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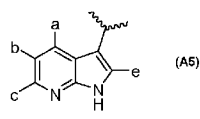
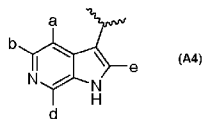
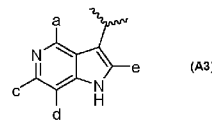
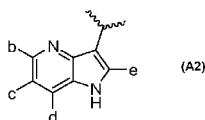
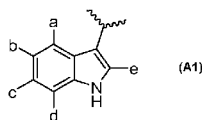
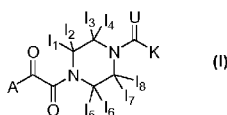
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(54) Title: THIOAMIDE, AMIDOXIME AND AMIDRAZONE DERIVATIVES AS HIV ATTACHMENT INHIBITORS



(57) Abstract: A compound of Formula (I), including pharmaceutically acceptable salts thereof: wherein A is selected from the group of Formula (A1), (A2), (A3), (A4) and (A5).



Declarations under Rule 4.17:

- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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THIOAMIDE, AMIDOXIME AND AMIDRAZONE DERIVATIVES AS HIV
ATTACHMENT INHIBITORS

CROSS REFERENCE TO RELATED APPLICATION

5 This non-provisional application claims the benefit of U.S. Provisional
Application Serial Number 61/474,324, filed April 12, 2011.

FIELD OF THE INVENTION

10 This invention provides compounds having drug and bio-affecting properties, their
pharmaceutical compositions and methods of use. In particular, the invention herein is
directed to piperazine thioamide, amidoxime and amidrazone derivatives as HIV
attachment inhibitors that possess unique antiviral activity.

BACKGROUND OF THE INVENTION

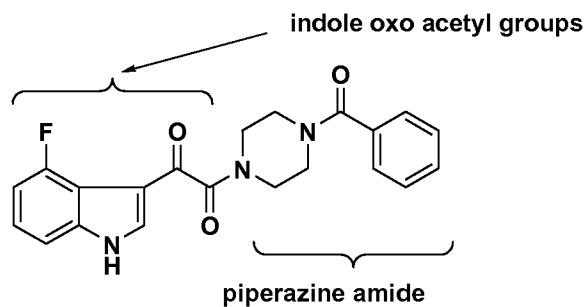
15 HIV-1 (human immunodeficiency virus -1) infection remains a major medical
problem, with an estimated 45 million people infected worldwide at the end of 2007. The
number of cases of HIV and AIDS (acquired immunodeficiency syndrome) has risen
rapidly. In 2005, approximately 5.0 million new infections were reported, and 3.1 million
people died from AIDS. Currently available drugs for the treatment of HIV include
20 nucleoside reverse transcriptase (RT) inhibitors zidovudine (or AZT or RETROVIR®),
didanosine (or VIDEX®), stavudine (or ZERIT®), lamivudine (or 3TC or EPIVIR®),
zalcitabine (or DDC or HIVID®), abacavir succinate (or ZIAGEN®), tenofovir
disoproxil fumarate salt (or VIREAD®), emtricitabine (or FTC - EMTRIVA®); non-
nucleoside reverse transcriptase inhibitors: nevirapine (or VIRAMUNE®), delavirdine (or
25 RESCRIPTOR®), efavirenz (or SUSTIVA®), etravirine (INTELENCE ®) and rilpivirine
(EDURANT ®), and peptidomimetic protease inhibitors or approved formulations:
saquinavir, indinavir, ritonavir, nelfinavir, amprenavir, lopinavir, KALETRA® (lopinavir
and Ritonavir), darunavir, atazanavir (REYATAZ®) and tipranavir (APTIVUS®), and
integrase inhibitors such as raltegravir (ISENTRISS ®), and entry inhibitors such as
30 enfuvirtide (T-20) (FUZEON ®) and maraviroc (SELZENTRY ®). Several single pill
combinations have been also approved, which include COMBIVIR® (contains
lamivudine and zidovudine), TRIZIVIR® (contains abacavir, zidovudine, and
lamivudine), Epzicom® (contains abacavir and lamivudine), TRUVADA® (contains

tenofovir disoproxil fumarate and emtricitabine), ATRIPLA® (contains efavirenz, emtricitabine and tenofovir disoproxil fumarate) and COMPLERA® (contains emtricitabine, rilpivirine, and tenofovir disoproxil fumarate).

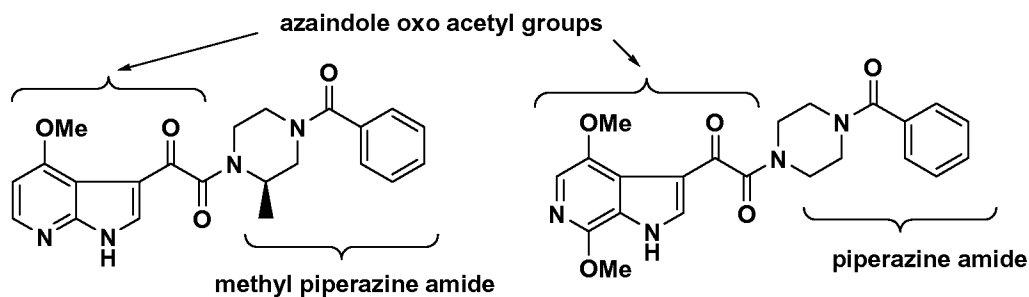
Each of these drugs can only transiently restrain viral replication if used alone.

5 However, when used in combination, these drugs have a profound effect on viremia and disease progression. In fact, significant reductions in death rates among AIDS patients have been documented as a consequence of the widespread application of combination therapy. However, despite these impressive results, 30 to 50% of patients may ultimately fail combination drug therapies. Insufficient drug potency, non-compliance, restricted
10 tissue penetration and drug-specific limitations within certain cell types (*e.g.*, most nucleoside analogs cannot be phosphorylated in resting cells) may account for the incomplete suppression of sensitive viruses. Furthermore, the high replication rate and rapid turnover of HIV-1 combined with the frequent incorporation of mutations, leads to the appearance of drug-resistant variants and treatment failures when sub-optimal drug
15 concentrations are present. Therefore, novel anti-HIV agents exhibiting distinct resistance patterns, and favorable pharmacokinetic as well as safety profiles are needed to provide more treatment options. Improved HIV fusion inhibitors and HIV entry coreceptor antagonists are two examples of new classes of anti-HIV agents further being studied by a number of investigators.

20 HIV attachment inhibitors are a novel subclass of antiviral compounds that bind to the HIV surface glycoprotein gp120, and interfere with the interaction between the surface protein gp120 and the host cell receptor CD4. Thus, they prevent HIV from attaching to the human CD4 T-cell, and block HIV replication in the first stage of the HIV life cycle. The properties of HIV attachment inhibitors have been improved in an
25 effort to obtain compounds with maximized utility and efficacy as antiviral agents. A disclosure describing indoles of which the structure shown below for BMS-705 is representative, has been disclosed (Antiviral Indoleoxoacetyl Piperazine Derivatives).

**BMS-705**

Two other compounds, referred to in the literature as BMS-806 and BMS-043 have been described in both the academic and patent art:

**BMS-806****BMS-043**

- 5 Some description of their properties in human clinical trials has been disclosed in the literature.

It should be noted that in all three of these structures, a piperazine amide (in these three structures a piperazine phenyl amide) is present and this group is directly attached to an oxoacetyl moiety. The oxoacetyl group is attached at the 3-position of 4-fluoro indole
10 in BMS-705 and to the 3 position of substituted azaindoles in BMS-806 and BMS-043.

In an effort to obtain improved anti-HIV compounds, later publications described in part, modified substitution patterns on the indoles and azaindoles. Examples of such efforts include: (1) novel substituted indoleoxoacetic piperazine derivatives, (2) substituted piperazinyloxoacetylindole derivatives, and (3) substituted azaindoleoxoacetic
15 piperazine derivatives.

Replacement of these groups with other heteroaromatics or substituted heteroaromatics or bicyclic hydrocarbons was also shown to be feasible. Examples include: (1) indole, azaindole and related heterocyclic amidopiperazine derivatives; (2) bicyclo [4.4.0] antiviral derivatives; and (3) diazaindole derivatives.

A select few replacements for the piperazine amide portion of the molecules have also been described in the art and among these examples are (1) some piperidine alkenes; (2) some pyrrolidine amides; (3) some N-aryl or heteroaryl piperazines; (4) some piperazinyl ureas; and (5) some carboline-containing compounds.

5 Method(s) for preparing prodrugs for this class of compounds are disclosed in Prodrugs of Piperazine and Substituted Piperidine Antiviral Agents (Ueda et al., U.S. Publication No. 2005/0209246 or WO 2005/090367 A1).

A published PCT patent application WO 2003/103607 A1 (June 11, 2003) discloses an assay useful for assaying some HIV inhibitors.

10 Several published patent applications describe combination studies with piperazine benzamide inhibitors, for example, U.S. Publication No. 2005/0215543 (WO 2005/102328 A1), U.S. Publication No. 2005/0215544 (WO 2005/102391 A1), and U.S. Publication No. 2005/0215545 (WO 2005/102392 A2).

15 A publication on new compounds in this class of attachment inhibitors (Wang, J. et al., *Org. Biol. Chem.*, 3:1781-1786 (2005)) and a patent application on some more remotely related compounds have appeared WO 2005/016344 published on February 24, 2005.

20 Published patent applications WO 2005/016344 and WO 2005/121094 also describe piperazine derivatives which are HIV inhibitors. Other references in the HIV attachment area include U.S. Publication Nos. 2007/0155702, 2007/0078141 and 2007/0287712, WO 2007/103456, as well as U.S. Patent Nos. 7,348,337 and 7,354,924. A literature reference is *J. Med. Chem.*, 50:6535 (2007).

What is therefore needed in the art are new HIV attachment inhibitor compounds, and compositions thereof, which are efficacious against HIV infection.

25 Of particular interest are new thioamide, amidoxime and amidrazone derivatives as HIV attachment inhibitor compounds, described herein. The compounds of the present invention are piperazine thioamide, amidoxime and amidrazone derivatives, which are believed to be structurally distinct from the piperazine aryl amide HIV attachment inhibitors set forth in the existing literature.

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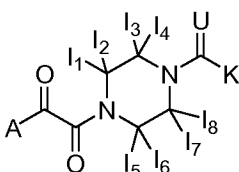
SUMMARY OF THE INVENTION

The present invention provides compounds of Formula I below, the pharmaceutically acceptable salts and/or solvates (*e.g.*, hydrates) thereof, their

pharmaceutical formulations, and their use in patients suffering from or susceptible to a virus such as HIV. The compounds of Formula I, their pharmaceutically acceptable salts and/or solvates are effective antiviral agents, particularly as inhibitors of HIV. They are useful for the treatment of HIV and AIDS.

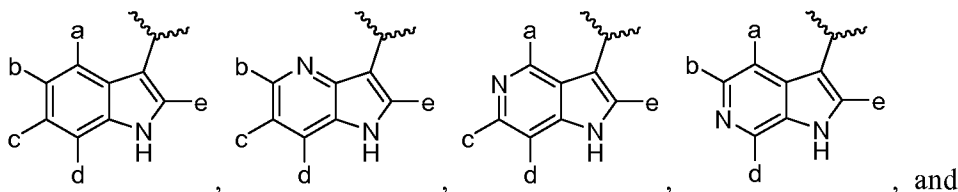
5 One embodiment of the present invention is directed to a compound of Formula I, including pharmaceutically acceptable salts thereof:

I



10

wherein A is selected from the group consisting of:



15

wherein

a, b, c, d and e are independently selected from the group consisting of hydrogen, halogen, cyano, nitro, COOR⁵⁶, XR⁵⁷, NA¹A², C(O)R⁷, C(O)NR⁵⁵R⁵⁶, B, Q, and E;

20

B is selected from the group consisting of -C(=NR⁴⁶)(R⁴⁷), C(O)NR⁴⁰R⁴¹, aryl, heteroaryl, heteroalicyclic, S(O)₂R⁸, C(O)R⁷, XR^{8a}, (C₁₋₆)alkylNR⁴⁰R⁴¹, (C₁₋₆)alkylCOOR^{8b}; wherein said aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to three same or different halogens or from one to three same or

different substituents selected from the group F; wherein aryl is naphthyl or substituted phenyl; wherein heteroaryl is a mono or bicyclic system which contains from 3 to 7 ring atoms for a mono cyclic system and up to 12 atoms in a fused bicyclic system, including from 1 to 4 heteroatoms; wherein heteroalicyclic is a 3 to 7 membered mono cyclic ring which may contain from 1 to 2 heteroatoms in the ring skeleton and which may be fused to a benzene or pyridine ring;

Q is selected from the group consisting of (C₁₋₆)alkyl and (C₂₋₆)alkenyl; wherein said (C₁₋₆)alkyl and (C₂₋₆)alkenyl are optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from the group consisting of C(O)NR⁵⁵R⁵⁶, hydroxy, cyano and XR⁵⁷;

E is selected from the group consisting of (C₁₋₆)alkyl and (C₂₋₆)alkenyl; wherein said (C₁₋₆)alkyl and (C₂₋₆)alkenyl are independently optionally substituted with a member selected from the group consisting of phenyl, heteroaryl, SMe, SPh, -C(O)NR₅₆R₅₇, C(O)R₅₇, SO₂(C₁₋₆)alkyl and SO₂Ph; wherein heteroaryl is a monocyclic system which contains from 3 to 7 ring atoms, including from 1 to 4 heteroatoms;

F is selected from the group consisting of (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C₁₋₆)alkoxy, aryloxy, (C₁₋₆)thioalkoxy, cyano, halogen, nitro, -C(O)R⁵⁷, benzyl, -NR⁴²C(O)-(C₁₋₆)alkyl, -NR⁴²C(O)-(C₃₋₆)cycloalkyl, -NR⁴²C(O)-aryl, -NR⁴²C(O)-heteroaryl, -NR⁴²C(O)-heteroalicyclic, a 4, 5, or 6 membered ring cyclic N-lactam, -NR⁴²S(O)₂-(C₁₋₆)alkyl, -NR⁴²S(O)₂-(C₃₋₆)cycloalkyl, -NR⁴²S(O)₂-aryl, -NR⁴²S(O)₂-heteroaryl, -NR⁴²S(O)₂-heteroalicyclic, S(O)₂(C₁₋₆)alkyl, S(O)₂aryl, -S(O)₂NR⁴²R⁴³, NR⁴²R⁴³, (C₁₋₆)alkylC(O)NR⁴²R⁴³, C(O)NR⁴²R⁴³, NHC(O)NR⁴²R⁴³, OC(O)NR⁴²R⁴³, NHC(O)OR⁵⁴, (C₁₋₆)alkylNR⁴²R⁴³, COOR⁵⁴, and (C₁₋₆)alkylCOOR⁵⁴; wherein said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, aryl, heteroaryl, heteroalicyclic, (C₁₋₆)alkoxy, and aryloxy, are optionally substituted with one to nine same or different halogens or from one to five same or different substituents selected from the group G; wherein aryl is phenyl; heteroaryl is a monocyclic system which contains from 3 to 7 ring atoms, including from 1 to 4 heteroatoms; heteroalicyclic is selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, piperidine, tetrahydrofuran, tetrahydropyran, azepine, and morpholine;

- G is selected from the group consisting of (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C₁₋₆)alkoxy, aryloxy, cyano, halogen, nitro, -C(O)R⁵⁷, benzyl, -NR⁴⁸C(O)-(C₁₋₆)alkyl, -NR⁴⁸C(O)-(C₃₋₆)cycloalkyl, -NR⁴⁸C(O)-aryl, -NR⁴⁸C(O)-
- 5 heteroaryl, -NR⁴⁸C(O)-heteroalicyclic, a 4, 5, or 6 membered ring cyclic N-lactam, -NR⁴⁸S(O)₂-(C₁₋₆)alkyl, -NR⁴⁸S(O)₂-(C₃₋₆)cycloalkyl, -NR⁴⁸S(O)₂-aryl, -NR⁴⁸S(O)₂-heteroaryl, -NR⁴⁸S(O)₂-heteroalicyclic, sulfinyl, sulfonyl, sulfonamide, NR⁴⁸R⁴⁹, (C₁₋₆)alkyl C(O)NR⁴⁸R⁴⁹, C(O)NR⁴⁸R⁴⁹, NHC(O)NR⁴⁸R⁴⁹, OC(O)NR⁴⁸R⁴⁹, NHC(O)OR⁵⁴, (C₁₋₆)alkylNR⁴⁸R⁴⁹, COOR⁵⁴, and (C₁₋₆)alkylCOOR⁵⁴; wherein aryl is
- 10 phenyl; heteroaryl is a monocyclic system which contains from 3 to 7 ring atoms, including from 1 to 4 heteroatoms; heteroalicyclic is selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, piperidine, tetrahydrofuran, tetrahydropyran, azepine, and morpholine;
- 15 R⁷ is selected from the group consisting of aryl, heteroaryl, and heteroalicyclic; wherein said aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to three same or different halogens or with from one to three same or different substituents selected from the group F;
- 20 wherein for R⁷, R⁸, R^{8a}, R^{8b} aryl is phenyl; heteroaryl is a mono or bicyclic system which contains from 3 to 7 ring atoms for mono cyclic systems and up to 10 atoms in a bicyclic system, including from 1 to 4 heteroatoms; wherein heteroalicyclic is selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, piperidine, tetrahydrofuran, tetrahydropyran, azepine, and morpholine;
- 25 R⁸ is selected from the group consisting of hydrogen, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₂₋₆)alkenyl, (C₃₋₇)cycloalkenyl, (C₂₋₆)alkynyl, aryl, heteroaryl, and heteroalicyclic; wherein said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₂₋₆)alkenyl, (C₃₋₇)cycloalkenyl, (C₂₋₆)alkynyl, aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to
- 30 six same or different halogens or from one to five same or different substituents selected from the group F or (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C₁₋₆)alkoxy, halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone,

amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, acyl sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric acid, boronic ester, boronic acid, squarate, squaric acid, oxime, hydrazine, peroxide, among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic; heteroaryl is selected from the group consisting of furanyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, triazolyl, pyridinyl, pyrazinyl, pyridazinyl, and pyrimidinyl;

10 R^{8a} is a member selected from the group consisting of aryl, heteroaryl, and heteroalicyclic; wherein each member is independently optionally substituted with one to six same or different halogens or from one to five same or different substituents selected from the group F;

15 R^{8b} is selected from the group consisting of hydrogen, (C₁₋₆)alkyl and phenyl;

R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, are each independently selected from the group consisting of hydrogen and (C₁₋₆)alkyl; wherein said (C₁₋₆)alkyl is optionally substituted with one to three same or different functional groups: (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C₁₋₆)alkoxy, halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, acyl sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric acid, boronic ester, boronic acid, squarate, squaric acid, oxime, hydrazine, peroxide, among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic; heteroaryl is selected from the group consisting of furanyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, triazolyl, pyridinyl, pyrazinyl, pyridazinyl, and pyrimidinyl;

30 X is selected from the group consisting of NH, NCH₃, O, and S;

R⁴⁰ and R⁴¹ are independently selected from the group consisting of

- (a) hydrogen; (b) (C₁₋₆)alkyl or (C₃₋₇)cycloalkyl substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F or different functional groups: (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C₁₋₆)alkoxy, halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, acyl sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric acid, boronic ester, boronic acid, squarate, squaric acid, oxime, hydrazine, peroxide, among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic; heteroaryl is selected from the group consisting of furanyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, triazolyl, pyridinyl, pyrazinyl, pyridazinyl, and pyrimidinyl; and (c) (C₁₋₆)alkoxy, aryl, heteroaryl or heteroalicyclic; or R⁴⁰ and R⁴¹ taken together with the nitrogen to which they are attached form a member selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, 4-NMe piperazine, piperidine, azepine, and morpholine; and wherein said aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F; wherein for R⁴⁰ and R⁴¹ aryl is phenyl; heteroaryl is a monocyclic system which contains from 3 to 6 ring atoms, including from 1 to 4 heteroatoms; heteroalicyclic is selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, piperidine, tetrahydrofuran, tetrahydropyran, azepine, and morpholine; provided when B is C(O)NR⁴⁰R⁴¹, at least one of R⁴⁰ and R⁴¹ is not selected from groups (a) or (b);
- R⁴² and R⁴³ are independently selected from the group consisting of hydrogen, (C₁₋₆)alkyl, allyl, (C₁₋₆)alkoxy, (C₃₋₇)cycloalkyl, aryl, heteroaryl and heteroalicyclic; or R⁴² and R⁴³ taken together with the nitrogen to which they are attached form a member selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, 4-NMe piperazine, piperidine, azepine, and morpholine; and wherein said (C₁₋₆)alkyl, (C₁₋₆)alkoxy, (C₃₋₇)cycloalkyl, aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group G or different functional groups: (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C₁₋₆)alkoxy,

halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, acyl sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric acid, boronic ester, boronic acid, squarate, squaric acid, oxime, hydrazine, peroxide, among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic; heteroaryl is selected from the group consisting of furanyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, triazolyl, pyridinyl, pyrazinyl, pyridazinyl, and pyrimidinyl; wherein for R⁴² and R⁴³ aryl is phenyl; heteroaryl is a monocyclic system which contains from 3 to 6 ring atoms, including from 1 to 4 heteroatoms; heteroalicyclic is a member selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, piperidine, tetrahydrofuran, tetrahydropyran, azepine, and morpholine;

