Title: HYDROXYDIHYDROPYRIDOPYRADOZINE-1,8-DIONES AND METHODS FOR INHIBITING HIV INTEGRASE

Abstract: Bi- or tricyclic compounds of formula (I) wherein R₁, R₂, and R₃ are as herein defined, A represents a single or double bond and two R₁, R₂, R₃, and R₄ can be joined to form a condensed or spiro ring. These compounds and their pharmaceutical acceptable salt are used in combinations or pharmaceutical compositions and are useful in methods for preventing or treating human immunodeficiency virus (HIV) infection or in methods for preventing, delaying or treating acquired immunodeficiency syndrome (AIDS).
HYDROXYDIHYDROPYRIDOPYRAZINE-1,8-DIONES AND METHODS FOR INHIBITING HIV INTEGRASE

This application claims the benefit of U. S. Provisional Application Serial No. 60/638,180, filed December 23, 2004, the entire disclosure of which is hereby incorporated by reference.

FIELD OF THE INVENTION

The present invention relates to novel compounds and method for the treatment or prevention of HIV infection/ AIDS.

BACKGROUND OF THE INVENTION

HIV integrase is an attractive therapeutic target for the development of drugs to treat HIV infection (Pommier Y et al: Antiviral. Chem. Chemother. 1997, 8, 463-83; De Clercq, E: Med Res Rev 2002, 22, 531-565; Nair V: Rev. Med. Virol. 2002, 12, 179-193). It is a protein of Mr 32000 encoded at the 3′-end of pol gene. This viral enzyme catalyses the integration of viral DNA into host cell chromosomal DNA to form a provirus. This essential step in the viral life cycle proceeds by integrase recognizing and binding to attachment sites located at the ends of linear viral DNA, followed by the cleavage of highly conserved CA dinucleotides from the 5′ and 3′ long-terminal repeats. This reaction, known as 3′-processing, occurs in the cytoplasm and exposes the 3′-OH group from the CA unit. This OH group subsequently acts as a nucleophile by attacking the host DNA in a transesterification reaction. This second
reaction, referred to as strand transfer or integration, occurs in the nucleus. These reactions are adequately represented in vitro using purified integrase, a double-stranded DNA template matching the viral DNA ends as a substrate surrogate along with a divalent metal ion (Mn$^{2+}$ or Mg$^{2+}$) cofactor. It has been reported that selective inhibition of strand transfer reaction results in the inhibition of HIV viral replication (Pais GCG & Burke TR Jr: Drugs of the Future, 2002, 27, 1101-1111).

HIV integrase is further attractive as a target for the development of anti-HIV drugs because there is apparently no functional equivalent of this enzyme in human cells. It has also been reported that integrase inhibitors in combination with either reverse transcriptase or protease inhibitors are potently synergistic against both wild-type HIV and reverse transcriptase inhibitor resistant viruses (Robinson WE Jr et al Antiviral Res. 1998, 39, 101-111; Beale K et al Antiviral Res 2000, 46, 223-232).

A number of integrase inhibitors have been reported, including nucleotide-based inhibitors, DNA binders, catechols, hydrazides, etc (Neamati N: Expert Opin Ther Patents 2002, 12, 709-724). Most of these compounds inhibit integrase function in extracellular oligonucleotide assays but often lack inhibitory potency when assayed using fully assembled preintegration complexes or fail to show antiviral effects against HIV-infected cells. A class of diketo-
containing integrase inhibitors has been found to inhibit viral replication by blocking the strand transfer step of integrase reactions (Pais CG & Burke TR Jr: Drugs of the Future, 2002, 27, 1101-1111). An inhibitor of this class has been in clinical trials for the treatment of HIV infection (Billich A: Curr. Opin. Investig. Drugs 2003, 4, 206-209). However, in spite of their high integrase inhibitory potencies, diketo-containing compounds are electrophilic and they bind covalently to human cellular proteins leading to potential cytotoxicity. In addition, it has been reported recently that some diketo-containing compounds interfere with DNA cleavage and disintegration activities of RAG1/2 which are essential for the development of mammalian immune system (Melek M et al: Proc. Natl. Acad. Sci. USA 2002, 99, 134-7).

SUMMARY OF THE INVENTION

In accordance with the present invention, there is provided a compound of formula I:

![Chemical Structure Image]

or a pharmaceutically acceptable salt thereof,
wherein

A is a single or double bond, and when A is a double bond R₂ or R'₂ and R₃ or R'₃ are absent;

R₁ is H, OH, optionally substituted C₆₋₁₀ aryl, optionally substituted 5-10 member heteroaryl, optionally substituted 4-10 member heterocycle, or C₁₋₁₀ alkyl optionally substituted with one or more substituents selected from optionally substituted C₃₋₁₀ cycloalkyl, optionally substituted C₆₋₁₀ aryl, optionally substituted 5-10 member heteroaryl, or optionally substituted 4-10 member heterocycle (e.g., R¹ can be optionally substituted (CH₂)₁₋₄ phenyl);

R₂, R'₂, R₃ and R'₃ are each, independently, hydrogen, optionally substituted C₁₋₁₀ alkyl, optionally substituted C₃₋₁₀ cycloalkyl, optionally substituted C₆₋₁₀ aryl, optionally substituted 5-10 member heteroaryl, optionally substituted 4-10 member heterocycle, COOR₆, CONR₇R'₇, or CR₆=NOR'₆;

R₂ or R'₂ can also be taken together with R₃ or R'₃, and the atoms to which they are attached, to form an optionally substituted C₃₋₁₀ cycloalkyl, an optionally substituted 4-10 member heterocycle, an optionally substituted C₆₋₁₀ aryl or an optionally substituted 5-10 member heteroaryl;

R₂ and R'₂ or R₃ and R'₃ can also be joined together, with the atoms to which they are attached, to form an
optionally substituted C₃₋₁₀ cycloalkyl or an optionally substituted 5-10 member heterocycle;

R₂ and R'₂ or R₃ and R'₃ can also be joined together to form a carbonyl (C=O);

R₄ is halogen, CN, azido, NO₂, amino, amido, sulfonamido, urea, guanidino, amidino, SO₄R₆, OCONR₇R'₇, NR₆SO₂NR₇R'₇, NR₆COOR₇, NR₆COCONR₇R'₇, CR₆=NOR₇, C₁₋₁₀alkoxy, optionally substituted C₆₋₁₀ aryloxy, optionally substituted C₆aryl-C₁₋₁₀alkyloxy, optionally substituted C₆₋₁₀ aryl, optionally substituted 5-10 member heterocycle, or optionally substituted 5-10 member heteroaryl;

n is 0, 1, or 2;

R₅ is hydrogen, halogen, OH, CN, azido, NO₂, COOR₆, C₁₋₁₀ alkyl, amino, amido, sulfonamido, urea, guanidino, amidino, SO₄R₆, OCONR₇R'₇, NR₆SO₂NR₇R'₇, NR₆COOR₇, CR₆=NOR₇, C₁₋₁₀alkoxy, optionally substituted C₆₋₁₀ aryl, optionally substituted 5-10 member heterocycle, or optionally substituted 5-10 member heteroaryl;

R₄ and R₅ can also be taken together, with the atoms to which they are attached, to form an optionally substituted C₅₋₁₀ cycloalkyl, optionally substituted 5-10 member heterocycle, optionally substituted 5-10 member heteroaryl, or optionally substituted C₆₋₁₀ aryl;
$R_6, R_7, R'_7$ are each independently hydrogen, optionally substituted C$_{1-10}$ alkyl, optionally substituted C$_{6-10}$ aryl, or optionally substituted C$_{7-12}$ aralkyl;

5 $R_6$ can also be taken together with $R_7$ or $R'_7$, with the atoms to which they are attached, to form a 5-10 member heterocycle; and

10 $R_7$ and $R'_7$ can be taken together, with the atom to which they are attached, to form a 4-10 member heterocycle.

