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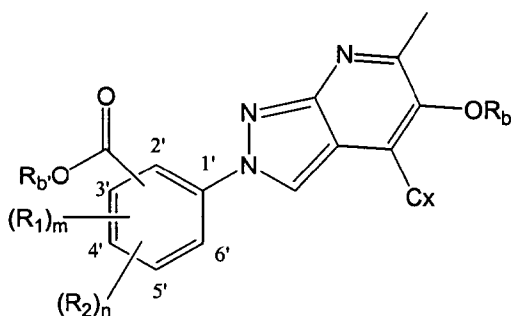
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(54) Title: PYRAZOLO[3,4-B]PYRIDIN-2-YL]-BENZOIC ACID DERIVATIVES AS HIV INTEGRASE INHIBITORS



(I)

(57) Abstract: The present invention provides compounds of formula (I) and pharmaceutically acceptable salts thereof, wherein C_x, m, n, R₁, R₂, R₃, R₄, R₅, R₆, R₇, R_a, R_b, R_b' are as defined herein.



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PYRAZOLO[3,4-B]PYRIDIN-2-YL]-BENZOIC ACID
DERIVATIVES
AS HIV INTEGRASE INHIBITORS

5

FIELD OF THE INVENTION

The present invention relates to a series of novel Pyrazolo[3,4-b]pyridin-2-yl]-benzoic acid derivatives which inhibit HIV Integrase and that have been characterized by specific structural and physicochemical features. This inhibitory property may be advantageously used to provide compounds with antiviral properties against retroviruses such as HIV viruses, including the HIV-1 and HIV-2 viruses. The Pyrazolo[3,4-b]pyridin-2-yl]-benzoic acid derivatives including pharmaceutical compositions thereof may be used to inhibit the activity of HIV integrase and therefore may be used to reduce HIV replication.

15

BACKGROUND OF THE INVENTION

The HIV (human immunodeficiency virus) retrovirus is the causative agent for AIDS (acquired immunodeficiency syndrome). The HIV-1 retrovirus primarily uses the CD4 receptor (a 58 kDa transmembrane protein) to gain entry into cells, through high-affinity interactions between the viral envelope glycoprotein (gp 120) and a specific region of the CD4 molecule found in CD4 (+) T-helper lymphocytes and certain other cells (Lasky L. A. et al., Cell vol. 50, p. 975 - 985 (1987)). HIV infection is characterized by a period immediately following infection called "asymptomatic" which is devoid of clinical manifestations in the patient. Progressive HIV-induced destruction of the immune system then leads to increased susceptibility to opportunistic infections, which eventually produces a syndrome called AIDS-related complex (ARC) characterized by symptoms such as persistent generalized lymphadenopathy, fever, weight loss, followed itself by full blown AIDS. After entry of the retrovirus into a cell, viral RNA is converted into DNA, which is then integrated into the host cell DNA. The reverse transcriptase encoded by the virus genome catalyzes the first of these reactions (Haseltine W. A. FASEB J. vol 5, p. 2349 - 2360 (1991)). At least three functions have been attributed to the reverse transcriptase: RNA-dependent DNA

polymerase activity which catalyzes the synthesis of the minus strand DNA from viral RNA, ribonuclease H (RNase H) activity which cleaves the RNA template from RNA-DNA hybrids and DNA-dependent DNA polymerase activity which catalyzes the synthesis of a second DNA strand from the minus strand DNA template (Goff S. P. J. *Acq. Imm. Defic. Syndr. Vol* 3, p. 817 - 831 (1990)). At the end of reverse transcription, the viral genome now in the form of DNA (called provirus) is integrated into host genomic DNA and serves as a template for viral gene expression by the host transcription system, which leads eventually to virus replication (Roth et al., 1989). The preintegration complex consists of integrase, reverse transcriptase, p17 and proviral DNA (Bukrinsky M. I., *Proc. Natn. Acad. Sci. USA* vol. 89 p.6580 - 6584 (1992)). The phosphorylated p17 protein plays a key role in targeting the preintegration complex into the nucleus of the host cell (Gallay et al., 1995).

The primary RNA transcripts made from the provirus are synthesized by the host cell RNA polymerase II which is modulated by two virus-encoded proteins called tat and rev. The viral proteins are formed as polyproteins.

Post-translational modifications of viral polyproteins include processing and glycosylation of Env (envelope) proteins, and myristylation of the N-terminal residue of the p17 protein in the Gag and Gag-Pol polyproteins. The viral protease is involved in processing polyproteins Gag and Gag-Pol into mature proteins, an essential step for virus infectivity.

A number of synthetic antiviral agents have been designed to block various stages in the replication cycle of HIV. These agents include compounds which interfere with viral binding to CD4 (+) T-lymphocytes (for example, soluble CD4), compounds which block viral reverse transcriptase (for example, didanosine and zidovudine (AZT)), budding of virion from the cell (interferon), or the viral protease (for example Ritonavir and Indinavir). Some of these agents proved ineffective in clinical tests. Others, targeting primarily early stages of viral replication, have no effect on the production of infectious virions in chronically infected cells. Furthermore, administration of many of these agents in effective therapeutic doses has led to cell-toxicity and unwanted side effects, such as anemia, neurotoxicity and bone marrow suppression. Anti-protease compounds in their present form are typically large and complex molecules of peptidic nature that tend to exhibit poor bioavailability and are not generally consistent with oral administration. These compounds often exhibit side effects such as nausea, diarrhea, liver abnormalities and kidney stones.

None of the known antiviral agents on the market target the HIV integrase.

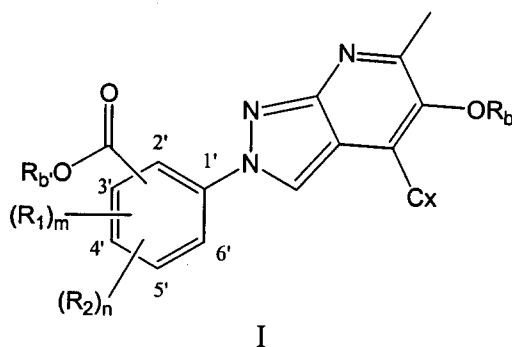
There exists a need for compounds that can effectively inhibit the action of HIV integrase and
5 that may be used for reducing HIV infections.

The present invention seeks to meet these and other needs.

SUMMARY OF THE INVENTION

10 The present invention relates to a class of pyrazolo[3,4-b]pyridin-2-yl]-benzoic acid compounds as well as their pharmaceutically acceptable derivatives (e.g., salts).

Accordingly, the present invention in a first aspect thereof provides a compound of formula I
15



and pharmaceutically acceptable derivatives thereof including where applicable, pharmaceutically acceptable salts or solvates thereof,

n may be, for example from 0 to 4 (0, 1, 2, 3 or 4), m may be, for example, from 0 to 4 (0, 1,
20 2, 3 or 4),

of course the total of n and m may not exceed the number of available positions (i.e., 4),

Cx may be selected from the group consisting of -CHO, -CH=N-OR₃ (for example, -
25 CH=N-OH), -CH=N-NR₃R₄ (for example, -CH=N-NH₂), -CH=N-R₅ and -CH(OR₃)₂

R₁ may be selected, for example, from the group consisting of -H, a straight alkyl group of 1 to 6 carbon atoms, a branched alkyl group of 3 to 6 carbon atoms, -F, -Cl, -Br, -I, -CN and -OR₃ (e.g. -OH),

- 5 R₂ may be selected, for example, from the group consisting of -H, -CO₂H, -CONR₃R₄ and -COR₆,

- 10 R₃ may be selected, for example, from the group consisting of -H, a straight alkyl group of 1 to 6 carbon atoms, a branched alkyl group of 3 to 6 carbon atoms, an allyl group, a cycloalkyl group of 3 to 8 carbon atoms, piperidine, pyrrolidine, morpholine and -R_a-COOH, where R_a may be a straight alkyl group of 1 to 6 carbon atoms,

- 15 R_b may be a cleavable unit (e.g., a physiologically cleavable unit), whereby upon cleavage of the unit, the compound releases an integrase inhibitor (an HIV integrase inhibitor). For example, R_b may be an enzymatically or metabolically cleavable unit or hydrolysable bond which may be cleaved under enteric and/or gastrointestinal conditions (pH) or other physiological conditions.

- 20 More particularly, R_b may be (independently) selected, for example, from the group consisting of -H, a straight alkyl group of 1 to 6 carbon atoms, a branched alkyl group of 3 to 6 carbon atoms, an allyl group, a cycloalkyl group of 3 to 8 carbon atoms, R_b'-CO-, (HO)₂P(O) and (MO)₂P(O), wherein M is an alkali metal (e.g. Na, K, Cs, etc) or alkaline earth metal (Ca, Mg, etc.),

- 25 R_b' may be selected, for example, from the group consisting of a straight or branched alkyl group of 1 to 6 carbon atoms (e.g. methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, *tert*-butyl-CH₂-, etc.), a cycloalkyl group having 3 to 6 carbon atoms (e.g. cyclopropyl-, cyclohexyl- etc.) and a cycloalkylalkyl group having 3 to 6 carbon atoms in the cycloalkyl part thereof and 1 to 3 carbon atoms in the alkyl part thereof, (e.g. cyclopropyl-CH₂-,
30 cyclohexyl-CH₂-, etc.),

R₄ may be selected, for example, from the group consisting of H, a straight alkyl group of 1 to 6 carbon atoms, a branched alkyl group of 3 to 6 carbon atoms, a cycloalkyl group of 3 to 8 carbon atoms, -CH₂CH₂OH, 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-(1,2,3,4-tetrahydroquinolyl, -

CO₂R₃, -CONR₃R₃, -COR₆, 2-hydroxy-6-methyl nicotinyl, formyl, benzyl (substituted (e.g., with a straight alkyl group of 1 to 6 carbon atoms, a branched alkyl group of 3 to 6 carbon atoms) or unsubstituted) and phenyl (unsubstituted or mono-, di-, tri- hydroxysubstituted phenyl, o, m, p, straight (1 to 6 carbon atoms) or branched alkyl (of 3 to 6 carbon atoms) substituted phenyl).

R₅ may be selected from the group consisting of piperidine (1-, 2-, 3- piperidine), morpholine (e.g., 1-morpholine),

R₆ may be selected from the group consisting of -H, a straight alkyl group of 1 to 6 carbon atoms, a branched alkyl group of 3 to 6 carbon atoms, a cycloalkyl group of 3 to 8 carbon atoms, -NH₂, phenyl, (unsubstituted or substituted phenyl such as mono, di, tri hydroxysubstituted phenyl, o, m, p straight (of 1 to 6 carbon atoms) and branched alkyl (of 3 to 6 carbon atoms) substituted phenyl, etc.), -CH₂CH₂OH, 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-(1,2,3,4-tetrahydroquinolyl), o, m, p straight and branched alkyl substituted pyridyl, nicotinyl (substituted nicotinyl (mono, di, tri) e.g., hydroxysubstituted nicotinyl, alkyl substituted nicotinyl, (e.g., 2-OH-6-Me nicotinyl) or unsubstituted nicotinyl) and -OR₇, and;

R₇ may be -H, a straight alkyl group of 1 to 6 carbon atoms, a branched alkyl group of 3 to 6 carbon atoms or a cycloalkyl group of 3 to 8 carbon atoms.

Exemplary embodiments of compounds of formula I encompassed by the present invention includes, compounds where C_x is selected, for example, from the group consisting of -CHO, -CHNO-R₄-COOH, -CHNOR₃, -CHN-NR₃R₄ and -CH=N-R₅, and wherein R₃ may more particularly be selected from the group consisting of -H and a straight alkyl group of 1 to 6 carbon atoms, where R₄ may be selected, for example from the group consisting of -H, -COR₆, formyl, benzyl substituted with a straight alkyl group of 1 to 6 carbon atoms or a branched alkyl group of 3 to 6 carbon atoms, unsubstituted benzyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, and phenyl substituted or not, where R₅ may be selected from the group consisting of piperidine and morpholine, where R₆ may be, more specifically selected from the group consisting of -NH₂, unsubstituted phenyl, mono-, di-, tri- hydroxysubstituted phenyl, phenyl substituted with a straight alkyl group of 1 to 6 carbon atoms, phenyl substituted with a branched alkyl group of 3 to 6 carbon atoms, an unsubstituted nicotinyl, a nicotinyl substituted with a straight alkyl group of 1 to 6 carbon atoms, a branched alkyl group of 3 to

6 carbon atoms, and/or at least one hydroxy group and -OR₇, and; where R₇ may be selected from the group consisting of -H, a straight alkyl group of 1 to 6 carbon atoms, a branched alkyl group of 3 to 6 carbon atoms and a cycloalkyl group of 3 to 8 carbon atoms.

- 5 Exemplary embodiments of compounds of formula I encompassed by the present invention also includes, for example, compounds where C_x is -CH=N-NR₃R₄ and R₃ is -H (such as in the group -CH=N-NHR₄) and wherein R₄ may more particularly be selected from the group consisting of -H, 2-pyridyl, 3-pyridyl, 4-pyridyl, formyl, benzyl (substituted (e.g., with a straight alkyl group of 1 to 6 carbon atoms, a branched alkyl group of 3 to 6 carbon atoms),
10 or unsubstituted), phenyl (substituted or not) and -COR₆ and wherein R₆ may be more particularly selected from the group consisting of -NH₂, -OR₇, a straight alkyl group of 1 to 6 carbon atoms, a branched alkyl group of 3 to 6 carbon atoms, a cycloalkyl group of 3 to 8 carbon atoms, phenyl (substituted or not; for example, mono, di or tri hydroxysubstituted phenyl, o, m, p straight and branched alkyl substituted phenyl, etc.,) and nicotinyl (substituted
15 nicotinyl (mono, di, tri) e.g., hydroxysubstituted nicotinyl, alkyl substituted nicotinyl, (e.g., 2-OH-6-Me nicotinyl) or unsubstituted nicotinyl) and wherein R₇ may be as defined herein.

In accordance with the present invention, C_x may be more particularly selected, for example, from the group consisting of -CHO, -CHNO-CH₂-COOH, -CHNO-Me, -CHNOEt, CHNO-
20 allyl, -CHNO-t-Bu, -CHNOH, -CHNNH₂, -CHN-1-piperidine, -CHN-1-morpholine, -CHN-NH-(CO-2-OH-6-Me nicotinyl), -CHN-NH-(CO-hydroxyphenyl) (e.g., -CHN-NH-(CO-2-OH-Phenyl)), -CHN-NH-(CO-di-hydroxyphenyl) (e.g., -CHN-NH-(CO-2, 3-Di OH-Phenyl)), -CHN-NH-(CO-tri-hydroxyphenyl) (e.g., -CHN-NH-(CO-2, 3,4 -Tri OH-Phenyl)), -CHN-NH-2-pyridine, -CHN-NH-formyl, -CHN-NH-(COOMe), -CHN-NH-(CONH₂), -CHN-NH-
25 Bz, -CHN-NH-(4-t-Bu Bz), etc.

In accordance with an embodiment of the invention, C_x may be chosen for example among the group consisting of -CHO, -CHNO-CH₂-COOH, -CHNO-Me, -CHNOEt, -CHNO-allyl, -
CHNO-t-Bu, -CHN-NH-(CO-2-OH-6-Me nicotinyl), -CHN-NH-2-pyridine, -CHN-NH-
30 formyl, -CHN-NH-(CO-hydroxyphenyl), -CHN-NH-Bz, and -CHN-NH-(4-t-Bu Bz).