15 R⁴⁶ is selected from the group consisting of H, OR⁵⁷, and NR⁵⁵R⁵⁶;

R⁴⁷ is selected from the group consisting of H, amino, halogen, phenyl, aryl, heteroaryl and (C₁₋₆)alkyl;

20 R⁴⁸ and R⁴⁹ are independently selected from the group consisting of hydrogen, (C₁₋₆)alkyl, phenyl, aryl and heteroaryl;

R⁵⁰ is selected from the group consisting of H, (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, and benzyl; wherein each of said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl and benzyl are optionally substituted with one to three same or different (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C₁₋₆)alkoxy, halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, acyl sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric acid, boronic ester, boronic acid, squarate, squaric acid, oxime, hydrazine, peroxide, among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic; heteroaryl is selected from the group consisting of furanyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl,

imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, triazolyl, pyridinyl, pyrazinyl, pyridazinyl, and pyrimidinyl

R⁵⁴ is selected from the group consisting of hydrogen and (C₁₋₆)alkyl;

5

R^{54'} is (C₁₋₆)alkyl;

R⁵⁵ and R⁵⁶ are independently selected from the group consisting of hydrogen and (C₁₋₆)alkyl; and

10

R⁵⁷ is selected from the group consisting of hydrogen, (C₁₋₆)alkyl, aryl, heteroaryl; and

A¹ and A² are independently selected from hydrogen, (C₁₋₆)alkyl, aryl, heteroaryl, SO₂D¹, SO₂ND²D³, COD⁴, COCOD⁴, COOD⁴, COND⁵D⁶, COCOND⁵D⁶, COCOD⁴,

15 C(=ND⁷)D⁸, C(=ND⁹)ND¹⁰D¹¹;

A¹ and A² can either never connect with each other, or conjoin to form a ring structure;

D¹, D², D³, D⁴, D⁵, D⁶, D⁷, D⁸, D⁹, D¹⁰, and D¹¹ are each independently selected from the

20

group consisting of H, C₁-C₅₀ alkyl, C₃-C₅₀ cycloalkyl, C₃-C₅₀ alkenyl, C₄-C₅₀ cycloalkenyl, phenyl, heteroaryl, C₃-C₅₀ amide and C₃-C₅₀ ether; heteroaryl is selected

from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl,

thienyl, benzothienyl, thiazolyl, isothiazolyl, oxazolyl, benzooxazolyl, isoxazolyl,

imidazolyl, benzoimidazolyl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-

25

2-yl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, tetrazinyl, triazinyl and triazolyl;

provided the carbon atoms which comprise the carbon-carbon double bond of said C₃-C₂₀

alkenyl or the carbon-carbon triple bond of said C₃-C₂₀ alkynyl are not the point of

attachment to the nitrogen to which D², D³, D⁵, D⁶, D⁷, D⁹, D¹⁰, and D¹¹ is attached;

wherein said C₁-C₅₀ alkyl, C₃-C₅₀ cycloalkyl, C₃-C₅₀ alkenyl, C₄-C₅₀ cycloalkenyl, aryl,

30

phenyl, heteroaryl, C₃-C₅₀ amide and C₃-C₅₀ ether is optionally substituted with one to

three same or different of the following functionalities: (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl,

cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C₁₋₆)alkoxy, halogen, benzyl,

primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether,

alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, acyl sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric acid, boronic ester, boronic acid, squarate, squaric acid, oxime, hydrazine, peroxide and steroid, among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic;

K is selected from group J or Ar;

Ar is selected from the group consisting of phenyl and heteroaryl; wherein said phenyl and heteroaryl are each independently optionally substituted with one to three same or different members selected from the group Ar-I; and heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, thienyl, benzothienyl, thiazolyl, isothiazolyl, oxazolyl, benzooxazolyl, isoxazolyl, imidazolyl, benzoimidazolyl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, tetrazinyl, triazinyl and triazolyl;

Ar-I is selected from the group consisting of (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C₁₋₆)alkoxy, halogen, primary amine, secondary amine, tertiary amine, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, oxime and hydrazine, among which ether, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic; wherein said (C₁₋₆)alkyl, (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl is optionally substituted with one to three same or different of the following functionalities: (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C₁₋₆)alkoxy, halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, oxime and hydrazine, among which ether, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic;

J is selected from the group consisting of H, C₁-C₃₀ alkyl, C₃-C₃₀ cycloalkyl, C₄-C₃₀ bicycloalkyl, C₅-C₃₀ tricycloalkyl, C₆-C₃₀ tetracycloalkyl, C₃-C₃₀ alkenyl, C₄-C₃₀ cycloalkenyl, C₅-C₃₀ bicycloalkenyl, C₇-C₃₀ tricycloalkenyl, C₉-C₃₀ tetracycloalkyl, phenyl, aryl, heteroaryl, C₁-C₃₀ amide, C₃-C₃₀ cyclic amide, C₁-C₃₀ amine, C₃-C₃₀ cyclic amine, C₂-C₃₀ ester, C₃-C₃₀ cyclic ester, C₂-C₃₀ ether, C₃-C₃₀ cyclic ether, C₁-C₃₀ sulfonamide, C₃-C₃₀ cyclic sulfonamide, C₂-C₃₀ sulfone, C₃-C₃₀ cyclic sulfone, C₂-C₃₀ sulfamide, C₃-C₃₀ cyclic sulfamide, C₂-C₃₀ acyl sulfamide, C₃-C₃₀ acyl sulfamide, C₂-C₃₀ urea, C₃-C₃₀ cyclic urea, C₂-C₃₀ amidine, C₃-C₃₀ cyclic amidine, C₂-C₃₀ guanidine, and C₃-C₃₀ cyclic guanidine; aryl or heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, thienyl, benzothienyl, thiazolyl, isothiazolyl, oxazolyl, benzooxazolyl, isoxazolyl, imidazolyl, benzoimidazolyl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, tetrazinyl, triazinyl, triazolyl, naphthalenyl, quinolinyl, isoquinolinyl, quinoxalinyl, indolyl, azaindolyl, indazolyl, azaindazolyl, benzoisoxazolyl, azabenzisoxazolyl, benzoisothiazole, azabenzothiazolyl; wherein said C₁-C₃₀ alkyl, C₃-C₃₀ cycloalkyl, C₄-C₃₀ bicycloalkyl, C₅-C₃₀ tricycloalkyl, C₆-C₃₀ tetracycloalkyl, C₃-C₃₀ alkenyl, C₄-C₃₀ cycloalkenyl, C₅-C₃₀ bicycloalkenyl, C₇-C₃₀ tricycloalkenyl, C₉-C₃₀ tetracycloalkyl, phenyl, aryl, heteroaryl, C₁-C₃₀ amide, C₃-C₃₀ cyclic amide, C₁-C₃₀ amine, C₃-C₃₀ cyclic amine, C₂-C₃₀ ester, C₃-C₃₀ cyclic ester, C₂-C₃₀ ether, C₃-C₃₀ cyclic ether, C₁-C₃₀ sulfonamide, C₃-C₃₀ cyclic sulfonamide, C₂-C₃₀ sulfone, C₃-C₃₀ cyclic sulfone, C₂-C₃₀ sulfamide, C₃-C₃₀ cyclic sulfamide, C₂-C₃₀ acyl sulfamide, C₃-C₃₀ acyl sulfamide, C₂-C₃₀ urea, C₃-C₃₀ cyclic urea, C₂-C₃₀ amidine, C₃-C₃₀ cyclic amidine, C₂-C₃₀ guanidine, and C₃-C₃₀ cyclic guanidine is optionally substituted with one to three same or different of the following functionalities: (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C₁₋₆)alkoxy, halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, acyl sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric acid, boronic ester, boronic acid, squarate, squaric acid, oxime, hydrazine, and peroxide, among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic;

I₁, I₂, I₃, I₄, I₅, I₆, I₇ and I₈ are each independently selected from the group consisting of H, (C₁₋₆)alkyl, (C₃₋₆) cycloalkyl, (C₂₋₆) alkenyl, (C₄₋₆) cycloalkenyl, (C₂₋₆) alkynyl, CR₈₁R₈₂OR₈₃, COR₈₄, COOR₈₅, or CONR₈₆R₈₇; wherein each of said alkyl and cycloalkyl being optionally substituted with one to three same or different cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C₁₋₆)alkoxy, halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, acyl sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric acid, boronic ester, boronic acid, squarate, squaric acid, oxime, hydrazine, peroxide, among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic; heteroaryl is selected from the group consisting of furanyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, triazolyl, pyridinyl, pyrazinyl, pyridazinyl, and pyrimidinyl;

15

R₈₁, R₈₂, R₈₃, R₈₄, R₈₅, R₈₆, and R₈₇ are each independently selected from the group consisting of H, (C₁₋₆)alkyl, (C₃₋₆) cycloalkyl, (C₂₋₆) alkenyl, (C₄₋₆) cycloalkenyl, (C₂₋₆) alkynyl;

20 U is selected from the group consisting of S, NOH, NOR₁₀₀, and NNR₁₀₁R₁₀₂;

R₁₀₀ is selected from the group consisting of C₁-C₆ alkyl;

R₁₀₁ and R₁₀₂ are J is selected from the group consisting of H, C₁-C₃₀ alkyl, C₃-C₃₀ cycloalkyl, C₄-C₃₀ bicycloalkyl, C₅-C₃₀ tricycloalkyl, C₆-C₃₀ tetracycloalkyl, C₃-C₃₀ alkenyl, C₄-C₃₀ cycloalkenyl, C₅-C₃₀ bicycloalkenyl, C₇-C₃₀ tricycloalkenyl, C₉-C₃₀ tetracycloalkyl, phenyl, aryl, heteroaryl, C₁-C₃₀ amide, C₃-C₃₀ cyclic amide, C₁-C₃₀ amine, C₃-C₃₀ cyclic amine, C₂-C₃₀ ester, C₃-C₃₀ cyclic ester, C₂-C₃₀ ether, C₃-C₃₀ cyclic ether, C₁-C₃₀ sulfonamide, C₃-C₃₀ cyclic sulfonamide, C₂-C₃₀ sulfone, C₃-C₃₀ cyclic sulfone, C₂-C₃₀ sulfamide, C₃-C₃₀ cyclic sulfamide, C₂-C₃₀ acyl sulfamide, C₃-C₃₀ acyl sulfamide, C₂-C₃₀ urea, C₃-C₃₀ cyclic urea, C₂-C₃₀ amidine, C₃-C₃₀ cyclic amidine, C₂-C₃₀ guanidine, and C₃-C₃₀ cyclic guanidine; aryl or heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, thienyl,

benzothienyl, thiazolyl, isothiazolyl, oxazolyl, benzooxazolyl, isoxazolyl, imidazolyl,
 benzoimidazolyl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl,
 oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, tetrazinyl, triazinyl, triazolyl,
 naphthalenyl, quinolinyl, isoquinolinyl, quinoxalinyl, indolyl, azaindolyl, indazolyl,
 5 azaindazolyl, benzoisoxazolyl, azabenzoisoxazolyl, benzoisothiazole, azabenzothiazolyl;
 wherein said C₁-C₃₀ alkyl, C₃-C₃₀ cycloalkyl, C₄-C₃₀ bicycloalkyl, C₅-C₃₀ tricycloalkyl,
 C₆-C₃₀ tetracycloalkyl, C₃-C₃₀ alkenyl, C₄-C₃₀ cycloalkenyl, C₅-C₃₀ bicycloalkenyl, C₇-
 C₃₀ tricycloalkenyl, C₉-C₃₀ tetracycloalkyl, phenyl, aryl, heteroaryl, C₁-C₃₀ amide, C₃-C₃₀
 cyclic amide, C₁-C₃₀ amine, C₃-C₃₀ cyclic amine, C₂-C₃₀ ester, C₃-C₃₀ cyclic ester, C₂-C₃₀
 10 ether, C₃-C₃₀ cyclic ether, C₁-C₃₀ sulfonamide, C₃-C₃₀ cyclic sulfonamide, C₂-C₃₀ sulfone,
 C₃-C₃₀ cyclic sulfone, C₂-C₃₀ sulfamide, C₃-C₃₀ cyclic sulfamide, C₂-C₃₀ acyl sulfamide,
 C₃-C₃₀ acyl sulfamide, C₂-C₃₀ urea, C₃-C₃₀ cyclic urea, C₂-C₃₀ amidine, C₃-C₃₀ cyclic
 amidine, C₂-C₃₀ guanidine, and C₃-C₃₀ cyclic guanidine is optionally substituted with one
 to three same or different of the following functionalities: (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl,
 15 cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C₁₋₆)alkoxy, halogen, benzyl,
 primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether,
 alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide,
 sulfamide, acyl sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric
 acid, boronic ester, boronic acid, squarate, squaric acid, oxime, hydrazine, and peroxide,
 20 among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium,
 ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic;

Another embodiment of the present invention is directed to a method for treating
 mammals infected with a virus, especially wherein the virus is HIV, comprising
 25 administering to said mammal an antiviral effective amount of a compound of Formula I
 above, and one or more pharmaceutically acceptable carriers, excipients or diluents.
 Optionally, the compound of Formula I can be administered in combination with an
 antiviral effective amount of an AIDS treatment agent selected from the group consisting
 of: (a) an AIDS antiviral agent; (b) an anti-infective agent; (c) an immunomodulator; and
 30 (d) other HIV entry inhibitors.

Another embodiment of the present invention is a pharmaceutical composition
 comprising an antiviral effective amount of a compound of Formula I and one or more
 pharmaceutically acceptable carriers, excipients, diluents and optionally in combination

with an antiviral effective amount of an AIDS treatment agent selected from the group consisting of: (a) an AIDS antiviral agent; (b) an anti-infective agent; (c) an immunomodulator; and (d) other HIV entry inhibitors.

In another embodiment of the invention there is provided one or more methods for making the compounds of Formula I.

The present invention is directed to these, as well as other important ends, hereinafter described.

DETAILED DESCRIPTION OF THE EMBODIMENTS

Since the compounds of the present invention may possess asymmetric centers and therefore occur as mixtures of diastereomers and enantiomers, the present disclosure includes the individual diastereoisomeric and enantiomeric forms of the compounds of Formula I in addition to the mixtures thereof.

Definitions

Unless otherwise specifically set forth elsewhere in the application, one or more of the following terms may be used herein, and shall have the following meanings:

The term "H" refers to hydrogen, including its isotopes.

The term "C₁₋₆ alkyl" as used herein and in the claims (unless specified otherwise) mean straight or branched chain alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *t*-butyl, amyl, hexyl and the like.

"C₁-C₄ fluoroalkyl" refers to F-substituted C₁-C₄ alkyl wherein at least one H atom is substituted with F atom, and each H atom can be independently substituted by F atom.

"Halogen" refers to chlorine, bromine, iodine or fluorine.

An "aryl" or "Ar" group refers to an all carbon monocyclic or fused-ring polycyclic (*i.e.*, rings which share adjacent pairs of carbon atoms) groups having a completely conjugated pi-electron system. Examples, without limitation, of aryl groups are phenyl, naphthalenyl and anthracenyl. The aryl group may be substituted or unsubstituted. When substituted the substituted group(s) is preferably one or more selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halogen, nitro, carbonyl, O-carbamyl, N-carbamyl, C-amido,

N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethyl, ureido, amino and $-NR^xR^y$, wherein R^x and R^y are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, carbonyl, C-carboxy, sulfonyl, trihalomethyl, and, combined, a five- or six-member heteroalicyclic ring.

5 As used herein, a “heteroaryl” group refers to a monocyclic or fused ring (*i.e.*, rings which share an adjacent pair of atoms) group having in the ring(s) one or more atoms selected from the group consisting of nitrogen, oxygen and sulfur and, in addition, having a completely conjugated pi-electron system. Unless otherwise indicated, the heteroaryl group may be attached at either a carbon or nitrogen atom within the heteroaryl
10 group. It should be noted that the term heteroaryl is intended to encompass an N-oxide of the parent heteroaryl if such an N-oxide is chemically feasible as is known in the art. Examples, without limitation, of heteroaryl groups are furyl, thienyl, benzothienyl, thiazolyl, imidazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, benzothiazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyranyl, tetrahydropyranyl, pyrazolyl,
15 pyridyl, pyrimidinyl, quinolinyl, isoquinolinyl, purinyl, carbazolyl, benzoxazolyl, benzimidazolyl, indolyl, isoindolyl, pyrazinyl, diazinyl, pyrazine, triazinyl, tetrazinyl, and tetrazolyl. When substituted the substituted group(s) is preferably one or more selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thioalkoxy, thiohydroxy, thioaryloxy, thioheteroaryloxy,
20 thioheteroalicycloxy, cyano, halogen, nitro, carbonyl, O-carbamyl, N-carbamyl, C-amido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethyl, ureido, amino, and $-NR^xR^y$, wherein R^x and R^y are as defined above.

As used herein, a “heteroalicyclic” group refers to a monocyclic or fused ring group having in the ring(s) one or more atoms selected from the group consisting of
25 nitrogen, oxygen and sulfur. Rings are selected from those which provide stable arrangements of bonds and are not intended to encompass systems which would not exist. The rings may also have one or more double bonds. However, the rings do not have a completely conjugated pi-electron system. Examples, without limitation, of heteroalicyclic groups are azetidiny, piperidyl, piperazinyl, imidazoliny, thiazolidiny, 3-
30 pyrrolidin-1-yl, morpholinyl, thiomorpholinyl and tetrahydropyranyl. When substituted the substituted group(s) is preferably one or more selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioalkoxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano,

halogen, nitro, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, C-thioamido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethanesulfonamido, trihalomethanesulfonyl, silyl, guanyl, guanidino, ureido, phosphonyl, amino and $-NR^xR^y$, wherein R^x and R^y are as defined
5 above.

An "alkyl" group refers to a saturated aliphatic hydrocarbon including straight chain and branched chain groups. Preferably, the alkyl group has 1 to 20 carbon atoms (whenever a numerical range; e.g., "1-20", is stated herein, it means that the group, in this case the alkyl group may contain 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc. up
10 to and including 20 carbon atoms). More preferably, it is a medium size alkyl having 1 to 10 carbon atoms. Most preferably, it is a lower alkyl having 1 to 4 carbon atoms. The alkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more individually selected from trihaloalkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy,
15 heteroalicycloxy, thiohydroxy, thioalkoxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halo, nitro, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, C-thioamido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethanesulfonamido, trihalomethanesulfonyl, and combined, a five- or six-member heteroalicyclic ring.

A "cycloalkyl" group refers to an all-carbon monocyclic or fused ring (*i.e.*, rings which share and adjacent pair of carbon atoms) group wherein one or more rings does not have a completely conjugated pi-electron system. Examples, without limitation, of cycloalkyl groups are cyclopropane, cyclobutane, cyclopentane, cyclopentene, cyclohexane, cyclohexene, cycloheptane, cycloheptene and adamantane. A cycloalkyl
20 group may be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more individually selected from alkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioalkoxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halo, nitro, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, C-thioamido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethanesulfonamido, trihalomethanesulfonyl, silyl, guanyl, guanidino, ureido,
25 phosphonyl, amino and $-NR^xR^y$ with R^x and R^y as defined above.

An “alkenyl” group refers to an alkyl group, as defined herein, having at least two carbon atoms and at least one carbon-carbon double bond.

An “alkynyl” group refers to an alkyl group, as defined herein, having at least two carbon atoms and at least one carbon-carbon triple bond.

5 A “hydroxy” group refers to an –OH group.

An “alkoxy” group refers to both an –O-alkyl and an –O-cycloalkyl group as defined herein.

