O-Ci-6 alkyl,
(5) O-C 1-6 alkyl substituted with O-C 1-6 alkyl,
(6) O-C 1-6 fluoroalkyl,
(7) C(O)O-C 1-6 alkyl,
(8) C 1-6 alkyl substituted with C(O)O-C 1-6 alkyl,
(9) C 1.6 alkyl substituted with C(O)OH,
(10) C 1.6 alkyl substituted with C(O)-C 1-6 alkyl,
(11) N(H)-C 1-6 alkyl, 
(12) N(-Ci-6 alkyl)2,
(13) Ci-6 alkyl substituted withNH2, N(H)-Ci-6 alkyl, or N(-Ci-6 alkyl)2,
(14) AryC,
(15) C 1.6 alkyl substituted with AryC,
(16) O-C 1-6 alkyl substituted with AryC,
(17) HetA,
(18) C 1-6 alkyl substituted with HetA,
(19) O-C 1-6 alkyl substituted with HetA,
(20) HetB, or
(21) O-HetB;

AryA is an aryl which is independently phenyl or naphthyl, wherein the phenyl or naphthyl is optionally substituted with from 1 to 4 YA wherein each YA independently has the same definition as XB;

AryB is an aryl which is independently phenyl or naphthyl, wherein the phenyl or naphthyl is optionally substituted with from 1 to 4 YA wherein each YA independently has the same definition as XB;

AryC is an aryl which is independently phenyl or naphthyl, wherein the phenyl or naphthyl is optionally substituted with from 1 to 4 YB wherein each YB independently has the same definition as XB;

HetA is a heteroaryl which is independently (i) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, or (ii) is a heterobicyclic ring selected from quinolinyl, isoquinolinyl, and quinoxalinyl; wherein the heteroaromatic ring (i) or the bicyclic ring (ii) is optionally substituted with from 1 to 4 YC wherein each YC independently has the same definition as XB; and
HetB is independently a 4- to 7-membered, saturated or unsaturated, non-aromatic heterocyclic ring containing at least one carbon atom and from 1 to 4 heteroatoms independently selected from N, O and S, where each S is optionally oxidized to S(O) or S(O)2, and wherein the saturated or unsaturated heterocyclic ring is optionally substituted with from 1 to 4 substituents each of which is independently halogen, CN, C1-6 alkyl, OH, oxo, O-Cj-6 alkyl, C1-6 haloalkyl, O-Ci-6 haloalkyl, C(0)NH2, C(0)N(H)-Ci-6 alkyl, C(O)N(-Ci-6 alkyl)2, C(O)H, C(O)-Ci-6 alkyl, CO2H, CO2-C1-6 alkyl, SO2H, or SO2-C1-6 alkyl.

2. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein

R1 is C1-6 alkyl or C1-6 alkyl substituted with AryA;

R2 is H, C1-6 alkyl, Cj-6 alkyl substituted with AryB, C(0)-Cj-6 alkyl, or SO2-C1-6 alkyl;

R3A is H or Cj-6 alkyl;

R3B is H or Cj-6 alkyl;

R4 is:

\[
\begin{align*}
(X^B)_m & \quad \begin{array}{c}
\text{or}
\end{array} \\
(X^C)_n & \\
(X^B)_m
\end{align*}
\]

each XB and each XC are independently selected from the group consisting of:

(1) Ci-3 alkyl,
(2) cyclopropyl,
(3) CF3,
(4) OH,
(5) O-Ci-3 alkyl,
(6) OCF3,
(7) Cl,
(8) Br,
(9) F,
(10) CN,
(H) NO₂,
(12) NH₂,
(13) N(H)-Ci. 3 alkyl,
(14) N(-Ci-3 alkyl)₂,
(15) C(O)-Ci-3 alkyl,
(16) CO₂H,
(17) C(O)O-C 1-3 alkyl,
(18) CH₂OH, and
(19) CH₂O-Ci-3 alkyl;

m is an integer equal to 0, 1, or 2;

n is an integer equal to 0, 1, or 2;

each XA is independently:

(D) Ci-3 alkyl,
(2) cyclopropyl,
(3) CF₃,
(4) OH,
(5) O-Ci-3 alkyl,
(6) OCF₃,
(7) Cl,
(8) Br,
(9) F,
(10) CN,
(H) NO₂,
(12) NH₂,
(13) N(H)-C 1-3 alkyl,
(14) N(-Ci-3 alkyl)₂,
(15) C(O)-Ci-3 alkyl,
(16) CO₂H,
(17) C(O)O-C 1-3 alkyl, or
(18) C 1-3 alkyl substituted with
   (a) cyclopropyl,
   (b) CF₃,
   (c) OH,
   (d) O-C 1-3 alkyl,
   (e) OCF₃,
(0) Cl,
(g) Br,
(h) F,
(i) CN,
(k) NO₂,
(l) NH₂,
(m) N(-Ci-3 alkyl)₂,
(n) C(O)-Ci-3 alkyl,
(o) CO₂H, or
(P) C(O)O-Ci-3 alkyl;

k is an integer equal to 0, 1, or 2;

or, alternatively, when two XA substituents are present on the phenyl ring and the two XA are attached to adjacent carbon atoms of the phenyl ring, the two XA are optionally taken together with the carbon atoms to which they are attached to form a 5- or 6-membered, saturated or unsaturated heterocycle fused to the phenyl ring, wherein the heterocycle contains from 1 to 2 heteroatoms independently selected from N, O and S;

R5 is H, Ci-6 alkyl, C(O)-Ci-6 alkyl, C(O)O-Ci-6 alkyl, C(0)N(-Ci-6 alkyl)₂, C(O)-HetA, C(O)OCH₂-HetA, C(O)-HetB, or C(O)O-HetB;

AryA is phenyl which is optionally substituted with from 1 to 3 substituents each of which is independently C1.3 alkyl, CF₃, OH, O-Ci-3 alkyl, OCF₃, Cl, Br, F, CN, NH₂, N(H)-Ci-3 alkyl, N(-Ci-3 alkyl)₂, C(O)-Cj.3 alkyl, CO₂H, C(O)O-Ci-3 alkyl, CH₂OH, CH₂O-Cj.3 alkyl, C(O)-Ci-3 alkyl, or SO₂-Ci-3 alkyl;

HetA is a heteroaryl selected from the group consisting of pyrrolyl, imidazolyl, pyridyl, pyrazinyl, quinolyl, isoquinolyl, and quinoxalinyl, wherein the heteroaryl is optionally substituted with from 1 to 3 substituents each of which is independently Ci-3 alkyl, CF₃, OH, O-Ci-3 alkyl, OCF₃, Cl, Br, F, CN, NH₂, N(H)-Ci-3 alkyl, N(Ci-3 alkyl)₂, C(0)-Ci-3 alkyl, CO₂-Ci-3 alkyl, or SO₂-Ci-3 alkyl; and

HetB is a saturated heterocyclic ring selected from the group consisting of tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, and thiomorpholinyl in which the S is optionally oxidized to S(O) or S(O)₂, and wherein the ring is optionally substituted with 1 or 2
substituents each of which is independently C1-3 alkyl, oxo, C(O)N(C1.3 alkyl)2, C(O)-C1.3 alkyl, CO2-C1-3 alkyl, or S(O)2-C1-3 alkyl.

3. The compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein:

R1 is CH3, CH2CH3, CH(CH3)2, CH2CH2CH3, CH2CH(CH3)2, CH2CH2CH2CH(CH3)2, or CH2CH2CH2CH2CH(CH3)2;

R2 is H or CH3;

R3A is H, CH3, CH2CH3, CH(CH3)2, CH2CH2CH3, CH2CH(CH3)2, C(CH3)3, CH2CH2CH2CH(CH3)2, or CH2CH2CH2CH2CH(CH3)2;

R3B is H or CH3;

each Xβ and each Xα are independently selected from the group consisting of:

(1) CH3,
(2) CH2CH3,
(3) CF3,
(4) OH,
(5) OCH3,
(6) OCF3,
(7) Cl,
(8) Br,
(9) F,
(10) CN,
(11) NH2,
(12) N(H)CH3,
(13) N(CH3)2,
(14) C(O)CH3,
(15) C(O)OCH3,
(16) CH2θ H, and
(17) CH2θ CH3;

each Xα is independently:

(1) CH3,
(2) CH2CH3,
(3) CF₃,
(4) OH,
(5) OCH₃,
(6) OCF₃,
(7) Cl,
(8) Br,
(9) F,
(10) CN,
(11) NH₂,
(12) N(H)CH₃,
(13) N(CH₃)₂,
(14) C(O)CH₃,
(15) C(O)OCH₃,
(16) CH₂OH,
(17) CH₂OCH₃,
(18) CH₂NH₂,
(19) CH₂N(H)CH₃,
(20) CH₂N(CH₃)₂,
(21) CH(CH₃)OH,
(22) CH(CH₃)OCH₃,
(23) CH(CH₃)NH₂,
(24) CH(CH₃)N(H)CH₃, or
(25) CH(CH₃)N(CH₃)₂;

or, alternatively, when two XA substituents are present on the phenyl ring and the two XA are attached to adjacent carbon atoms of the phenyl ring, the two XA are optionally taken together with the carbon atoms to which they are attached to form a 5- or 6-membered, saturated or unsaturated heterocycle fused to the phenyl ring, wherein the heterocycle contains from 1 to 2 heteroatoms independently selected from N, O and S; and