Also in accordance with a specific embodiment of the invention, C_x may be selected from the group consisting of -CHO, CHNO-CH₂-COOH, -CHNOEt, -CHN-NH-(CO-2-OH-6-Me nicotinyl) and -CHN-NH-(CO-hydroxyphenyl).

The -CHN-NH-(CO-hydroxyphenyl) group may be more particularly selected from the group of, a -CHN-NH-(CO-mono-hydroxyphenyl), -CHN-NH-(CO-di-hydroxyphenyl), -CHN-NH-(CO-tri-hydroxyphenyl) etc., such as, for example, -CHN-NH-(CO-2-OH-Phenyl), -CHN-NH-(CO-3-OH-Phenyl), -CHN-NH-(CO-4-OH-Phenyl), -CHN-NH-(CO-5-OH-Phenyl), -CHN-NH-(CO-2, 3-Di-OH-Phenyl), -CHN-NH-(CO-2, 4-Di-OH-Phenyl), -CHN-NH-(CO-3, 4-Di-OH-Phenyl), -CHN-NH-(CO-2, 3,4 -Tri-OH-Phenyl), -CHN-NH-(CO-3, 4, 5 -Tri-OH-Phenyl) etc.

10 In an embodiment of the present invention, compounds of formula I encompass those, for example, where -COOH or alternatively -H group may be found at position 3'.

Exemplary embodiments of compounds which are encompassed herewith includes, for example,

- 15 - compounds of formula I, where m may be 0, 1 or 2;
- compounds of formula I, where n may be 0, 1 or 2;
- compounds of formula I, where the -COOR_b' group may be found at a 3' or 4' position;
- compounds of formula I, where R_b' may be, for example -H;
- 20 - compounds of formula I, where R_b may be more particularly selected from the group consisting of -H, (HO)₂P(O) and (MO)₂P(O), where M may be, for example, an alkali metal or alkaline earth metal thereof;
- compounds of formula I, where C_x is -CHO and/or,
- compounds of formula I, where R₁ and R₂ are both - H or wherein m and n are both 0.
- 25

In a further embodiment of the present invention, compounds of formula I where R₂ may be, more specifically H or -COOH are encompassed herewith. Other exemplary embodiments of the invention are compounds where n may be, for example, 0 or 1.

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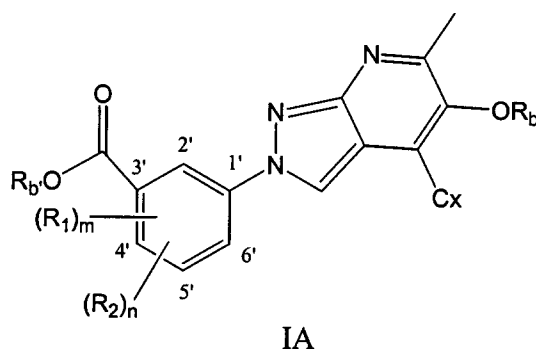
In another embodiment of the present invention, compounds of formula I where R₁ may be more specifically, -H, -F, -Cl, -Br and -OH are encompassed herewith. More particularly, Cl may be found, for example, at position 2', 4' and/or 6'. In accordance with the present invention, m may more particularly be 0, 1 or 2.

For example, compounds where Cx is -CHO, R₁ and R₂ are both -H or wherein m and n are both 0, where the -COOR_{b'} group is at a 4' position, where R_{b'} is H and where R_b is H are encompassed herewith.

5

Compounds of the present invention also includes, for example, compounds of formula I, wherein R₁ may be -OH and R₂ may be -CO₂H and wherein R₂ may be, more particularly CO₂H at position 4'

10 In a further aspect, the present invention relates to compound of formula IA



, and pharmaceutically acceptable derivatives thereof including where applicable pharmaceutically acceptable salts or solvates thereof. Cx, m, n, R₁, R₂, R₃, R₄, R₅, R₆, R₇, R_a,
 15 R_b, R_{b'} may be as defined herein.

In accordance with the present invention, Cx may be more particularly selected from the group consisting of -CHO, -CHNO-CH₂-COOH, -CHNO-Me, -CHNOEt, -CHNO-allyl, -CHNO-t-Bu, -CHNOH, -CHNNH₂, -CHN-1-piperidine, -CHN-1-morpholine, -CHN-NH-
 20 (CO-2-OH-6-Me nicotinyl), -CHN-NH-(CO-hydroxyphenyl), -CHN-NH-2-pyridine, -CHN-NH-formyl, -CHN-NH-(COOMe), -CHN-NH-(CONH₂), -CHN-NH-Bz, and -CHN-NH-(4-t-Bu Bz).

More particularly, Cx may thus be selected from the group consisting of -CHO, -CHNO-
 25 CH₂-COOH, -CHNO-Me, -CHNOEt, -CHNO-allyl, -CHNO-t-Bu, -CHN-NH-(CO-2-OH-6-Me nicotinyl), -CHN-NH-2-pyridine, -CHN-NH-formyl, -CHN-NH-(CO-hydroxyphenyl), -CHN-NH-Bz, and -CHN-NH-(4-t-Bu Bz).

Even more particularly, Cx may be selected from the group consisting of -CHO, CHNO-CH₂-COOH, -CHNOEt, -CHN-NH-(CO-2-OH-6-Me nicotinyll) and -CHN-NH-(CO-hydroxyphenyl).

5

Particular embodiments of compounds of the present invention includes those where Cx may be, for example, -CHO.

10

In an embodiment compounds of formula IA encompassed by the present invention may include, for example, a compound where Cx may be -CHO, n may be 1 and R₂ may be -COOH at position 4' or 5'. Other embodiments of the present invention include compounds of formula IA where m may be 0 or R₁ may be H. Compounds of formula IA where R_b is, for example H are also encompassed by the present invention. Also encompassed are compounds of formula IA where R_b is, for example, H.

15

In further embodiments the present invention provides compounds of formula IA where Cx may be -CHO, n may be 1, R₂ may be -COOH, for example, at position 5', m may be 1 and R₁ may be -OH, for example, at position 4'.

20

Also in accordance with the present invention, compounds of formula IA may include, for example, compounds where Cx may be -CHO, m may be 1 and R₁ may be -Cl, for example, at position 4' or 6'.

25

Other particular exemplary embodiments of compounds of the present invention include those where Cx may be -CHNO-CH₂-COOH.

30

In more specific embodiments of the invention, compounds of formula IA where Cx may be -CHNO-CH₂-COOH, where m may be 0, n may be 1 and R₂ may be -COOH are also encompassed herein. In accordance with the present invention, R₂ may be, for example, at position 5'.

Other exemplary embodiments of the present invention include compounds of formula IA where Cx may be -CHNO-CH₂-COOH, where m may be 1, n may be 0 and R₁ may be -Cl. In accordance with the present invention, R₁ may be, for example, at position 4'.

In additional exemplary embodiments of the present invention Cx may be, for example, -CHN-NH-(CO-2-OH-6-Me nicotinyll).

- 5 More particularly and in accordance with the present invention, compounds of formula IA where Cx may be -CHN-NH-(CO-2-OH-6-Me nicotinyll), where m may be 0, n may be 1 and R₂ may be -COOH are also encompassed herein. In accordance with the present invention, R₂ may be at position 5'.
- 10 Also in accordance with the present invention, compounds of formula IA where Cx may be -CHN-NH-(CO-2-OH-6-Me nicotinyll), where m may be 1, n may be 0 and R₁ may be -Cl are also encompassed herewith. In accordance with the present invention, R₁ may be, more particularly at position 4'.
- 15 In a further exemplary embodiment of the invention, Cx may be, for example, -CH=N-NH-COR₆ where R₆ may be, for example, a phenyl group (substituted or not; for example, mono, di or tri hydroxysubstituted phenyl).

In other embodiments of the invention, Cx, may be for example, -CHN-NH-(CO-2-OH-Phenyl), -CHN-NH-(CO-2, 3-Di OH-Phenyl) or -CHN-NH-(CO-2, 3, 4 -Tri OH-Phenyl) or other hydroxyphenyl. Also in accordance with the present invention, m may be 0, n may be 1 and R₂ may be -COOH. R₂ may be found, for example, at position 5'.

Further embodiments of the invention includes, for example, compounds of formula IA, where Cx may be -CHNO-Allyl, m may be 1, R₁ may be Cl and n may be 0 or R₂ may be -H.

Exemplary embodiments of compounds which are encompassed herewith includes, for example,

- 30
- compounds of formula IA where R₂ may be more particularly, H or -COOH or even more particularly, -COOH;
 - compounds of formula IA where R₁ may be more specifically selected from the group consisting of -H, -F, -Cl, -Br and -OH or even more particularly, -Cl or -OH;

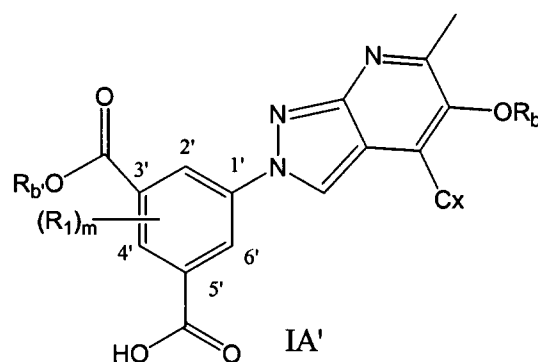
- compounds of formula IA where m may be 0, 1 or 2;
- compounds of formula IA where n may be 0, 1 or 2;
- compounds of formula IA where the $-\text{COOR}_b$ group may be at a 3', 4' or 5' position;
- 5 - compounds of formula IA where R_b may be, for example, $-\text{H}$;
- compounds of formula IA where R_b may be selected, for example, from the group consisting of $-\text{H}$, $(\text{HO})_2\text{P}(\text{O})$ and $(\text{MO})_2\text{P}(\text{O})$, wherein M is an alkali metal or alkaline earth metal thereof;
- compounds of formula IA where R_2 may be $-\text{COOH}$ at position 4' or 5';
- 10 - compounds of formula IA where R_1 may be $-\text{Cl}$ or $-\text{OH}$ at position 4' or 6';
- compounds of formula IA where R_b and $\text{R}_{b'}$ may both be $-\text{H}$;
- compounds of formula IA where R_2 may be $-\text{COOH}$ at position 4' or 5' and wherein m is 0 or 1 and n is 1 or 2; and/or,
- compounds of formula IA where R_1 may be $-\text{Cl}$ or $-\text{OH}$ at position 4' or 6' and
- 15 wherein m is 1, 2 or 3 and n is 0 or 1.

Examples of compounds of formula IA encompassed by the present invention thus includes, without limitation;

- a compound of formula IA where C_x is $-\text{CHO}$, R_b and $\text{R}_{b'}$ are both $-\text{H}$, R_2 is $-\text{COOH}$ at position 4' and where m is 0,
- 20 - a compound of formula IA where C_x is $-\text{CHO}$, R_b and $\text{R}_{b'}$ are both $-\text{H}$, R_2 is $-\text{COOH}$ at position 5' and where R_1 is $-\text{OH}$ at position 4';
- a compound of formula IA where C_x is $-\text{CHO}$, R_b and $\text{R}_{b'}$ are both $-\text{H}$, where R_2 is H , where R_1 is $-\text{Cl}$ at position 4';
- 25 - a compound of formula IA where C_x is $-\text{CHO}$, R_b and $\text{R}_{b'}$ are both $-\text{H}$, where R_2 is H , where R_1 is $-\text{Cl}$ at position 6';
- a compound of formula IA where C_x is $-\text{CHNO}-\text{CH}_2-\text{COOH}$, R_b and $\text{R}_{b'}$ are both $-\text{H}$, R_2 is $-\text{COOH}$ at position 5' and where m is 0
- a compound of formula IA where C_x is $-\text{CHNO}-\text{CH}_2-\text{COOH}$, R_b and $\text{R}_{b'}$ are both $-\text{H}$, R_1 is $-\text{Cl}$ at position 4' and where n is 0;
- 30 - a compound of formula IA where C_x is $-\text{CHN}-\text{NH}-(\text{CO}-2-\text{OH}-6-\text{Me nicotinyll})$, where R_b and $\text{R}_{b'}$ are both $-\text{H}$, where R_2 is $-\text{COOH}$ at position 5' and where m is 0;
- a compound of formula IA where C_x is $-\text{CHN}-\text{NH}-(\text{CO}-2-\text{OH}-6-\text{Me nicotinyll})$, where R_b and $\text{R}_{b'}$ are both $-\text{H}$, where R_1 is $-\text{Cl}$ at position 4' and wherein n is 0;

- a compound of formula IA where Cx is CHN-NH-(CO-hydroxyphenyl), where R_b and R_{b'} are both -H, where R₂ is -COOH at position 5' and where m is 0;
- a compound of formula IA where Cx is -CHNOR₃ and wherein R₃ is selected from the group consisting of -H, a straight alkyl group of 1 to 6 carbon atoms, where R_b and R_{b'} are both -H, where R₁ is Cl at position 4' and wherein n is 0;
- a compound of formula IA where Cx is -CHNO-Allyl, where R_b and R_{b'} are both -H, where R₁ is Cl at position 4' and wherein n is 0;
- a compound of formula IA where Cx is -CHNO-Alkyl, where R_b and R_{b'} are both -H, where R₁ is Cl at position 4' and wherein n is 0;
- a compound of formula IA where Cx is -CHN-NH-Bz, where R_b and R_{b'} are both -H, where R₁ is Cl at position 4' and where n is 0;
- a compound of formula IA where Cx is -CHN-NH-(4-t-Bu Bz) where R_b and R_{b'} are both -H, where R₁ is Cl at position 4' and where n is 0;
- a compound of formula IA where Cx is -CHN-NH(COOMe), where R_b and R_{b'} are both -H, where R₁ is Cl at position 4' and where n is 0; and;
- a compound of formula IA where Cx is -CHN-NH(CONH₂), where R_b and R_{b'} are both -H, where R₁ is Cl at position 4' and where n is 0.

In an additional aspect, the present invention relates to compounds of formula IA'



, and pharmaceutically acceptable derivatives thereof including where applicable or pharmaceutically acceptable salts or solvates thereof, wherein Cx, m, R₁, R₃, R₄, R₅, R₆, R₇, R_a, R_b, R_{b'} are as defined herein.

In accordance with the present invention, Cx may be more particularly selected from the group consisting of -CHO, -CHNO-CH₂-COOH, -CHNO-Me, -CHNOEt, -CHNO-allyl, -CHNO-t-Bu, -CHNOH, -CHNNH₂, -CHN-1-piperidine, -CHN-1-morpholine, -CHN-NH-(CO-2-OH-6-Me nicotinyll), -CHN-NH-(CO-hydroxyphenyl), -CHN-NH-2-pyridine, -CHN-NH-formyl, -CHN-NH-(COOMe), -CHN-NH-(CONH₂), -CHN-NH-Bz, and -CHN-NH-(4-t-Bu Bz).

More particularly, Cx may thus be selected from the group consisting of -CHO, -CHNO-CH₂-COOH, -CHNO-Me, -CHNOEt, -CHNO-allyl, -CHNO-t-Bu, -CHN-NH-(CO-2-OH-6-Me nicotinyll), -CHN-NH-2-pyridine, -CHN-NH-formyl, -CHN-NH-(CO-hydroxyphenyl), -CHN-NH-Bz, and -CHN-NH-(4-t-Bu Bz).

Even more particularly, Cx may be selected from the group consisting of -CHO, CHNO-CH₂-COOH, -CHNOEt, -CHN-NH-(CO-2-OH-6-Me nicotinyll) and -CHN-NH-(CO-hydroxyphenyl) (e.g., -CHN-NH-(CO-mono-hydroxyphenyl), -CHN-NH-(CO-di-hydroxyphenyl), -CHN-NH-(CO-tri-hydroxyphenyl) etc.).