An “aryloxy” group refers to both an –O-aryl and an –O-heteroaryl group, as defined herein.

10 A “heteroaryloxy” group refers to a heteroaryl-O- group with heteroaryl as defined herein.

A “heteroalicycloxy” group refers to a heteroalicyclic-O- group with heteroalicyclic as defined herein.

A “thiohydroxy” group refers to an –SH group.

15 A “thioalkoxy” group refers to both an S-alkyl and an –S-cycloalkyl group, as defined herein.

A “thioaryloxy” group refers to both an –S-aryl and an –S-heteroaryl group, as defined herein.

20 A “thioheteroaryloxy” group refers to a heteroaryl-S- group with heteroaryl as defined herein.

A “thioheteroalicycloxy” group refers to a heteroalicyclic-S- group with heteroalicyclic as defined herein.

25 A “carbonyl” group refers to a –C(=O)-R'' group, where R'' is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), as each is defined herein.

An “aldehyde” group refers to a carbonyl group where R'' is hydrogen.

A “thiocarbonyl” group refers to a –C(=S)-R'' group, with R'' as defined herein.

30 A “Keto” group refers to a –CC(=O)C- group wherein the carbon on either or both sides of the C=O may be alkyl, cycloalkyl, aryl or a carbon of a heteroaryl or heteroalicyclic group.

A “trihalomethanecarbonyl” group refers to a Z₃CC(=O)- group with said Z being a halogen.

A "C-carboxy" group refers to a $-C(=O)O-R''$ groups, with R'' as defined herein.

An "O-carboxy" group refers to a $R''C(O)O$ -group, with R'' as defined herein.

A "carboxylic acid" group refers to a C-carboxy group in which R'' is hydrogen.

A "trihalomethyl" group refers to a $-CZ_3$, group wherein Z is a halogen group as
5 defined herein.

A "trihalomethanesulfonyl" group refers to an $Z_3CS(=O)_2$ - groups with Z as defined above.

A "trihalomethanesulfonamido" group refers to a $Z_3CS(=O)_2NR^x$ - group with Z as defined above and R^x being H or (C_{1-6}) alkyl.

10 A "sulfinyl" group refers to a $-S(=O)-R''$ group, with R'' being (C_{1-6}) alkyl.

A "sulfonyl" group refers to a $-S(=O)_2R''$ group with R'' being (C_{1-6}) alkyl.

A "S-sulfonamido" group refers to a $-S(=O)_2NR^xR^y$, with R^x and R^y independently being H or (C_{1-6}) alkyl.

15 A "N-Sulfonamido" group refers to a $R''S(=O)_2NR_x$ - group, with R_x being H or (C_{1-6}) alkyl.

A "O-carbamyl" group refers to a $-OC(=O)NR^xR^y$ group, with R^x and R^y independently being H or (C_{1-6}) alkyl.

A "N-carbamyl" group refers to a $R^xOC(=O)NR^y$ group, with R^x and R^y independently being H or (C_{1-6}) alkyl.

20 A "O-thiocarbamyl" group refers to a $-OC(=S)NR^xR^y$ group, with R^x and R^y independently being H or (C_{1-6}) alkyl.

A "N-thiocarbamyl" group refers to a $R^xOC(=S)NR^y$ - group, with R^x and R^y independently being H or (C_{1-6}) alkyl.

An "amino" group refers to an $-NH_2$ group.

25 A "C-amido" group refers to a $-C(=O)NR^xR^y$ group, with R^x and R^y independently being H or (C_{1-6}) alkyl.

A "C-thioamido" group refers to a $-C(=S)NR^xR^y$ group, with R^x and R^y independently being H or (C_{1-6}) alkyl.

30 A "N-amido" group refers to a $R^xC(=O)NR^y$ - group, with R^x and R^y independently being H or (C_{1-6}) alkyl.

An "ureido" group refers to a $-NR^xC(=O)NR^yR^{y2}$ group, with R^x , R^y , and R^{y2} independently being H or (C_{1-6}) alkyl.

A “guanidino” group refers to a $-R^xNC(=N)NR^yR^{y2}$ group, with R^x , R^y , and R^{y2} independently being H or (C_{1-6}) alkyl.

A “guanyl” group refers to a $R^xR^yNC(=N)-$ group, with R^x and R^y independently being H or (C_{1-6}) alkyl.

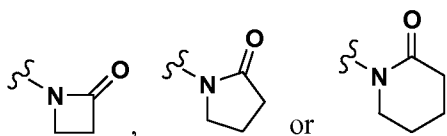
5 A “cyano” group refers to a $-CN$ group.

A “silyl” group refers to a $-Si(R'')_3$, with R'' being (C_{1-6}) alkyl or phenyl.

A “phosphonyl” group refers to a $P(=O)(OR^x)_2$ with R^x being (C_{1-6}) alkyl.

A “hydrazino” group refers to a $-NR^xNR^yR^{y2}$ group, with R^x , R^y , and R^{y2} independently being H or (C_{1-6}) alkyl.

10 A “4, 5, or 6 membered ring cyclic N-lactam” group refers to



Any two adjacent R groups may combine to form an additional aryl, cycloalkyl, heteroaryl or heterocyclic ring fused to the ring initially bearing those R groups.

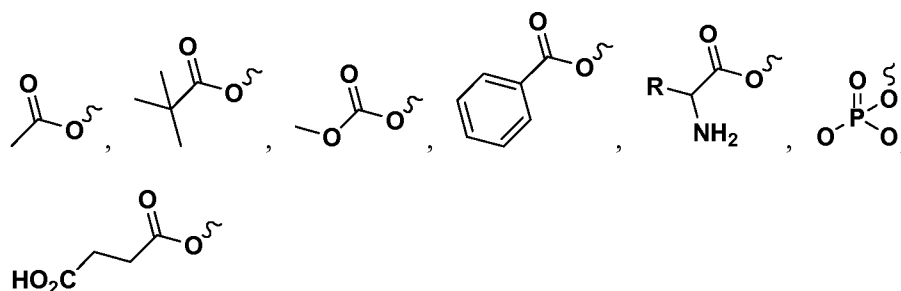
It is known in the art that nitrogen atoms in heteroaryl systems can be
 15 “participating in a heteroaryl ring double bond”, and this refers to the form of double bonds in the two tautomeric structures which comprise five-member ring heteroaryl groups. This dictates whether nitrogens can be substituted as well understood by chemists in the art. The disclosure and claims of the present disclosure are based on the known general principles of chemical bonding. It is understood that the claims do not
 20 encompass structures known to be unstable or not able to exist based on the literature.

Pharmaceutically acceptable salts and prodrugs of compounds disclosed herein are within the scope of this disclosure. The term “pharmaceutically acceptable salt” as used herein and in the claims is intended to include nontoxic base addition salts. Suitable salts include those derived from organic and inorganic acids such as, without limitation,
 25 hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, tartaric acid, lactic acid, sulfinic acid, citric acid, maleic acid, fumaric acid, sorbic acid, aconitic acid, salicylic acid, phthalic acid, and the like. The term “pharmaceutically acceptable salt” as used herein is also intended to include salts of
 30 acidic groups, such as a carboxylate, with such counterions as ammonium, alkali metal salts, particularly sodium or potassium, alkaline earth metal salts, particularly calcium or

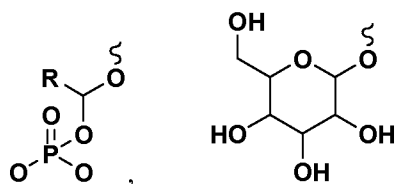
magnesium, and salts with suitable organic bases such as lower alkylamines (methylamine, ethylamine, cyclohexylamine, and the like) or with substituted lower alkylamines (*e.g.*, hydroxyl-substituted alkylamines such as diethanolamine, triethanolamine or tris(hydroxymethyl)-aminomethane), or with bases such as piperidine or morpholine.

As stated above, the compounds of the invention also include “prodrugs”. The term “prodrug” as used herein encompasses both the term “prodrug esters” and the term “prodrug ethers”. The term “prodrug esters” as employed herein includes esters and carbonates formed by reacting one or more hydroxyls of compounds of Formula I with either alkyl, alkoxy, or aryl substituted acylating agents or phosphorylating agent employing procedures known to those skilled in the art to generate acetates, pivalates, methylcarbonates, benzoates, amino acid esters, phosphates, half acid esters such as malonates, succinates or glutarates, and the like. In certain embodiments, amino acid esters may be especially preferred.

Examples of such prodrug esters include

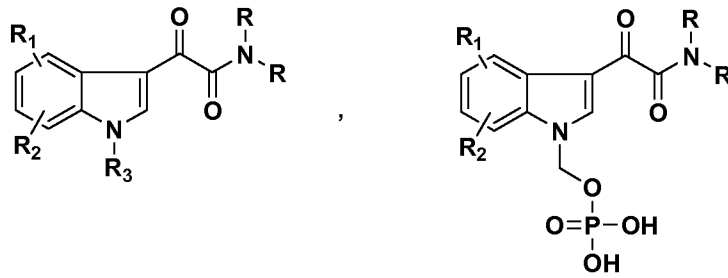


The term “prodrug ethers” include both phosphate acetals and O-glucosides. Representative examples of such prodrug ethers include



Prodrug derivatives in which the prodrug moiety is attached to the indole N atom are also considered part of this invention. These prodrugs can be prepared by substitution of the indole N with a moiety that modifies the physical properties of the compound and can be unmasked either by chemical or enzymatic degradation. Examples of R₃ include acyl derivatives similar to those described above. A preferred prodrug is the

phosphonoxymethyl moiety which can be introduced using methods previously described and converted to pharmaceutically acceptable salt forms that confer chemical stability and advantageous physical properties:

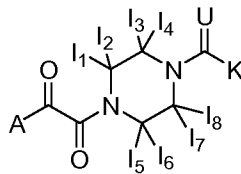


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As set forth above, the invention is directed to compounds of Formula I, including pharmaceutically acceptable salts thereof:

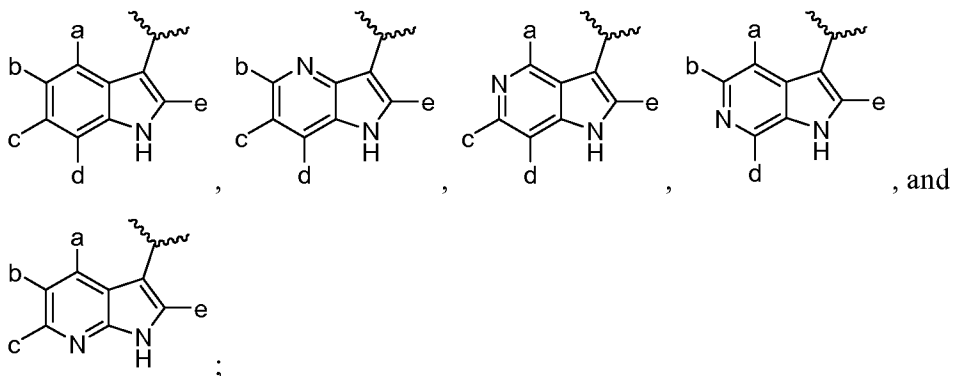
10

I



wherein A is selected from the group consisting of:

15



wherein

a, b, c, d and e are independently selected from the group consisting of hydrogen, halogen, cyano, nitro, COOR⁵⁶, XR⁵⁷, NA¹A², C(O)R⁷, C(O)NR⁵⁵R⁵⁶, B, Q, and E;

- B is selected from the group consisting of -C(=NR⁴⁶)(R⁴⁷), C(O)NR⁴⁰R⁴¹, aryl, heteroaryl, heteroalicyclic, S(O)₂R⁸, C(O)R⁷, XR^{8a}, (C₁₋₆)alkylNR⁴⁰R⁴¹, (C₁₋₆)alkylCOOR^{8b}; wherein said aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from the group F; wherein aryl is naphthyl or substituted phenyl; wherein heteroaryl is a mono or bicyclic system which contains from 3 to 7 ring atoms for a mono cyclic system and up to 12 atoms in a fused bicyclic system, including from 1 to 4 heteroatoms; wherein heteroalicyclic is a 3 to 7 membered mono cyclic ring which may contain from 1 to 2 heteroatoms in the ring skeleton and which may be fused to a benzene or pyridine ring;
- Q is selected from the group consisting of (C₁₋₆)alkyl and (C₂₋₆)alkenyl; wherein said (C₁₋₆)alkyl and (C₂₋₆)alkenyl are optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from the group consisting of C(O)NR⁵⁵R⁵⁶, hydroxy, cyano and XR⁵⁷;
- E is selected from the group consisting of (C₁₋₆)alkyl and (C₂₋₆)alkenyl; wherein said (C₁₋₆)alkyl and (C₂₋₆)alkenyl are independently optionally substituted with a member selected from the group consisting of phenyl, heteroaryl, SMe, SPh, -C(O)NR₅₆R₅₇, C(O)R₅₇, SO₂(C₁₋₆)alkyl and SO₂Ph; wherein heteroaryl is a monocyclic system which contains from 3 to 7 ring atoms, including from 1 to 4 heteroatoms;
- F is selected from the group consisting of (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C₁₋₆)alkoxy, aryloxy, (C₁₋₆)thioalkoxy, cyano, halogen, nitro, -C(O)R⁵⁷, benzyl, -NR⁴²C(O)-(C₁₋₆)alkyl, -NR⁴²C(O)-(C₃₋₆)cycloalkyl, -NR⁴²C(O)-aryl, -NR⁴²C(O)-heteroaryl, -NR⁴²C(O)-heteroalicyclic, a 4, 5, or 6 membered ring cyclic N-lactam, -NR⁴²S(O)₂-(C₁₋₆)alkyl, -NR⁴²S(O)₂-(C₃₋₆)cycloalkyl, -NR⁴²S(O)₂-aryl, -NR⁴²S(O)₂-heteroaryl, -NR⁴²S(O)₂-heteroalicyclic, S(O)₂(C₁₋₆)alkyl, S(O)₂aryl, -S(O)₂NR⁴²R⁴³, NR⁴²R⁴³, (C₁₋₆)alkylC(O)NR⁴²R⁴³, C(O)NR⁴²R⁴³, NHC(O)NR⁴²R⁴³, OC(O)NR⁴²R⁴³, NHC(O)OR⁵⁴, (C₁₋₆)alkylNR⁴²R⁴³, COOR⁵⁴, and (C₁₋

₆alkylCOOR⁵⁴; wherein said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, aryl, heteroaryl,
 heteroalicyclic, (C₁₋₆)alkoxy, and aryloxy, are optionally substituted with one to nine
 same or different halogens or from one to five same or different substituents selected
 from the group G; wherein aryl is phenyl; heteroaryl is a monocyclic system which
 5 contains from 3 to 7 ring atoms, including from 1 to 4 heteroatoms; heteroalicyclic is
 selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine,
 piperidine, tetrahydrofuran, tetrahydropyran, azepine, and morpholine;

G is selected from the group consisting of (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, aryl, heteroaryl,
 10 heteroalicyclic, hydroxy, (C₁₋₆)alkoxy, aryloxy, cyano, halogen, nitro, -C(O)R⁵⁷, benzyl,
 -NR⁴⁸C(O)-(C₁₋₆)alkyl, -NR⁴⁸C(O)-(C₃₋₆)cycloalkyl, -NR⁴⁸C(O)-aryl, -NR⁴⁸C(O)-
 heteroaryl, -NR⁴⁸C(O)-heteroalicyclic, a 4, 5, or 6 membered ring cyclic N-
 lactam, -NR⁴⁸S(O)₂-(C₁₋₆)alkyl, -NR⁴⁸S(O)₂-(C₃₋₆)cycloalkyl, -NR⁴⁸S(O)₂-
 aryl, -NR⁴⁸S(O)₂-heteroaryl, -NR⁴⁸S(O)₂-heteroalicyclic, sulfinyl, sulfonyl, sulfonamide,
 15 NR⁴⁸R⁴⁹, (C₁₋₆)alkyl C(O)NR⁴⁸R⁴⁹, C(O)NR⁴⁸R⁴⁹, NHC(O)NR⁴⁸R⁴⁹, OC(O)NR⁴⁸R⁴⁹,
 NHC(O)OR⁵⁴, (C₁₋₆)alkylNR⁴⁸R⁴⁹, COOR⁵⁴, and (C₁₋₆)alkylCOOR⁵⁴; wherein aryl is
 phenyl; heteroaryl is a monocyclic system which contains from 3 to 7 ring atoms,
 including from 1 to 4 heteroatoms; heteroalicyclic is selected from the group consisting of
 aziridine, azetidine, pyrrolidine, piperazine, piperidine, tetrahydrofuran, tetrahydropyran,
 20 azepine, and morpholine;

R⁷ is selected from the group consisting of aryl, heteroaryl, and heteroalicyclic; wherein
 said aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to three same
 or different halogens or with from one to three same or different substituents selected
 25 from the group F;

wherein for R⁷, R⁸, R^{8a}, R^{8b} aryl is phenyl; heteroaryl is a mono or bicyclic system which
 contains from 3 to 7 ring atoms for mono cyclic systems and up to 10 atoms in a bicyclic
 system, including from 1 to 4 heteroatoms; wherein heteroalicyclic is selected from the
 30 group consisting of aziridine, azetidine, pyrrolidine, piperazine, piperidine,
 tetrahydrofuran, tetrahydropyran, azepine, and morpholine;

R⁸ is selected from the group consisting of hydrogen, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl,

(C₂₋₆)alkenyl, (C₃₋₇)cycloalkenyl, (C₂₋₆)alkynyl, aryl, heteroaryl, and heteroalicyclic; wherein said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₂₋₆)alkenyl, (C₃₋₇)cycloalkenyl, (C₂₋₆)alkynyl, aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to six same or different halogens or from one to five same or different substituents selected
5 from the group F or (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C₁₋₆)alkoxy, halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, acyl sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric acid, boronic ester, boronic acid,
10 squarate, squaric acid, oxime, hydrazine, peroxide, among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic; heteroaryl is selected from the group consisting of furanyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, triazolyl, pyridinyl, pyrazinyl, pyridazinyl,
15 and pyrimidinyl;

R^{8a} is a member selected from the group consisting of aryl, heteroaryl, and heteroalicyclic; wherein each member is independently optionally substituted with one to six same or different halogens or from one to five same or different substituents selected
20 from the group F;

R^{8b} is selected from the group consisting of hydrogen, (C₁₋₆)alkyl and phenyl;

R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, are each independently selected from the group
25 consisting of hydrogen and (C₁₋₆)alkyl; wherein said (C₁₋₆)alkyl is optionally substituted with one to three same or different functional groups: (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C₁₋₆)alkoxy, halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, acyl
30 sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric acid, boronic ester, boronic acid, squarate, squaric acid, oxime, hydrazine, peroxide, among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic; heteroaryl is selected from the

group consisting of furanyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, triazolyl, pyridinyl, pyrazinyl, pyridazinyl, and pyrimidinyl;

5 X is selected from the group consisting of NH, NCH₃, O, and S;

R⁴⁰ and R⁴¹ are independently selected from the group consisting of

(a) hydrogen; (b) (C₁₋₆)alkyl or (C₃₋₇)cycloalkyl substituted with one to three same or different halogens or from one to two same or different substituents selected from the
10 group F or different functional groups: (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C₁₋₆)alkoxy, halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, acyl sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric acid, boronic ester,
15 boronic acid, squarate, squaric acid, oxime, hydrazine, peroxide, among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic; heteroaryl is selected from the group consisting of furanyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, triazolyl, pyridinyl, pyrazinyl,
20 pyridazinyl, and pyrimidinyl; and (c) (C₁₋₆)alkoxy, aryl, heteroaryl or heteroalicyclic; or R⁴⁰ and R⁴¹ taken together with the nitrogen to which they are attached form a member selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, 4-NMe piperazine, piperidine, azepine, and morpholine; and wherein said aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to three same or different halogens or
25 from one to two same or different substituents selected from the group F; wherein for R⁴⁰ and R⁴¹ aryl is phenyl; heteroaryl is a monocyclic system which contains from 3 to 6 ring atoms, including from 1 to 4 heteroatoms; heteroalicyclic is selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, piperidine, tetrahydrofuran, tetrahydropyran, azepine, and morpholine; provided when B is C(O)NR⁴⁰R⁴¹, at least one
30 of R⁴⁰ and R⁴¹ is not selected from groups (a) or (b);