R₅ is H, CH₃, C(O)CH₃, C(O)OCH₃, C(O)OC(CH₃)₃, C(O)N(CH₃)₂, C(O)-morpholinyl, C(O)-pyridyl, or C(O)-O-CH₂-pyridyl.

The compound according to claim 3, or a pharmaceutically acceptable salt thereof, wherein:

R₄ is:
there are 1 or 2 XA groups on the phenylsulfonyl moiety wherein one XA is in the para position on the phenyl ring and is CH3, Cl, Br, F, NH2, CH2NH2, C(O)CH3, CH2OH, or CH(CH3)OH; and the other, optional XA is in the meta position on the phenyl ring and is Cl, Br, or F;

or, alternatively, when two XA substituents are present on the phenyl ring and the two XA are attached to adjacent carbon atoms, the two XA are optionally taken together with the carbon atoms to which they are attached to form -OCH2O- or -OCH2CH2O-; and

R5 is H, CH3, C(O)OCH3, C(O)OC(CH3)3, or C(O)O-CH2-pyridyl.

5. The compound according to any one of claims 1 to 4, which is a compound of Formula II:

or a pharmaceutically acceptable salt thereof.

6. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

A is N-R1;

B is N-R2;

R1 is C3-6 alkyl or CH2-AryA;
R2 is H or Cl-6 alkyl;

R3A is H or C1-6 alkyl;

R3B is H or Cl-6 alkyl;

R4 is:

\[
\begin{array}{c}
\text{(X_B)^m} \\
\text{(X_C)^n}
\end{array}
\]

each XB and each XC are independently selected from the group consisting of:

0) Cl₃ alkyl,  
(1) cyclopropyl,  
(2) CF₃,  
(3) OH,  
(4) O-Ci-3 alkyl,  
(5) OCF₃,  
(6) Cl,  
(7) Br,  
(8) F,  
(9) CN,  
(10) NO₂,  
(11) NH₂,  
(12) N(H)-C\text{-Cl}_3 .3 alkyl,  
(13) N(-Ci-3 alkyl)₂,  
(14) C(O)-Ci-3 alkyl,  
(15) CO₂H,  
(16) C(O)O-Ci-3 alkyl,  
(17) CH₂OH, and  
(18) CH₂O-Ci-3 alkyl;

m is an integer equal to 0, 1, or 2;

n is an integer equal to 0, 1, or 2;

each XA is independently:
(D) Cl-3 alkyl,
(2) cyclopropyl,
(3) CF₃,
(4) OH,
(5) O-Ci-3 alkyl,
(6) OCF₃,
(7) Cl,
(8) Br,
(9) F,
(10) CN,
(H) NO₂,
(12) NH₂,
(13) N(H)-Ci-3 alkyl,
(14) N(-Cl-3 alkyl)₂,
(15) C(O)-C] 3 alkyl,
(16) CO₂H,
(17) C(O)O-C 1-3 alkyl, or
(18) Cl-3 alkyl substituted with
(a) cyclopropyl,
(b) CF₃,
(c) OH,
(d) O-Cl-3 alkyl,
(e) OCF₃,
(f) Cl₁,
(g) Br₁,
(h) F,
(i) CN,
(o) NO₂,
(k) NH₂,
(o) N(H)-C 1-3 alkyl,
(m) N(-Ci-3 alkyl)₂,
(n) C(O)-C 1-3 alkyl,
(o) CO₂H, or
(p) C(O)O-C 1-3 alkyl;

k is an integer equal to 0, 1, or 2;
or, alternatively, when two XA substituents are present on the phenyl ring and the two XA are attached to adjacent carbon atoms of the phenyl ring, the two XA are optionally taken together with the carbon atoms to which they are attached to form a 5- or 6-membered, saturated or unsaturated heterocycle fused to the phenyl ring, wherein the heterocycle contains from 1 to 2 heteroatoms independently selected from N, O and S;

R5 is C(O)O-C1-6 alkyl; and

AryA is phenyl which is optionally substituted with from 1 to 3 substituents each of which is independently C1.3 alkyl, CF3, OH, O-C1-3 alkyl, OCF3, Cl, Br, F, CN, NH2, N(H)-Cj.3 alkyl, N(-Cj-3 alkyl)2, C(O)-Cj-3 alkyl, CO2H, C(O)O-Cj-3 alkyl, CH2OH, CH2O-CL alkyl, C(O)-Q-3 alkyl, or SO2-C1.3 alkyl.