The compound of formula I can also be in the form of a pharmaceutically acceptable solvate or a solvate of a pharmaceutically acceptable salt thereof.

In one embodiment, there is provided a method of preventing or treating HIV infection in a subject which comprises administering to the subject a therapeutically effective amount of a compound, a combination or a pharmaceutical composition of the present invention.

In one embodiment, there is provided a method of preventing, delaying or treating AIDS in a subject which comprises administering to the subject a therapeutically effective amount of a compound, a combination or a pharmaceutical composition of the present invention.
In one embodiment, there is provided a method of inhibiting HIV integrase in a subject which comprises administering to the subject a therapeutically effective amount of a compound, a combination or a pharmaceutical composition of the present invention.

In one embodiment, there is provided a method of preventing integration of HIV DNA into host cell DNA in a subject which comprises administering to the subject a therapeutically effective amount of a compound, a combination or a pharmaceutical composition of the present invention.

In one embodiment, there is provided a method of preventing HIV DNA strand transfer to the host cell DNA in a subject which comprises administering to the subject a therapeutically effective amount of a compound, a combination or a pharmaceutical composition of the present invention.

In another embodiment, the invention provides the use of a compound or combination of the present invention for the manufacture of a medicament for preventing or treating HIV infection or preventing, delaying or treating AIDS.

In another embodiment, the invention provides the use of a compound or combination of the present invention for the manufacture of a medicament for preventing any one of HIV replication, integration of HIV DNA into host cell DNA, 3'-end processing of HIV DNA or HIV DNA strand transfer to the host cell DNA.
In another aspect, the present invention provides a combination comprising a therapeutically effective amount of compound of the present invention, and a therapeutically effective amount of at least one antiviral agent.

A further aspect of the invention is therefore presented as a pharmaceutical composition comprising a compound or combination of the present invention together with at least one pharmaceutically acceptable carrier or excipient thereof.

**DETAILED DESCRIPTION OF THE INVENTION**

In one embodiment, compounds of the present invention comprise those wherein the following embodiments are present, either independently or in combination.

In accordance with the present invention, there is provided a compound of formula I:

![Chemical Structure](image)

or a pharmaceutically acceptable salt thereof,

wherein
A is a single or double bond, and when A is a double bond \( R_2 \) or \( R'_2 \) and \( R_3 \) or \( R'_3 \) are absent;

5 \( R_1 \) is \( \text{H, OH, optionally substituted } C_{6-10} \text{ aryl, optionally substituted } 5-10 \text{ member heteroaryl, optionally substituted } 4-10 \text{ member heterocycle, or } C_{1-10} \text{ alkyl optionally substituted with one or more substituents selected from optionally substituted } C_{3-10} \text{ cycloalkyl, optionally substituted } C_{6-10} \text{ aryl, optionally substituted } 5-10 \text{ member heteroaryl, or optionally substituted } 4-10 \text{ member heterocycle } \) \( \) \( \text{e.g., } R_1 \) can be optionally substituted \( (\text{CH}_2)_{1-4} \text{ phenyl} \);  

10 \( R_2, R'_2, R_3 \) and \( R'_3 \) are each, independently, hydrogen, optionally substituted \( C_{1-10} \text{ alkyl, optionally substituted } C_{3-10} \text{ cycloalkyl, optionally substituted } C_{5-10} \text{ aryl, optionally substituted } 5-10 \text{ member heteroaryl, optionally substituted } 4-10 \text{ member heterocycle, COOR}_6, \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) \( \) CONR_7R'_7, or \( CR_6=\text{NOR}'_6; \)

15 \( R_2 \) or \( R'_2 \) can also be taken together with \( R_3 \) or \( R'_3 \), and the atoms to which they are attached, to form an optionally substituted \( C_{3-10} \text{ cycloalkyl, an optionally substituted } 4-10 \text{ member heterocycle, an optionally substituted } C_{5-10} \text{ aryl or an optionally substituted } 5-10 \text{ member heteroaryl}; \)

20 \( R_2 \) and \( R'_2 \) or \( R_3 \) and \( R'_3 \) can also be joined together, with the atoms to which they are attached, to form an

9

SUBSTITUTE SHEET (RULE 26)
optionally substituted C_{3-10} cycloalkyl or an optionally substituted 5-10 member heterocycle;

R_2 and R'_2 or R_3 and R'_3 can also be joined together to form a carbonyl (C=O);

R_4 is halogen, CN, azido, NO_2, amino, amido, sulfonamido, urea, guanidino, amidino, SO_{2}R_6, OCONR_7R'_7, NR_5SO_2NR_7R'_7, NR_6COOR_7, NR_5COCONR_7R'_7, CR_5=NOR_7, C_{1-10}alkoxy, optionally substituted C_{6-10} aryl, optionally substituted 5-10 member heterocycle, or optionally substituted 5-10 member heteroaryl;

n is 0, 1, or 2;

R_5 is hydrogen, halogen, OH, CN, azido, NO_2, COOR_6, C_{1-10} alkyl, amino, amido, sulfonamido, urea, guanidino, amidino, SO_{2}R_6, OCONR_7R'_7, NR_5SO_2NR_7R'_7, NR_6COOR_7, CR_5=NOR_7, C_{1-10}alkoxy, optionally substituted C_{6-10} aryl, optionally substituted 5-10 member heterocycle, or optionally substituted 5-10 member heteroaryl;

R_4 and R_5 can also be taken together, with the atoms to which they are attached, to form a optionally substituted C_{5-10} cycloalkyl, optionally substituted 5-10 member heterocycle, optionally substituted 5-10 member heteroaryl, or optionally substituted C_{6-10} aryl;

R_6, R_7, R'_7 are each independently hydrogen, optionally substituted C_{1-10} alkyl, optionally substituted C_{6-10} aryl, or optionally substituted C_{7-12}aralkyl;
R₆ can also be taken together with R₇ or R’₇, with the atoms to which they are attached, to form a 5-10 member heterocycle; and

R₇ and R’₇ can be taken together, with the atom to which they are attached, to form a 4-10 member heterocycle.

The compound of formula I can also be in the form of a pharmaceutically acceptable solvate or a solvate of a pharmaceutically acceptable salt thereof.

In one embodiment of the invention, A is a single bond.

R₄ can be H, OH, optionally substituted C₆-10 aryl, optionally substituted 5-10 member heteroaryl, optionally substituted 4-10 member heterocycle, optionally substituted cycloalkylalkyl wherein the cycloalkyl portion has 3 to 10 carbon atoms and the alkyl portion has 1 to 10 carbon atoms, optionally substituted aralkyl wherein the aryl portion has 6 to 10 carbon atoms and the alkyl portion has 1 to 10 carbon atoms, optionally substituted heteroaralkyl wherein the heteroarylam portion is a 5-10 member heteroaryl and the alkyl portion has 1 to 10 carbon atoms, or optionally substituted heterocyclic-alkyl wherein the heterocyclic portion is a 4-10 member heterocycle and the alkyl portion has 1 to 10 carbon atoms.

In one embodiment of the invention, R₁ is hydrogen.
In one embodiment of the invention, R₁ is hydroxy.

In one embodiment of the invention, R₁ is C₁₋₄ alkyl substituted by an optionally substituted aryl group.