In an exemplary embodiment of the invention, Cx may be for example -CH=N-OR₃. In accordance with the present invention R₃ may be selected, for example, from the group consisting of -H, a straight alkyl group of 1 to 6 carbon atoms, a branched alkyl group of 3 to 6 carbon atoms and an allyl group.

In other exemplary embodiments of the invention compounds of formula IA', where Cx may be -CHNNH₂ are also encompassed herewith as well as compounds of formula IA' where Cx may be -CHN-1-piperidine, -CHN-1-morpholine, -CHN-NH-2-pyridine or -CHN-NH-formyl.

In accordance with the present invention, compounds of formula IA' may include, for example, compounds where m is 0 or R₁ is -H. Compounds of formula IA' where R_b is, for example H and R_{b'} is, for example, H are also encompassed by the present invention.

Exemplary embodiments of compounds which are encompassed herewith includes, for example,

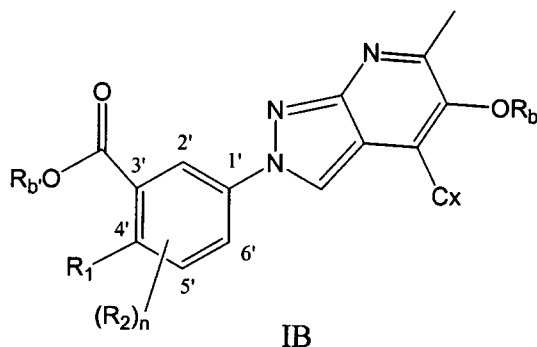
- compounds of formula IA' where R_b and R_{b'} are both -H;

- compounds of formula IA' where R_1 is selected from the group consisting of -H, -OH, -F, -Cl, -Br and -I or more particularly, where R_1 is -OH or -Cl, and/or;
- compounds of formula IA' where m is 0, 1 or 2.

5 Examples of compounds of formula IA' encompassed by the present invention thus includes, without limitation;

- compounds of formula IA' where R_b and $R_{b'}$ are both -H, where Cx is -CHO and where m is 0;
- compounds of formula IA' where R_b and $R_{b'}$ are both -H, where Cx is -CHNOMe, and where m is 0;
- 10 - compounds of formula IA' where R_b and $R_{b'}$ are both -H, where Cx is -CHNOEt and where m is 0;
- compounds of formula IA' where R_b and $R_{b'}$ are both -H, where Cx is -CHNO-Allyl and where m is 0;
- 15 - compounds of formula IA' where R_b and $R_{b'}$ are both -H, where Cx is -CHNO-t-Butyl and where m is 0;
- compounds of formula IA' where R_b and $R_{b'}$ are both -H, where Cx is -CHNOH and where m is 0;
- compounds of formula IA' where R_b and $R_{b'}$ are both -H, where Cx is -CHNNH₂ and where m is 0;
- 20 - compounds of formula IA' where R_b and $R_{b'}$ are both -H, where Cx is -CHN-1-piperidine and where m is 0;
- compounds of formula IA' where R_b and $R_{b'}$ are both -H, where Cx is -CHN-1-morpholine and where m is 0;
- 25 - compounds of formula IA' where R_b and $R_{b'}$ are both -H, where Cx is -CHN-NH-2-pyridine and where m is 0;
- compounds of formula IA' where R_b and $R_{b'}$ are both -H, where Cx is -CHN-NH-formyl and where m is 0; and,
- compounds of formula IA' where R_b and $R_{b'}$ are both -H, where Cx is CHN-NH-(CO-hydroxyphenyl) and where m is 0.
- 30

In a further aspect, the present invention thus relates to compound of formula IB



, and pharmaceutically acceptable derivatives thereof including, where applicable, pharmaceutically acceptable salts or solvates thereof. Cx, n, R₂, R₃, R₄, R₅, R₆, R₇, R_a, R_b, R_b' are as defined herein.

5

In accordance with the present invention, Cx may be selected, for example, from the group consisting of -CHO, CHNO-CH₂-COOH, -CHNOEt, -CHN-NH-(CO-2-OH-6-Me nicotinyll) and -CHN-NH-(CO-hydroxyphenyl).

10 In accordance with the present invention, exemplary compounds of formula IB may include, for example, a compound where n is 0 or R₂ is -H. Compounds of formula IB where R_b is, for example H and R_b' is, for example, H are also encompassed by the present invention.

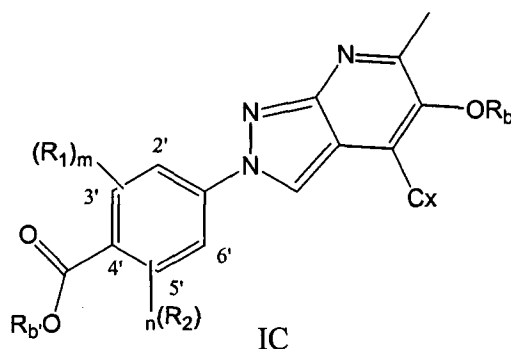
In accordance with the present R₁ may be one of, for example, -OH, -Cl, -F, -Br, -I etc.

15

Further in accordance with the present invention, Cx may be, for example, -CH=N-NR₃R₄, for example, -CHN-NH-(COOMe), -CHN-NH-(CONH₂). In accordance, with the present invention, R₃ and R₄ may be as defined herein, for example, R₃ may be H and R₄ may be benzyl (unsubstituted or substituted) for example, -CHN-NH-Bz, CHN-NH-(4-t-Bu Bz), etc.

20

In yet another aspect, the present invention also encompasses compounds of formula IC



, and pharmaceutically acceptable derivatives thereof including, where applicable, pharmaceutically acceptable salts or solvates thereof. Cx, m, R₁, R₂, R₃, R₄, R₅, R₆, R₇, R_a,
 5 R_b, R_{b'} are as defined herein.

In accordance with the present invention, Cx may more specifically be selected from the group consisting of -CHO, -CHNO-CH₂-COOH, -CHNO-Me, -CHNOEt, -CHNO-allyl, -CHNO-t-Bu, -CHN-NH-(CO-2-OH-6-Me nicotinyll), -CHN-NH-2-pyridine, -CHN-NH-formyl, -CHN-NH-(CO-hydroxyphenyl), -CHN-NH-Bz, and -CHN-NH-(4-t-Bu Bz).
 10

Even more specifically, Cx may be selected from the group consisting of -CHO, CHNO-CH₂-COOH, -CHNOEt, -CHN-NH-(CO-2-OH-6-Me nicotinyll) and -CHN-NH-(CO-hydroxyphenyl).
 15

Also in accordance with the present invention, R₁ may be selected from the group consisting of -H, -Cl, -F, -Br, -I and -OH and more particularly from the group consisting of -H, -Cl and -OH.

20 Further in accordance with the present invention, R₂ may be as described herein and more particularly, may be, for example, -H or -COOH.

The present invention also relates to a pharmaceutical composition comprising at least one compound of formula I, IA, IA' IB and/or IC and a pharmaceutically acceptable carrier. The pharmaceutical composition may comprise, for example, a pharmaceutically effective amount
 25 of such one or more compounds of this invention. The pharmaceutical compositions may be

used to inhibit integrase, including HIV integrase, thus providing protection against HIV infection.

5 The present invention further relates to the use of at least one compound of formula I, IA, IA' IB and/or IC, for making a pharmaceutical composition, medicament or drug. The compound of formula I, IA, IA' IB and/or IC may be used in the making of a drug for the treatment and/or prevention of HIV infection and/or for the prevention of the apparition of acquired immunodeficiency syndrome (AIDS), and/or for reducing HIV replication and/or its cytopathic effects and/or inhibiting the HIV integrase enzyme etc.

10 The present invention further relates to the use of the at least one compound of formula I, IA, IA' IB and/or IC, for treating and/or preventing HIV infection and/or AIDS for reducing HIV replication and/or its cytopathic effects and/or inhibiting the HIV integrase enzyme or else in an individual in need thereof.

15 The invention also relates to a method of treating and/or preventing HIV infection and/or AIDS (e.g., for delaying the apparition of AIDS), for reducing HIV replication and/or its cytopathic effects and/or for inhibiting the HIV integrase enzyme or else in an individual in need thereof. In accordance with the present invention, the method may comprise
20 administering a compound of formula I, IA, IA' IB and/or IC (or a pharmaceutical composition, drug etc.) to (in) an individual in need thereof.

The present invention more particularly relates to a method of reducing the replication (e.g., integration) of HIV, the method may comprise providing a cell with a compound of formula
25 I, IA, IA' IB and/or IC (or a pharmaceutical composition, drug etc.) or administering such compound to (in) an individual in need thereof.

The present invention also relates to a process or method for preparing a compound of formula I, IA, IA' IB and/or IC and the use of intermediate compounds for that purpose.

30 The compounds of this invention may include pharmaceutically acceptable derivatives of the compounds of formula I, IA, IA' IB and/or IC as defined above. A "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt (e.g., Na, K, Cs, etc),

acetals (i.e., dimethylacetal, diethylacetal, etc), oxime, or ester (as for example, but not limited to methyl, ethyl, propyl, isopropyl esters, etc) of a compound of this invention.

Furthermore, the expression “pharmaceutically acceptable derivative” is to be understood as referring to any other compound having a structure such that, upon administration to a recipient, it is capable of providing (directly or indirectly) a compound of this invention or an antivirally active metabolite or residue thereof. Thus, the compounds of this invention may be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral bioavailability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

The compounds of the present invention including where applicable their pharmaceutically acceptable derivatives have an affinity for integrase, in particular, HIV integrase. Therefore, these compounds may be useful as inhibitors of such integrase, i.e. they are in particular useful as HIV integrase inhibitors. These compounds may be used alone or in combination with other therapeutic or prophylactic agents, such as antivirals, antibiotics, immunomodulators or vaccines, for the treatment or prophylaxis of viral infection or for reducing the probability of infection or reducing the probability of developing ARC and/or AIDS.

According to the present invention, the compounds of this invention may be capable of inhibiting HIV viral replication in human CD4⁺ T-cells, by inhibiting the ability of HIV integrase to integrate the double stranded DNA into host genomic DNA for further virus replication by the host cell machinery (Sakai H., J. Virol. Vol. 67 p. 1169 - 1174 (1993)). These novel compounds may thus serve to reduce the production of infectious virions from acutely infected cells, and may inhibit the initial or further infection of host cells. Accordingly, these compounds are useful as therapeutic and prophylactic agents to treat or prevent infection by HIV (e.g., HIV-1) and related viruses, which may result in asymptomatic HIV-1 infection, AIDS-related complex (ARC), acquired immunodeficiency syndrome (AIDS), AIDS-related dementia, or similar diseases of the immune system.

The terms “HIV integrase” and “integrase” as used herein are used interchangeably and refer to the integrase enzyme encoded by the human immunodeficiency virus type 1 or 2. In particular this term includes the human immunodeficiency virus type 1 integrase.

5 The term “pharmaceutically effective amount” refers to an amount effective in treating or preventing HIV infection in a patient (e.g., reducing HIV replication, delaying the apparition of AIDS, lowering the probability of infection, lowering the probability of developing AIDS, etc.). It is also to be understood herein that a “pharmaceutically effective amount” may be interpreted as an amount giving a desired therapeutic effect, either taken into one dose or in
10 any dosage or route or taken alone or in combination with other therapeutic agents. In the case of the present invention, a “pharmaceutically effective amount” may be understood as an amount having an inhibitory effect on HIV (HIV-1 and HIV-2 as well as related viruses (e.g., HTLV-I and HTLV-II, and simian immunodeficiency virus)) infection cycle (e.g., inhibition of replication, reinfection, maturation, budding etc.) and on any organism depending on
15 integrase for their life cycle.

The term “prophylactically effective amount” refers to an amount effective in preventing HIV infection in a patient or preventing AIDS (e.g., delaying the apparition of AIDS, lowering the probability of infection, lowering the probability of developing AIDS, etc.). As used herein,
20 the term “patient” refers to a mammal, including a human.

The terms “pharmaceutically acceptable carrier”, “pharmaceutically acceptable adjuvant” and “physiologically acceptable vehicle” refer to a non-toxic carrier or adjuvant that may be administered to a patient, together with a compound of this invention, and which does not
25 destroy the pharmacological activity thereof.

It is to be understood herein that a “straight alkyl group of 1 to 6 carbon atoms” includes for example, methyl, ethyl, propyl, allyl, butyl, pentyl, hexyl.

30 It is to be understood herein that a “branched alkyl group of 3 to 6 carbon atoms” includes for example, without limitation, *iso*-butyl, *tert*-butyl, 2-pentyl, 3-pentyl, etc.

It is to be understood herein, that a "cycloalkyl group having 3 to 6 carbon" includes for example, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclocyclohexyl (i.e., C₆H₁₁).

- 5 Salts derived from appropriate bases include alkali metal (e.g., sodium), alkaline earth metal (e.g., magnesium), ammonium and N - (C₁₋₄ alkyl)₄⁺ salts.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to
10 compounds, which possess stability sufficient to allow manufacture and administration to a mammal by methods known in the art.

It is to be understood herein, that if a "range" or "group of substances" is mentioned with respect to a particular characteristic (e.g., temperature, concentration, time and the like) of the
15 present invention, the present invention relates to and explicitly incorporates herein each and every specific member and combination of sub-ranges or sub-groups therein whatsoever. Thus, any specified range or group is to be understood as a shorthand way of referring to each and every member of a range or group individually as well as each and every possible sub-ranges or sub-groups encompassed therein; and similarly with respect to any sub-ranges or
20 sub-groups therein. Thus, for example,

- with respect to the number of carbon atoms, the mention of the range of 1 to 6 carbon atoms is to be understood herein as incorporating each and every individual number of carbon atoms as well as sub-ranges such as, for example, 1 carbon atoms, 3 carbon atoms, 4 to 6 carbon atoms, etc.
- 25 - with respect to reaction time, a time of 1 minute or more is to be understood as specifically incorporating herein each and every individual time, as well as sub-range, above 1 minute, such as for example 1 minute, 3 to 15 minutes, 1 minute to 20 hours, 1 to 3 hours, 16 hours, 3 hours to 20 hours etc.;
- and similarly with respect to other parameters such as concentrations, elements, etc...