7. The compound according to claim 6, or a pharmaceutically acceptable salt thereof, wherein:

R1 is CH(CH3)2, CH2CH2CH3, CH2CH(CH3)2, CH2CH2CH(CH3)2, or benzyl;

R2 is H or CH3;

R3A is H, CH3, CH2CH3, CH(CH3)2, CH2CH2CH3, CH2CH2CH(CH3)2, C(CH3)3, CH2CH2CH(CH3)2, or CH2CH2CH2CH(CH3)2

R3B is H or CH3;

each XB and each XC are independently selected from the group consisting of:

(1) CH3,
(2) CH2CH3,
(3) CF3,
(4) OH,
(5) OCH3,
(6) OCF3,
(7) Cl,
(8) Br,
(9) F,
(10) CN,
(11) NH2,
(12) N(H)CH₃,
(13) N(CH₃)₂,
(14) C(O)CH₃,
(15) C(O)OCH₃,
(16) CH₂OH, and
(17) CH₂OCH₃;

m is an integer equal to 0, 1, or 2;

n is an integer equal to 0, 1, or 2;

each Xᵢ is independently:

(1) CH₃,
(2) CH₂CH₃,
(3) CF₃,
(4) OH,
(5) OCH₃,
(6) OCF₃,
(7) Cl,
(8) Br,
(9) F,
(10) CN,
(11) NH₂,
(12) N(H)CH₃,
(13) N(CH₃)₂,
(14) C(O)CH₃,
(15) C(O)OCH₃,
(16) CH₂OH,
(17) CH₂OCH₃,
(18) CH₂NH₂,
(19) CH₂N(H)CH₃,
(20) CH₂N(CH₃)₂,
(21) CH(CH₃)OH,
(22) CH(CH₃)OCH₃,
(23) CH(CH₃)NH₂,
(24) CH(CH₃)N(H)CH₃, or
(25) CH(CH₃)N(CH₃)₂;

k is an integer equal to 0, 1, or 2;
or, alternatively, when two XA substituents are present on the phenyl ring and the two XA are attached to adjacent carbon atoms of the phenyl ring, the two XA are optionally taken together with the carbon atoms to which they are attached to form a 5- or 6-membered, saturated or unsaturated heterocycle fused to the phenyl ring, wherein the heterocycle contains from 1 to 2 heteroatoms independently selected from N, O and S; and

R5 is C(O)OCH3 or C(O)OC(CH3)3-

8. The compound according to claim 7, or a pharmaceutically acceptable salt thereof, wherein:

R1 is CH(CH3)2, CH2CH(CH3)2, CH2CH2CH(CH3)2, or CH2CH2CH2CH(CH3)2;

either (i) R3A i, H, CH3, CH2CH3, CH(CH3)2, CH2CH2CH3, CH2CH3, CH(CH3)3,
CH2CH2CH(CH3)2, or CH2CH2CH2CH(CH3)2, and R3B i, H; or (ii) R3A and R3B are both CH3;

R4 is:

there are 1 or 2 XA groups on the phenylsulfonyl moiety wherein one XA is in the para position on the phenyl ring and is CH3, Cl, Br, F, NH2, CH2NH2, C(O)CH3, CH2OH, or CH(CH3)OH; and the other, optional XA is in the meta position on the phenyl ring and is Cl, Br, or F;

or, alternatively, when two XA substituents are present on the phenyl ring and the two XA are attached to adjacent carbon atoms, the two XA are optionally taken together with the carbon atoms to which they are attached to form -OCH2O- or -OCH2CH2O-; and

R5 is C(O)OCH3.