In another embodiment of the invention, R₁ is (CH₂)₁₋₄ phenyl where phenyl is unsubstituted or substituted with one or more substituents independently selected from:

- halogen,
- amino,
- amidino,
- amido,
- azido,
- cyano,
- guanidino,
- hydroxyl,
- nitro,
- nitroso,
- urea,
- S(O)ₓ₋₂Rₓ (wherein Rₓ is H, C₁₋₁₀ alkyl, C₆₋₁₀ aryl or 3₋₁₀ member heterocycle),
- C₁₋₁₀ alkyl,
- C₇₋₁₀ aralkyl,
- C₆₋₁₀ aryl,
- 5₋₁₀ member heteroaryl
- C₁₋₁₀ alkoxy,
- C₆₋₁₀ aryl-C₁₋₁₀ alkoxy,
- C₆₋₁₀ aryloxy,
- 3₋₁₀ member heterocycle,
C(0)R_b (wherein R_b is H, C1-10 alkyl, C6-10 aryl, C7-12 aralkyl or 3-10 member heterocycle),
C(0)OR_b (wherein R_b is H, C1-10 alkyl, C6-10 aryl, C7-12 aralkyl—or 3-10 member heterocycle),
5 NR_b C(O) R_b' (wherein R_b and R_b' are each independently H, C1-10 alkyl, C6-10 aryl, C7-12 aralkyl or 3-10 member heterocycle, or R_b and R_b' are taken together with the atoms to which they are attached to form a 5-10 member heterocycle),
SO2NR_b R_b' (wherein R_b and R_b' are each independently H, C1-10 alkyl, C6-10 aryl, C7-12 aralkyl or 3-10 member heterocycle, or R_b and R_b' are taken together with the atoms to which they are attached to form a 5-10 member heterocycle),
10 NR_b SO2R_b' (wherein R_b and R_b' are each independently H, C1-10 alkyl, C6-10 aryl, C7-12 aralkyl or 3-10 member heterocycle, or R_b and R_b' are taken together with the atoms to which they are attached to form a 5-10 member heterocycle),
NR_b SO2NR_b' R_c (wherein R_b, R_b' and R_c are each independently H, C1-10 alkyl, C6-10 aryl, C7-12 aralkyl or 3-10 member heterocycle, or R_b' and R_c are taken together with the atoms to which they are attached to form a 5-10 member heterocycle),
20 CR_b N=OR_b' (wherein R_b and R_b' are each independently H, C1-10 alkyl, C6-10 aryl, C7-12 aralkyl or 3-10 member heterocycle), and
NR_b COO R_b' (wherein R_b and R_b' are each independently H, C1-10 alkyl, C6-10 aryl, C7-12 aralkyl or 3-10 member heterocycle).
In another embodiment R₁ is (CH₂)₁₋₄phenyl where phenyl is unsubstituted or substituted with one or more substituents independently selected from:
halogen,

5
amino,
amido,
ocyano,
hydroxyl,
urea,

10 OC₁₋₁₀ alkyl,
S(O)₀₋₂Rₐ (wherein Rₐ is H, C₁₋₁₀ alkyl, C₆₋₁₀ aryl or 3-10 member heterocycle),
C₁₋₁₀ alkyl,
C₆₋₁₀ aryl,

15 5-10 member heteroaryl
3-10 member heterocycle,
C(O)ORₜ (wherein Rₜ is H, C₁₋₁₀ alkyl, C₇₋₁₂ aralkyl or 3-10 member heterocycle),
NRₚC(O)Rₚ' (wherein Rₚ and Rₚ' are each independently H, C₁₋₁₀ alkyl, C₇₋₁₂ aralkyl or 3-10 member heterocycle, or Rₚ and Rₚ' are taken together with the atoms to which they are attached to form a 5-10 member heterocycle),
NRₚSO₂Rₚ' (wherein Rₚ and Rₚ' are each independently H, C₁₋₁₀ alkyl, C₇₋₁₂ aralkyl or 3-10 member heterocycle, or Rₚ and Rₚ' are taken together with the atoms to which they are attached to form a 5-10 member heterocycle),
CRₚN=ORₚ' (wherein Rₚ and Rₚ' are each independently H, C₁₋₁₀ alkyl, C₆₋₁₀ aryl, C₇₋₁₂ aralkyl or 3-10 member heterocycle), and
NR_6\text{COOR}_b\)' (wherein \(R_b\) and \(R_b'\) are each independently H, C_{1-10} alkyl, C_{6-10} aryl, C_{7-12} aralkyl or 3-10 member heterocycle).

In another embodiment \(R_1\) is \((\text{CH}_2)_1\text{-phenyl}\) where phenyl is substituted with one or more substituents independently selected from:
fluoro,
bromo,
chloro,
CONHCH_3,
CON(\text{CH}_3)_2,
CF_3,
NHCOCH_3,
NHCONHCH_3, and
SO_2NHCH_3.

In another embodiment \(R_1\) is \(\text{CH}_2\)\text{-}(4-fluorophenyl).
In another embodiment \(R_1\) is \(\text{CH}_2\)\text{-}(3,4 dichlorophenyl).
In another embodiment \(R_1\) is \(\text{CH}_2\)\text{-}(3-chloro-4-fluorophenyl).
In another embodiment \(R_1\) is \(\text{CH}_2\)\text{-}(2-N-methylamido-4-fluorophenyl).

In one embodiment, \(R_2\) and \(R_2'\) are each independently chosen from:
H,
optionally substituted phenyl,
optionally substituted C_{1-6}alkyl,
COOC_{1-6}alkyl,
CONR_7R_7', and
CR₆=NOR'₆.

In one embodiment, R₂ and R'₂ are each independently chosen from:

- H;
- unsubstituted phenyl or phenyl substituted by one or more substituents independently selected from halogens, hydroxy, -NH₂, -NHR₃ and -NR₃R₄, -CONH₂, -CONHR₄, -CONR₅R₆, -NHCOR₇, -NR₃COR₇, carboxy, CF₃, NR₃COR₇, NR₃CONR₅R₆, and SO₂NR₃R₆ wherein R₃ and R₆ are each independently selected from C₁₋₁₀ alkyl;
- unsubstituted C₁₋₆alkyl or C₁₋₆alkyl substituted by one or more substituents independently selected from halogens, hydroxy, -NH₂, -NHR₃ and -NR₃R₄, wherein R₃ and R₄ are each independently selected from C₁₋₁₀ alkyl, -CONH₂, -CONHR₃, -CONR₅R₆, -NHCOR₇, -NR₃COR₇, -NR₃CONR₅R₆, and carboxy, wherein R₅ and R₆ are each independently selected from C₁₋₁₀ alkyl;
- COOC₁₋₆alkyl;
- CONR₇R'₇; and
- CR₆=NOR'₆.

In one embodiment, R₂ and R'₂ are each independently chosen from:

- H,
- Phenyl,
C_{1-6}alkyl,
COOC_{1-6}alkyl,
CONR_7R'_7, and
CR_6=NOR'_6.

In one embodiment, R_3 and R'_3 are each independently chosen from:
H,
optionally substituted phenyl,
optionally substituted C_{1-6}alkyl,
COOC_{1-6}alkyl,
CONR_7R'_7, and
CR_6=NOR'_6.

In one embodiment, R_3 and R'_3 are each independently chosen from:
H;
unsubstituted phenyl or phenyl substituted by one or more substituents independently selected from halogens, hydroxy, \(-\text{NH}_2\), \(-\text{NHR}_4\) and \(-\text{NR}_4\text{R}_8\), \(-\text{CONH}_2\), \(-\text{CONHR}_4\), \(-\text{CONR}_4\text{R}_8\), \(-\text{NHCOR}_4\), \(-\text{NR}_4\text{COR}_4\), carboxy, \(\text{CF}_3\), \(\text{NR}_4\text{COR}_4\), \(\text{NR}_4\text{CONR}_4\text{R}_8\), and \(\text{SO}_2\text{NR}_4\text{R}_8\) wherein \(\text{R}_4\) and \(\text{R}_8\) are each independently selected from C_{1-10} alkyl;

unsubstituted C_{1-6}alkyl or C_{1-6}alkyl substituted by one or more substituents independently selected from halogens, hydroxy, \(-\text{NH}_2\), \(-\text{NHR}_4\) and \(-\text{NR}_4\text{R}_8\), wherein \(\text{R}_4\) and \(\text{R}_8\) are each independently selected from C_{1-10} alkyl, \(-\text{CONH}_2\), \(-\text{CONHR}_4\), \(-\text{CONR}_4\text{R}_8\), \(-\text{NHCOR}_4\), \(-\text{NR}_4\text{COR}_4\), and carboxy,
wherein \( R_4 \) and \( R_6 \) are each independently selected from:
\( C_{1-10} \) alkyl;
COOC\(_{1-6}\)alkyl;
5
CONR\(_7\)R\(_7'\); and
CR\(_6\)=NOR\(_6'\).