R⁴² and R⁴³ are independently selected from the group consisting of hydrogen,

(C₁₋₆)alkyl, allyl, (C₁₋₆)alkoxy, (C₃₋₇)cycloalkyl, aryl, heteroaryl and heteroalicyclic; or R⁴² and R⁴³ taken together with the nitrogen to which they are attached form a member selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, 4-NMe piperazine, piperidine, azepine, and morpholine; and wherein said (C₁₋₆)alkyl, (C₁₋₆)alkoxy, (C₃₋₇)cycloalkyl, aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group G or different functional groups: (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C₁₋₆)alkoxy, halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, acyl sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric acid, boronic ester, boronic acid, squarate, squaric acid, oxime, hydrazine, peroxide, among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic; heteroaryl is selected from the group consisting of furanyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, triazolyl, pyridinyl, pyrazinyl, pyridazinyl, and pyrimidinyl; wherein for R⁴² and R⁴³ aryl is phenyl; heteroaryl is a monocyclic system which contains from 3 to 6 ring atoms, including from 1 to 4 heteroatoms; heteroalicyclic is a member selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, piperidine, tetrahydrofuran, tetrahydropyran, azepine, and morpholine;

R⁴⁶ is selected from the group consisting of H, OR⁵⁷, and NR⁵⁵R⁵⁶;

R⁴⁷ is selected from the group consisting of H, amino, halogen, phenyl, aryl, heteroaryl and (C₁₋₆)alkyl;

R⁴⁸ and R⁴⁹ are independently selected from the group consisting of hydrogen, (C₁₋₆)alkyl, phenyl, aryl and heteroaryl;

R⁵⁰ is selected from the group consisting of H, (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, and benzyl; wherein each of said (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl and benzyl are optionally substituted with one to three same or different (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, cyano, phenyl, aryl,

heteroaryl, heteroalicyclic, hydroxy, (C₁₋₆)alkoxy, halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, acyl sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric acid, boronic ester, boronic acid, squarate, squaric acid, oxime, hydrazine, peroxide, among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic; heteroaryl is selected from the group consisting of furanyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, triazolyl, pyridinyl, pyrazinyl, pyridazinyl, and pyrimidinyl

R⁵⁴ is selected from the group consisting of hydrogen and (C₁₋₆)alkyl;

R^{54'} is (C₁₋₆)alkyl;

R⁵⁵ and R⁵⁶ are independently selected from the group consisting of hydrogen and (C₁₋₆)alkyl; and

R⁵⁷ is selected from the group consisting of hydrogen, (C₁₋₆)alkyl, aryl, heteroaryl; and

A¹ and A² are independently selected from hydrogen, (C₁₋₆)alkyl, aryl, heteroaryl, SO₂D¹, SO₂ND²D³, COD⁴, COCOD⁴, COOD⁴, COND⁵D⁶, COCOND⁵D⁶, COCOD⁴, C(=ND⁷)D⁸, C(=ND⁹)ND¹⁰D¹¹;

A¹ and A² can either never connect with each other, or conjoin to form a ring structure;

D¹, D², D³, D⁴, D⁵, D⁶, D⁷, D⁸, D⁹, D¹⁰, and D¹¹ are each independently selected from the group consisting of H, C₁-C₅₀ alkyl, C₃-C₅₀ cycloalkyl, C₃-C₅₀ alkenyl, C₄-C₅₀ cycloalkenyl, phenyl, heteroaryl, C₃-C₅₀ amide and C₃-C₅₀ ether; heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, thienyl, benzothienyl, thiazolyl, isothiazolyl, oxazolyl, benzooxazolyl, isoxazolyl, imidazolyl, benzoimidazolyl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, tetrazinyl, triazinyl and triazolyl;

provided the carbon atoms which comprise the carbon-carbon double bond of said C₃-C₂₀ alkenyl or the carbon-carbon triple bond of said C₃-C₂₀ alkynyl are not the point of attachment to the nitrogen to which D², D³, D⁵, D⁶, D⁷, D⁹, D¹⁰, and D¹¹ is attached; wherein said C₁-C₅₀ alkyl, C₃-C₅₀ cycloalkyl, C₃-C₅₀ alkenyl, C₄-C₅₀ cycloalkenyl, aryl, phenyl, heteroaryl, C₃-C₅₀ amide and C₃-C₅₀ ether is optionally substituted with one to three same or different of the following functionalities: (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C₁₋₆)alkoxy, halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, acyl sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric acid, boronic ester, boronic acid, squarate, squaric acid, oxime, hydrazine, peroxide and steroid, among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic;

15

K is selected from group J or Ar;

Ar is selected from the group consisting of phenyl and heteroaryl; wherein said phenyl and heteroaryl are each independently optionally substituted with one to three same or different members selected from the group Ar-I; and heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, thienyl, benzothienyl, thiazolyl, isothiazolyl, oxazolyl, benzooxazolyl, isoxazolyl, imidazolyl, benzoimidazolyl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, tetrazinyl, triazinyl and triazolyl;

25

Ar-I is selected from the group consisting of (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C₁₋₆)alkoxy, halogen, primary amine, secondary amine, tertiary amine, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, oxime and hydrazine, among which ether, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic; wherein said (C₁₋₆)alkyl, (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl is optionally substituted with one to three same or different of the following functionalities: (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, cyano,

30

phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C₁₋₆)alkoxy, halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, oxime and hydrazine, among which ether, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic;

J is selected from the group consisting of H, C₁-C₃₀ alkyl, C₃-C₃₀ cycloalkyl, C₄-C₃₀ bicycloalkyl, C₅-C₃₀ tricycloalkyl, C₆-C₃₀ tetracycloalkyl, C₃-C₃₀ alkenyl, C₄-C₃₀ cycloalkenyl, C₅-C₃₀ bicycloalkenyl, C₇-C₃₀ tricycloalkenyl, C₉-C₃₀ tetracycloalkyl, phenyl, aryl, heteroaryl, C₁-C₃₀ amide, C₃-C₃₀ cyclic amide, C₁-C₃₀ amine, C₃-C₃₀ cyclic amine, C₂-C₃₀ ester, C₃-C₃₀ cyclic ester, C₂-C₃₀ ether, C₃-C₃₀ cyclic ether, C₁-C₃₀ sulfonamide, C₃-C₃₀ cyclic sulfonamide, C₂-C₃₀ sulfone, C₃-C₃₀ cyclic sulfone, C₂-C₃₀ sulfamide, C₃-C₃₀ cyclic sulfamide, C₂-C₃₀ acyl sulfamide, C₃-C₃₀ acyl sulfamide, C₂-C₃₀ urea, C₃-C₃₀ cyclic urea, C₂-C₃₀ amidine, C₃-C₃₀ cyclic amidine, C₂-C₃₀ guanidine, and C₃-C₃₀ cyclic guanidine; aryl or heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, thienyl, benzothienyl, thiazolyl, isothiazolyl, oxazolyl, benzooxazolyl, isoxazolyl, imidazolyl, benzoimidazolyl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, tetrazinyl, triazinyl, triazolyl, naphthalenyl, quinolinyl, isoquinolinyl, quinoxalinyl, indolyl, azaindolyl, indazolyl, azaindazolyl, benzoisoxazolyl, azabenzisoxazolyl, benzoisothiazole, azabenzothiazolyl; wherein said C₁-C₃₀ alkyl, C₃-C₃₀ cycloalkyl, C₄-C₃₀ bicycloalkyl, C₅-C₃₀ tricycloalkyl, C₆-C₃₀ tetracycloalkyl, C₃-C₃₀ alkenyl, C₄-C₃₀ cycloalkenyl, C₅-C₃₀ bicycloalkenyl, C₇-C₃₀ tricycloalkenyl, C₉-C₃₀ tetracycloalkyl, phenyl, aryl, heteroaryl, C₁-C₃₀ amide, C₃-C₃₀ cyclic amide, C₁-C₃₀ amine, C₃-C₃₀ cyclic amine, C₂-C₃₀ ester, C₃-C₃₀ cyclic ester, C₂-C₃₀ ether, C₃-C₃₀ cyclic ether, C₁-C₃₀ sulfonamide, C₃-C₃₀ cyclic sulfonamide, C₂-C₃₀ sulfone, C₃-C₃₀ cyclic sulfone, C₂-C₃₀ sulfamide, C₃-C₃₀ cyclic sulfamide, C₂-C₃₀ acyl sulfamide, C₃-C₃₀ acyl sulfamide, C₂-C₃₀ urea, C₃-C₃₀ cyclic urea, C₂-C₃₀ amidine, C₃-C₃₀ cyclic amidine, C₂-C₃₀ guanidine, and C₃-C₃₀ cyclic guanidine is optionally substituted with one to three same or different of the following functionalities: (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C₁₋₆)alkoxy, halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid,

aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, acyl sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric acid, boronic ester, boronic acid, squarate, squaric acid, oxime, hydrazine, and peroxide, among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic;

I₁, I₂, I₃, I₄, I₅, I₆, I₇ and I₈ are each independently selected from the group consisting of H, (C₁₋₆)alkyl, (C₃₋₆) cycloalkyl, (C₂₋₆) alkenyl, (C₄₋₆) cycloalkenyl, (C₂₋₆) alkynyl, CR₈₁R₈₂OR₈₃, COR₈₄, COOR₈₅, or CONR₈₆R₈₇; wherein each of said alkyl and cycloalkyl being optionally substituted with one to three same or different cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C₁₋₆)alkoxy, halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, acyl sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric acid, boronic ester, boronic acid, squarate, squaric acid, oxime, hydrazine, peroxide, among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic; heteroaryl is selected from the group consisting of furanyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, triazolyl, pyridinyl, pyrazinyl, pyridazinyl, and pyrimidinyl;

R₈₁, R₈₂, R₈₃, R₈₄, R₈₅, R₈₆, and R₈₇ are each independently selected from the group consisting of H, (C₁₋₆)alkyl, (C₃₋₆) cycloalkyl, (C₂₋₆) alkenyl, (C₄₋₆) cycloalkenyl, (C₂₋₆) alkynyl;

U is selected from the group consisting of S, NOH, NOR₁₀₀, and NNR₁₀₁R₁₀₂;

R₁₀₀ is selected from the group consisting of C₁-C₆ alkyl;

R₁₀₁ and R₁₀₂ are J is selected from the group consisting of H, C₁-C₃₀ alkyl, C₃-C₃₀ cycloalkyl, C₄-C₃₀ bicycloalkyl, C₅-C₃₀ tricycloalkyl, C₆-C₃₀ tetracycloalkyl, C₃-C₃₀ alkenyl, C₄-C₃₀ cycloalkenyl, C₅-C₃₀ bicycloalkenyl, C₇-C₃₀ tricycloalkenyl, C₉-C₃₀ tetracycloalkyl, phenyl, aryl, heteroaryl, C₁-C₃₀ amide, C₃-C₃₀ cyclic amide, C₁-C₃₀

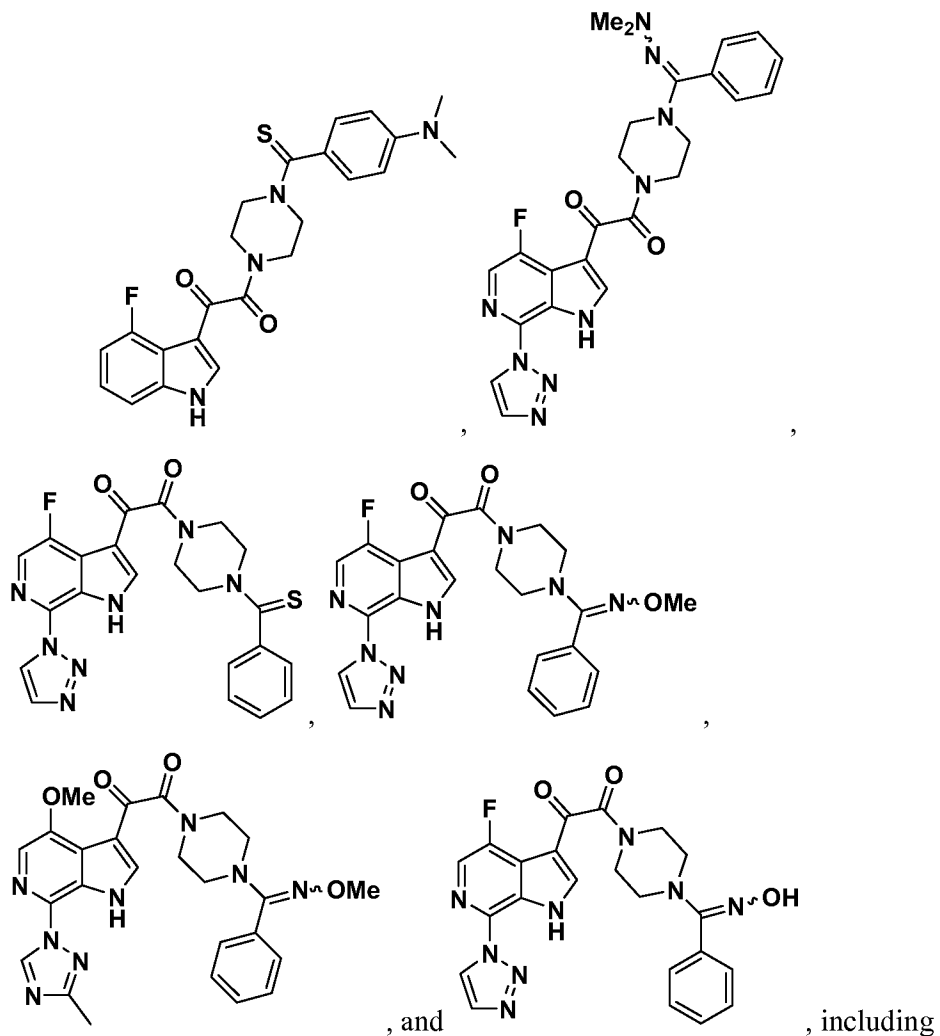
amine, C₃-C₃₀ cyclic amine, C₂-C₃₀ ester, C₃-C₃₀ cyclic ester, C₂-C₃₀ ether, C₃-C₃₀ cyclic ether, C₁-C₃₀ sulfonamide, C₃-C₃₀ cyclic sulfonamide, C₂-C₃₀ sulfone, C₃-C₃₀ cyclic sulfone, C₂-C₃₀ sulfamide, C₃-C₃₀ cyclic sulfamide, C₂-C₃₀ acyl sulfamide, C₃-C₃₀ acyl sulfamide, C₂-C₃₀ urea, C₃-C₃₀ cyclic urea, C₂-C₃₀ amidine, C₃-C₃₀ cyclic amidine, C₂-C₃₀ guainidine, and C₃-C₃₀ cyclic guainidine; aryl or heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, thienyl, benzothienyl, thiazolyl, isothiazolyl, oxazolyl, benzooxazolyl, isoxazolyl, imidazolyl, benzoimidazolyl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, tetrazinyl, triazinyl, triazolyl, naphthalenyl, quinolinyl, isoquinolinyl, quinoxalinyl, indolyl, azaindolyl, indazolyl, azaindazolyl, benzoisoxazolyl, azabenzoisoxazolyl, benzoisothiazole, azabenzothiazolyl; wherein said C₁-C₃₀ alkyl, C₃-C₃₀ cycloalkyl, C₄-C₃₀ bicycloalkyl, C₅-C₃₀ tricycloalkyl, C₆-C₃₀ tetracycloalkyl, C₃-C₃₀ alkenyl, C₄-C₃₀ cycloalkenyl, C₅-C₃₀ bicycloalkenyl, C₇-C₃₀ tricycloalkenyl, C₉-C₃₀ tetracycloalkyl, phenyl, aryl, heteroaryl, C₁-C₃₀ amide, C₃-C₃₀ cyclic amide, C₁-C₃₀ amine, C₃-C₃₀ cyclic amine, C₂-C₃₀ ester, C₃-C₃₀ cyclic ester, C₂-C₃₀ ether, C₃-C₃₀ cyclic ether, C₁-C₃₀ sulfonamide, C₃-C₃₀ cyclic sulfonamide, C₂-C₃₀ sulfone, C₃-C₃₀ cyclic sulfone, C₂-C₃₀ sulfamide, C₃-C₃₀ cyclic sulfamide, C₂-C₃₀ acyl sulfamide, C₃-C₃₀ acyl sulfamide, C₂-C₃₀ urea, C₃-C₃₀ cyclic urea, C₂-C₃₀ amidine, C₃-C₃₀ cyclic amidine, C₂-C₃₀ guainidine, and C₃-C₃₀ cyclic guainidine is optionally substituted with one to three same or different of the following functionalities: (C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C₁₋₆)alkoxy, halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, acyl sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric acid, boronic ester, boronic acid, squarate, squaric acid, oxime, hydrazine, and peroxide, among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic;

In a further embodiment of Formula I above, there is the proviso that at least one of a-e is selected from the group B or E.

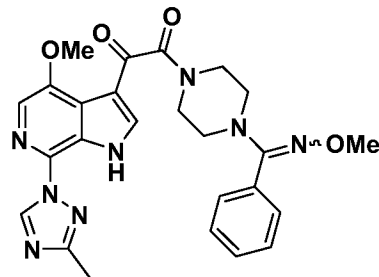
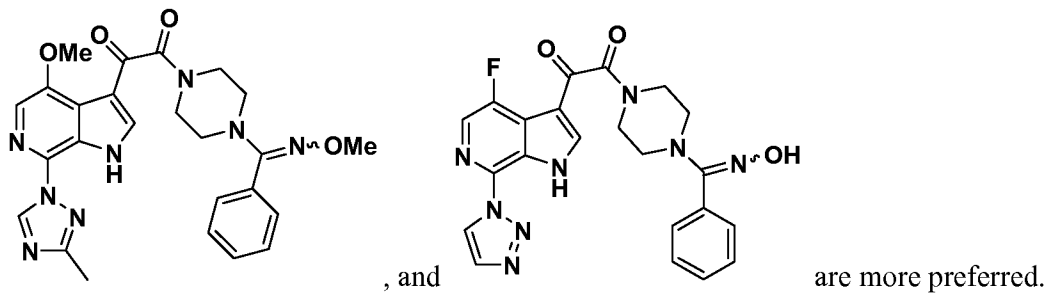
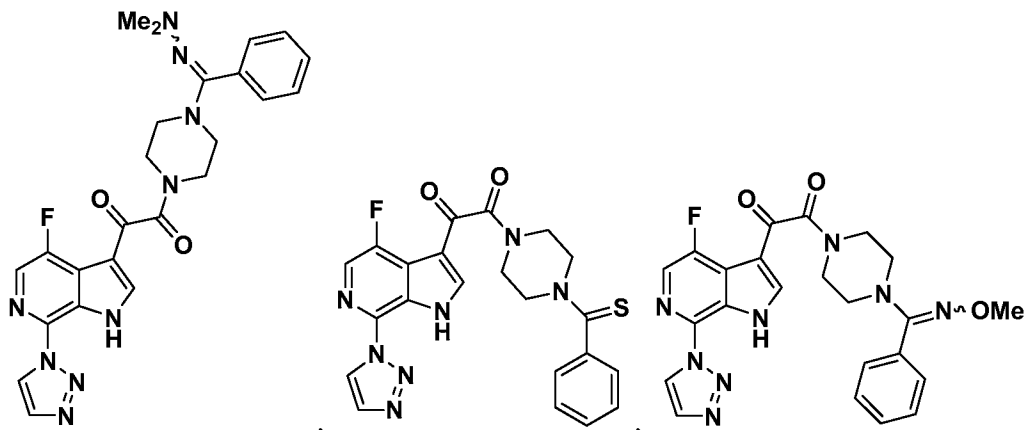
In a further embodiment of the invention, U is preferred to be S, NOH and NOR₁₀₀. Even more preferably, U is S or NOR₁₀₀.

It is also preferred that K is aryl, and even more preferably phenyl.

More preferred compounds of Formula I include those which are selected from the
 5 group consisting of:



10 pharmaceutically acceptable salts thereof. Of these, the compounds



Especially preferred is the compound

5 The compounds of the present invention, according to all the various embodiments described above, may be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, and by other means, in dosage unit formulations containing non-toxic pharmaceutically acceptable carriers, excipients and
10 diluents available to the skilled artisan. One or more adjuvants may also be included.