30

It is in particular to be understood herein that the compound formulae each include each and every individual compound described thereby as well as each and every possible class or sub-

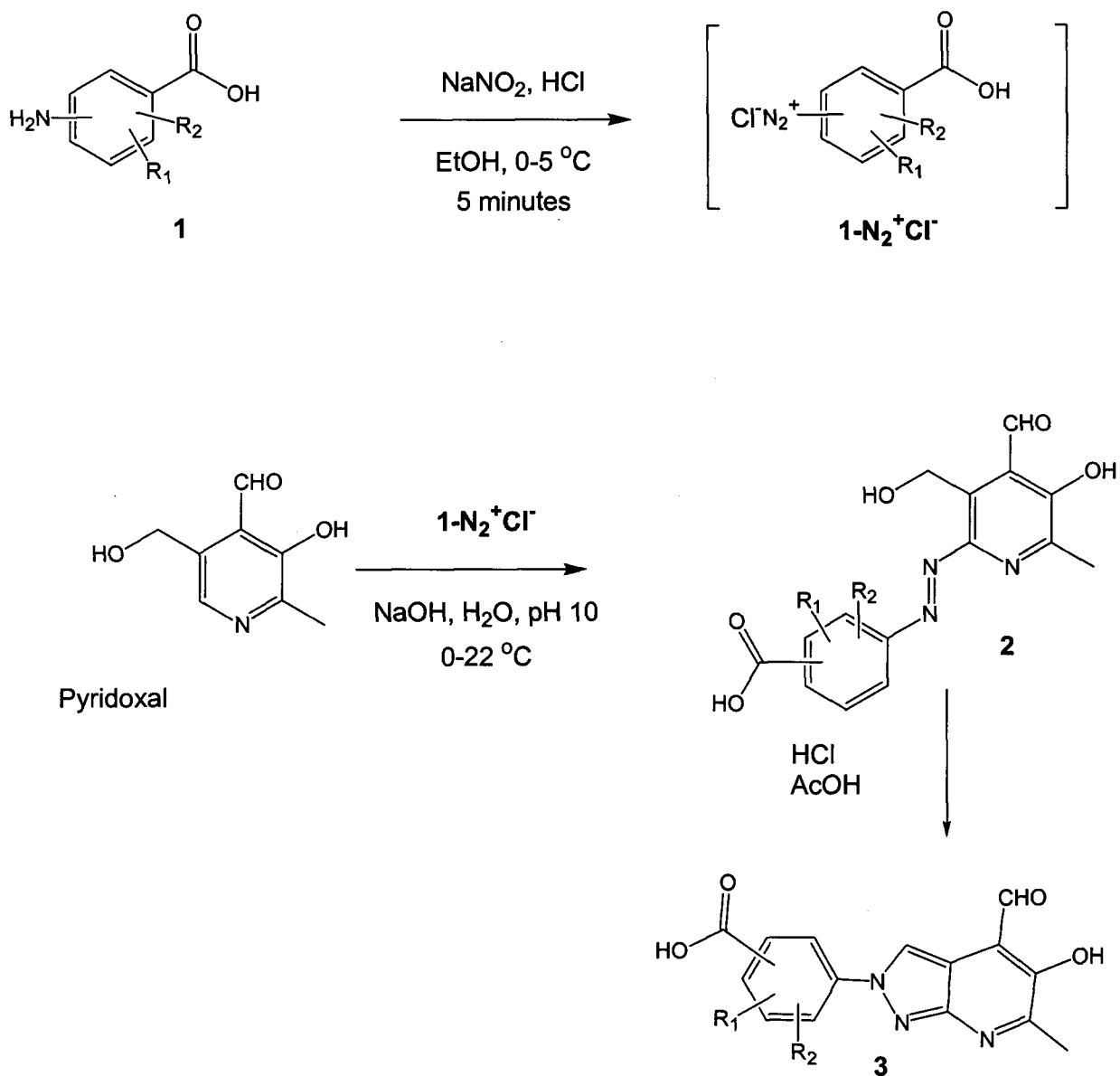
group or sub-class of compounds whether such class or sub-class is defined as positively including particular compounds, as excluding particular compounds or a combination thereof; for example an exclusionary definition for the formula (e.g. I) may read as follows: “provided that when one of A and B is -COOH and the other is H, -COOH may not occupy the X’ position”.

The compounds of this invention may be readily prepared using conventional techniques from commercially available and cheap starting materials. In general, the derivatives of the present invention may be readily obtained from pyridoxal through sequences recognized by those knowledgeable in the art as straightforward, requiring readily available reagents and easy techniques. Using standard techniques, pyridoxal may be transformed to the desired HIV integrase inhibitors according to approaches as below.

Scheme 1 illustrates a generic example for the coupling of aminoaryl carboxylic acid **1** with pyridoxal.

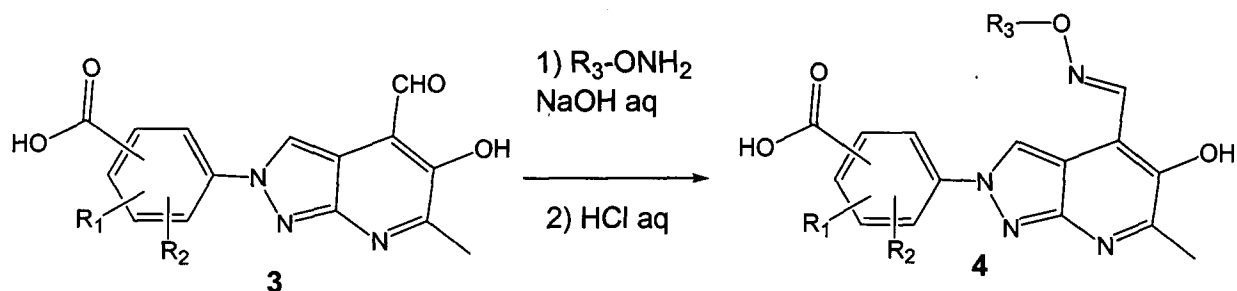
Diazotation of an appropriate aminoaryl carboxylic acid **1** (i.e., *ortho*, *meta* or *para*) upon treatment with NaNO₂ and hydrochloric acid gave the corresponding diazonium salt intermediate (1-N₂⁺Cl⁻) which is immediately added to a basic solution of pyridoxal. The resulting reaction mixture gave compound **2** in 65% average yield. Compound **2** is then treated with an acid in an appropriate polar solvent such as Water or Acetic acid to give the title compounds **3** in 65-95% yields.

Scheme 1

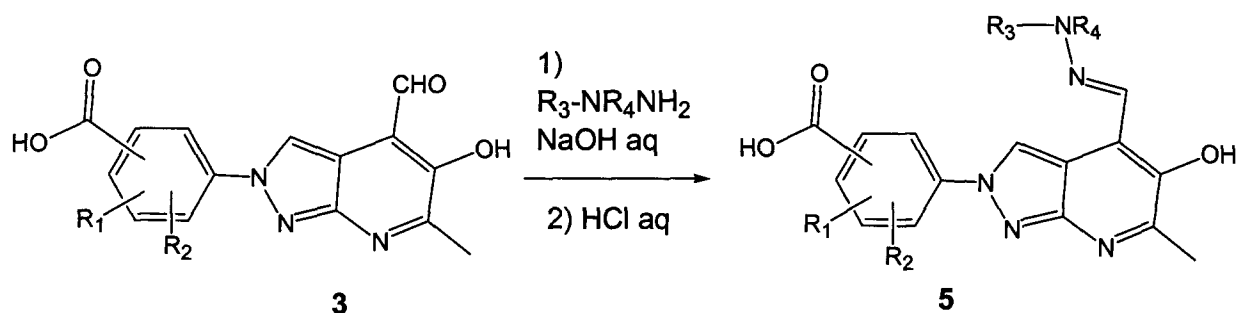


Title compounds 3 may further be modified by reaction with appropriately *O*-substituted oximes, *N'*-substituted hydrazines, *N'*-substituted hydrazides, *N'*, *N'*-disubstituted hydrazines, or *N'*, *N'*-disubstituted hydrazides to give title compounds 4 or 5 (Scheme 2)

Scheme 2



Scheme 3



5

As may be appreciated by the skilled person, the above synthetic schemes are not intended to comprise a comprehensive list of all means by which the compounds described and claimed in this application may be synthesized. Further methods will be evident to those of ordinary skill in the art.

10

The novel compounds of the present invention are excellent ligands for integrase, particularly HIV-1, and most likely HIV-2 and HTLV-1 integrase. Accordingly, these compounds are capable of targeting and inhibiting an early stage event in the replication, i.e. the integration of viral DNA into the human genome, thus preventing the replication of the virus.

15

In addition to their use in the prophylaxis or treatment of HIV infection or AIDS, the compounds according to this invention may also be used as inhibitory or interruptive agents for other viruses which depend on integrases, similar to HIV integrases, for obligatory events in their life cycle. Such compounds inhibit the viral replication cycle by inhibiting integrase.

5 Because integrase is essential for the production of mature virions, inhibition of that process effectively blocks the spread of virus by inhibiting the production and reproduction of infectious virions, particularly from acutely infected cells. The compounds of this invention advantageously inhibit enzymatic activity of integrase and inhibit the ability of integrase to catalyze the integration of the virus into the genome of human cells.

10 The compounds of this invention may be employed in a conventional manner for the treatment or prevention of infection by HIV and other viruses which depend on integrases for obligatory events in their life cycle. Such methods of treatment, their dosage levels and requirements may be selected by those of ordinary skill in the art from available methods and

15 techniques. For example, a compound of this invention may be combined with a pharmaceutically acceptable adjuvant for administration to a virally infected patient in a pharmaceutically acceptable manner and in an amount effective to lessen the severity of the viral infection. Also, a compound of this invention may be combined with pharmaceutically acceptable adjuvants conventionally employed in vaccines and administered in

20 prophylactically effective amounts to protect individuals over an extended period of time against viral infections, such as HIV infection. As such, the novel integrase inhibitors of this invention may be administered as agents for treating or preventing viral infections, including HIV infection, in a mammal. The compounds of this invention may be administered to a

25 healthy or HIV-infected patient either as a single agent or in combination with other antiviral agents which interfere with the replication cycle of HIV. By administering the compounds of this invention with other antiviral agents which target different events in the viral replication cycle, the therapeutic effect of these compounds may be potentiated. For instance, the co-administered antiviral agent may be one which targets early events in the life cycle of the virus, such as cell entry, reverse transcription and viral DNA integration into cellular DNA.

30 Antiviral agents targeting such early life cycle events include, didanosine (ddI), zalcitabine (ddC), stavudine (d4T), zidovudine (AZT), polysulfated polysaccharides, sT4 (soluble CD4) - which blocks attachment or adsorption of the virus to host cells -- and other compounds which block binding of virus to CD4 receptors on CD4-bearing T-lymphocytes. Other retroviral reverse transcriptase inhibitors, such as derivatives of AZT, may also be co-

administered with the compounds of this invention to provide therapeutic treatment for substantially reducing or eliminating viral infectivity and the symptoms associated therewith. Examples of other antiviral agents include ganciclovir, dideoxycytidine, trisodium phosphonoformate, eflornithine, ribavirin, acyclovir, alpha interferon and trimenotrexate.

5 Additionally, non-ribonucleoside inhibitors of reverse transcriptase, such as TIBO, nevirapine or delavirdine, may be used to potentiate the effect of the compounds of this invention, as may viral uncoating inhibitors, inhibitors of trans-activating proteins such as tat or rev, or inhibitors of the viral protease. These compounds may also be co-administered with other inhibitors of HIV integrase.

10 Combination therapies according to this invention exert a synergistic effect in inhibiting HIV replication because each component agent of the combination acts on a different site of HIV replication. The use of such combinations also advantageously reduces the dosage of a given conventional anti-retroviral agent that would be required for a desired therapeutic or prophylactic effect as compared to when that agent is administered as a monotherapy. These combinations may reduce or eliminate the side effects of conventional single anti-retroviral agent therapies while not interfering with the anti-retroviral activity of those agents. These combinations reduce potential of resistance to single agent therapies, while minimizing any associated toxicity. These combinations may also increase the efficacy of the conventional agent without increasing the associated toxicity. Preferred combination therapies include the administration of a compound of this invention with AZT, 3TC, ddI, ddC, d4T, combivir, 15 ziagen, sustiva, nevirapine and delavirdine.

25 Alternatively, the compounds of this invention may also be co-administered with other HIV protease inhibitors such as saquinavir, indinavir, nelfinavir, ritonavir and amprenavir to increase the effect of therapy or prophylaxis against various viral mutants or members of other HIV quasi species.

30 The compounds of this invention may be administered as single agents or in combination with retroviral reverse transcriptase inhibitors, such as derivatives of AZT or HIV aspartyl protease inhibitors. Co-administration of the compounds of this invention with retroviral reverse transcriptase inhibitors or HIV aspartyl protease inhibitors may exert a substantial synergistic effect, thereby preventing, substantially reducing, or completely eliminating viral infectivity and its associated symptoms.

The compounds of this invention may also be administered in combination with immunomodulators (e.g., bropirimine, anti-human alpha interferon antibody, IL-2, GM-CSF, methionine enkephalin, interferon alpha, diethyldithiocarbante, tumor necrosis factor, naltrexone and rEPO); antibiotics (e.g., pentamidine isethionate) or vaccines to prevent or combat infection and disease associated with HIV infection, such as AIDS and ARC.

When the compounds of this invention are administered in combination therapies with other agents, they may be administered sequentially or concurrently to the patient. Alternatively, pharmaceutical or prophylactic compositions according to this invention may be comprised of a combination of an integrase inhibitor of this invention and another therapeutic or prophylactic agent.

Although this invention focuses on the use of the compounds disclosed herein for preventing and treating HIV infection, the compounds of this invention may also be used as inhibitory agents for other viruses that depend on similar integrases for obligatory events in their life cycle. These viruses include, but are not limited to, other diseases caused by retroviruses, such as simian immunodeficiency viruses, HTLV-I and HTLV-II.

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

The pharmaceutical compositions of this invention may be administered orally, parenterally by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted

reservoir. Oral administration or administration by injection are thus contemplated by the present invention. The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically acceptable carriers, adjuvants or vehicles. The term “parenteral” as used herein includes subcutaneous, intracutaneous, intravenous,
5 intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

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

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, and aqueous
25 suspension and solutions. In the case of tablets for oral and carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or
30 flavoring and/or coloring agents may be added.

The pharmaceutical compositions of this invention may also be administered in the form of suppositories for rectal administration. These compositions may be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room

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

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

20 The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions may be prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

25 Dosage levels of between about 0.01 and about 25 mg/kg body weight per day, between about 0.5 and about 25 mg/kg body weight per day of the active ingredient compound are useful in the prevention and treatment of viral infection, including HIV infection. Typically, the pharmaceutical compositions of this invention may be administered from about 1 to about
30 5 times per day or alternatively, as a continuous infusion. Such administration may be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form may vary depending upon the patient treated and the particular mode of administration. A typical preparation may contain from

about 5% to about 75% active compound (w/w), for example, from about 20% to about 50% active compound.

5 Upon improvement of a patient's condition, a maintenance dose of a compound, composition or combination of this invention may be administered if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained. When the symptoms have been alleviated to the desired level, treatment may cease. Patients may, however, require intermittent treatment on a long-term basis, upon any recurrence of disease symptoms, especially for
10 AIDS.

As the skilled artisan will appreciate, lower or higher doses than those recited above may be required. Specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body
15 weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the infection, the patient's disposition to the infection and the judgment of the treating physician.

The compounds of this invention are also useful as commercial reagents which effectively
20 bind to integrases, particularly HIV integrase. As commercial reagent, the compounds of this invention, and their derivatives, may be used to block integration of a target DNA molecule by integrase, or may be derivatized to bind to a stable resin as a tethered substrate for affinity chromatography applications. These and other uses which characterize commercial integrase inhibitors will be evident to those of ordinary skill in the art.

25

In the description herein, the following abbreviations are used:

<u>Abbreviation</u>	<u>Meaning</u>
30 AcOH	Acetic acid
Ar	Argon
ARC	AIDS-related complex
AIDS	Acquired Immunodeficiency Syndrome
AZT	3-Azido-3-deoxythymine (Zidovudine)

	BSA	Bovine serum albumin
	DABCYL	4-[[4'-(dimethylamino)phenyl]azo]benzoic acid
	DCE	Dichloroethane
	DMF	Dimethylformamide
5	DNA	Deoxyribonucleic acid
	EtOH	Ethyl alcohol
	g	gram
	HPLC	High pressure liquid chromatography
	HIV-1, -2	Human immunodeficiency virus type 1, type 2
10	HTLV-I, -II	Human T-cell lymphotropic virus type I, type II
	IL-2	Interleukine-2
	M	Molar
	MeOH	Methyl alcohol
	mg	Milligram
15	mp	Melting point
	min	Minute
	mL	Milliliter
	mmol	Millimole
	nM	Nanomolar
20	rEPO	Recombinant erythropoietin
	RNA	Ribonucleic acid
	3TC	2',3'-Dideoxy-3-thiacytidine
	THF	Tetrahydrofuran
	°C	degree Celcius

25

This section describes the synthesis of several molecules that are presented in this document. These examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way. This section presents the detailed synthesis of compounds of this invention.