In another embodiment \( R_3 \) and \( R_3' \) are each independently chosen from:
H,
Phenyl,
C\(_{1-6}\)alkyl,
10 COOC\(_{1-6}\)alkyl,
CONR\(_7\)R\(_7'\), and
CR\(_6\)=NOR\(_6'\).

In one embodiment, \( R_4 \) is:
20 H,
halogen,
amino,
amidino,
amido,
25 azido,
cyano,
guanidino,
nitro,
nitroso,
30 urea,
$S(O)_{0-2}R_a$ (wherein $R_a$ is H, C$_{1-10}$ alkyl, C$_{6-10}$ aryl or 3-10 member heterocycle),
C$_{1-10}$alkyl,
C$_{7-12}$ aralkyl,
5
C$_{6-10}$aryl,
5-10 member heteroaryl
C$_{1-10}$alkoxy,
C$_5$aryle-C$_{1-10}$alkyloxy,
C$_{5-10}$ aroyloxy,
10
3-10 member heterocycle,
C(O)R$_b$ (wherein $R_b$ is H, C$_{1-10}$ alkyl, C$_{6-10}$ aryl, C$_{7-12}$
aralkyl—or 3-10 member heterocycle),
C(O)OR$_b$ (wherein $R_b$ is H, C$_{1-10}$ alkyl, C$_{6-10}$ aryl, C$_{7-12}$
aralkyl or 3-10 member heterocycle),
15
NR$_b$C(O)R$_b'$ (wherein $R_b$ and $R_b'$ are each independently H, C$_{1-10}$
alcohol, C$_{6-10}$ aryl, C$_{7-12}$ aralkyl or 3-10 member heterocycle, or $R_b$ and $R_b'$
are taken together with the atoms to which they are attached to form a 5-10 member heterocycle),
20
SO$_2$NR$_b$R$_b'$ (wherein $R_b$ and $R_b'$ are each independently H, C$_{1-10}$
alcohol, C$_{6-10}$ aryl, C$_{7-12}$ aralkyl or 3-10 member heterocycle, or $R_b$ and $R_b'$
are taken together with the atoms to which they are attached to form a 5-10 member heterocycle),
25
NR$_b$SO$_2$R$_b'$ (wherein $R_b$ and $R_b'$ are each independently H, C$_{1-10}$
alcohol, C$_{6-10}$ aryl, C$_{7-12}$ aralkyl or 3-10 member heterocycle, or $R_b$ and $R_b'$
are taken together with the atoms to which they are attached to form a 5-10 member heterocycle),
30
NR$_b$SO$_2$NR$_b'$R$_c$ (wherein $R_b$, $R_b'$ and $R_c$ are each independently H, C$_{1-10}$
alcohol, C$_{6-10}$ aryl, C$_{7-12}$ aralkyl or
3-10 member heterocycle, or \( R_b \) and \( R_c \) are taken together with the atoms to which they are attached to form a 5-10 member heterocycle),
\[ \text{CR}_b\text{N} = \text{OR}_b' \] (wherein \( R_b \) and \( R_b' \) are each independently \( H \), \( \text{C}_{1-10} \) alkyl, \( \text{C}_{6-10} \) aryl, \( \text{C}_{7-12} \) aralkyl or 3-10 member heterocycle),
\[ \text{NR}_b\text{COOR}_b' \] wherein \( R_b \) and \( R_b' \) are each independently \( H \) or \( \text{C}_{1-10} \) alkyl, \( \text{C}_{6-10} \) aryl, \( \text{C}_{7-12} \) aralkyl or 3-10 member heterocycle, or
\[ \text{NR}_b\text{COCONR}_b'R_c \] (wherein \( R_b' \), \( R_b \) and \( R_c \) are each independently \( H \) or \( \text{C}_{1-10} \) alkyl, \( \text{C}_{6-10} \) aryl, \( \text{C}_{7-12} \) aralkyl or 3-10 member heterocycle, or \( R_b' \) and \( R_c \) are taken together with the atoms to which they are attached to form a 4-10 member heterocycle).

In another embodiment \( R_4 \) is halogen,
amino,
amido,
cyano,
urea,
\( \text{C}_{1-6}\text{alkoxy} \),
\( \text{S(O)}_n \text{R}_a \) (wherein \( R_a \) is \( H \), \( \text{C}_{1-10} \) alkyl, \( \text{C}_{6-10} \) aryl or 3-10 member heterocycle),
\( \text{C}_{6-10}\text{aryl} \),
5-10 member heteroaryl,
3-10 member heterocycle,
\[ \text{NR}_b\text{C(O)}R_b' \] (wherein \( R_b \) and \( R_b' \) are each independently \( H \), \( \text{C}_{1-10} \) alkyl, \( \text{C}_{6-10} \) aryl, \( \text{C}_{7-12} \) aralkyl or 3-10 member heterocycle, or \( R_b \) and \( R_b' \) are taken together with the
atoms to which they are attached to form a 5-10 member heterocycle),
NR₆SO₂R₇ (wherein R₆ and R₇ are each independently H, C₁₋₁₀ alkyl, C₆₋₁₀ aryl, C₇₋₁₂ aralkyl or 3-10 member heterocycle, or R₆ and R₇ are taken together with the atoms to which they are attached to form a 5-10 member heterocycle),
NR₆SO₂NR₇R₈ (wherein R₆, R₇ and R₈ are each independently H, C₁₋₁₀ alkyl, C₆₋₁₀ aryl, C₇₋₁₂ aralkyl or 3-10 member heterocycle, or R₇ and R₈ are taken together with the atoms to which they are attached to form a 5-10 member heterocycle),
NR₆COOR₇ (wherein R₆ and R₇ are each independently H, C₁₋₁₀ alkyl, C₆₋₁₀ aryl, C₇₋₁₂ aralkyl or 3-10 member heterocycle, or R₇ is halogen,
NR₆SO₂R₇ (wherein R₆ and R₇ are each independently H, C₁₋₁₀ alkyl, C₆₋₁₀ aryl, C₇₋₁₂ aralkyl or 3-10 member heterocycle, or R₆ and R₇ are taken together with the atoms to which they are attached to form a 5-10 member heterocycle),
NR₆SO₂NR₇R₈ (wherein R₆, R₇, R₈ are each independently H, C₁₋₁₀ alkyl, C₆₋₁₀ aryl, C₇₋₁₂ aralkyl or 3-10 member heterocycle, or R₇ and R₈ are taken together with the atoms to which they are attached to form a 5-10 member heterocycle).
3-10 member heterocycle, or \( R_b' \) and \( R_c \) are taken together with the atoms to which they are attached to form a 5-10 member heterocycle,

\[ NR_b C(O) R_b' \] (wherein \( R_b \) and \( R_b' \) are each independently \( H, C_{1-10} \) alkyl, \( C_{6-10} \) aryl, \( C_{7-12} \) aralkyl or 3-10 member heterocycle, or \( R_b \) and \( R_b' \) are taken together with the atoms to which they are attached to form a 5-10 member heterocycle),

or

\[ NR_b COCONR_b' R_c \] (wherein \( R_b, R_b' \) and \( R_c \) are each independently \( H, C_{1-10} \) alkyl, \( C_{6-10} \) aryl, \( C_{7-12} \) aralkyl or 3-10 member heterocycle, or \( R_b' \) and \( R_c \) are taken together with the atoms to which they are attached to form a 4-10 member heterocycle).