Thus, in accordance with the present disclosure, there is further provided a method of treatment, and a pharmaceutical composition, for treating viral infections such as HIV infection and AIDS. The treatment involves administering to a patient in need of such treatment a pharmaceutical composition which contains an antiviral effective amount of
15 one or more of the compounds of Formula I, together with one or more pharmaceutically

acceptable carriers, excipients or diluents. As used herein, the term “antiviral effective amount” means the total amount of each active component of the composition and method that is sufficient to show a meaningful patient benefit, *i.e.*, inhibiting, ameliorating, or healing of acute conditions characterized by inhibition of the HIV infection. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously. The terms “treat, treating, treatment” as used herein and in the claims means preventing, ameliorating or healing diseases associated with HIV infection.

The pharmaceutical compositions of the invention may be in the form of orally administrable suspensions or tablets; as well as nasal sprays, sterile injectable preparations, for example, as sterile injectable aqueous or oleaginous suspensions or suppositories. Pharmaceutically acceptable carriers, excipients or diluents may be utilized in the pharmaceutical compositions, and are those utilized in the art of pharmaceutical preparations.

When administered orally as a suspension, these compositions are prepared according to techniques typically known in the art of pharmaceutical formulation and may contain microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners/flavoring agents known in the art. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents, and lubricants known in the art.

The injectable solutions or suspensions may be formulated according to known art, using suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer’s solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

The compounds of this disclosure can be administered orally to humans in a dosage range of 1 to 100 mg/kg body weight in divided doses, usually over an extended period, such as days, weeks, months, or even years. One preferred dosage range is 1 to 10 mg/kg body weight orally in divided doses. Another preferred dosage range is 1 to 20

mg/kg body weight in divided doses. It will be understood, however, that 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.

Also contemplated herein are combinations of the compounds of Formula I herein set forth, together with one or more agents useful in the treatment of AIDS. For example, the compounds of this disclosure may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of the AIDS antivirals, immunomodulators, anti-infectives, or vaccines, such as those in the following non-limiting table:

ANTIVIRALS

| Drug Name | Manufacturer | Indication |
|---------------------------------|----------------|--|
| Rilpivirine | Tibotec | HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor) |
| Complera ® | Gilead | HIV infection, AIDS, ARC; combination with emtricitabine, rilpivirine, and tenofovir disoproxil fumarate |
| 097 | Hoechst/Bayer | HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase (RT) inhibitor) |
| Amprenavir 141 W94 GW 141 | Glaxo Wellcome | HIV infection, AIDS, ARC (protease inhibitor) |
| Abacavir (1592U89) | Glaxo Wellcome | HIV infection, |

| | | | |
|----|---|--|---|
| | GW 1592 | | AIDS, ARC (RT inhibitor) |
| 5 | Acemannan | Carrington Labs (Irving, TX) | ARC |
| | Acyclovir | Burroughs Wellcome | HIV infection, AIDS, ARC |
| 10 | AD-439 | Tanox Biosystems | HIV infection, AIDS, ARC |
| | AD-519 | Tanox Biosystems | HIV infection, AIDS, ARC |
| 15 | Adefovir dipivoxil AL-721 | Gilead Sciences Ethigen (Los Angeles, CA) | HIV infection ARC, PGL HIV positive, AIDS |
| 20 | Alpha Interferon | Glaxo Wellcome | Kaposi's sarcoma, HIV in combination w/Retrovir |
| | Ansamycin LM 427 | Adria Laboratories (Dublin, OH) Erbamont (Stamford, CT) | ARC |
| 25 | | | |
| | Antibody which Neutralizes pH Labile alpha aberrant Interferon | Advanced Biotherapy Concepts (Rockville, MD) | AIDS, ARC |
| 30 | | | |
| | AR177 | Aronex Pharm | HIV infection, AIDS, ARC |
| 35 | | | |
| | Beta-fluoro-ddA | Nat'l Cancer Institute | AIDS-associated diseases |
| | BMS-234475 (CGP-61755) | Bristol-Myers Squibb/ Novartis | HIV infection, AIDS, ARC (protease inhibitor) |
| 40 | | | |
| | CI-1012 | Warner-Lambert | HIV-1 infection |

| | | | |
|----|----------------------------------|--|--|
| | Cidofovir | Gilead Science | CMV retinitis, herpes, papillomavirus |
| 5 | Curdlan sulfate | AJI Pharma USA | HIV infection |
| | Cytomegalovirus Immune globin | MedImmune | CMV retinitis |
| 10 | Cytovene | Syntex | Sight threatening |
| | Ganciclovir | | CMV peripheral CMV retinitis |
| 15 | Darunavir | Tibotec- J & J | HIV infection, AIDS, ARC (protease inhibitor) |
| 20 | Delaviridine | Pharmacia-Upjohn | HIV infection, AIDS, ARC (RT inhibitor) |
| 25 | Dextran Sulfate | Ueno Fine Chem. Ind. Ltd. (Osaka, Japan) | AIDS, ARC, HIV positive asymptomatic |
| | ddC Dideoxycytidine | Hoffman-La Roche | HIV infection, AIDS, ARC |
| 30 | ddI Dideoxyinosine | Bristol-Myers Squibb | HIV infection, AIDS, ARC; combination with AZT/d4T |
| 35 | DMP-450 | AVID (Camden, NJ) | HIV infection, AIDS, ARC (protease inhibitor) |

| | | | |
|----|--|-------------------------------------|---|
| 5 | Efavirenz (DMP 266, Sustiva [®]) (-)-6-Chloro-4-(S)- cyclopropylethynyl- 4(S)-trifluoro- methyl-1,4-dihydro- 2H-3,1-benzoxazin- 2-one, STOCRINE | Bristol Myers Squibb | HIV infection, AIDS, ARC (non-nucleoside RT inhibitor) |
| 10 | EL10 | Elan Corp, PLC (Gainesville, GA) | HIV infection |
| 15 | Etravirine | Tibotec/ J & J | HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor) |
| 20 | Famciclovir | Smith Kline | herpes zoster, herpes simplex |
| 25 | GS 840 | Gilead | HIV infection, AIDS, ARC (reverse transcriptase inhibitor) |
| 30 | HBY097 | Hoechst Marion Roussel | HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor) |
| 35 | Hypericin | VIMRx Pharm. | HIV infection, AIDS, ARC |
| 40 | Recombinant Human Interferon Beta | Triton Biosciences (Alameda, CA) | AIDS, Kaposi's sarcoma, ARC |
| 45 | Interferon alfa-n3 | Interferon Sciences | ARC, AIDS |
| | Indinavir | Merck | HIV infection, AIDS, ARC, asymptomatic HIV positive, also in combination with AZT/ddI/ddC |

| | | | |
|----|--------------------------------|-----------------------------------|---|
| | ISIS 2922 | ISIS Pharmaceuticals | CMV retinitis |
| | KNI-272 | Nat'l Cancer Institute | HIV-assoc. diseases |
| 5 | Lamivudine, 3TC | Glaxo Wellcome | HIV infection, AIDS, ARC (reverse transcriptase inhibitor); also with AZT |
| 10 | Lobucavir | Bristol-Myers Squibb | CMV infection |
| 15 | Nelfinavir | Agouron Pharmaceuticals | HIV infection, AIDS, ARC (protease inhibitor) |
| 20 | Nevirapine | Boeheringer Ingelheim | HIV infection, AIDS, ARC (RT inhibitor) |
| | Novapren | Novaferon Labs, Inc. (Akron, OH) | HIV inhibitor |
| 25 | Peptide T Octapeptide Sequence | Peninsula Labs (Belmont, CA) | AIDS |
| 30 | Trisodium Phosphonoformate | Astra Pharm. Products, Inc. | CMV retinitis, HIV infection, other CMV infections |
| 35 | PNU-140690 | Pharmacia Upjohn | HIV infection, AIDS, ARC (protease inhibitor) |
| | Probucol | Vyrex | HIV infection, AIDS |
| 40 | RBC-CD4 | Sheffield Med. Tech (Houston, TX) | HIV infection, AIDS, ARC |
| | Ritonavir | Abbott | HIV infection, AIDS, ARC |

| | | | |
|----|--|------------------------------|---|
| | | | (protease inhibitor) |
| 5 | Saquinavir | Hoffmann-LaRoche | HIV infection, AIDS, ARC (protease inhibitor) |
| 10 | Stavudine; d4T Didehydrodeoxy-Thymidine | Bristol-Myers Squibb | HIV infection, AIDS, ARC |
| | Tipranavir | Boehringer Ingelheim | HIV infection, AIDS, ARC (protease inhibitor) |
| 15 | Valaciclovir | Glaxo Wellcome | Genital HSV & CMV Infections |
| | Virazole Ribavirin | Viratek/ICN (Costa Mesa, CA) | asymptomatic HIV positive, LAS, ARC |
| 20 | VX-478 | Vertex | HIV infection, AIDS, ARC |
| 25 | Zalcitabine | Hoffmann-LaRoche | HIV infection, AIDS, ARC, with AZT |
| 30 | Zidovudine; AZT | Glaxo Wellcome | HIV infection, AIDS, ARC, Kaposi's sarcoma, in combination with other therapies |
| 35 | Tenofovir disoproxil, fumarate salt (Viread [®]) | Gilead | HIV infection, AIDS, (reverse transcriptase inhibitor) |
| 40 | Emtriva [®] (Emtricitabine) (FTC) | Gilead | HIV infection, AIDS, (reverse transcriptase inhibitor) |
| 45 | Combivir [®] | GSK | HIV infection, AIDS, (reverse transcriptase inhibitor) |
| | Abacavir succinate | GSK | HIV infection, |

| | | | |
|----|---|----------------------|--|
| | (or Ziagen [®]) | | AIDS, (reverse transcriptase inhibitor) |
| 5 | Reyataz [®] (or atazanavir) | Bristol-Myers Squibb | HIV infection AIDs, protease inhibitor |
| 10 | Fuzeon [®] (Enfuvirtide or T-20) | Roche / Trimeris | HIV infection AIDs, viral Fusion inhibitor |
| 15 | Lexiva [®] (or Fosamprenavir calcium) | GSK/Vertex | HIV infection AIDs, viral protease inhibitor |
| 20 | Selzentry Maraviroc; (UK 427857) | Pfizer | HIV infection AIDs, (CCR5 antagonist, in development) |
| 25 | Trizivir [®] | GSK | HIV infection AIDs, (three drug combination) |
| 30 | Sch-417690 (vicriviroc) | Schering-Plough | HIV infection AIDs, (CCR5 antagonist, in development) |
| 35 | TAK-652 | Takeda | HIV infection AIDs, (CCR5 antagonist, in development) |
| 40 | GSK 873140 (ONO-4128) | GSK/ONO | HIV infection AIDs, (CCR5 antagonist, in development) |
| 45 | Integrase Inhibitor MK-0518 Raltegravir | Merck | HIV infection AIDs |
| | Truvada [®] | Gilead | Combination of Tenofovir disoproxil fumarate salt (Viread [®]) and Emtriva [®] (Emtricitabine) |
| | Integrase Inhibitor | Gilead/Japan Tobacco | HIV Infection |

| | | | |
|----|--|-----------------------------|--|
| | GS917/JTK-303 Elvitegravir | | AIDs in development |
| 5 | Triple drug combination Atripla [®] | Gilead/Bristol-Myers Squibb | Combination of Tenofovir disoproxil fumarate salt (Viread [®]), Emtriva [®] (Emtricitabine), and Sustiva [®] (Efavirenz) |
| 10 | Festinavir [®] | Oncolys BioPharma | HIV infection AIDs in development |
| 15 | CMX-157 Lipid conjugate of nucleotide tenofovir | Chimerix | HIV infection AIDs |
| 20 | GSK1349572 Integrase inhibitor | GSK | HIV infection AIDs |

IMMUNOMODULATORS

| | <i>Drug Name</i> | <i>Manufacturer</i> | <i>Indication</i> |
|----|------------------|---------------------------------------|-----------------------------------|
| 25 | AS-101 | Wyeth-Ayerst | AIDS |
| | Bropirimine | Pharmacia Upjohn | Advanced AIDS |
| 30 | Acemannan | Carrington Labs, Inc. (Irving, TX) | AIDS, ARC |
| | CL246,738 | Wyeth Lederle Labs | AIDS, Kaposi's sarcoma |
| 35 | FP-21399 | Fuki ImmunoPharm | Blocks HIV fusion with CD4+ cells |
| | Gamma Interferon | Genentech | ARC, in combination |

| | | | |
|----|--|-------------------------------------|---|
| | | | w/TNF (tumor necrosis factor) |
| 5 | Granulocyte Macrophage Colony Stimulating Factor | Genetics Institute Sandoz | AIDS |
| 10 | Granulocyte Macrophage Colony Stimulating Factor | Hoechst-Roussel Immunex | AIDS |
| 15 | Granulocyte Macrophage Colony Stimulating Factor | Schering-Plough | AIDS, combination w/AZT |
| | HIV Core Particle Immunostimulant | Rorer | Seropositive HIV |
| 20 | IL-2 Interleukin-2 | Cetus | AIDS, in combination w/AZT |
| | IL-2 Interleukin-2 | Hoffman-LaRoche Immunex | AIDS, ARC, HIV, in combination w/AZT |
| 25 | IL-2 Interleukin-2 (aldeslukin) | Chiron | AIDS, increase in CD4 cell counts |
| 30 | Immune Globulin Intravenous (human) | Cutter Biological (Berkeley, CA) | Pediatric AIDS, in combination w/AZT |
| 35 | IMREG-1 | Imreg (New Orleans, LA) | AIDS, Kaposi's sarcoma, ARC, PGL |
| | IMREG-2 | Imreg (New Orleans, LA) | AIDS, Kaposi's sarcoma, ARC, PGL |
| 40 | Imuthiol Diethyl Dithio Carbamate | Merieux Institute | AIDS, ARC |
| | Alpha-2 Interferon | Schering Plough | Kaposi's sarcoma w/AZT, AIDS |

| | | | |
|----|---------------------------------------|--|--|
| | Methionine-Enkephalin | TNI Pharmaceutical (Chicago, IL) | AIDS, ARC |
| 5 | MTP-PE Muramyl-Triptide | Ciba-Geigy Corp. | Kaposi's sarcoma |
| 10 | Granulocyte Colony Stimulating Factor | Amgen | AIDS, in combination w/AZT |
| | Remune | Immune Response Corp. | Immunotherapeutic |
| 15 | rCD4 Recombinant Soluble Human CD4 | Genentech | AIDS, ARC |
| 20 | rCD4-IgG hybrids | | AIDS, ARC |
| | Recombinant Soluble Human CD4 | Biogen | AIDS, ARC |
| 25 | Interferon Alfa 2a | Hoffman-La Roche | Kaposi's sarcoma AIDS, ARC, in combination w/AZT |
| 30 | SK&F106528 Soluble T4 | Smith Kline | HIV infection |
| | Thymopentin | Immunobiology Research Institute (Annandale, NJ) | HIV infection |
| 35 | Tumor Necrosis Factor; TNF | Genentech | ARC, in combination w/gamma Interferon |

ANTI-INFECTIVES

| | | | |
|----|------------------|---------------------|-------------------|
| 40 | <i>Drug Name</i> | <i>Manufacturer</i> | <i>Indication</i> |
|----|------------------|---------------------|-------------------|

| | | | |
|----|--|-------------------------|---|
| | Clindamycin with Primaquine | Pharmacia Upjohn | PCP |
| 5 | Fluconazole | Pfizer | Cryptococcal meningitis, candidiasis |
| 10 | Pastille Nystatin Pastille | Squibb Corp. | Prevention of oral candidiasis |
| | Ornidyl Eflornithine | Merrell Dow | PCP |
| 15 | Pentamidine Isethionate (IM & IV) | LyphoMed (Rosemont, IL) | PCP treatment |
| | Trimethoprim | | Antibacterial |
| 20 | Trimethoprim/sulfa | | Antibacterial |
| | Piritrexim | Burroughs Wellcome | PCP treatment |
| 25 | Pentamidine Isethionate for Inhalation | Fisons Corporation | PCP prophylaxis |
| | Spiramycin | Rhone-Poulenc diarrhea | Cryptosporidial |
| 30 | Intraconazole-R51211 | Janssen-Pharm. | Histoplasmosis; cryptococcal meningitis |
| 35 | Trimetrexate | Warner-Lambert | PCP |
| | Daunorubicin | NeXstar, Sequus | Kaposi's sarcoma |
| 40 | Recombinant Human Erythropoietin | Ortho Pharm. Corp. | Severe anemia assoc. with AZT therapy |

| | | | |
|----|----------------------------------|-------------------------------|--|
| | Recombinant Human Growth Hormone | Serono | AIDS-related wasting, cachexia |
| 5 | Megestrol Acetate | Bristol-Myers Squibb | Treatment of anorexia assoc. W/AIDS |
| 10 | Testosterone | Alza, Smith Kline | AIDS-related wasting |
| | Total Enteral Nutrition | Norwich Eaton Pharmaceuticals | Diarrhea and malabsorption related to AIDS |

15

Additionally, the compounds of the disclosure herein set forth may be used in combination with other HIV entry inhibitors. Examples of such HIV entry inhibitors are discussed in *Drugs of the Future*, 24(12):1355-1362 (1999); *Cell*, 9:243-246 (Oct. 29, 1999); and *Drug Discovery Today*, 5(5):183-194 (May 2000) and Meanwell, N.A. et al., “Inhibitors of the entry of HIV into host cells”, *Curr. Op. Drug Disc. Dev*, 6(4):451-461 (2003). Specifically the compounds can be utilized in combination with other attachment inhibitors, fusion inhibitors, and chemokine receptor antagonists aimed at either the CCR5 or CXCR4 coreceptor.

It will be understood that the scope of combinations of the compounds of this disclosure with AIDS antivirals, immunomodulators, anti-infectives, HIV entry inhibitors or vaccines is not limited to the list in the above Table but includes, in principle, any combination with any pharmaceutical composition useful for the treatment of AIDS.

Preferred combinations are simultaneous or alternating treatments with a compound of the present disclosure and an inhibitor of HIV protease and/or a non-nucleoside inhibitor of HIV reverse transcriptase. An optional fourth component in the combination is a nucleoside inhibitor of HIV reverse transcriptase, such as AZT, 3TC, ddC or ddI. A preferred inhibitor of HIV protease is REYATAZ® (active ingredient Atazanavir). Typically a dose of 300 to 600mg is administered once a day. This may be co-administered with a low dose of Ritonavir (50 to 500mgs). Another preferred inhibitor of HIV protease is KALETRA®. Another useful inhibitor of HIV protease is

indinavir, which is the sulfate salt of N-(2(R)-hydroxy-1-(S)-indanyl)-2(R)-phenylmethyl-4-(S)-hydroxy-5-(1-(4-(3-pyridyl-methyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide ethanolate, and is synthesized according to U.S. Patent No. 5,413,999.

Indinavir is generally administered at a dosage of 800 mg three times a day. Other preferred protease inhibitors are nelfinavir and ritonavir. Another preferred inhibitor of HIV protease is saquinavir which is administered in a dosage of 600 or 1200 mg tid. Preferred non-nucleoside inhibitors of HIV reverse transcriptase include efavirenz. These combinations may have unexpected effects on limiting the spread and degree of infection of HIV. Preferred combinations include those with the following (1) indinavir with efavirenz, and, optionally, AZT and/or 3TC and/or ddI and/or ddC; (2) indinavir, and any of AZT and/or ddI and/or ddC and/or 3TC, in particular, indinavir and AZT and 3TC; (3) stavudine and 3TC and/or zidovudine; (4) zidovudine and lamivudine and 141W94 and 1592U89; (5) zidovudine and lamivudine. (The preparation of ddC, ddI and AZT are also described in EP 0 484 071.)

In such combinations the compound of the present disclosure and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

GENERAL CHEMISTRY (METHODS OF SYNTHESIS)

The present invention comprises compounds of Formula I, their pharmaceutical formulations, and their use in patients suffering from or susceptible to HIV infection. The compounds of Formula I include pharmaceutically acceptable salts thereof. General procedures to construct compounds of Formula I and intermediates useful for their synthesis are described in the following Schemes (after the Abbreviations).