30

Materials and Methods

Analytical thin layer chromatography (TLC) was carried out with 0.25 mm silica gel E. Merck 60 F₂₅₄ plates and eluted with the indicated solvent systems. Preparative

chromatography was performed by flash chromatography, using silica gel 60 (EM Science) with the indicated solvent systems and positive air pressure to allow proper rate of elution. Detection of the compounds was carried out by exposing eluted plates (analytical or preparative) to iodine, UV light and/or treating analytical plates with a 2% solution of *p*-anisaldehyde in ethanol containing 3% sulfuric acid and 1% acetic acid followed by heating. Alternatively, analytical plates may be treated with a 0.3% ninhydrin solution in ethanol containing 3% acetic acid and/or a CAM solution made of 20 g (NH₄)₆Mo₇O₂₄ and 8.3 g Ce(SO₄)₂ polyhydrate in water (750 mL) containing concentrated sulfuric acid (90 mL).

Unless otherwise indicated, all starting materials were purchased from a commercial source such as Aldrich Co. or Sigma Co.

Melting points (mp) were determined on a Büchi 530 melting point apparatus in capillary tubes and were uncorrected.

Mass spectra were recorded on a Hewlett Packard LC/MSD 1100 system APCI either in negative mode or positive mode.

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AMX 500 equipped with a reversed or QNP probe. Samples were dissolved in deuteriochloroform (CDCl₃), deuterium oxide (D₂O) or deuterodimethylsulfoxide (DMSO-d₆) for data acquisition using tetramethylsilane as internal standard. Chemical shifts (*) are expressed in parts per million (ppm), the coupling constants (*J*) are expressed in hertz (Hz) whereas multiplicities are denoted as s for singlet, d for doublet, dd for doublet of doublets, t for triplet, q for quartet, quint for quintet m for multiplet, and br s for broad singlet.

GENERAL PROCEDURES

A. General procedure for the coupling of pyridoxal to diazobenzoic acid

Method A :

1 mmol of an aminobenzoic acid was dissolved in 5 mL 2N HCl (with ethanol to help dissolution if necessary) and cooled to 0-5°C in an ice/salt bath. 1 mmol of NaNO₂ was added

portionwise and the diazonium salt was formed during 5 min. Then, 1 mmol (263 mg) of pyridoxal was dissolved in 10 mL of ice water with addition of 0.5 mL of saturated NaOH. The diazonium salt was the added portionwise over a 1 min period and the resulting orange red solution left for 15 min. The solution was then warmed to RT for 1-4 h. The red solution
5 was then cooled in an ice bath and 6N HCl was added dropwise forming a red precipitate. The precipitate was filtered off, washed with ice water and dried. The yield for this reaction ranged from 20 to 90%.

Method B :

10 1 mmol of an aminobenzoic was dissolved in 2 mL 2N HCl (with 5 mL ethanol to help dissolution if necessary) and cooled to 0-5°C in an ice/salt bath. 1 mmol of NaNO₂ was added portionwise and the diazonium salt was formed during 5 min. Then, 1 mmol (263 mg) of pyridoxal was dissolved in 2 mL of ice water with addition of 0.5 mL of saturated NaOH. The diazonium salt was the added portionwise over a 1 min period and the resulting orange
15 red solution left for 15 min. The solution was then warmed to RT for 1-4 h. The red solution was then cooled in an ice bath until a yellow precipitate results. The precipitate was filtered and dried. The yield for this reaction ranged from 20 to 80%.

B. General procedure for the Pyrazolo formation

20 To a suspension of a pyridoxal derivative (5 mmol) in 5 mL acetic acid was added 2 mL 12 N HCl And heated to 80°C . The solution became deep red-brown as the product was formed. The solution was then filtered hot and the filtrated poured on crushed ice. A yellow brown precipitate was filtered and dried. (> 90% yield).

C. General procedure for the oxime formation

25 A Pyrazolo[3,4-b]pyridin-2-yl]-benzoic acid derivative (0.1 mmol) was added to a 20% solution of hydroxylamine hydrochloride in 2-5 mL, pH 6 buffered water and stirred for 20
30 min. The pH was adjusted with hydrochloric acid until precipitation of the product was completed. The precipitate was filtered and dried (~ 65-95% yield).

D. General procedure for the hydrazone formation

A Pyrazolo[3,4-b]pyridin-2-yl]-benzoic acid derivative (0.1 mmol) was added to a 20% solution of hydrazine hydrochloride in 2-5 mL, pH 6 buffered water and stirred for 20 min.

- 5 The pH was adjusted with hydrochloric acid until precipitation of the product was completed. The precipitate was filtered and dried (~ 65% yield).

DETAILED DESCRIPTION OF THE INVENTION

10 **EXAMPLES:**

Specific examples for the preparation of derivatives of general formula I

- The following compounds were prepared from either from pyridoxal- using the procedures summarized in schemes 1, 2, and 3.
- 15

Example 1. Preparation of 5-(4-Formyl-5-hydroxy-6-methyl-pyrazolo[3,4-b]pyridin-2-yl)-isophthalic acid

20

This product was obtained from commercially available 3, 5-amino-isophthalic acid and pyridoxal as described in general procedures A, method B and B. The final product was obtained in 85% yield.

- 25 LC/MS M+1 = 342.1 95%

¹H NMR (DMSO-d₆) σ ; 2.59 s 3H, 8.43 s 1H, 8.72 s 2H, 9.25 s 1H, 10.6 s 1H

Example 2. Preparation of 2-Chloro-5-(4-formyl-5-hydroxy-6-methyl-pyrazolo[3,4-b]pyridin-2-yl)-benzoic acid

30

This product was obtained from commercially available 2 Chloro 5-amino-benzoic acid and pyridoxal as described in general procedures A, method A and B. The final product was obtained in 70% yield.

- 35 LC/MS M+1 = 332.1

¹H NMR D₂O/ NaOD 2.10 s 3H, 8.0 d (J=7.4 Hz) 1H, 8.32 d (J= 7.4 Hz) 1H, 8.47 s 1H, 9.28 s 1H, 10.6 s 1H

Example 3. Preparation of 4-Chloro-3-(4-formyl-5-hydroxy-6-methyl-pyrazolo[3,4-b]pyridin-2-yl)-benzoic acid

This product was obtained from commercially available 4-Chloro, 5-amino-benzoic acid and pyridoxal as described in general procedures A, method A and B. The final product was obtained in 88% yield.

LC/MS M+1 = 332.1

¹H NMR (DMSO-d₆) σ; 2.65 s 3H, 7.89 d (8 Hz) 1H, 8.09 d (8 Hz) 1H, 9.20 s 1H, 10.59 s 1H

Example 4. Preparation of 4-(4-Formyl-5-hydroxy-6-methyl-pyrazolo[3,4-b]pyridin-2-yl)-benzoic acid

This product was obtained from commercially available 4-amino-benzoic acid and pyridoxal as described in general procedures A, method A and B. The final product was obtained in 95% yield.

LC/MS M+1 = 298.1

¹H NMR (DMSO-d₆) σ; 2.65 s 3H, 8.11 d (J=8Hz) 1H, 8.25 d(J=8Hz)1H, 9.20 s 1H, 10.59 s

Example 5. Preparation of 4-(4-Formyl-5-hydroxy-6-methyl-pyrazolo[3,4-b]pyridin-2-yl)-phthalic acid

This product was obtained from commercially available 3-amino-phthalic acid and pyridoxal as described in general procedures A, method A and B. The final product was obtained in 85% yield.

LC/MS M+1 = 342.1

¹H NMR (DMSO-d₆) σ ; 2.65 s 3H, 8.00 d(J=7.4) 1H, 8.32 d (J=7.4) 1H, 8.47 s 1H, 9.28 s 1H, 10.6 s 1H.

5 **Example 6. Preparation of 5-(4-Formyl-5-hydroxy-6-methyl-pyrazolo[3,4-b]pyridin-2-yl)-2-hydroxy-isophthalic acid**

This product was obtained from commercially available 2 Hydroxy, 5-amino-isophthalic acid and pyridoxal as described in general procedures A, method A and B. The final product was
10 obtained in 65% yield.

LC/MS M+1 = 358.2

¹H NMR D₂O/ NaOD; 2.33 s 3H, 7.33 s 2H, 8.26 s 2H, 9.92 s 2H
15

Example 7. Preparation of 5-[4-(Carboxymethoxyimino-methyl)-5-hydroxy-6-methyl-pyrazolo[3,4-b]pyridin-2-yl]-isophthalic acid

20 This product was obtained from commercially available 5-amino-isophthalic acid and pyridoxal as described in general procedures A, method A and B (Example 1). The filtered product was then reacted with carboxy methoxyl amine by general procedure C and obtained in 80% yield.

25 LC/MS M+1 =415.1

¹H NMR (DMSO-d₆) σ ; 2.58 s 3H, 4.90 s 2H, 8.46 s 1H, 8.67 s 2H, 8.84 s 1H, 9.05 s 1H

30 **Example 8. Preparation of 5-[5-Hydroxy-4-(methoxyimino-methyl)-6-methyl-pyrazolo[3,4-b]pyridin-2-yl]-isophthalic acid**

This product was obtained from commercially available 5-amino-isophthalic acid and pyridoxal as described in general procedures A, method A and B (Example 1). The filtered
35 product was then reacted with methoxyl amine by general procedure G and obtained in 80% yield.

LC/MS M+1 = 371.1

¹H NMR (DMSO-d₆) σ; 2.51 s 3H, 4.13 , 3H, 8.45 s 1H, 8.70 s 2H, 8.76 s 1H, 9.10 s 1H, 10.0 s 1H

Example 9. Preparation of 5-[4-(Ethoxyimino-methyl)-5-hydroxy-6-methyl-pyrazolo[3,4-b]pyridin-2-yl]-isophthalic acid

This product was obtained from commercially available 5-amino-isophthalic acid and pyridoxal as described in general procedures A, method A and B (Example 1). The filtered product was then reacted with Ethoxyl amine by general procedure C and obtained in 80% yield.

LC/MS M+1 = 385.1

¹H NMR (DMSO-d₆) σ; 1.35 t(6Hz) 3H, 2.60 s 3H, 4.45 q(J=6Hz) 2H, 8.70 s 2H, 8.80 s 1H, 9.1 s 1H, 10.0 s 1H

Example 10. Preparation of 5-[4-(Allyloxyimino-methyl)-5-hydroxy-6-methyl-pyrazolo[3,4-b]pyridin-2-yl]-isophthalic acid

This product was obtained from commercially available 5-amino-isophthalic acid and pyridoxal as described in general procedures A, method A and B (Example 1). The filtered product was then reacted with Allyloxyl amine by general procedure C and obtained in 80% yield.

LC/MS M+1 = 397.1

¹H NMR (DMSO-d₆) σ; 2.55 s 3H, 4.77 d (J= 6Hz) 2H, 5.31 d (J=6Hz) 1H, 5.40 d (J=15hz) 1H, 5.98-6.10m 1H, 8.36 s 1H, 8.65 s 2H, 8.71 s1H, 9.01 s 1H, 10.01 s 1H.

Example 11. Preparation of 5-[4-(tert-Butoxyimino-methyl)-5-hydroxy-6-methyl-pyrazolo[3,4-b]pyridin-2-yl]-isophthalic acid

This product was obtained from commercially 5-amino-isophthalic acid and pyridoxal as described in general procedures A, method A and B (Example 1). The filtered product was then reacted with t- Butoxyl amine by general procedure C and obtained in 80% yield.

LC/MS M+1 = 413.1

¹H NMR (DMSO-d₆) σ; 1.41 s 9H, 2.56 s 3H, 8.45 s 1H, 8.67 s 2H, 8.78 s 1H 9.09 s 1H, 10.05 s 1H

Example 12. Preparation of PL-402

This product was obtained from commercially 2 Chloro 5-amino-benzoic acid and pyridoxal as described in general procedures A, method A and B (Example 2). The filtered product was then reacted with Allyloxyl amine by general procedure C and obtained in 80% yield.

LC/MS M+1 = 387.1

¹H NMR (DMSO-d₆) σ; 2.54 s 3H, 4.76 brs 2H, 5.31 d (J=6Hz) 1H, 5.49 q (J=6Hz) 1H, 6.01 m 1H, 7.7 d (J= 8Hz) 1H, 8.22 d (J= 8Hz) 1H, 8.42 s 1H, 8.78 s 1H, 8.99 s 1H

Example 13. Preparation of 3-[4-(Carboxymethoxyimino-methyl)-5-hydroxy-6-methyl-pyrazolo[3,4-b]pyridin-2-yl]-4-chloro-benzoic acid

This product was obtained from commercially 2 Chloro 5-amino-benzoic acid and pyridoxal as described in general procedures A, method A and B (Example 2). The filtered product was then reacted with Carboxy methoxyl amine by general procedure C and obtained in 80% yield.

LC/MS M+1 = 405.0

¹H NMR (DMSO-d₆) σ; 2.61 s 3H, 4.95 s 2H, 7.76 d (J=8Hz) 1H, 8.22 d (J=8Hz) 1H, 8.46 s 1H, 8.73 s 1H, 9.00 s 1H

Example 14. Preparation of 5-[5-Hydroxy-4-(hydroxyimino-methyl)-6-methyl-pyrazolo[3,4-b]pyridin-2-yl]-isophthalic acid

This product was obtained from commercially 5-amino-isophthalic acid and pyridoxal as described in general procedures A, method A and B (Example 1). The filtered product was then reacted with Hydroxyl amine by general procedure C and obtained in 70% yield.

LC/MS M+1 = 357

5 ^1H NMR (DMSO- d_6) σ ; 2.55 s 3H, 8.61 s 2H, 8.74 s 1H, 9.15 s 1H, 10.18 s 1H, 12.01 s 1H.

Example 15. Preparation of 5-(4-Hydrazonomethyl-5-hydroxy-6-methyl-pyrazolo[3,4-b]pyridin-2-yl)-isophthalic acid

10

This product was obtained from commercially available 5-amino-isophthalic acid and pyridoxal as described in general procedures A, method A and B (Example 1). The filtered product was then reacted with Hydrazine by general procedure D and obtained in 80% yield.

15

LC/MS M+1 = 356.1

^1H NMR D_2O σ 2.25 s 3H, 8.12 s 1H, 8.17 s 2H, 8.25 s 1H, 8.37 s 1H.

20

Example 16. Preparation of 5-[5-Hydroxy-6-methyl-4-(piperidin-1-yliminomethyl)-pyrazolo[3,4-b]pyridin-2-yl]-isophthalic acid

25 This product was obtained from commercially available 5-amino-isophthalic acid and pyridoxal as described in general procedures A, method A and B (Example 1). The filtered product was then reacted with 1- amino piperidine by general procedure D and obtained in 69 % yield.

30

LC/MS M+1 =424.2

Example 17. Preparation of 5-[5-Hydroxy-6-methyl-4-(morpholin-4-yliminomethyl)-pyrazolo[3,4-b]pyridin-2-yl]-isophthalic acid

35

This product was obtained from commercially available 5-amino-isophthalic acid and pyridoxal as described in general procedures A, method A and B (Example 1). The filtered product was then reacted with 4 - amino morpholine by general procedure D and obtained in 69 % yield.