15 In another embodiment, \( R_4 \) is

\[ \text{Br, NHCOCON(CH}_3\text{)}_2, \]

In another embodiment, \( R_4 \) is optionally substituted \( C_{1-10} \) alkoxy (e.g., \( C_1-6 \)-alkoxy), optionally substituted \( C_{6-10} \) aryloxy, or optionally substituted \( C_6 \)aryl-\( C_{1-10} \)alkyloxy.

In another embodiment, \( R_4 \) is optionally substituted \( C_{1-10} \) alkoxy (e.g., \( C_1-6 \)-alkoxy).

In another embodiment, \( R_4 \) is optionally substituted \( C_6-10 \) aryloxy (e.g., phenoxy, 4-fluorophenoxy).
In another embodiment, $R_4$ is optionally substituted C$_6$aryl-C$_{1-10}$alkyloxy.

In another embodiment, $R_4$ is optionally halogenated C$_{1-10}$ alkoxy (e.g., C$_{1-6}$alkoxy).

In another embodiment, $R_4$ is optionally halogenated C$_6$aryl-C$_{1-10}$ aryloxy.

In another embodiment, $R_4$ is optionally halogenated C$_6$aryl-C$_{1-10}$ alkylxy.

According to a further aspect of the invention, $R_4$ is an optionally substituted 5-10 member heterocycle, or optionally substituted 5-10 member heteroaryl. Suitable heterocycle and heteroaryl for $R_4$ include: piperidinyl, morpholinyl, pyrrolidinyl, tetrahydrofuranyl, and pyrazinyl.

According to a further aspect of the invention, $R_4$ is an amino group selected from NH$_2$, monoalkylamino in which the alkyl group has 1 to 6, preferably 1 to 4, carbon atoms, and dialkylamino in which each alkyl group has, independently, 1 to 6, preferably 1 to 4, carbon atoms, and -N(C$_{1-4}$-alkyl)-aryl wherein the aryl is optionally substituted (e.g., phenylamino wherein the phenyl group is substituted by halogen such as F).

According to a further aspect of the invention, $R_4$ is an optionally substituted -O-heterocycle wherein the
heterocycle group has 5-10 members, or optionally substituted \(-O\)-heteroaryl wherein the heteroaryl group has 5-10 members. Suitable heterocycle and heteroaryl for \(R_4\) include: piperidinyl, morpholiny, pyrrolidinyl, tetrahydrofurany, pyrazinyl, dioxany, and pyridinyl).

According to a further aspect of the invention, \(R_4\) is an optionally substituted \(-O-C_{1-4}\)-alkyl-heterocycle wherein the heterocycle group has 5-10 members, or optionally substituted \(-O-C_{1-4}\)-alkyl-heteroaryl wherein the heteroaryl group has 5-10 members (e.g., morpholinyethoxy, tetrahydropyranymethoxy, 1,3-dioxanylmethoxy, dimethyl-1,3-dioxanylmethoxy, 1,3-dioxolanylmethoxy, piperidinylethoxy, thienylethoxy, pyridinylmethoxy, and oxo-tetrahydrofuranylmethoxy).

In one embodiment, \(R_5\) is

Halogen,
Amino,

Hydroxy,

\(C_{1-6}\) alkyl,
5-10 member heteroaryl,
\(C_{6-10}\) aryl, or
\(CONR_6R'_6\).

In another embodiment, \(R_4\) and \(R_5\) are joined to form a 5-10 member heterocycle, or \(C_{6-10}\) member aryl.
In accordance with a further embodiment of the invention, the compounds are selected from subformulas Ia-Ijj, which correspond, respectively, to Formula I, but which exhibit the following groups:

5

Ia  A is a single bond; and

R⁴ is C₁₋₁₀ alkoxy (e.g., methoxy, ethoxy, propoxy, isopropanoxy, fluoroethoxy, difluoroethoxy, trifluoromethoxy, fluoropropoxy, cyclopropylmethoxy, cyclopropylethoxy, cyclobutylmethoxy, cyclopentylmethoxy, and cyclohexylmethoxy) optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, or N(C₁₋₄-alkyl)₂, phenoxy optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂, or benzyloxy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂.

15

Ib  A is a single bond;

20

R², R¹², R³, and R¹³ are each H; and
R^4 is C_{1-10} alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, fluoroethoxy, difluoroethoxy, trifluoromethoxy, fluoro propoxy, cyclopropylmethoxy, cyclopropylethoxy, cyclobutylmethoxy, cyclopentylmethoxy, and cyclohexylmethoxy) optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C_{1-4-}alkyl, CO-C_{1-4-}alkyl, NH_2, NHC_{1-4}-alkyl, or N(C_{1-4}-alkyl)_2, phenox y optionally substituted by F, Cl, Br, C_{1-4}-alkyl, cyan o, hydroxy, carboxy, COO-C_{1-4}-alkyl, CO-C_{1-4}-alkyl, NH_2, NHC_{1-4}-alkyl, N(C_{1-4}-alkyl)_2, CONH_2, CONHC_{1-4}-alkyl, or CON(C_{1-4}-alkyl)_2, or benzyloxy, phénethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C_{1-4}-alkyl, cyano, hydroxy, carboxy, COO-C_{1-4}-alkyl, CO-C_{1-4}-alkyl, NH_2, NHC_{1-4}-alkyl, N(C_{1-4}-alkyl)_2, CONH_2, CONHC_{1-4}-alkyl, or CON(C_{1-4}-alkyl)_2.

Ic A is a single bond;

R^2, R'^2, R^3, and R'^3 are each H;
R₁ is benzyl, phenethyl, phenpropyl, or naphthylmethyl, in each case optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂; and

R₄ is C₁₋₁₀ alkoxy (e.g., methoxy, ethoxy, propoxy, isoproxy, fluoroethoxy, difluoroethoxy, trifluoromethoxy, fluoropropoxy, cyclopropylmethoxy, cyclopropylethoxy, cyclobutylmethoxy, cyclopentylmethoxy, and cyclohexylmethoxy) optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, or N(C₁₋₄-alkyl)₂, phenoxy optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂, or benzyloxy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂.

Id A is a single bond;
$R^2$, $R^1$, $R^3$, and $R^1$ are each H;

$R^1$ is benzyl optionally substituted by F, Cl, Br, C$_{1-4}$-alkyl, cyano, hydroxy, carboxy, COO-C$_{1-4}$-alkyl, CO-C$_{1-4}$-alkyl, NH$_2$, NHC$_{1-4}$-alkyl, N(C$_{1-4}$-alkyl)$_2$, CONH$_2$, CONHC$_{1-4}$-alkyl, or CON(C$_{1-4}$-alkyl)$_2$; and

$R^4$ is C$_{1-10}$ alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, fluoroethoxy, difluoroethoxy, trifluoromethoxy, fluoropropoxy, cyclopropylmethoxy, cyclopropylethoxy, cyclobutylmethoxy, cyclopentylmethoxy, and cyclohexylmethoxy) optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C$_{1-4}$-alkyl, CO-C$_{1-4}$-alkyl, NH$_2$, NHC$_{1-4}$-alkyl, or N(C$_{1-4}$-alkyl)$_2$, phenoxy optionally substituted by F, Cl, Br, C$_{1-4}$-alkyl, cyano, hydroxy, carboxy, COO-C$_{1-4}$-alkyl, CO-C$_{1-4}$-alkyl, NH$_2$, NHC$_{1-4}$-alkyl, N(C$_{1-4}$-alkyl)$_2$, CONH$_2$, CONHC$_{1-4}$-alkyl, or CON(C$_{1-4}$-alkyl)$_2$, or benzyloxy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C$_{1-4}$-alkyl, cyano, hydroxy, carboxy, COO-C$_{1-4}$-alkyl, CO-C$_{1-4}$-alkyl, NH$_2$, NHC$_{1-4}$-alkyl, N(C$_{1-4}$-alkyl)$_2$, CONH$_2$, CONHC$_{1-4}$-alkyl, or CON(C$_{1-4}$-alkyl)$_2$.