Abbreviations

One or more of the following abbreviations, most of which are conventional abbreviations well known to those skilled in the art, may be used throughout the description of the disclosure and the examples:

h = hour(s)

rt = room temperature

- mol = mole(s)
mmol = millimole(s)
g = gram(s)
mg = milligram(s)
- 5 mL = milliliter(s)
TFA = trifluoroacetic Acid
DCE = 1,2-Dichloroethane
CH₂Cl₂ = dichloromethane
TPAP = tetrapropylammonium perruthenate
- 10 THF = tetrahydrofuran
DEPBT = 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one
DMAP = 4-dimethylaminopyridine
P-EDC = polymer supported 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
- 15 DMF = *N,N*-dimethylformamide
Hunig's Base = *N,N*-diisopropylethylamine
MCPBA = *meta*-chloroperbenzoic acid
azaindole = 1*H*-pyrrolo-pyridine
4-azaindole = 1*H*-pyrrolo[3,2-*b*]pyridine
- 20 5-azaindole = 1*H*-pyrrolo[3,2-*c*]pyridine
6-azaindole = 1*H*-pyrrolo[2,3-*c*]pyridine
7-azaindole = 1*H*-pyrrolo[2,3-*b*]pyridine
PMB = 4-methoxybenzyl
DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
- 25 OTf = trifluoromethanesulfonyl
NMM = 4-methylmorpholine
PIP-COPh = 1-benzoylpiperazine
NaHMDS = sodium hexamethyldisilazide
EDAC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
- 30 TMS = trimethylsilyl
DCM = dichloromethane
DCE = dichloroethane
MeOH = methanol

THF = tetrahydrofuran

EtOAc = ethyl acetate

LDA = lithium diisopropylamide

TMP-Li = 2,2,6,6-tetramethylpiperidinyl lithium

5 DME = dimethoxyethane

DIBALH = diisobutylaluminum hydride

HOBT = 1-hydroxybenzotriazole

CBZ = benzyloxycarbonyl

PCC = pyridinium chlorochromate

10 TBTU = O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate

DEBPT = 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one

BOP = benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphoniumhexafluorophosphate

15 *Preparation of Compounds of Formula I*

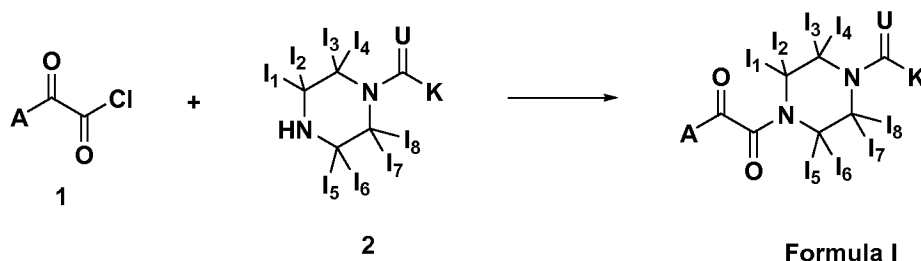
Preparation of template A-CO-CO-Cl and A-CO-CO-OH has been described in detail in WO-00076521, WO-00162255, WO-00204440, WO-02062423, WO-02085301, WO-03068221 and US-2004/0063744.

20

Standard conditions such as reacting amine with acyl halide **1** (**Scheme 1a**) and carboxyl acid **3** (**Scheme 1b**) can be used to convert the ketone to the desired amide products. Some general references of these methodologies and directions for use are contained in "Comprehensive Organic Transformation" by Richard C. Larock, Wiley-

25 VCH, New York, 1989, 972 (Carboxylic acids to amides), 979 (Acid halides to amides).

Scheme 1a

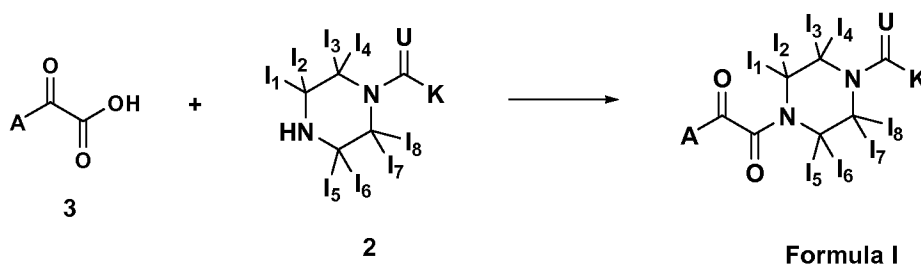


5

Scheme 1a depicts a general method for forming an amide from piperazine derivative **2** and acyl chloride **1**. An appropriate base (from catalytic to an excess amount) selected from sodium hydride, potassium carbonate, triethylamine, DBU, pyridine, DMAP or di-isopropyl ethyl amine was added into a solution of piperazine derivative **2** and acyl chloride **1** in an appropriate solvent selected from dichloromethane, chloroform, benzene, toluene, THF, diethyl ether, dioxane, acetone, N,N-dimethylformamide or pyridine at room temperature. Then reaction was carried out at either room temperature or evaluated temperature up to 150°C over a period of time (30 minutes to 16 hours) to afford the structure of Formula I. Some selected references involving such reactions include a) *Indian J. Chem., Sect B* **1990**, 29, 1077; 2) *Chem. Sci.* **1998**, 53, 1216; 3) *Chem. Pharm. Bull.* **1992**, 40, 1481; 4) *Chem. Heterocycl. Compd.* **2002**, 38, 539.

20

Scheme 1b



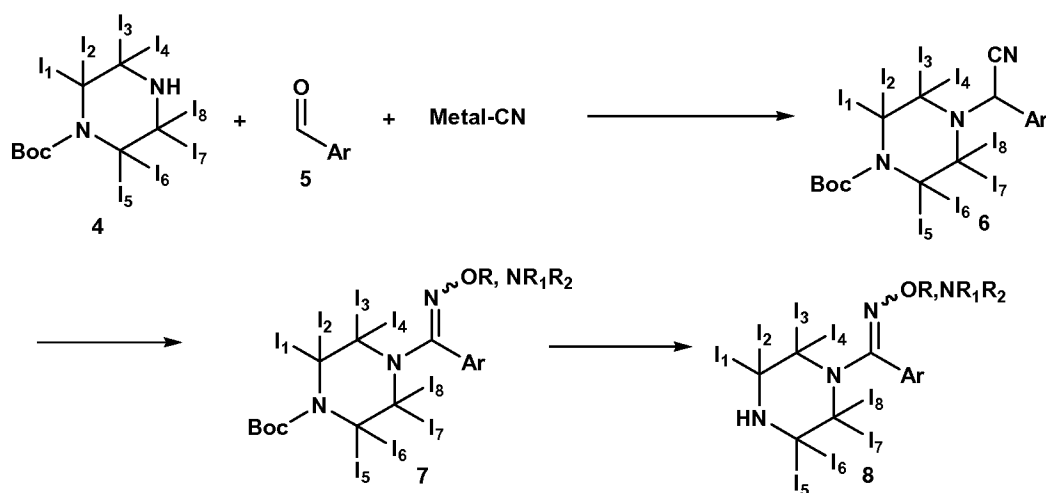
Alternatively, as shown in **Scheme 1b**, a piperazine derivative **2** can be coupled with an acid **3** using standard amide bond or peptide bond forming coupling reagents. Many reagents for amide bond couplings are known by an organic chemist skilled in the art and nearly all of these are applicable for realizing coupled amide products. The

combination of EDAC and triethylamine in tetrahydrofuran or BOPCl and diisopropyl ethyl amine in chloroform have been utilized most frequently but DEPBT, or other coupling reagents such as PyBop could be utilized. Another useful coupling condition employs HATU ((a) *J.Chem.Soc. Chem Comm.* **1994**, 201; (b) *J. Am. Chem. Soc.* 1994, 116,11580). Additionally, DEPBT (3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one) and *N,N*-diisopropylethylamine, commonly known as Hunig's base, represents another efficient method to form the amide bond and provide compounds of Formula I. DEPBT is either purchased from Aldrich or prepared according to the procedure described in *Organic Lett.*, **1999**, 1, 91. Typically an inert solvent such as DMF or THF is used but other aprotic solvents could be used.

The piperazine oxime and hydrazone derivatives used in **Scheme 1a** and **Scheme 1b** may be prepared by methods described in **Scheme 2**.

15

Scheme 2

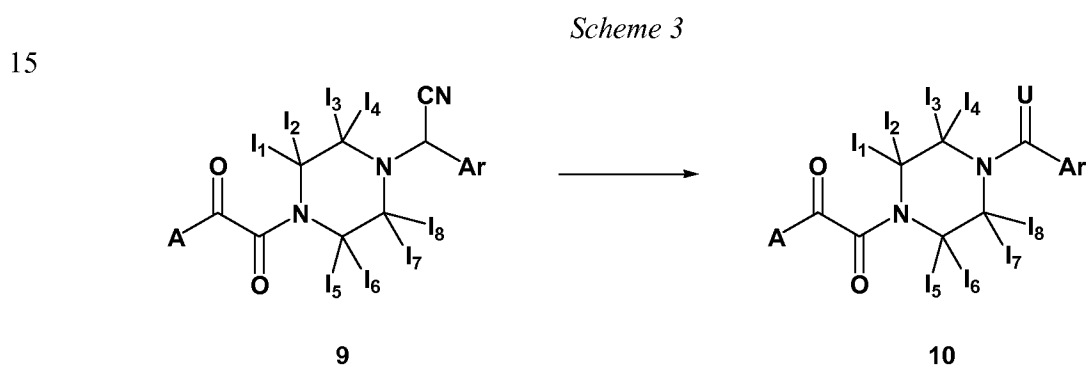


Scheme 2 presents a general route for the preparation of aryl piperazinyl oximes and hydrazones **8**, by using N-Boc piperazine **4** as the starting material. In a mixed solvent of water and alcohol such as methanol and ethanol, at a temperature between -78°C and 50°C with ambient temperature being preferred, in the presence of NaCN or KCN and NaHSO₃, N-Boc piperazine **4** can react with an aryl aldehyde **5** to offer 2-aryl 2-(piperazin-1-yl)acetonitrile **6**. The intermediate **6** can be oxidized by NiO₂-H₂O or MnO₂ in the presence of an alkoxyamine or an *N,N*-disubstituted hydrazine (*Tetrahedron*

Lett. **2005**, *46*, 4919), to produce an aryl N-Boc piperazinyl oxime or hydrazone **7**. The reaction solvent could be THF, DME, dioxane, DMF, EtOH, MeOH and water alone, or a mixture of two or three of these solvents and temperatures would range from ambient to reflux with ambient being the initial temperature evaluated. A well established

5 deprotection of the Boc group under acidic conditions in solution could provide an aryl piperazinyl oxime or hydrazone **8**. TFA and HCl are the typical acids used for this deprotection, while the most commonly used solvents are ether and dichloromethane or neat TFA, but other acidic agents and solvents could be used. Some selected references involving such reactions include 1) *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2777; 2) *Zh. Org.*

10 *Khim.* **1996**, *32*, 1010; 3) *J. Fluorine Chem.* **1996**, *76*, 177; 4) *Synth. Commun.* **1996**, *26*, 3549; 5) *J. Heterocycl. Chem.* **1994**, *31*, 841; 6) *J. Org. Chem.* **1964**, *29*, 794.



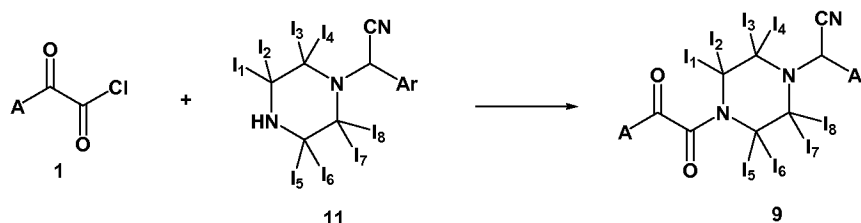
Alternatively, compounds of **Formula I** with K equal to Ar (compound **10**) could also be synthesized from an aryl piperazinyl acetonitrile intermediate **9** by oxidization

20 using NiO₂-H₂O or MnO₂ in the presence of an NH₂-containing agent including N,N-disubstituted hydrazines or O-substituted hydroxyl amines (**Scheme 3**, *Tetrahedron Lett.* **2005**, *46*, 4919). An excess amount of NiO₂-H₂O or MnO₂ could be added into a solution of compound **9** and the NH₂-containing agent in a suitable solvent to afford compound

10. THF, DME, dioxane, DMF, EtOH, MeOH and water alone, or their mixture, can be

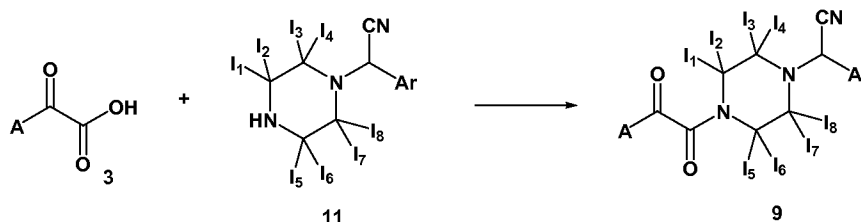
25 utilized as the solvent.

Scheme 4



5 Aryl piperazinyl acetonitrile intermediate **9** could be prepared *via* the reaction of a 2-keto acyl halide **1** and aryl piperazinyl acetonitrile **11**, as shown in **Scheme 4**. An appropriate base (from catalytic to an excess amount) selected from sodium hydride, potassium carbonate, triethylamine, DBU, pyridine, DMAP or diisopropyl ethyl amine would be added into a solution of the aryl piperazinyl acetonitrile **11** and the 2-keto acyl chloride **1** in an appropriate solvent selected from dichloromethane, chloroform, benzene, toluene, THF, diethyl ether, dioxane, acetone, N,N-dimethylformamide or pyridine at room temperature. Then the reaction was carried out at either room temperature or an appropriate temperature up to 150°C over a period of time (30 minutes to 16 hours) to afford compound **9**. Some selected references involving such reactions include a) *Indian*
 10 *J. Chem., Sect B* **1990**, 29, 1077; 2) *Chem. Sci.* **1998**, 53, 1216; 3) *Chem. Pharm. Bull.* **1992**, 40, 1481; 4) *Chem. Heterocycl. Compd.* **2002**, 38, 539.

Scheme 5



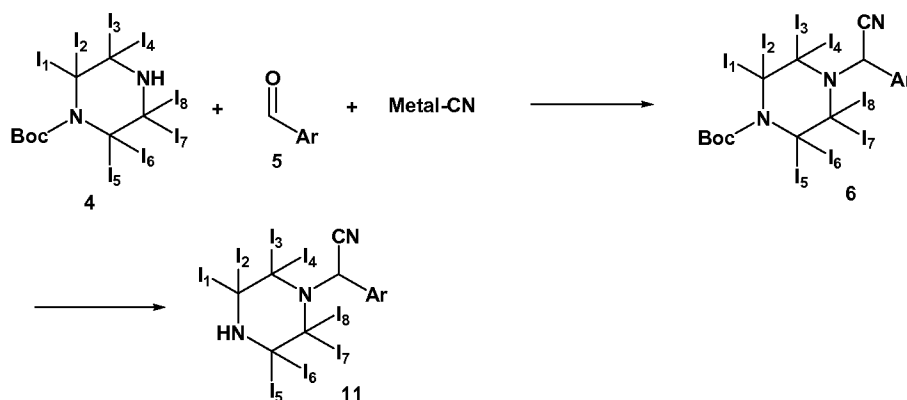
20 As shown in **Scheme 5**, an aryl piperazinyl acetonitrile **11** could be coupled with a 2-keto acid **3** using standard amide bond or peptide bond forming coupling reagents. Many reagents for amide bond couplings are known by an organic chemist skilled in the art and nearly all of these are applicable for realizing coupled amide products. The combination of EDAC and triethylamine in tetrahydrofuran or BOPCl and diisopropyl ethyl amine in chloroform have been utilized most frequently but DEPBT, or other coupling reagents such as PyBop could be utilized. Another useful coupling condition

employs HATU ((a) *J. Chem. Soc. Chem Comm.* **1994**, 201; (b) *J. Am. Chem. Soc.* 1994, 116,11580). Additionally, DEPBT (3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one) and *N,N*-diisopropylethylamine, commonly known as Hunig's base, represents another efficient method to form the amide bond and provide compound **9**.

- 5 DEPBT is either purchased commercially or prepared according to the procedure described in *Organic Lett.*, **1999**, 1, 91. Typically an inert solvent such as DMF or THF is used but other aprotic solvents could be used.

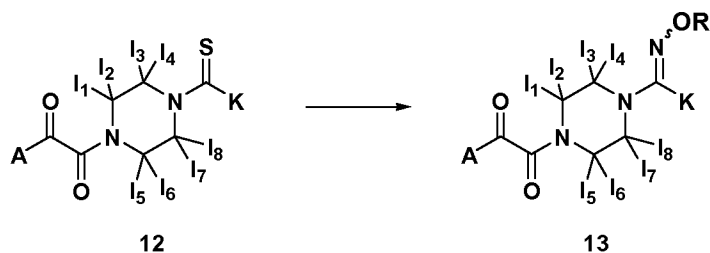
Scheme 6

10



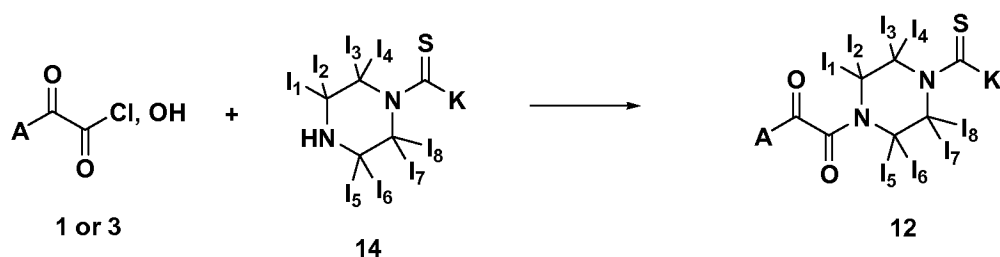
- Aryl piperazinyl acetonitrile **11** could be prepared *via* a Strecker reaction involving N-Boc piperazine **4**, an aryl aldehyde **5** and a cyanide agent, followed by
- 15 removal of the Boc group from the N atom under acidic condition as described earlier. In the Strecker reaction, the cyanide agent can be selected from TMS-CN, NaCN, KCN, $Al(CN)_3$, $Zn(CN)_2$, CuCN, or HCN (gas or solution). The solvent could be an aprotic (e.g., THF, DMF, DMSO, benzene) or protic solvent (e.g., MeOH, EtOH, PrOH, BuOH, water). Usually a protic solvent or a co-solvent with a protic component is preferred.
- 20 Some selected references involving Strecker reactions include a) *Aust. J. Chem.* **1997**, 50, 747; b) *Tetrahedron* **1997**, 53, 8941; c) *Can. J. Chem.* **1996**, 74, 88; d) *J. Org. Chem.* **1995**, 60, 588; e) *Synthesis* **1995**, 659; f) *Chem. Ber.* **1994**, 127, 1761.

Scheme 7



- 5 Substituted piperazinyl oxime **13** could be prepared *via* a displacement reaction of thione **12** with hydroxyamine, with or without a mercury reagent, and with or without a base. The mercury reagent can be selected from HgO, Hg(OAc)₂, HgF₂, HgCl₂, HgBr₂, HgI₂. The base can be selected from K₂CO₃, Na₂CO₃, KHCO₃, NaHCO₃, NaOH, KOH, AcONa, AcOK, pyridine, iPr₂NEt, Et₃N. The solvent could be an aprotic (e.g., THF,
- 10 DMF, DMSO, benzene, pyridine) or protic solvent (e.g., MeOH, EtOH, PrOH, BuOH, water). Some selected references include a) *Canadian Journal of Chemistry* **1985**, 63, 3089; b) *European Journal of Medicinal Chemistry* **1990**, 25, 403; c) *Journal of Organic Chemistry* **1980**, 45, 4198; d) *Journal of the Chemical Society, Section A: Inorganic, Physical, Theoretical* **1968**, 1519; e) *European Journal of Medicinal Chemistry* **1987**, 22,
- 15 485; f) *Pest Management Science* **2002**, 58, 1205.

Scheme 8



20

Thione **12** can be synthesized according to the conditions described in **Scheme 1a** and **Scheme 1b**, using substituted piperazinyl thione **14** as the starting material.

Reaction conditions and methods given in the specific examples are broadly applicable to compounds with other substitution and to other transformations in this application.

Examples

5

The following examples illustrate typical syntheses of the compounds of Formula I as described generally above. These examples are illustrative only and are not intended to limit the disclosure in any way. The reagents and starting materials are readily available to one of ordinary skill in the art.