LC/MS M+1 = 426

- 5 ¹H NMR (DMSO-d₆) σ; 2.43 br s 4H, 2.55 s 3H, 3.66 br s 4H, 3.80 br s 4H, 8.20 s 1H, 8.41 s 1H 8.66 s 2H, 9.34 s 1H.

10 **Example 18. Preparation of 5-{5-Hydroxy-4-[(2-hydroxy-6-methyl-pyridine-3-carbonyl)-hydrazonomethyl]-6-methyl-pyrazolo[3,4-b]pyridin-2-yl}-isophthalic acid**

This product was obtained from commercially available 5-amino-isophthalic acid and pyridoxal as described in general procedures A, method A and B (Example 1). The filtered
15 product was then reacted with 2-Hydroxy-6 Methyl nicotinyl hydrazide by general procedure D and obtained in 79 % yield.

20 LC/MS M+1 = 491

¹H NMR (DMSO-d₆) σ; 2.33 s 3H, 2.62 s 3H, 6.43 d 1H J= 7, 8.32 d 1H J= 7, 8.41 s 1H, 8.72 s 2H, 9.00 s 1H, 9.40 s 1H, 11.5 s 1H, 12.7 s 1H, 13.3 s 1H.

25 **Example 19. Preparation of 5-{4-[(2,3-Dihydroxy-benzoyl)-hydrazonomethyl]-5-hydroxy-6-methyl-pyrazolo[3,4-b]pyridin-2-yl}-isophthalic acid**

This product was obtained from commercially available 5-amino-isophthalic acid and
30 pyridoxal as described in general procedures A, method A and B (Example 1). The filtered product was then reacted with 2, 3- DiHydroxy-Benzoic hydrazide by general procedure D and obtained in 77 % yield.

LC/MS M+1 = 492

- 35 ¹H NMR (DMSO-d₆) σ; 2.55 s 3H, 6.71 t j=6, 7.03 d 1H J=6, 7.48 d 1H J= 6, 8.4 s 1H, 8.7 s 2H, 9.1 s 1H, 9.3 s 1H 12.55 s 1H.

Example 20. Preparation of 5-{5-Hydroxy-6-methyl-4-[(2,3,4-trihydroxy-benzoyl)-hydrazonomethyl]-pyrazolo[3,4-b]pyridin-2-yl}-isophthalic acid

5 This product was obtained from commercially available 5-amino-isophthalic acid and pyridoxal as described in general procedures A, method A and B (Example 1). The filtered product was then reacted with 2, 3, 4- TriHydroxy-Benzoic hydrazide by general procedure D and obtained in 77 % yield.

10 LC/MS M+1 = 508

¹H NMR (DMSO-d₆) σ; 2.61 s 3H, 6.45 d 1H J=7, 7.45 d 1H J= 7, 8.45 s 1H, 8.70 s 2H, 9.00 s 1H, 9.31 s 1H, 12.41 s 1H.

15

Example 21. Preparation of 5-[5-Hydroxy-6-methyl-4-(pyridin-2-yl-hydrazonomethyl)-pyrazolo[3,4-b]pyridin-2-yl]-isophthalic acid

This product was obtained from commercially available 5-amino-isophthalic acid and
20 pyridoxal as described in general procedures A, method A and B (Example 1). The filtered product was then reacted with 2-pyridyl hydrazine by general procedure D and obtained in 65 % yield.

25 PI- 388
LC/MS M+1 = 433.1

¹H NMR (DMSO-d₆) σ; 2.64 s 3H, 7.11 s 1H, 7.40 t (J= 7Hz) 1H, 8.02-8.18 m 2H, 8.80 s 2H, 8.91 s 1H, 9.55 s 1H

30

Example 22. Preparation of 5-[4-(Formyl-hydrazonomethyl)-5-hydroxy-6-methyl-pyrazolo[3,4-b]pyridin-2-yl]-isophthalic acid

35 This product was obtained from commercially available 5-amino-isophthalic acid and pyridoxal as described in general procedures A, method A and B (Example 1). The filtered product was then reacted with formyl hydrazide by general procedure D and obtained in 85 % yield.

LC/MS M+1 = 384.1

5 **Example 23. Preparation of 5-{5-Hydroxy-4-[(2-hydroxy-benzoyl)-hydrazonomethyl]-6-methyl-pyrazolo[3,4-b]pyridin-2-yl}-isophthalic acid**

10 This product was obtained from commercially available 5-amino-isophthalic acid and pyridoxal as described in general procedures A, method A and B (Example 1). The filtered product was then reacted with Salicyl hydrazide by general procedure D and obtained in 88 % yield.

LC/MS M+1 = 476.1

15 ¹H NMR (DMSO-d₆) σ ; 2.62 s 3H, 6.92-7.03 m 2H, 7.46 brs 1H, 7.93 d (J=6.8 Hz) 1H, 8.44 s 1H, 8.71 s 2H, 9.00 s 1H, 9.32 s 1H, 11.3 brs 1H, 11.67 brs 1H, 12.30 s 1H.

20 ¹H NMR dmso

Example 25. Preparation of 2-Chloro-5-[5-hydroxy-4-(methoxycarbonyl-hydrazonomethyl)-6-methyl-pyrazolo[3,4-b]pyridin-2-yl]-benzoic acid

25 This product was obtained from commercially 2 Chloro 5-amino-benzoic acid and pyridoxal as described in general procedures A, method A and B (Example 2). The filtered product was then reacted with NH₂NHCOOMe by general procedure D and obtained in 80% yield.

30 PI- 423
LC/MS M+1 = 404.8

35 **Example 26. Preparation of 2-Chloro-5-[5-hydroxy-4-(aminocarbonyl-hydrazonomethyl)-6-methyl-pyrazolo[3,4-b]pyridin-2-yl]-benzoic acid**

This product was obtained from commercially 2 Chloro 5-amino-benzoic acid and pyridoxal

as described in general procedures A, method A and B (Example 2). The filtered product was then reacted with semicarbazide by general procedure D and obtained in 80% yield.

LC/MS M+1 = 389.1

5

Example 27. Preparation of 5-[4-(Benzoyl-hydrazonomethyl)-5-hydroxy-6-methyl-pyrazolo[3,4-b]pyridin-2-yl]-2-chloro-benzoic acid

10 This product was obtained from commercially 2 Chloro 5-amino-benzoic acid and pyridoxal as described in general procedures A, method A and B (Example 2). The filtered product was then reacted with Benzoyl hydrazide by general procedure D and obtained in 80% yield.

15 LC/MS M+1 = 450.8

Example 28. Preparation of 5-{4-[(4-tert-Butyl-benzoyl)-hydrazonomethyl]-5-hydroxy-6-methyl-pyrazolo[3,4-b]pyridin-2-yl}-2-chloro-benzoic acid

20

This product was obtained from commercially 2 Chloro 5-amino-benzoic acid and pyridoxal as described in general procedures A, method A and B (Example 2). The filtered product was then reacted with 4-t Butyl- Benzoyl Hydrazide by general procedure D and obtained in 80% yield.

25

LC/MS M+1 = 506.2

Example 28. Preparation of 2-Chloro-5-{5-hydroxy-4-[(2-hydroxy-6-methyl-pyridine-3-carbonyl)-hydrazonomethyl]-6-methyl-pyrazolo[3,4-b]pyridin-2-yl}-benzoic acid

30

This product was obtained from commercially 2 Chloro 5-amino-benzoic acid and pyridoxal as described in general procedures D, method A and B (Example 2). The filtered product was then reacted with 2-Hydroxy-6 Methyl nicotinyl hydrazide by general procedure D and
35 obtained in 80% yield.

LC/MS M+1 = 481.8

5 BIOLOGICAL EVALUATION

Integrase inhibition assay *in vitro*

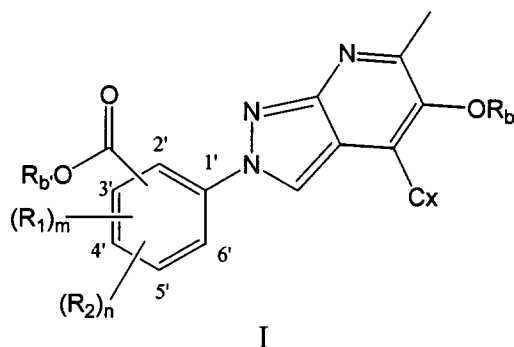
For the purpose of Table 1, the HIV-1 integrase inhibition assay was carried out following a
10 known procedure (IGEN International, Inc. 2002; ORIGEN® HIV Integrase assay, A highly
Sensitive and Rapid method to measure Integrase Activity and to Identify Inhibitors), Using
an M8 Electroluminescence analyzer (IGEN International).

15 Anti-viral and cytotoxicity assays *in vitro*

- To evaluate the EC₅₀ of our compounds, various drug concentrations were incubated with
the infected cell for six days and then the metabolic activity of the cells was monitored by
the MTT assay. (See A. J. Japour et al, Antimicrobial Agents and Chemotherapy, 37,
20 1095-1101, 1993 and R. Pauwels et al. Journal of Virological Methods, 20, 309-321,
1988)
- We used the laboratory viral strain NL4.3 as wild type virus and the cell line used was
MT-4 which is a T-cell line highly sensitive to HIV-1. We also used some WT clinical
strains. To address the resistance issue we assayed the inhibitors with NL4.3 mutants
25 which are designed to be resistant to specific commercially available inhibitors
- The same MTT assay was used to evaluate the CCIC₅₀ of our compounds except that the
virus was omitted.

The compounds listed in Table 1 were prepared by following Scheme 1, 2, 3; and more
30 particularly as described in each example listed above. The numbers of the compounds listed
in Table 1 (Ex. No.) correspond to the example numbers presented above. The activities of
the compounds are also listed in the same table demonstrating their potential usefulness. In
Table 1 are shown compounds of formula I wherein carbon 2', 3', 4', 5' and in a case 6' are
substituted as presented in Table 1. IC₅₀, EC₅₀ as well as CCIC₅₀ results for compound of
35 formula I and Ib are also presented in Table 1 illustrating their potential usefulness.

Table 1. Anti-integrase activity of Pyrazolo[3,4-b]pyridin-2-yl]-benzoic acid derivatives of formula I



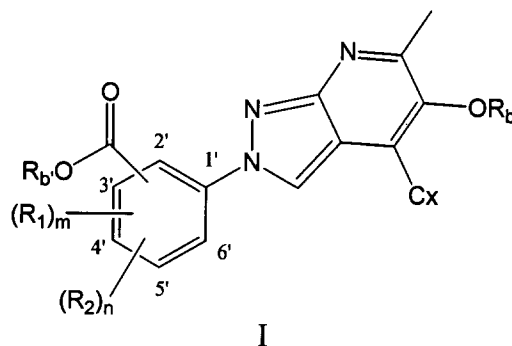
Ex. No.	Cx	2'	3'	4'	5'	6'	IC ₅₀ (nM)	EC ₅₀ (nM)	CCIC ₅₀ (nM)
1	CHO	H	COOH	H	COOH	H	500-800	800	> 100000
2	CHO	H	COOH	Cl	H	H	1900	18000	> 100000
3	CHO	H	COOH	H	H	Cl	9000	32000	> 100000
4	CHO	H	H	COOH	H	H	2700	7000	> 100000
5	CHO	H	COOH	COOH	H	H	500	14000	> 100000
6	CHO	H	COOH	OH	COOH	H	200	5000	> 100000
7	CHNO-CH ₂ -CO ₂ H	H	COOH	H	COOH	H	700	700	> 100000
8	CHNOMe	H	COOH	H	COOH	H	1000	3200	> 100000
9	CHNOEt	H	COOH	H	COOH	H	500	2000	> 100000
10	CHNO-Allyl	H	COOH	H	COOH	H	2500	2500	> 100000
11	CHNO-t-Bu	H	COOH	H	COOH	H	4000	4000	> 100000
12	CHNO-Allyl	H	COOH	Cl	H	H	6000	ND	> 100000
13	CHNO-CH ₂ -CO ₂ H	H	COOH	Cl	H	H	1200	20000	> 100000
14	CHNOH	H	COOH	H	COOH	H	19000	19000	> 100000
15	CHNNH ₂	H	COOH	H	COOH	H	15000	15000	> 100000
16	CHN-1- piperidine	H	COOH	H	COOH	H	12000	15000	> 100000
17	CHN-1-morpholine	H	COOH	H	COOH	H	90000	ND	> 100000
18	CHN-NH- (CO-2-OH-6-Me Nicotinyll)	H	COOH	H	COOH	H	500	1000	> 100000
19	CHN-NH- (CO-2, 3-Di-OH-Phenyl)	H	COOH	H	COOH	H	300	1000	50000
20	CHN-NH- (CO-2, 3, 4-Tri-OH-Phenyl)	H	COOH	H	COOH	H	200	200	8000
21	CHN-NH-2-Pyridine	H	COOH	H	COOH	H	2000	4000	30000
22	CHN-NH-formyl	H	COOH	H	COOH	H	2500	50000	> 100000
23	CHN-NH- (CO-2-OH-Phenyl)	H	COOH	H	COOH	H	500	1000	50000
24	CHN-NH-(COOMe)	H	COOH	Cl	H	H	27000	20000	> 100000
25	CHN-NH-(CONH ₂)	H	COOH	Cl	H	H	29000	17000	> 100000
26	CHN-NH-Bz	H	COOH	Cl	H	H	6000	15000	> 100000
27	CHN-NH- (4- t-Bu Bz)	H	COOH	Cl	H	H	5900	23000	> 100000
28	CHN-NH- (CO-2-OH-6-Me Nicotinyll)	H	COOH	Cl	H	H	5200	12000	> 100000

5

In compounds 1 to 28 exemplified above, R_b and R_b' are both H.

WE CLAIM:

1. A compound of formula I



and pharmaceutically acceptable salts or solvates thereof,

wherein n is 0, 1, 2, 3 or 4,

wherein m is 0, 1, 2, 3 or 4,

wherein Cx is selected from the group consisting of -CHO, -CH=N-OR₃, -CH=N-NR₃R₄, -CH=N-R₅, and -CH(OR₃)₂,

wherein R₁ is selected from the group consisting of -H, a straight alkyl group of 1 to 6 carbon atoms, a branched alkyl group of 3 to 6 carbon atoms, -F, -Cl, -Br, -I, -CN and -OR₃,

wherein R₂ is selected from the group consisting of -H, -CO₂H, -CONR₃R₄ and -COR₆,

wherein R₃ is selected from the group consisting of -H, a straight alkyl group of 1 to 6 carbon atoms, a branched alkyl group of 3 to 6 carbon atoms, an allyl group, a cycloalkyl group of 3 to 8 carbon atoms, piperidine, pyrrolidine, morpholine and -R_a-COOH,

wherein R_a is a straight alkyl group of 1 to 6 carbon atoms,

wherein R_b is selected from the group consisting of -H, a straight alkyl group of 1 to 6 carbon atoms, a branched alkyl group of 3 to 6 carbon atoms, an allyl group, a cycloalkyl group of 3 to 8 carbon atoms, R_b -CO-, $(HO)_2P(O)$ and $(MO)_2P(O)$,

5 wherein M is an alkali metal or alkaline earth metal thereof,

wherein R_b is selected from the group consisting of H, a straight or branched alkyl group of 1 to 6 carbon atoms, a cycloalkyl group having 3 to 6 carbon atoms and a cycloalkylalkyl group having 3 to 6 carbon atoms in the cycloalkyl part thereof and 1 to 3 carbon atoms in the alkyl part thereof,

10

wherein R_4 is selected from the group consisting of H, a straight alkyl group of 1 to 6 carbon atoms, a branched alkyl group of 3 to 6 carbon atoms, a cycloalkyl group of 3 to 8 carbon atoms, -CH₂CH₂OH, 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-(1,2,3,4-tetrahydroquinolyl), -CO₂R₃, -CONR₃R₃, -COR₆, 2-hydroxy-6-methyl nicotinyl, formyl, benzyl substituted with a straight alkyl group of 1 to 6 carbon atoms or a branched alkyl group of 3 to 6 carbon atoms, unsubstituted benzyl, unsubstituted phenyl, mono-, di- or tri- hydroxysubstituted phenyl, phenyl substituted with a straight alkyl group of 1 to 6 carbon atoms and phenyl substituted with a branched alkyl group of 3 to 6 carbon atoms,

15

20 wherein R_5 is selected from the group consisting of piperidine and morpholine,

wherein R_6 is selected from the group consisting of -H, a straight alkyl group of 1 to 6 carbon atoms, a branched alkyl group of 3 to 6 carbon atoms, a cycloalkyl group of 3 to 8 carbon atoms, -NH₂, unsubstituted phenyl, mono-, di- or tri- hydroxysubstituted phenyl, phenyl substituted with a straight alkyl group of 1 to 6 carbon atoms, phenyl substituted with a branched alkyl group of 3 to 6 carbon atoms, -CH₂CH₂OH, 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-(1,2,3,4-tetrahydroquinolyl), an unsubstituted pyridyl, a pyridyl substituted with a straight alkyl group of 1 to 6 carbon atoms, a pyridyl substituted with a branched alkyl group of 3 to 6 carbon atoms, an unsubstituted nicotinyl, a nicotinyl substituted with a straight alkyl group of 1 to 6 carbon atoms, a branched alkyl group of 3 to 6 carbon atoms, and/or at least one hydroxy group and -OR₇, and;

25

30

wherein R₇ is selected from the group consisting of -H, a straight alkyl group of 1 to 6 carbon atoms, a branched alkyl group of 3 to 6 carbon atoms and a cycloalkyl group of 3 to 8 carbon atoms.