Ie A is a single bond;
R², R³, and R⁴ are each H;

R⁵ is hydrogen, halogen, cyano, hydroxy, C₁-₄-alkyl, hydroxymethyl having 1 to 4 carbon atoms, C₂-₄-alkenyl, COOH, COO-C₁-₄-alkyl, NH₂, NHC₁-₄-alkyl, or N(C₁-₄-alkyl)₂; and R⁴ is C₁-₁₀ alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, fluoroethoxy, difluoroethoxy, trifluoromethoxy, fluoropropoxy, cyclopropylmethoxy, cyclopropylethoxy, cyclobutylmethoxy, cyclopentylmethoxy, and cyclohexylmethoxy) optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C₁-₄-alkyl, CO-C₁-₄-alkyl, NH₂, NHC₁-₄-alkyl, or N(C₁-₄-alkyl)₂, phenoxy optionally substituted by F, Cl, Br, C₁-₄-alkyl, cyano, hydroxy, carboxy, COO-C₁-₄-alkyl, CO-C₁-₄-alkyl, NH₂, NHC₁-₄-alkyl, N(C₁-₄-alkyl)₂, CONH₂, CONHC₁-₄-alkyl, or CON(C₁-₄-alkyl)₂, or benzyloxy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C₁-₄-alkyl, cyano, hydroxy, carboxy, COO-C₁-₄-alkyl, CO-C₁-₄-alkyl, NH₂, NHC₁-₄-alkyl, N(C₁-₄-alkyl)₂, CONH₂, CONHC₁-₄-alkyl, or CON(C₁-₄-alkyl)₂.

If A is a single bond;

R², R³, and R⁴ are each H;
R^5 is hydrogen, halogen, cyano, hydroxy, C_{1-4}-alkyl, hydroxyalkyl having 1 to 4 carbon atoms, C_{2-4}-alkenyl, COOH, COO-C_{1-4}-alkyl, NH_2, NHC_{1-4}-alkyl, or N(C_{1-4}-alkyl)_2;

R^1 is benzyl, phenethyl, phenpropyl, or naphthylmethyl, in each case optionally substituted by F, Cl, Br, C_{1-4}-alkyl, cyano, hydroxy, carboxy, COO-C_{1-4}-alkyl, CO-C_{1-4}-alkyl, NH_2, NHC_{1-4}-alkyl, N(C_{1-4}-alkyl)_2, CONH_2, CONHC_{1-4}-alkyl, or CON(C_{1-4}-alkyl)_2, and R^4 is C_{1-10} alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, fluoroethoxy, difluoroethoxy, trifluoromethoxy, fluoroisopropoxy, cyclopropylmethoxy, cyclopropylethoxy, cyclobutylmethoxy, cyclopentylmethoxy, and cyclohexylmethoxy) optionally substituted by F, Cl, Br,methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C_{1-4}-alkyl, CO-C_{1-4}-alkyl, NH_2, NHC_{1-4}-alkyl, or N(C_{1-4}-alkyl)_2, phenoxy optionally substituted by F, Cl, Br, C_{1-4}-alkyl, cyano, hydroxy, carboxy, COO-C_{1-4}-alkyl, CO-C_{1-4}-alkyl, NH_2, NHC_{1-4}-alkyl, N(C_{1-4}-alkyl)_2, CONH_2, CONHC_{1-4}-alkyl, or CON(C_{1-4}-alkyl)_2, or benzyloxy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C_{1-4}-alkyl, cyano, hydroxy, carboxy, COO-C_{1-4}-alkyl, CO-C_{1-4}-alkyl, NH_2, NHC_{1-4}-alkyl, N(C_{1-4}-alkyl)_2, CONH_2, CONHC_{1-4}-alkyl, or CON(C_{1-4}-alkyl)_2.
Ig  A is a single bond;

\[ R^2, R'^2, R^3, \text{ and } R'^3 \text{ are each } H; \]

5  \[ R^5 \text{ is hydrogen}; \text{ and} \]

\[ R^4 \text{ is } C_{1-10} \text{ alkoxy (e.g., methoxy, ethoxy, propoxy, isoproxy, fluoroethoxy, difluoroethoxy, trifluoromethoxy, fluoropropoxy, cyclopropylmethoxy, cyclopropylethoxy, cyclobutylmethoxy, cyclopentylmethoxy, and cyclohexylmethoxy) optionally substituted by } F, Cl, Br, \text{ methoxy, ethoxy, cyano, hydroxy, carboxy, } COO-C_{1-4}-alkyl, CO-C_{1-4}-alkyl, NH_2, NHC_{1-4}-alkyl, \text{ or } N(C_{1-4}-alkyl)_2, \text{ phenoxy optionally substituted by } F, Cl, Br, C_{1-4}-alkyl, \text{ cyano, hydroxy, carboxy, } COO-C_{1-4}-alkyl, CO-C_{1-4}-alkyl, NH_2, NHC_{1-4}-alkyl, N(C_{1-4}-alkyl)_2, CONH_2, CONHC_{1-4}-alkyl, \text{ or } CON(C_{1-4}-alkyl)_2, \text{ or benzylxoy, phenethoxy, or phenpropoxy, in each case optionally substituted by } F, Cl, Br, C_{1-4}-alkyl, \text{ cyano, hydroxy, carboxy, } COO-C_{1-4}-alkyl, CO-C_{1-4}-alkyl, NH_2, NHC_{1-4}-alkyl, N(C_{1-4}-alkyl)_2, CONH_2, CONHC_{1-4}-alkyl, \text{ or } CON(C_{1-4}-alkyl)_2. \]

Ih  A is a single bond;

\[ R^2, R'^2, R^3, \text{ and } R'^3 \text{ are each } H; \]
R^5 is hydrogen;

R^1 is benzyl, phenethyl, phenpropyl, or naphthylmethyl, in each case optionally substituted by F, Cl, Br, C_{1-4}-alkyl, cyano, hydroxy, carboxy, COO-C_{1-4}-alkyl, CO-C_{1-4}-alkyl, NH_2, NHC_{1-4}-alkyl, N(C_{1-4}-alkyl)_2, CONH_2, CONHC_{1-4}-alkyl, or CON(C_{1-4}-alkyl)_2; and

R^4 is C_{1-10} alkoxy (e.g., methoxy, ethoxy, propoxy, isoproxy, fluoroethoxy, difluoroethoxy, trifluoromethoxy, fluoropropoxy, cyclopropylmethoxy, cyclopentyldimethoxy, cyclobutylmethoxy, and cyclohexylmethoxy) optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C_{1-4}-alkyl, CO-C_{1-4}-alkyl, NH_2, NHC_{1-4}-alkyl, or N(C_{1-4}-alkyl)_2, phenoxy optionally substituted by F, Cl, Br, C_{1-4}-alkyl, cyano, hydroxy, carboxy, COO-C_{1-4}-alkyl, CO-C_{1-4}-alkyl, NH_2, NHC_{1-4}-alkyl, N(C_{1-4}-alkyl)_2, CONH_2, CONHC_{1-4}-alkyl, or CON(C_{1-4}-alkyl)_2, or benzyloxy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C_{1-4}-alkyl, cyano, hydroxy, carboxy, COO-C_{1-4}-alkyl, CO-C_{1-4}-alkyl, NH_2, NHC_{1-4}-alkyl, N(C_{1-4}-alkyl)_2, CONH_2, CONHC_{1-4}-alkyl, or CON(C_{1-4}-alkyl)_2.
A is a single bond;