10

Chemistry Experimental

Typical Procedures and Characterization of Selected Examples:

- 15 Unless otherwise stated, solvents and reagents were used directly as obtained from commercial sources, and reactions were performed under a nitrogen atmosphere. Flash chromatography was conducted on Silica gel 60 (0.040-0.063 particle size; EM Science supply). ¹H NMR spectra were recorded on Bruker DRX-500f at 500 MHz (or Bruker DPX-300B or Varian Gemini 300 at 300 MHz as stated). The chemical shifts were
- 20 reported in ppm on the δ scale relative to $\delta_{\text{TMS}} = 0$. The following internal references were used for the residual protons in the following solvents: CDCl₃ (δ_{H} 7.26), CD₃OD (δ_{H} 3.30), and DMSO-*d*₆ (δ_{H} 2.50). Standard acronyms were employed to describe the multiplicity patterns: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), b (broad), app (apparent). The coupling constant (*J*) is in Hertz. All Liquid
- 25 Chromatography (LC) data were recorded on a Shimadzu LC-10AS liquid chromatograph using a SPD-10AV UV-Vis detector with Mass Spectrometry (MS) data determined using a Micromass Platform for LC in electrospray mode.

HPLC Method (i.e., compound isolation)

- 30 Compounds purified by preparative HPLC were diluted in methanol (1.2 mL) and purified using a Shimadzu LC-8A or LC-10A automated preparative HPLC system.

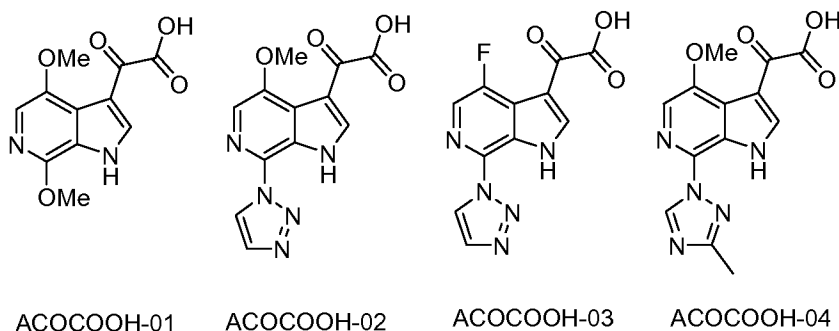
Typical Procedures and Characterization of Selected Examples:

Typical procedure to prepare amide derivatives from amino-indole precursors

5 *General Procedures:*

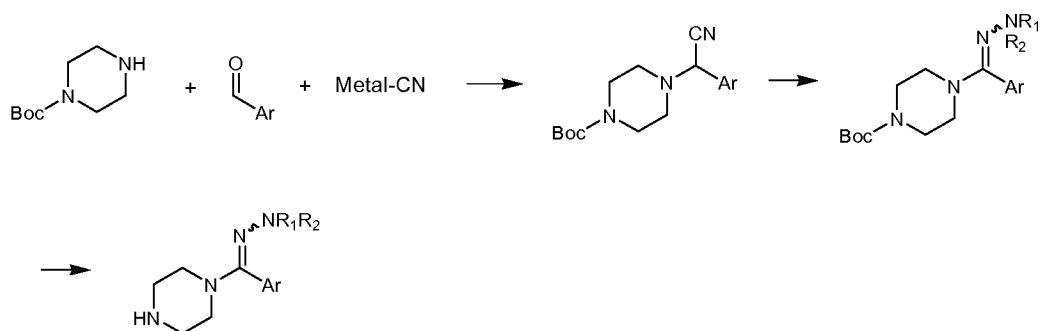
Intermediate ACOCOOH:

- 10 Preparation of intermediate ACOCOOH was described in the previous published applications (T. Wang, et al. WO-2001062255 and T. Wang, et al. WO-2002062423). Some examples of ACOCOOH are listed in below.



15

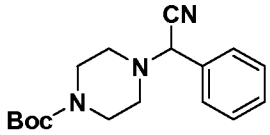
Aryl Piperazinyl Amidrazone Intermediates:



- 20 Step 1: A solution of aryl aldehyde (1 eq.) in MeOH was added into a aqueous solution of NaHSO₃ (1-5 eq.), followed by an amine (1 - 2 eq.) in aqueous MeOH. The mixture was

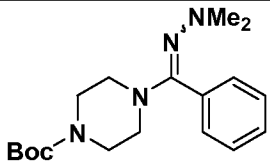
cooled before the addition of cyanide (2-10 eq.) in water. After stirring for 24 hours at room temperature, ethyl ether was added. The organic layer was separated, washed with water, dried over MgSO_4 and concentrated to give a residue, which was purified by silica gel column chromatography to afford the aryl piperazine acetonitrile.

5

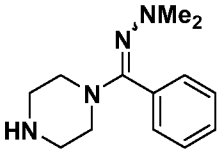
| | |
|---|----------------------------------|
|  | |
| MS (M+Na) ⁺ Calcd. | 324.2 |
| MS (M+Na) ⁺ Observ. | 324.1 |
| Retention Time | 1.69 min |
| LC Conditions | |
| Solvent A | 90% Water -10% Methanol-0.1% TFA |
| Solvent B | 10% Water -90% Methanol-0.1% TFA |
| Start % B | 0 |
| Final % B | 100 |
| Gradient Time | 2 min |
| Flow Rate | 5 mL/min |
| Wavelength | 220 |
| Solvent Pair | Water - Methanol- TFA |
| Column | Xterra MS C18 5um 4.6 x 30mm |

Step 2: An excess amount of $\text{NiO}_2\text{-H}_2\text{O}$ or MnO_2 (5-100 eq.) was added into a solution of an aryl piperazine acetonitrile (1 eq.) and a N,N-disubstituted hydrazine (5-100 eq.) in THF or DMF. The reaction mixture was stirred for 1-5 days. The solids were removed by filtration. The filtrate was concentrated under vacuum to give a residue which was purified by silica gel column chromatography or a Shimadzu automated preparative HPLC System.

10

|  | |
|---|----------------------------------|
| MS (M+H) ⁺ Calcd. | 333.2 |
| MS (M+H) ⁺ Observ. | 333.3 |
| Retention Time | 1.97 min |
| LC Conditions | |
| Solvent A | 90% Water -10% Methanol-0.1% TFA |
| Solvent B | 10% Water -90% Methanol-0.1% TFA |
| Start % B | 0 |
| Final % B | 100 |
| Gradient Time | 2 min |
| Flow Rate | 5 mL/min |
| Wavelength | 220 |
| Solvent Pair | Water - Methanol- TFA |
| Column | XTERRA 4.6 x 30mm S5 |

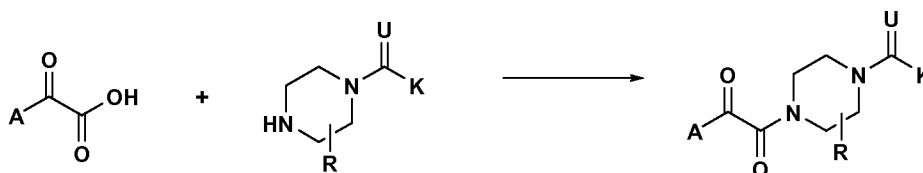
- Step 3: An aryl N-Boc piperazinyl amidrazone derivative was dissolved in an acidic solution of TFA or HCl in CH₂Cl₂, ether, dioxane or alcohol. After 0.5 to 17 hours, the solution was concentrated under vacuum to give residual salt, which was used in the next
- 5 step without purification. Alternatively, if the salt precipitated out of solution, it was filtered and washed with CH₂Cl₂, ether, dioxane or alcohol before further use.

|  | |
|---|----------------------------------|
| MS (M+H) ⁺ Calcd. | 233.2 |
| MS (M+H) ⁺ Observ. | 233.3 |
| Retention Time | 0.24 min |
| LC Conditions | |
| Solvent A | 90% Water -10% Methanol-0.1% TFA |
| Solvent B | 10% Water -90% Methanol-0.1% TFA |
| Start % B | 0 |
| Final % B | 100 |
| Gradient Time | 2 min |
| Flow Rate | 5 mL/min |
| Wavelength | 220 |
| Solvent Pair | Water - Methanol- TFA |
| Column | Xterra MS C18 5um 4.6 x 30mm |

General procedure to prepare compounds 1001 to 1003.

Method A:

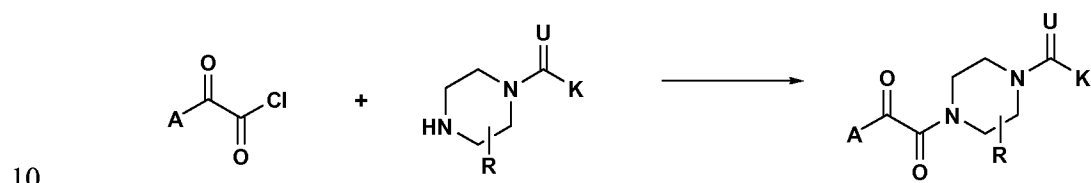
5



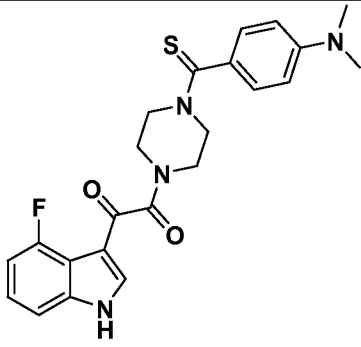
2-Keto acid (1 eq.), piperazine agent (1-5 eq.), 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one (DEPBT) or O-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU) (1-5 eq.) or (2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (HATU) (1-5 eq.) and Hunig's base or N-methyl morpholine (1-100 eq.) were combined in THF or DMF. The mixture was stirred at room temperature or at 115^oC for 17 hours. The THF or DMF was

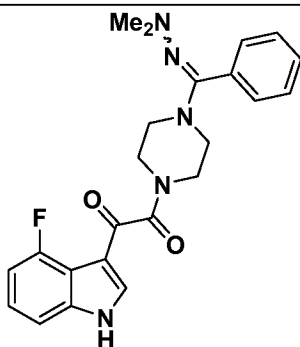
removed *via* evaporation at reduced pressure and the residue was partitioned between ethyl acetate and saturated NaHCO₃ aqueous solution. The aqueous layer was extracted with ethyl acetate. The organic phase was combined and dried over anhydrous MgSO₄. Concentration in *vacuo* provided a crude product, which was purified by titration,
5 recrystallization, or silica gel column chromatography, or on Shimadzu automated preparative HPLC System.

Method B:



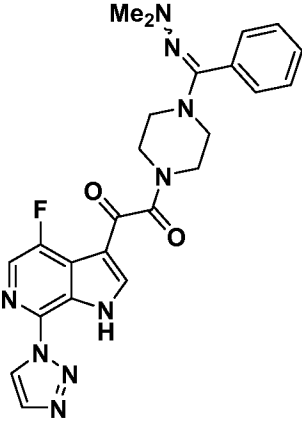
Et₃N (1-100 eq.) was added to a solution of a 2-keto acyl chloride (1 eq.) and piperazine (1-5 eq.) in an aprotic solvent (such as THF, DMF, dioxane, ether, acetonitrile) and the reaction mixture was stirred at room temperature for 17 hours before being quenched with
15 saturated aqueous NaHCO₃ solution. The aqueous layer was extracted with ethyl acetate. The organic phase was combined and dried over anhydrous MgSO₄. Concentration in *vacuo* provided a crude product, which was purified by titration, recrystallization, or silica gel column chromatography, or Shimadzu automated preparative HPLC System.

| | |
|---|----------------------------------|
|  1001 | |
| Preparative Method | B |
| MS (M+H) ⁺ Calcd. | 439.2 |
| MS (M+H) ⁺ Observ. | 439.2 |
| Retention Time | 1.95 min |
| LC Conditions | |
| Solvent A | 90% Water -10% Methanol-0.1% TFA |
| Solvent B | 10% Water -90% Methanol-0.1% TFA |
| Start % B | 0 |
| Final % B | 100 |
| Gradient Time | 2 min |
| Flow Rate | 5 mL/min |
| Wavelength | 220 |
| Solvent Pair | Water - Methanol- TFA |
| Column | XTERRA 4.6 x 30mm S5 |

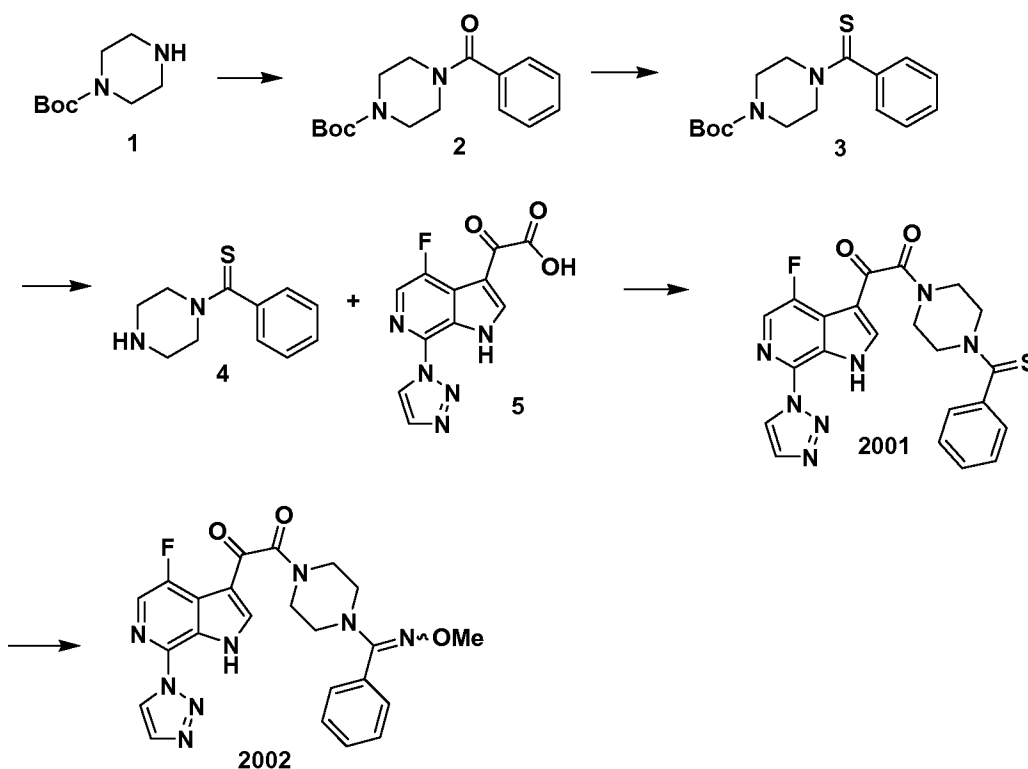


1002

| | |
|-------------------------------|----------------------------------|
| Preparative Method | B |
| MS (M+H) ⁺ Calcd. | 422.2 |
| MS (M+H) ⁺ Observ. | 422.2 |
| Retention Time | 1.77 min |
| LC Conditions | |
| Solvent A | 90% Water -10% Methanol-0.1% TFA |
| Solvent B | 10% Water -90% Methanol-0.1% TFA |
| Start % B | 0 |
| Final % B | 100 |
| Gradient Time | 2 min |
| Flow Rate | 5 mL/min |
| Wavelength | 220 |
| Solvent Pair | Water - Methanol- TFA |
| Column | XTERRA 4.6 x 30mm S5 |

| | |
|---|--|
|  1003 | |
| Preparative Method | A |
| MS (M+H) ⁺ Calcd. | 490.2 |
| MS (M+H) ⁺ Observ. | 490.1 |
| Retention Time | 1.54 min |
| LC Conditions | |
| Solvent A | 90% Water -10% Methanol-0.1% TFA |
| Solvent B | 10% Water -90% Methanol-0.1% TFA |
| Start % B | 0 |
| Final % B | 100 |
| Gradient Time | 2 min |
| Flow Rate | 4 mL/min |
| Wavelength | 220 |
| Solvent Pair | Water - Methanol- TFA |
| Column | PHENOMENEX-LUNA 4.6 x 30mm S10 |
| NMR | |
| ¹ H NMR (300 MHz, MeOD) δ ppm | 2.61 - 2.75 (br.s, 6 H), 3.30 - 4.61 (m, 8 H), 7.49 - 7.65 (m, 5 H), 7.93 (s, 1 H), 8.04 (s, 1 H), 8.38 (s, 1 H), 8.77 (s, 1 H). |

- Preparation of 1-(4-fluoro-7-(1H-1,2,3-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)-2-(4-(phenylcarbonothioyl)piperazin-1-yl)ethane-1,2-dione (2001) and 1-(4-fluoro-7-(1H-1,2,3-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)-2-(4-((methoxyimino)(phenyl)methyl)piperazin-1-yl)ethane-1,2-dione (2002)



- 5 Step 1: A 100ml three necked round bottom flask was charged with BOC-piperazine (2.0 g), dry potassium carbonate (2.96 g) and dry CH₃CN (20 mL) under a nitrogen atmosphere. The reaction mixture was cooled to 0°C and benzoyl chloride (1.8 g) was slowly added to the reaction mixture at 0°C. The reaction mixture was stirred at room temperature for 24 hours, before being diluted with ice-cold water (20 mL). The
- 10 precipitated white solid was filtered, washed with water (4 x 50 mL) and dried under vacuum to afford compound **2** (2 g) as a pure product. ¹H NMR (400 MHz, CDCl₃): δ ppm 1.49 (s, 9H), 3.45 (t, 2H), 3.60 (t, 2H), 3.71 (t, 2H), 4.22 (t, 2H), 7.28-7.41 (m, 5H). LCMS: 290.9 (M + H)⁺. HPLC: 87 % (0.1%TFA/ACN; Column: C18 BDS, 250 × 4.6 mm).
- 15 Step 2: To a stirred solution of compound **2** (1.0 g) in dry THF (10 mL), Lawesson's reagent (2.0 g) was added under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 4 hours before being concentrated. The crude material was purified by column chromatography using EtOAc/hexane (1 : 9) as eluent to afford

compound **3** (1 g) as pale yellow solid. ¹H NMR (400 MHz, CDCl₃): δ ppm 1.48 (s, 9H), 3.42 (t, 2H), 3.59 (t, 2H), 3.68 (t, 2H), 4.41 (t, 2H), 7.27-7.38 (m, 5H).

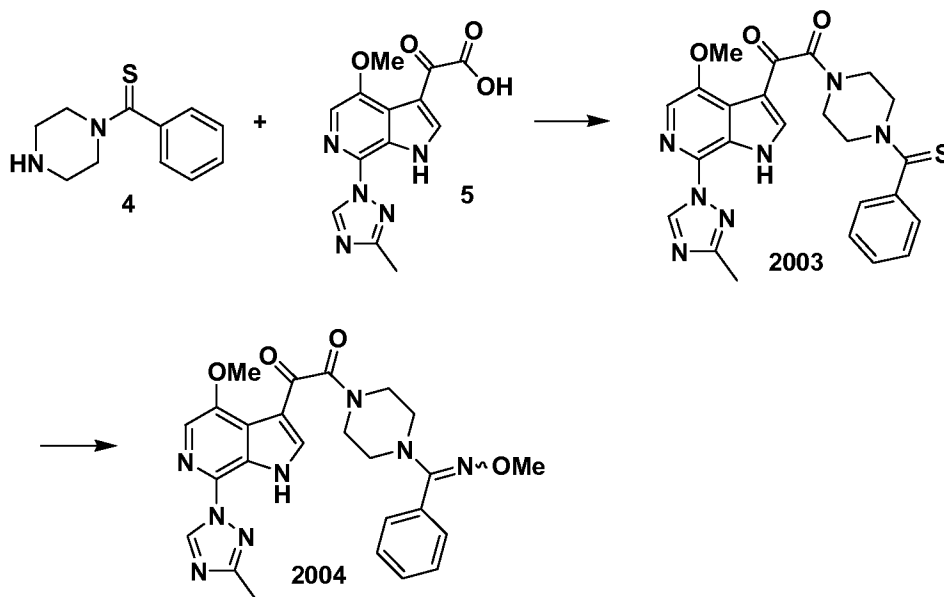
Step 3: TFA (1 mL) was added to the solution of the BOC-protected amine **3** (0.3 g) in
5 dry CH₂Cl₂ (10 mL) at 0°C. The reaction mixture was stirred at room temperature for 24
hours. The volatiles were completely removed under reduced pressure and the crude
material was diluted with CH₂Cl₂ (10 mL). The organic layer was washed with saturated
NaHCO₃ solution (2 × 10 mL), brine (20 mL) and dried over Na₂SO₄. Evaporation of the
solvent gave the amine **4** (0.25 g), which was used without any further purification. ¹H
10 NMR (400 MHz, CDCl₃): δ ppm 2.87 (t, 2H), 3.11 (t, 2H), 3.59 (t, 2H), 4.44 (t, 2H),
7.27-7.38 (m, 5H). LCMS: 207.1 (M + H)⁺.