9. The compound according to any one of claims 6 to 8, or a pharmaceutically acceptable salt thereof, which is a compound of Formula 111:
10. A compound selected from the group consisting of:

\[ N-(2-\{(3R,4R)-[4-\text{((4-aminophenyl)sulfonyl)(3-methylbutyl)amino}]-\text{pyrroldin-3-yl}\amino}\text{ethyl})-N\alpha-(\text{methoxycarbonyl})-\beta\text{-phenyl-L-phenylalaninamide}; \]

\[ N-\{(25)-1-\{(3R,4R)-[4-\text{((4-aminophenyl)sulfonyl)(3-methylbutyl)amino}]-\text{pyrroldin-3-yl}\amino}\text{propan-2-yl}\} \]

\[ N-\{(25)-1-\{(3R,4R)-[4-\text{((4-aminophenyl)sulfonyl)(3-methylbutyl)amino}]-\text{pyrroldin-3-yl}\amino}\text{butan-2-yl}\} \]

\[ N-\{(25)-1-\{(3R,4R)-[4-\text{((4-aminophenyl)sulfonyl)(3-methylbutyl)amino}]-\text{pyrroldin-3-yl}\amino}\text{-2-methylpropan-2-yl}\} \]

\[ N-\{(25)-1-\{(3R,4R)-[4-\text{((4-aminophenyl)sulfonyl)(3-methylbutyl)amino}]-\text{pyrroldin-3-yl}\amino}\text{ethyl}\} \]

\[ N-(3\text{-\{(3R,4R)-[4-\text{((4-aminophenyl)sulfonyl)(3-methylbutyl)amino}]-\text{pyrroldin-3-yl}\amino}\text{propyl}\}} \]

and pharmaceutically acceptable salts thereof.

11. A pharmaceutical composition comprising an effective amount of a compound according to any one of claims 1 to 10 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
12. A method for the inhibition of HTV protease, or for the treatment or prophylaxis of infection by HIV, or for the treatment, prophylaxis, or delay in the onset of AIDS in a subject in need thereof, which comprises administering to the subject an effective amount of the compound according to any one of claims 1 to 10 or a pharmaceutically acceptable salt thereof.

13. A method for the inhibition of HIV protease, or for the treatment or prophylaxis of infection by HIV, or for the treatment, prophylaxis, or delay in the onset of AIDS in a subject in need thereof, which comprises administering to the subject an effective amount of the pharmaceutical composition according to claim 11.

14. A compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, for use in the preparation of a medicament for the inhibition of HIV protease, for the treatment or prophylaxis of infection by HIV, or for the treatment, prophylaxis, or delay in the onset of AIDS in a subject in need thereof.

15. A pharmaceutical composition according to claim 11 for use in the preparation of a medicament for the inhibition of HIV protease, for the treatment or prophylaxis of infection by HIV, or for the treatment, prophylaxis, or delay in the onset of AIDS in a subject in need thereof.
A CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61 K 31/1 6; A61 K 31/1 8 (201 0.01 )
USPC - 514/613; 514/601

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- 514/613, 514/601

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC- 514/617, 514/357, 514/252 1, 514/475, 514/595 514/489, 514/378, 514/605, 546/532, 564/84 (keywords below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (USPT, PGPB, EPAB, JPAB), Google Patents/Scholar pyrrolidine core, HIV, amino pyrrolidine sulfonil, phenylalanine

C DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>SPECKER et al., Unexpected novel binding mode of pyrrolidine-based aspartyl protease inhibitors design, sunthesis and crystal structure in complex with HIV protease Chem Med Chem, January 2006, Vol 1, No 1, pp 106-1 17, pg 107, right col, para 2, pg 109, Scheme 2, pg 1 10, left col, para 5. Table 2</td>
<td>1-10</td>
</tr>
<tr>
<td>Y</td>
<td>WI 2009/042093 A1 (COBURN et al) 02 April 2009 (02 04 2009) pg 2, In 21-26, 29-30, pg 3, In 32, 34-37, pg 4, In 26, pg 5, In 33 to pg 6, In 5, pg 6, In 1-13, pg 7, In 32, 34, 36, 38, pg 8, In 1-6, pg 30, In 1-17</td>
<td>1-10</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C

D

- 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 claims/ 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
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  "Y" 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
  "&" 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
  "T" document member of the same patent family

Date of the actual completion of the international search 29 July 2010 (29 07 2010)

Date of mailing of the international search report 13 AUG 2010

Name and mailing address of the ISAJS
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Authorized officer Lee W Young
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PCT DSP 571 272 7774

Form PCT/ISA/210 (second sheet) (July 2009)
This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos. [1] because they relate to subject matter not required to be searched by this Authority, namely

2. [ ] Claims Nos. [2] because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically

3. [ ] Claims Nos. [1,15] because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims

2. [ ] As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims. It is covered by claims Nos.

Remark on Protest: [ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation

[ ] No protest accompanied the payment of additional search fees