R², R¹², R³, and R¹³ are each H;

R⁵ is hydrogen;

R¹ is benzyl optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂; and

R⁴ is C₁₋₁₀ alkoxy (e.g., methoxy, ethoxy, propoxy, isoproxy, fluoroethoxy, difluoroethoxy, trifluoromethoxy, fluoroisoproxy, cyclopropylmethoxy, cyclopentyloxy, cyclobutylmethoxy, and cyclohexylmethoxy) optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, or N(C₁₋₄-alkyl)₂, phenoxy optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂, or benzyloxy, phenethoxy, or phenprooxy, in each case optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂.
Ij  A is a single bond; and

\[ R_4 \text{ is an a 5-10 member heterocycle, or 5-10 member heteroaryl (e.g. piperidinyl, morpholiny1, pyrrolidinyl, pyridinyl, tetrahydrofuranyl, and pyrazinyl) optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C_4-alkyl, CO-C_4-alkyl, NH_2, NHC_4-alkyl, or N(C_4-alkyl)_2, phenoxy optionally substituted by F, Cl, Br, C_4-alkyl, cyano, hydroxy, carboxy, COO-C_4-alkyl, CO-C_4-alkyl, NH_2, NHC_4-alkyl, N(C_4-alkyl)_2, CONH_2, CONHC_4-alkyl, or CON(C_4-alkyl)_2, or benzyloxy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C_4-alkyl, cyano, hydroxy, carboxy, COO-C_4-alkyl, CO-C_4-alkyl, NH_2, NHC_4-alkyl, N(C_4-alkyl)_2, CONH_2, CONHC_4-alkyl, or CON(C_4-alkyl)_2.} \]

Ik  A is a single bond;

\[ R^2, R'^2, R^3, \text{ and } R'^3 \text{ are each H; and} \]
R₄ is an a 5-10 member heterocycle, or 5-10 member heteroaryl (e.g. piperidinyl, morpholinyl, pyrrolidinyl, pyridinyl, tetrahydrofuranyl, and pyrazinyl) optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, or N(C₁₋₄-alkyl)₂, phenoxy optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂, or benzyloxy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂.

A is a single bond;

R¹, R¹', R², and R³ are each H;

R¹ is benzyl, phenethyl, phenpropyl, or naphthylmethyl, in each case optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂; and

SUBSTITUTE SHEET (RULE 26)
R₄ is an a 5-10 member heterocycle, or 5-10 member heteroaryl (e.g. piperidinyl, morpholinylo, pyrrolidinyl, pyridinyl, tetrahydrofuranyl, and pyrazinyl) optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C₄-alkyl, CO-C₄-alkyl, NH₂, NHC₄-alkyl, or N(C₄-alkyl)₂, phenoxy optionally substituted by F, Cl, Br, C₄-alkyl, cyano, hydroxy, carboxy, COO-C₄-alkyl, CO-C₄-alkyl, NH₂, NHC₄-alkyl, N(C₄-alkyl)₂, CONH₂, CONHC₄-alkyl, or CON(C₄-alkyl)₂, or benzylxy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C₄-alkyl, cyano, hydroxy, carboxy, COO-C₄-alkyl, CO-C₄-alkyl, NH₂, NHC₄-alkyl, N(C₄-alkyl)₂, CONH₂, CONHC₄-alkyl, or CON(C₄-alkyl)₂.

A is a single bond;

R₂, R'₂, R³, and R'³ are each H;

R¹ is benzyl optionally substituted by F, Cl, Br, C₄-alkyl, cyano, hydroxy, carboxy, COO-C₄-alkyl, CO-C₄-alkyl, NH₂, NHC₄-alkyl, N(C₄-alkyl)₂, CONH₂, CONHC₄-alkyl, or CON(C₄-alkyl)₂; and
R₄ is an a 5-10 member heterocycle, or 5-10 member heteroaryl (e.g. piperidinyl, morpholinyl, pyrrolidinyl, pyridinyl, tetrahydrofuranyl, and pyrazinyl) optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, or N(C₁₋₄-alkyl)₂, phenoxy optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂, or benzyloxy, phenethoxy, or phenproproxy, in each case optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂.

In A is a single bond;

R², R⁴, R⁵, and R⁷ are each H;

R⁵ is hydrogen, halogen, cyano, hydroxy, C₁₋₄-alkyl, hydroxyalkyl having 1 to 4 carbon atoms, C₂₋₄-alkenyl, COOH, COO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, or N(C₁₋₄-alkyl)₂; and
R₄ is an a 5-10 member heterocycle, or 5-10 member heteroaryl (e.g. piperidinyl, morpholinyl, pyrrolidinyl, pyridinyl, tetrahydrofuranyl, and pyrazinyl) optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, or N(C₁₋₄-alkyl)₂, phenoxy optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONH₂, CONH₂, CONH₂, or CONH₂, or benzylxy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONH₂, CONH₂, CONH₂, or CONH₂.

R², R¹², R³, and R¹³ are each H;

R⁵ is hydrogen, halogen, cyano, hydroxy, C₁₋₄-alkyl, hydroxyalkyl having 1 to 4 carbon atoms, C₂₋₄-alkenyl, COOH, COO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, or N(C₁₋₄-alkyl)₂;
R³ is benzyl, phenethyl, phenpropyl, or naphthylmethyl, in each case optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂; and

R₄ is an a 5-10 member heterocycle, or 5-10 member heteroaryl (e.g. piperidinyl, morpholinyl, pyrrolidinyl, pyridinyl, tetrahydrofuranyl, and pyrazinyl) optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, or N(C₁₋₄-alkyl)₂, phenoxy optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂, or benzyl oxy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂.

Ip A is a single bond;

R², R¹², R³, and R¹³ are each H;

R⁵ is hydrogen; and
R₄ is an a 5-10 member heterocycle, or 5-10 member heteroaryl (e.g. piperidinyl, morpholinyl, pyrrolidinyl, pyridinyl, tetrahydrofuranyl, and pyrazinyl) optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, or N(C₁₋₄-alkyl)₂, phenoxy optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂, or benzyloxy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂.

Iq A is a single bond;

R², R'², R³, and R'³ are each H;

R⁵ is hydrogen;

R¹ is benzyl, phenethyl, phenpropyl, or naphthylmethyl, in each case optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂; and
R₄ is a 5-10 member heterocycle, or 5-10 member heteroaryl (e.g. piperidinyl, morpholinyl, pyrrolidinyl, pyridinyl, tetrahydrofuranyl, and pyrazinyl) optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, or N(C₁₋₄-alkyl)₂, phenoxy optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂, or benzyloxy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂.

Ir A is a single bond;

R², R'², R³, and R'³ are each H;

R⁵ is hydrogen;

R¹ is benzyl optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂; and
R₄ is an a 5-10 member heterocycle, or 5-10 member heteroaryl (e.g. piperidinyl, morpholinyl, pyrrolidinyl, pyridinyl, tetrahydrofuranyl, and pyrazinyl) optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C₄-alkyl, CO-C₄-alkyl, NH₂, NHC₄-alkyl, or N(C₄-alkyl)₂, phenoxy optionally substituted by F, Cl, Br, C₄-alkyl, cyano, hydroxy, carboxy, COO-C₄-alkyl, CO-C₄-alkyl, NH₂, NHC₄-alkyl, N(C₄-alkyl)₂, CONH₂, CONHC₄-alkyl, or CON(C₄-alkyl)₂, or benzyloxy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C₄-alkyl, cyano, hydroxy, carboxy, COO-C₄-alkyl, CO-C₄-alkyl, NH₂, NHC₄-alkyl, N(C₄-alkyl)₂, CONH₂, CONHC₄-alkyl, or CON(C₄-alkyl)₂.