Step 4: To a stirred solution of compound **5** (200 mg) in dry DMF (10 mL), amine **4** (156
mg), TBTU (236 mg) and iPr₂NEt (0.2 mL) were added. The reaction mixture was stirred
15 at room temperature for 24 hours and the solvent was removed under reduced pressure.
The resulting oil was diluted with EtOAc (50 mL), washed with 10% NaHCO₃ (10 mL)
and brine (10 mL). The organic layer was dried over anhydrous Na₂SO₄ and concentrated
using a rotary evaporator. The crude material was purified by column chromatography
using MeOH/CHCl₃ (1 : 9) as eluent to afford compound **2001** (80 mg) as a pale yellow
20 solid. ¹H NMR (400 MHz, DMSO - d₆): δ ppm 3.72 (m, 2H), 3.89 (m, 2H), 4.27 (m, 2H),
4.26 (m, 2H), 7.28-7.43 (m, 5H), 8.12 (s, 1H), 8.31 (m, 1H), 8.39 (m, 1H), 9.03 (m, 1H),
13.10 (bs, 1H). LCMS: 465.2 (M + H)⁺. HPLC: 97.4 % (0.1%TFA/ACN; Column: C18
BDS, 50 × 4.6 mm).

25 Step 5: To a stirred solution of compound **2001** (200 mg) in dry DMF (5 mL),
methoxyamino hydrochloride (71.6 mg), mercuric oxide (139 mg) and Et₃N (0.267 mL)
were added. The reaction mixture was stirred at room temperature for 24 hours before the
solvents were removed under reduced pressure. The resulting oil was diluted with
dichloromethane (50 mL), washed with 10% NaHCO₃ (10 mL) and brine (10 mL). The
30 organic layer was dried over anhydrous Na₂SO₄ and concentrated using a rotary
evaporator. The crude material was purified by column chromatography using
MeOH/CHCl₃ (0.5 : 9.5) as eluent to afford compound **2002** (26 mg) as pale yellow solid.

LCMS: 477.0 (M + H)⁺. HPLC: 97.93% (0.1% TFA /ACN; Column: Hypersil C18 BDS, 4.6 × 50 mm).

Preparation of Compound 2003, and Compound 2004, 1-(4-methoxy-7-(3-methyl-1*H*-1,2,4-triazol-1-yl)-1*H*-pyrrolo[2,3-*c*]pyridin-3-yl)-2-(4-((methoxyimino)(phenyl)methyl)piperazin-1-yl)ethane-1,2-dione:



10 Step 1: To a stirred solution of compound **5** (300 mg) in dry DMF (15 mL), amine **4** (226 mg), TBTU (350 mg) and *i*Pr₂NEt (0.5 mL) were added. The reaction mixture was stirred at room temperature for 24 hours, before the solvents were removed under reduced pressure. The resulting oil was diluted with ethyl acetate (50 mL), washed with 10% NaHCO₃ (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na₂SO₄

15 and concentrated using rotary evaporator. The crude material was purified by column chromatography using MeOH/CHCl₃ (1:9) as eluent to afford compound **2003** (160 mg) as yellow solid. ¹H NMR (400 MHz, DMSO - d₆): δ ppm 2.50 (s, 3H), 3.67 (m, 2H), 3.71 (m, 4H), 3.99 (s, 3H), 4.44 (m, 2H), 7.30-7.40 (m, 5H), 7.88 (s, 1H), 8.24 (m, 1H), 8.31 (m, 1H), 9.23 (s, 1H), 12.43 (bs, 1H). LCMS: 490.0 (M + H)⁺.

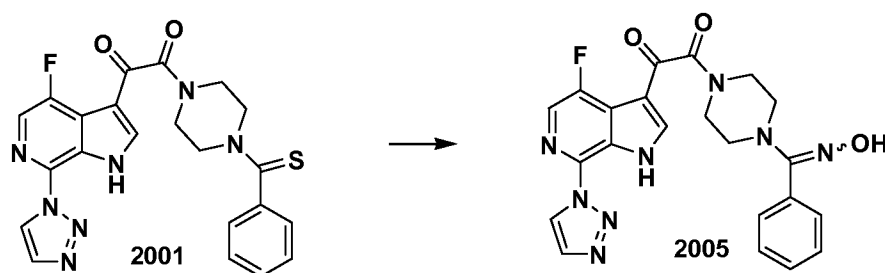
20

Step 2: To a stirred solution of compound **2003** (160 mg) in dry DMF (5 mL), methoxyamino hydrochloride (54 mg), mercuric oxide (103 mg) and Et₃N (0.27 mL) were added. The reaction mixture was stirred at room temperature for 24 hours, before the

solvents were removed under reduced pressure. The resulting oil was diluted with dichloromethane (50 mL), washed with 10% NaHCO₃ (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na₂SO₄ and concentrated using rotary evaporator. The crude material was purified by column chromatography using MeOH/CHCl₃ (1.0:9.0) as eluent to afford compound **2004** (16 mg) as white solid. ¹H NMR (400 MHz, DMSO – d₆): δ ppm 2.50 (s, 3H), 2.97 (t, 2H), 3.27 (t, 2H), 3.33 (m, 2H), 3.56 (s, 3H), 3.63 (t, 2H), 3.99 (s, 3H), 7.34-7.44 (m, 5H), 7.89 (s, 1H), 8.22 (s, 1H), 9.24 (s, 1H), 12.42 (bs, 1H). LCMS: 503.1 (M + H)⁺. HPLC: 99.34% (0.1% TFA /ACN; Column: Hypersil C18 BDS, 4.6 × 50 mm).

10

Preparation of Compound 2005, -1-(4-fluoro-7-(1*H*-1,2,3-triazol-1-yl)-1*H*-pyrrolo[2,3-*c*]pyridin-3-yl)-2-(4-((hydroxyimino)(phenyl)methyl)piperazin-1-yl)ethane-1,2-dione:



15

To a solution of compound **2001** (0.1 g) dissolved in ethanol (1 mL), hydroxylamine (0.05 mL, 50% wt in water) was added. The reaction mixture was refluxed for 18 hours with vigorous stirring. The progress of the reaction was monitored by TLC. After consumption of starting material, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was treated with methanol and the solvent decanted. The process was repeated 2 to 3 times to leave compound **2005** (1.5 mg) as an off white solid. LCMS: 463.1 (M + H)⁺. HPLC: 87 % (0.1%TFA/ACN; Column: C18 BDS, 250 × 4.6 mm).

25

Biology Data for the Examples

- “μM” means micromolar;
- “mL” means milliliter;

- “μl” means microliter;
- “mg” means milligram;

The materials and experimental procedures used to obtain the results reported in
5 Table 1 are described below.

Cells:

- Virus production - Human embryonic Kidney cell line, 293T (HEK 293T), was propagated in Dulbecco’s Modified Eagle Medium (Invitrogen, Carlsbad, CA)
10 containing 10% fetal bovine serum (FBS, Sigma, St. Louis, MO). The human T-cell leukemia cell MT2 (AIDS Research and Reference Reagent Program, Cat. 237) was propagated in RPMI 1640 (Invitrogen, Carlsbad, CA) containing 10% fetal bovine serum (FBS, Hyclone, Logan , UT)
- Virus infection - Single-round infectious reporter virus was produced by co-
15 transfecting HEK 293T cells with plasmide expressing the HIV-1 LAI envelope along with a plasmid containing an HIV-1 LAI proviral cDNA with the envelope gene replaced by a firefly luciferase reporter gene (Chen *et al.*, Ref. 41). Transfections were performed using lipofectAMINE PLUS reagent as described by the
20 manufacturer (Invitrogen, Carlsbad, CA).

Experimental Procedure

1. MT2 cells were plated in black, 384 well plates at a cell density of 5×10^3 cells per well in 25 μl RPMI 1640 containing 10% FBS.
- 25 2. Compound (diluted in dimethylsulfoxide and growth medium) was added to cells at 12.5 μl/well, so that the final assay concentration would be ≤ 50 nM.
3. 12.5 μl of single-round infectious reporter virus in Dulbecco’s Modified Eagle
Medium was added to the plated cells and compound at an approximate multiplicity
30 of infection (MOI) of 0.01, resulting in a final volume of 50 μl per well.

4. Virus-infected cells were incubated at 37 degrees Celsius in a CO₂ incubator and harvested 72 h after infection.

5. Viral infection was monitored by measuring luciferase expression in the infected cells using a luciferase reporter gene assay kit (Steady-Glo, Promega, Madison, WI) as described by the manufacturer. Luciferase activity was then quantified by measuring luminescence using an EnVision Multilabel Plate Readers (PerkinElmer, Waltham, MA).

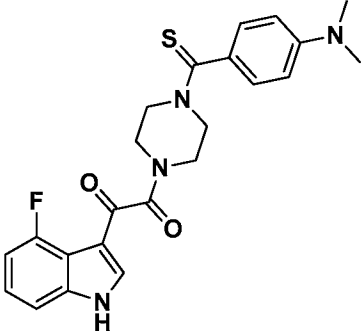
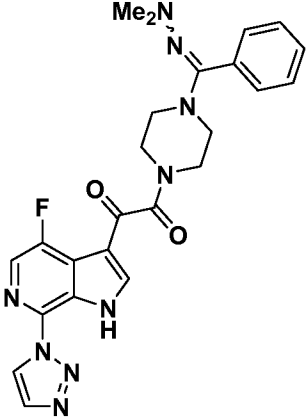
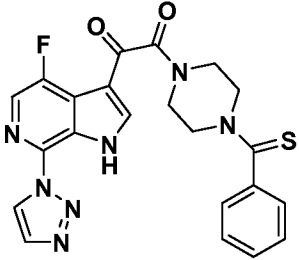
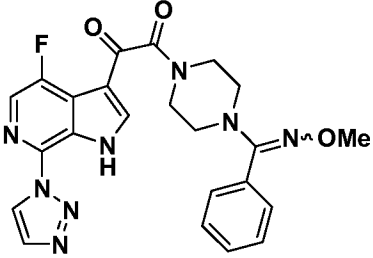
6. The percent inhibition for each compound was calculated by quantifying the level of luciferase expression in cells infected in the presence of each compound as a percentage of that observed for cells infected in the absence of compound and subtracting such a determined value from 100.

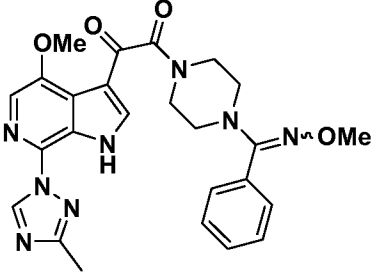
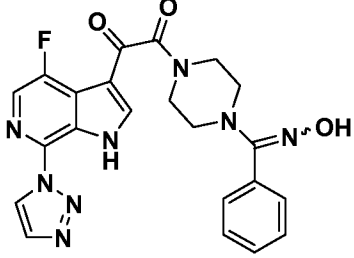
7. An EC₅₀ provides a method for comparing the antiviral potency of the compounds of this disclosure. The effective concentration for fifty percent inhibition (EC₅₀) was calculated with the Microsoft Excel Xlfit curve fitting software. For each compound, curves were generated from percent inhibition calculated at 10 different concentrations by using a four parameter logistic model (model 205). The EC₅₀ data for the compounds is shown in Table 2. Table 1 is the key for the data in Table 2.

Table 1. Biological Data Key for EC₅₀

| | |
|---|---|
| Compounds with EC ₅₀ >0.5 μM | Compounds with EC ₅₀ <0.5 μM |
| Group B | Group A |

Table 2

| Compd. Number | Structure | EC_{50} Group from Table 1 |
|---------------|---|---------------------------------|
| 1001 |  | B |
| 1003 |  | A |
| 2001 |  | A 0.027 nM |
| 2002 |  | A |

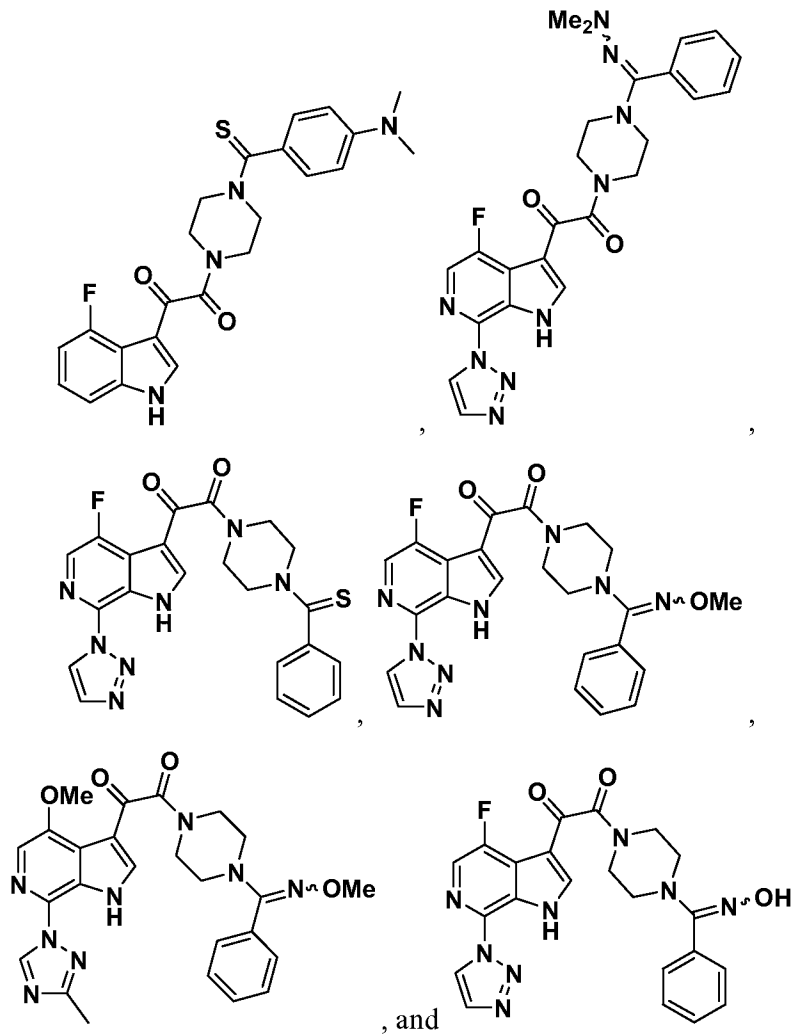
| Compd. Number | Structure | EC_{50} Group from Table 1 |
|---------------|---|---------------------------------|
| 2004 |  | A 0.019 nM |
| 2005 |  | A 0.121 nM |

The foregoing description is merely illustrative and should not be understood to limit the scope or underlying principles of the invention in any way. Indeed, various
5 modifications of the invention, in addition to those shown and described herein, will become apparent to those skilled in the art from the following examples and the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

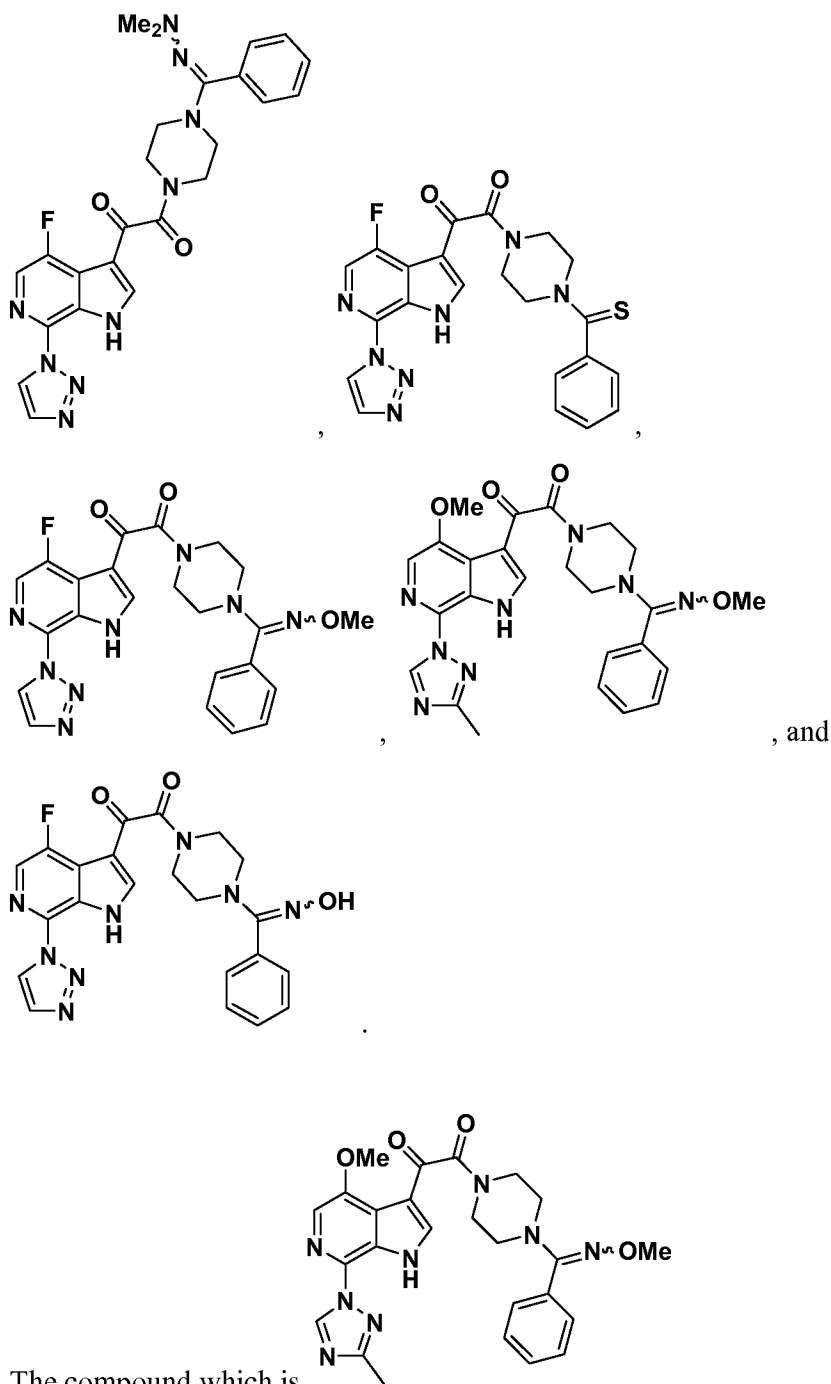
CLAIMS

What is claimed is:

1. A compound, including pharmaceutically acceptable salts thereof, which is selected from the group consisting of:



2. The compound as claimed in claim 1, which is selected from the group consisting of:



3. The compound which is .
4. A pharmaceutical composition which comprises an antiviral effective amount of one or more of the compounds of Formula I as claimed in claim 2, together with one or more pharmaceutically acceptable carriers, excipients or diluents.

5. The pharmaceutical composition of claim 4, useful for treating infection by HIV, which additionally comprises an antiviral effective amount of an AIDS treatment agent selected from the group consisting of:

- (a) an AIDS antiviral agent;
- (b) an anti-infective agent;
- (c) an immunomodulator; and
- (d) another HIV entry inhibitor.

6. A method for treating a mammal infected with the HIV virus comprising administering to said mammal an antiviral effective amount of a compound of Formula I as claimed in claim 2, and one or more pharmaceutically acceptable carriers, excipients or diluents.

7. The method of claim 6, comprising administering to said mammal an antiviral effective amount of a compound of Formula I, in combination with an antiviral effective amount of an AIDS treatment agent selected from the group consisting of an AIDS antiviral agent; an anti-infective agent; an immunomodulator; and another HIV entry inhibitor.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/033007

| | | |
|--|--|-----------------------|
| A. CLASSIFICATION OF SUBJECT MATTER INV. A61P31/18 A61K31/496 C07D209/18 C07D471/04 ADD. | | |
| According to International Patent Classification (IPC) or to both national classification and IPC | | |
| B. FIELDS SEARCHED | | |
| Minimum documentation searched (classification system followed by classification symbols) A61K C07D | | |
| Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched | | |
| Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data | | |
| C. DOCUMENTS CONSIDERED TO BE RELEVANT | | |
| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X | US 2007/078141 A1 (WANG TAO [US] ET AL) 5 April 2007 (2007-04-05) page 1, paragraph 4 - paragraph 5 page 4, paragraph 63 - paragraph 64 page 28; table table c page 42; table table c page 43; table table c page 45; examples AM-70; table table c ----- | 1-7 |
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| Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016 | Authorized officer <p style="text-align: center;">Terenzi, Carla</p> | |

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