- 5 2. The compound of claim 1, wherein C_x is selected from the group consisting of -CHO, -CHNO-R_a-COOH, -CHNOR₃, -CHN-NR₃R₄ and -CH=N-R₅,

wherein R₃ is selected from the group consisting of -H and a straight alkyl group of 1 to 6 carbon atoms,

10

wherein R₄ is selected from the group consisting of -H, -COR₆, formyl, benzyl substituted with a straight alkyl group of 1 to 6 carbon atoms or a branched alkyl group of 3 to 6 carbon atoms, unsubstituted benzyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, unsubstituted phenyl, mono-, di- or tri- hydroxysubstituted phenyl, phenyl substituted with a straight
15 alkyl group of 1 to 6 carbon atoms and phenyl substituted with a branched alkyl group of 3 to 6 carbon atoms,

wherein R₅ is selected from the group consisting of piperidine and morpholine,

- 20 wherein R₆ is selected from the group consisting of -NH₂, unsubstituted phenyl, mono-, di- or tri- hydroxysubstituted phenyl, phenyl substituted with a straight alkyl group of 1 to 6 carbon atoms, phenyl substituted with a branched alkyl group of 3 to 6 carbon atoms, an unsubstituted nicotinyl, a nicotinyl substituted with a straight alkyl group of 1 to 6 carbon atoms, a branched alkyl group of 3 to 6 carbon atoms, and/or at least one hydroxy group
25 and -OR₇, and;

wherein R₇ is selected from the group consisting of -H, a straight alkyl group of 1 to 6 carbon atoms, a branched alkyl group of 3 to 6 carbon atoms and a cycloalkyl group of 3 to 8 carbon atoms.

30

3. The compound of claim 2, wherein C_x is selected from the group consisting of -CHO, -CHNO-CH₂-COOH, -CHNO-Me, -CHNOEt, -CHNO-allyl, -CHNO-t-Bu, -CHNOH, -CHNNH₂, -CHN-1-piperidine, -CHN-1-morpholine, -CHN-NH-(CO-2-OH-6-Me

nicotinyll), -CHN-NH-(CO-hydroxyphenyl), -CHN-NH-2-pyridine, -CHN-NH-formyl, -CHN-NH-(COOMe), -CHN-NH-(CONH₂), -CHN-NH-Bz, and -CHN-NH-(4-t-Bu Bz).

4. The compound of claim 3, wherein Cx is selected from the group consisting of -CHO, -CHNO-CH₂-COOH, -CHNO-Me, -CHNOEt, -CHNO-allyl, -CHNO-t-Bu, -CHN-NH-(CO-2-OH-6-Me nicotinyll), -CHN-NH-2-pyridine, -CHN-NH-formyl, -CHN-NH-(CO-hydroxyphenyl), -CHN-NH-Bz, and -CHN-NH-(4-t-Bu Bz).
5. The compound of claim 4, wherein Cx is selected from the group consisting of -CHO, CHNO-CH₂-COOH, -CHNOEt, -CHN-NH-(CO-2-OH-6-Me nicotinyll) and -CHN-NH-(CO-hydroxyphenyl).
6. The compound of claim 5, wherein Cx is -CHN-NH-(CO-mono-hydroxyphenyl).
7. The compound of claim 5, wherein Cx is -CHN-NH-(CO-di-hydroxyphenyl).
8. The compound of claim 5, wherein Cx is -CHN-NH-(CO-tri-hydroxyphenyl).
9. The compound of claim 6, wherein Cx is -CHN-NH-(CO-2-OH-Phenyl).
10. The compound of claim 7, wherein Cx is -CHN-NH-(CO-2, 3-Di-OH-Phenyl).
11. The compound of claim 8, wherein Cx is -CHN-NH-(CO-2, 3,4 -Tri-OH-Phenyl).
12. The compound of claim 1, wherein Cx is -CH=N-NR₃R₄,
wherein R₃ is -H;

wherein R₄ is selected from the group consisting of -H, 2-pyridyl, 3-pyridyl, 4-pyridyl, formyl, unsubstituted benzyl, benzyl substituted with a straight alkyl group of 1 to 6 carbon atoms or a branched alkyl group of 3 to 6 carbon atoms, unsubstituted phenyl, mono-, di- or tri- hydroxysubstituted phenyl, phenyl substituted with a straight alkyl group of 1 to 6 carbon atoms, phenyl substituted with a branched alkyl group of 3 to 6 carbon atoms and -COR₆;

wherein R_6 is selected from the group consisting of $-NH_2$, $-OR_7$, a straight alkyl group of 1 to 6 carbon atoms, a branched alkyl group of 3 to 6 carbon atoms, a cycloalkyl group of 3 to 8 carbon atoms, unsubstituted phenyl, mono-, di-, tri- hydroxysubstituted phenyl, phenyl substituted with a straight alkyl group of 1 to 6 carbon atoms, phenyl substituted with a branched alkyl group of 3 to 6 carbon atoms, an unsubstituted nicotiny, a nicotiny substituted with a straight alkyl group of 1 to 6 carbon atoms, a branched alkyl group of 3 to 6 carbon atoms, and/or at least one hydroxy group and;

wherein R_7 is as defined in claim 1.

13. The compound of any one of claims 1 to 12, wherein R_1 is selected from the group consisting of $-H$, $-F$, $-Cl$, $-Br$ and $-OH$.

14. The compound of any one of claims 1 to 13, wherein m is 0, 1 or 2.

15. The compound of any one of claims 1 to 14, wherein n is 0, 1 or 2.

16. The compound of any one of claims 1 to 15, wherein the $-COOR_{b'}$ group is at a 3' or 4' position.

17. The compound of any one of claims 1 to 16, wherein $R_{b'}$ is $-H$.

18. The compound of any one of claims 1 to 17, wherein R_b is selected from the group consisting of $-H$, $(HO)_2P(O)$ and $(MO)_2P(O)$, wherein M is an alkali metal or alkaline earth metal thereof.

19. The compound of claim 5, wherein C_x is $-CHO$.

20. The compound of claim 19, wherein R_1 and R_2 are both $-H$ or wherein m and n are both 0.

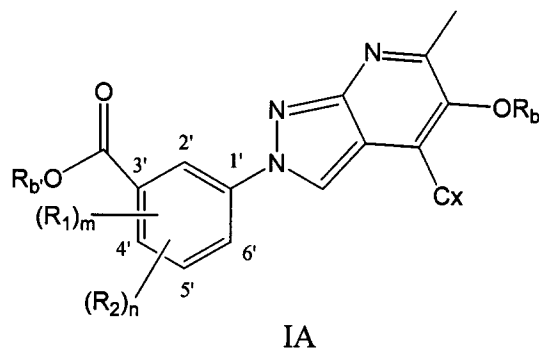
21. The compound of claim 20, wherein the $-COOR_{b'}$ group is at a 4' position.

22. The compound of claim 21, wherein $R_{b'}$ is H .

23. The compound of any one of claims 19 to 22, wherein R_b is H.

24. A compound of formula IA

5



, and pharmaceutically acceptable salts or solvates thereof,

wherein n is 0, 1, 2, 3 or 4,

10

wherein m is 0, 1, 2, 3 or 4,

wherein C_x is selected from the group consisting of $-CHO$, $-CH=N-OR_3$, $-CH=N-NR_3R_4$, $-CH=N-R_5$, and $-CH(OR_3)_2$,

15

wherein R_1 is selected from the group consisting of $-H$, a straight alkyl group of 1 to 6 carbon atoms, a branched alkyl group of 3 to 6 carbon atoms, $-F$, $-Cl$, $-Br$, $-I$, $-CN$ and $-OR_3$,

20

wherein R_2 is selected from the group consisting of $-H$, $-CO_2H$, $-CONR_3R_4$ and $-COR_6$,

wherein R_3 is selected from the group consisting of $-H$, a straight alkyl group of 1 to 6 carbon atoms, a branched alkyl group of 3 to 6 carbon atoms, an allyl group, a cycloalkyl group of 3 to 8 carbon atoms, piperidine, pyrrolidine, morpholine and $-R_a-COOH$,

25

wherein R_a is a straight alkyl group of 1 to 6 carbon atoms,

wherein R_b is selected from the group consisting of -H, a straight alkyl group of 1 to 6 carbon atoms, a branched alkyl group of 3 to 6 carbon atoms, an allyl group, a cycloalkyl group of 3 to 8 carbon atoms, R_b -CO-, $(HO)_2P(O)$ and $(MO)_2P(O)$,

5 wherein M is an alkali metal or alkaline earth metal thereof,

wherein R_b is selected from the group consisting of H, a straight or branched alkyl group of 1 to 6 carbon atoms, a cycloalkyl group having 3 to 6 carbon atoms and a cycloalkylalkyl group having 3 to 6 carbon atoms in the cycloalkyl part thereof and 1 to 3 carbon atoms in the alkyl part thereof,

wherein R_4 is selected from the group consisting of H, a straight alkyl group of 1 to 6 carbon atoms, a branched alkyl group of 3 to 6 carbon atoms, a cycloalkyl group of 3 to 8 carbon atoms, -CH₂CH₂OH, 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-(1,2,3,4-tetrahydroquinolyl), -CO₂R₃, -CONR₃R₃, -COR₆, 2-hydroxy-6-methyl nicotinyl, formyl, benzyl substituted with a straight alkyl group of 1 to 6 carbon atoms or a branched alkyl group of 3 to 6 carbon atoms, unsubstituted benzyl, unsubstituted phenyl, mono-, di- or tri- hydroxysubstituted phenyl, phenyl substituted with a straight alkyl group of 1 to 6 carbon atoms and phenyl substituted with a branched alkyl group of 3 to 6 carbon atoms,

20 wherein R_5 is selected from the group consisting of piperidine and morpholine,

wherein R_6 is selected from the group consisting of -H, a straight alkyl group of 1 to 6 carbon atoms, a branched alkyl group of 3 to 6 carbon atoms, a cycloalkyl group of 3 to 8 carbon atoms, -NH₂, unsubstituted phenyl, mono-, di-, tri- hydroxysubstituted phenyl, phenyl substituted with a straight alkyl group of 1 to 6 carbon atoms, phenyl substituted with a branched alkyl group of 3 to 6 carbon atoms, -CH₂CH₂OH, 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-(1,2,3,4-tetrahydroquinolyl), an unsubstituted pyridyl, a pyridyl substituted with a straight alkyl group of 1 to 6 carbon atoms, a pyridyl substituted with a branched alkyl group of 3 to 6 carbon atoms, an unsubstituted nicotinyl, a nicotinyl substituted with a straight alkyl group of 1 to 6 carbon atoms, a branched alkyl group of 3 to 6 carbon atoms, and/or at least one hydroxy group and -OR₇, and;

wherein R₇ is selected from the group consisting of -H, a straight alkyl group of 1 to 6 carbon atoms, a branched alkyl group of 3 to 6 carbon atoms and a cycloalkyl group of 3 to 8 carbon atoms.

- 5 25. The compound of claim 24, wherein C_x is selected from the group consisting of -CHO, -CHNO-R_a-COOH, -CHNOR₃, -CHN-NR₃R₄ and -CH=N-R₅,

wherein R₃ is selected from the group consisting of -H, a straight alkyl group of 1 to 6 carbon atoms,

10

wherein R₄ is selected from the group consisting of -H, -COR₆, formyl, benzyl substituted with a straight alkyl group of 1 to 6 carbon atoms or a branched alkyl group of 3 to 6 carbon atoms, unsubstituted benzyl, 2-pyridyl, 3-pyridyl, 4-pyridyl,

- 15 wherein R₅ is selected from the group consisting of piperidine and morpholine,

wherein R₆ is selected from the group consisting of -NH₂, unsubstituted phenyl, mono-, di-, tri- hydroxysubstituted phenyl, an unsubstituted nicotinyll, a nicotinyll substituted with a straight alkyl group of 1 to 6 carbon atoms, a branched alkyl group of 3 to 6 carbon atoms, and/or at least one hydroxy group and -OR₇, and;

20

wherein R₇ is selected from the group consisting of -H and a straight alkyl group of 1 to 6 carbon atoms.

- 25 26. The compound of claim 25, wherein C_x is selected from the group consisting of -CHO, -CHNO-CH₂-COOH, -CHNO-Me, -CHNOEt, -CHNO-allyl, -CHNO-t-Bu, -CHNOH, -CHNNH₂, -CHN-1-piperidine, -CHN-1-morpholine, -CHN-NH-(CO-2-OH-6-Me nicotinyll), -CHN-NH-(CO-hydroxyphenyl), -CHN-NH-2-pyridine, -CHN-NH-formyl, -CHN-NH-(COOMe), -CHN-NH-(CONH₂), -CHN-NH-Bz, and -CHN-NH-(4-t-Bu Bz).

30

27. The compound of claim 26, wherein C_x is selected from the group consisting of -CHO, -CHNO-CH₂-COOH, -CHNO-Me, -CHNOEt, -CHNO-allyl, -CHNO-t-Bu, -CHN-NH-(CO-2-OH-6-Me nicotinyll), -CHN-NH-2-pyridine, -CHN-NH-formyl, -CHN-NH-(CO-hydroxyphenyl), -CHN-NH-Bz, and -CHN-NH-(4-t-Bu Bz).

28. The compound of claim 27, wherein Cx is selected from the group consisting of -CHO, CHNO-CH₂-COOH, -CHNOEt, -CHN-NH-(CO-2-OH-6-Me nicotinyll) and -CHN-NH-(CO-hydroxyphenyl).
- 5
29. The compound of claim 28, wherein Cx is selected from the group consisting of -CHN-NH-(CO-mono-hydroxyphenyl), -CHN-NH-(CO-dihydroxyphenyl), and -CHN-NH-(CO-trihydroxyphenyl).
- 10
30. The compound of any one of claims 24 to 29, wherein R₂ is H or -COOH.
31. The compound of any one of claims 24 to 30, wherein R₁ is selected from the group consisting of -H, -F, -Cl, -Br and -OH.
- 15
32. The compound of claim 31, wherein R₁ is -Cl or -OH.
33. The compound of claim 32, wherein m is 0, 1 or 2.
34. The compound of any one of claims 30 to 33, wherein n is 0, 1 or 2.
- 20
35. The compound of any one of claims 24 to 34, wherein the -COOR_b group is at a 3', 4' or 5' position.
36. The compound of any one of claims 24 to 35, wherein R_b is -H.
- 25
37. The compound of any one of claims 24 to 36, wherein R_b is selected from the group consisting of -H, (HO)₂P(O) and (MO)₂P(O), wherein M is an alkali metal or alkaline earth metal thereof.
- 30
38. The compound of claim 24, wherein R₂ is -COOH.
39. The compound of claim 38, wherein R₂ is at position 4' or 5'.
40. The compound of claim 24 or 39, wherein R₁ is -Cl or -OH.

41. The compound of claim 40, wherein R_1 is at position 4' or 6'.

42. The compound of any one of claims 38 to 41, wherein R_b and $R_{b'}$ are both H.

5

43. The compound of claim 26 or 27, wherein R_2 is $-\text{COOH}$ at position 4' or 5' and wherein m is 0 or 1.

44. The compound of claim 26 or 27, wherein R_1 is $-\text{Cl}$ or $-\text{OH}$ at position 4' or 6' and wherein n is 0 or 1.

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45. The compound of any one of claims 43 to 44, wherein R_b is H, $(\text{HO})_2\text{P}(\text{O})$ or $(\text{MO})_2\text{P}(\text{O})$, wherein M is an alkali metal or alkaline earth metal thereof and $R_{b'}$ is H.

15 46. The compound of claim 27, wherein C_x is $-\text{CHO}$.

47. The compound of claim 46, wherein R_b and $R_{b'}$ are both $-\text{H}$.

48. The compound of claim 47, wherein R_2 is $-\text{H}$ or $-\text{COOH}$.

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49. The compound of claim 48, wherein R_2 is $-\text{COOH}$ at position 4' and wherein m is 0.

50. The compound of claim 48, wherein R_2 is $-\text{COOH}$ at position 5' and wherein R_1 is $-\text{OH}$.

25 51. The compound of claim 50, wherein R_1 is at position 4'.

52. The compound of claim 48, wherein R_2 is H.

53. The compound of claim 52, wherein R_1 is $-\text{Cl}$.

30

54. The compound of claim 53, wherein R_1 is at position 4'.

55. The compound of claim 54, wherein R_1 is at position 6'.

56. The compound of claim 26 or 27, wherein C_x is -CHNO-CH₂-COOH.

57. The compound of claim 56, wherein R_b and R_{b'} are both -H.

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58. The compound of claim 57, wherein R₂ is -COOH and wherein m is 0.

59. The compound of claim 58, wherein R₂ is at position 5'.

10 60. The compound of claim 57, wherein R₁ is -Cl and wherein n is 0.

61. The compound of claim 60, wherein R₁ is at position 4'.

62. The compound of claim 26 or 27, wherein C_x is -CHN-NH-(CO-2-OH-6-Me nicotinyll).

15

63. The compound of claim 62, wherein R_b and R_{b'} are both -H.

64. The compound of claim 63, wherein R₂ is -COOH and wherein m is 0.

20 65. The compound of claim 64, wherein R₂ is at position 5'.

66. The compound of claim 63, wherein R₁ is -Cl and wherein n is 0.

67. The compound of claim 66, wherein R₁ is at position 4'.

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68. The compound of claim 27, wherein C_x is -CHN-NH-(CO-hydroxyphenyl).

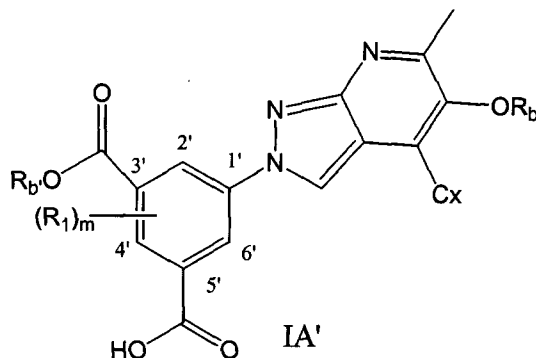
69. The compound of claim 68, wherein R_b and R_{b'} are both -H.

30 70. The compound of claim 69, wherein R₂ is -COOH and wherein m is 0.

71. The compound of claim 70, wherein R₂ is at position 5'.

72. The compound of claim 71, wherein Cx is -CHN-NH-(CO-2-OH-Phenyl).
73. The compound of claim 71, wherein Cx is -CHN-NH-(CO-2, 3-Di-OH-Phenyl).
- 5 74. The compound of claim 71, wherein Cx is -CHN-NH-(CO-2, 3, 4-Tri-OH-Phenyl).
75. The compound of claim 25, wherein Cx is -CHNOR₃ and wherein R₃ is selected from the group consisting of -H, a straight alkyl group of 1 to 6 carbon atoms.
- 10 76. The compound of claim 75, wherein R_b and R_{b'} are both -H.
77. The compound of claim 76, wherein R₁ is Cl and wherein n is 0.
78. The compound of claim 77, wherein R₁ is at position 4'.
- 15 79. The compound of claim 78, wherein Cx is -CHNO-Allyl.
80. The compound of claim 27, wherein Cx is -CHN-NH-Bz, or -CHN-NH-(4-t-Bu Bz).
- 20 81. The compound of claim 80, wherein R_b and R_{b'} are both -H.
82. The compound of claim 81, wherein R₁ is Cl and wherein n is 0.
83. The compound of claim 82, wherein R₁ is at position 4'.
- 25 84. The compound of claim 26, wherein Cx is selected from the group consisting of -CHN-NH(COOMe) and -CHN-NH(CONH₂).
85. The compound of claim 84, wherein R_b and R_{b'} are both -H.
- 30 86. The compound of claim 85, wherein R₁ is Cl and wherein n is 0.
87. The compound of claim 86, wherein R₁ is at position 4'.

88. A compound of formula IA'



5 , and pharmaceutically acceptable salts or solvates thereof, wherein Cx, m, R₁, R₃, R₄, R₅, R₆, R₇, R_a, R_b, R_b' are as defined in claim 1.

89. The compound of claim 88, wherein Cx is selected from the group consisting of -CHO, -CHNO-CH₂-COOH, -CHNO-Me, -CHNOEt, -CHNO-allyl, -CHNO-t-Bu, -CHNOH, -CHNNH₂, -CHN-1-piperidine, -CHN-1-morpholine, -CHN-NH-(CO-2-OH-6-Me nicotinyll), -CHN-NH-(CO-hydroxyphenyl), -CHN-NH-2-pyridine, -CHN-NH-formyl, -CHN-NH-(COOMe), -CHN-NH-(CONH₂), -CHN-NH-Bz, and -CHN-NH-(4-t-Bu Bz).

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90. The compound of claim 89, wherein Cx is selected from the group consisting of -CHO, -CHNO-CH₂-COOH, -CHNO-Me, -CHNOEt, -CHNO-allyl, -CHNO-t-Bu, -CHN-NH-(CO-2-OH-6-Me nicotinyll), -CHN-NH-2-pyridine, -CHN-NH-formyl, -CHN-NH-(CO-hydroxyphenyl), -CHN-NH-Bz, and -CHN-NH-(4-t-Bu Bz).

15

91. The compound of claim 90, wherein Cx is selected from the group consisting of -CHO, -CHNO-CH₂-COOH, -CHNOEt, -CHN-NH-(CO-2-OH-6-Me nicotinyll) and -CHN-NH-(CO-hydroxyphenyl).

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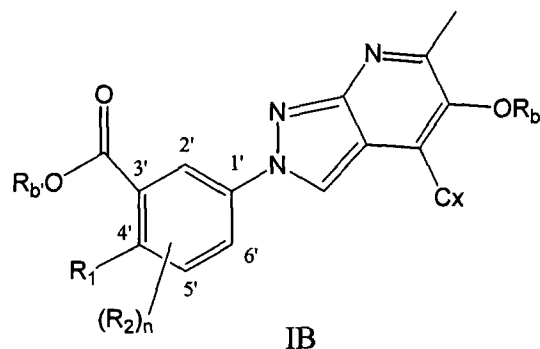
92. The compound of claim 91, wherein Cx is -CHN-NH-(CO-mono-hydroxyphenyl), -CHN-NH-(CO-di-hydroxyphenyl) or -CHN-NH-(CO-tri-hydroxyphenyl).

25

93. The compound of claim 88, wherein R_b and R_b' are both -H.

94. The compound of claim 93, wherein R_1 is selected from the group consisting of -H, -OH, -F, -Cl, -Br and -I.
- 5 95. The compound of claim 94, wherein R_1 is -OH or -Cl.
96. The compound of claim 95, wherein m is 0, 1 or 2.
- 10 97. The compound of claim 96, C_x is -CHO and wherein m is 0.
98. The compound of claim 96, wherein C_x is -CHNOMe, and wherein m is 0.
99. The compound of claim 96, wherein C_x is -CHNOEt and wherein m is 0.
- 15 100. The compound of claim 96, wherein C_x is -CHNO-Allyl and wherein m is 0.
101. The compound of claim 96, wherein C_x is -CHNO-*t*-Butyl and wherein m is 0.
- 20 102. The compound of claim 96, wherein C_x is -CHNOH and wherein m is 0.
103. The compound of claim 96, wherein C_x is -CHNNH₂ and wherein m is 0.
104. The compound of claim 96, wherein C_x is -CHN-1-piperidine and wherein m is 0.
- 25 105. The compound of claim 96, wherein C_x is -CHN-1-morpholine and wherein m is 0.
106. The compound of claim 96, wherein C_x is -CHN-NH-2-pyridine and wherein m is 0.
- 30 107. The compound of claim 96, wherein C_x is -CHN-NH-formyl and wherein m is 0.
108. The compound of claim 96, wherein C_x is CHN-NH-(CO-hydroxyphenyl) and wherein m is 0.

109. A compound of formula IB



5 , and pharmaceutically acceptable salts or solvates thereof,
wherein Cx, n, R₂, R₃, R₄, R₅, R₆, R₇, R_a, R_b, R_b' are as defined in claim 1.

110. The compound of claim 109, wherein Cx is selected from the group consisting of -
CHO, -CHNO-CH₂-COOH, -CHNO-Me, -CHNOEt, -CHNO-allyl, -CHNO-t-Bu, -
10 CHNOH, -CHNNH₂, -CHN-1-piperidine, -CHN-1-morpholine, -CHN-NH-(CO-2-OH-6-
Me nicotinyll), -CHN-NH-(CO-hydroxyphenyl), -CHN-NH-2-pyridine, -CHN-NH-
formyl, -CHN-NH-(COOMe), -CHN-NH-(CONH₂), -CHN-NH-Bz, and -CHN-NH-(4-t-
Bu Bz).

15 111. The compound of claim 110, wherein Cx is selected from the group consisting of -
CHO, -CHNO-CH₂-COOH, -CHNO-Me, -CHNOEt, -CHNO-allyl, -CHNO-t-Bu, -CHN-
NH-(CO-2-OH-6-Me nicotinyll), -CHN-NH-2-pyridine, -CHN-NH-formyl, -CHN-NH-
(CO-hydroxyphenyl), -CHN-NH-Bz, and -CHN-NH-(4-t-Bu Bz).

20 112. The compound of claim 111, wherein Cx is selected from the group consisting of -
CHO, CHNO-CH₂-COOH, -CHNOEt, -CHN-NH-(CO-2-OH-6-Me nicotinyll) and -
CHN-NH-(CO-hydroxyphenyl).

113. The compound of any one of claims 109 to 112, wherein n is 0 or R₂ is -H.

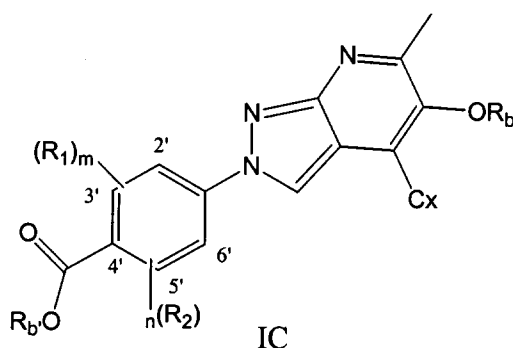
25

114. The compound of claim 113, wherein R_b is H, $(HO)_2P(O)$ or $(MO)_2P(O)$, wherein M is an alkali metal or alkaline earth metal thereof and $R_{b'}$ is H.

115. The compound of any one of claims 109 to 114, wherein R_1 is selected from the group consisting of -Cl, -F, -Br, -I and -OH.

116. The compound of claim 115, wherein R_1 is -OH or Cl.

117. A compound of formula IC



, and pharmaceutically acceptable salts or solvates thereof, wherein C_x , m , R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_a , R_b , $R_{b'}$ are as defined in claim 1.

118. The compound of claim 117, wherein C_x is selected from the group consisting of -CHO, -CHNO-CH₂-COOH, -CHNO-Me, -CHNOEt, -CHNO-allyl, -CHNO-t-Bu, -CHNOH, -CHNNH₂, -CHN-1-piperidine, -CHN-1-morpholine, -CHN-NH-(CO-2-OH-6-Me nicotinyll), -CHN-NH-(CO-hydroxyphenyl), -CHN-NH-2-pyridine, -CHN-NH-formyl, -CHN-NH-(COOMe), -CHN-NH-(CONH₂), -CHN-NH-Bz, and -CHN-NH-(4-t-Bu Bz).

119. The compound of claim 118, wherein C_x is selected from the group consisting of -CHO, -CHNO-CH₂-COOH, -CHNO-Me, -CHNOEt, -CHNO-allyl, -CHNO-t-Bu, -CHN-NH-(CO-2-OH-6-Me nicotinyll), -CHN-NH-2-pyridine, -CHN-NH-formyl, -CHN-NH-(CO-hydroxyphenyl), -CHN-NH-Bz, and -CHN-NH-(4-t-Bu Bz).

120. The compound of claim 119, wherein Cx is selected from the group consisting of -CHO, CHNO-CH₂-COOH, -CHNOEt, -CHN-NH-(CO-2-OH-6-Me nicotinyll) and -CHN-NH-(CO-hydroxyphenyl).

121. The compound of any one of claims 117 to 120, wherein R_b is H, (HO)₂P(O) or (MO)₂P(O), wherein M is an alkali metal or alkaline earth metal thereof and R_{b'} is H.

122. The compound of any one of claims 117 to 121, wherein R₁ is selected from the group consisting of -H, -Cl, -F, -Br, -I and -OH.

123. The compound of claim 122, wherein R₁ is -H, -Cl or -OH.

124. The compound of claim 123, wherein R₂ is -H or -COOH.

125. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 124 and a pharmaceutically acceptable carrier.

126. The use of a compound as defined in any one of claims 1 to 124 for making a pharmaceutical composition for the treatment or prevention of HIV infection or for the treatment or prevention of AIDS or for reducing HIV replication.

127. The use of at least one compound as defined in any one of claims 1 to 124 for treating or preventing HIV infection or AIDS or for reducing HIV replication.

128. A method of treating or preventing HIV infection or AIDS or for reducing HIV replication in an individual in need thereof, the method comprising administering at least one compound as defined in any one of claims 1 to 124.