Is A is a single bond; and
R₄ is an -O-heterocycle wherein the heterocycle group has 5-10 members, or -O-heteroaryl wherein the heteroaryl group has 5-10 members (e.g. piperidinyl, morpholinyl, pyrrolidinyl, tetrahydrofuranyl, pyrazinyl, dioxanyl, and pyridinyl) optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, or N(C₁₋₄-alkyl)₂, phenoxy optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂, or benzyloxy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂.

It A is a single bond;

R², R₁², R³, and R₁³ are each H; and
R₄ is an -O-heterocycle wherein the heterocycle group has 5-10 members, or -O-heteroaryl wherein the heteroaryl group has 5-10 members (e.g. piperidinyl, morpholiny1, pyrrolidinyl, tetrahydrofuranyl, pyrazinyl, dioxanyl, and pyridinyl) optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, or N(C₁₋₄-alkyl)₂, phenoxy optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONH-C₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂, or benzylxoy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONH-C₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂.

Tu A is a single bond;

R², R¹², R³, and R¹³ are each H;

R¹ is benzyl, phenethyl, phenpropyl, or naphthylmethyl, in each case optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONH-C₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂; and
R₄ is an -O-heterocycle wherein the heterocycle group has 5-10 members, or -O-heteroaryl wherein the heteroaryl group has 5-10 members (e.g. piperidinyl, morpholinyl, pyrrolidinyl, tetrahydrofuryl, pyrazinyl, dioxanyl, and pyridinyl) optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, or N(C₁₋₄-alkyl)₂, phenoxy optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHNC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂, or benzyloxy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHNC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂.

Iv A is a single bond;

R², R'², R³, and R'³ are each H;

R² is benzyl optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHNC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂; and
R₄ is an -O-heterocycle wherein the heterocycle group has 5-10 members, or -O-heteroaryl wherein the heteroaryl group has 5-10 members (e.g. piperidinyl, morpholinyl, pyrrolidinyl, tetrahydrofuranyl, pyrazinyl, dioxanyl, and pyridinyl) optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, or N(C₁₋₄-alkyl)₂, phenoxy optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂, or benzyloxy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂.

Iw A is a single bond;

R², R¹², R³, and R¹³ are each H;

R⁵ is hydrogen, halogen, cyano, hydroxy, C₁₋₄-alkyl, hydroxyalkyl having 1 to 4 carbon atoms, C₂₋₄-alkenyl, COOH, COO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, or N(C₁₋₄-alkyl)₂; and
R₄ is an -O-heterocycle wherein the heterocycle group has 5-10 members, or -O-heteroaryl wherein the heteroaryl group has 5-10 members (e.g. piperidinyl, morpholinyl, pyrrolidinyl, tetrahydrofuranyl, pyrazinyl, dioxanyl, and pyridinyl) optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, or N(C₁₋₄-alkyl)₂, phenoxy optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂, or benzyloxy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂.

Ix  A is a single bond;

R², R¹², R³, and R¹³ are each H;

R⁵ is hydrogen, halogen, cyano, hydroxy, C₁₋₄-alkyl, hydroxyalkyl having 1 to 4 carbon atoms, C₂₋₄-alkenyl, COOH, COO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, or N(C₁₋₄-alkyl)₂;
R₁ is benzyl, phenethyl, phenpropyl, or naphthylmethyl, in each case optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂; and

R₄ is an -O-heterocycle wherein the heterocycle group has 5-10 members, or -O-heteroaryl wherein the heteroaryl group has 5-10 members (e.g. piperidinyl, morpholinyl, pyrrolidinyl, tetrahydrofuranyl, pyrazinyl, dioxanyl, and pyridinyl) optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, or N(C₁₋₄-alkyl)₂, phenoxy optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂, or benzylxoy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂.

Iy A is a single bond;

R₂, R₁², R³, and R₁³ are each H;
R⁵ is hydrogen; and

R₄ is an -O-heterocycle wherein the heterocycle group has 5-10 members, or -O-heteroaryl wherein the heteroaryl group has 5-10 members (e.g. piperidinyl, morpholinyl, pyrrolidinyl, tetrahydrofuranyl, pyrazinyl, dioxanyl, and pyridinyl) optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, or N(C₁₋₄-alkyl)₂, phenoxy optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂, or benzyloxy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂.

Iz A is a single bond;

R², R¹², R³, and R¹³ are each H;

R⁵ is hydrogen;
R¹ is benzyl, phenethyl, phenpropyl, or naphthylmethyl, in each case optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂; and

R₄ is an -O-heterocycle wherein the heterocycle group has 5-10 members, or -O-heteroaryl wherein the heteroaryl group has 5-10 members (e.g. piperidinyl, morpholinyl, pyrrolidinyl, tetrahydrofuranyl, pyrazinyl, dioxanyl, and pyridinyl) optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, or N(C₁₋₄-alkyl)₂, phenoxy optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂, or benzyloxy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂.

Ia  A is a single bond;

R², R¹², R³, and R¹³ are each H;
R^5 is hydrogen;

R^1 is benzyl optionally substituted by F, Cl, Br, C_{1-4}-alkyl, cyano, hydroxy, carboxy, COO-C_{1-4}-alkyl, CO-C_{1-4}-alkyl, NH_2, NHC_{1-4}-alkyl, N(C_{1-4}-alkyl)_2, CONH_2, CONHC_{1-4}-alkyl, or CON(C_{1-4}-alkyl)_2; and

R_4 is an -O-heterocycle wherein the heterocycle group has 5-10 members, or -O-heteroaryl wherein the heteroaryl group has 5-10 members (e.g. piperidinyl, morpholinyl, pyrrolidinyl, tetrahydrofuranyl, pyrazinyl, dioxanyl, and pyridinyl) optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C_{1-4}-alkyl, CO-C_{1-4}-alkyl, NH_2, NHC_{1-4}-alkyl, or N(C_{1-4}-alkyl)_2, phenoxy optionally substituted by F, Cl, Br, C_{1-4}-alkyl, cyano, hydroxy, carboxy, COO-C_{1-4}-alkyl, CO-C_{1-4}-alkyl, NH_2, NHC_{1-4}-alkyl, N(C_{1-4}-alkyl)_2, CONH_2, CONHC_{1-4}-alkyl, or CON(C_{1-4}-alkyl)_2, or benzyloxy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C_{1-4}-alkyl, cyano, hydroxy, carboxy, COO-C_{1-4}-alkyl, CO-C_{1-4}-alkyl, NH_2, NHC_{1-4}-alkyl, N(C_{1-4}-alkyl)_2, CONH_2, CONHC_{1-4}-alkyl, or CON(C_{1-4}-alkyl)_2.

Ibb A is a single bond; and
R₄ is an -O-Cl-4-alkyl-heterocycle wherein the heterocycle group has 5-10 members, -O-Cl-4-alkyl-heteroaryl wherein the heteroaryl group has 5-10 members (e.g., morpholinylethoxy, tetrahydropyranylmethoxy, 1,3-dioxanylethoxy, dimethyl-1,3-dioxanylethoxy, 1,3-dioxolanylmethoxy, piperidinylethoxy, thiénylethoxy, pyridinylethoxy, and oxo-tetrahydrofuranylmethoxy) optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C₁-₄-alkyl, CO-C₁-₄-alkyl, NH₂, NHC₁-₄-alkyl, or N(C₁-₄-alkyl)₂, phenoxy optionally substituted by F, Cl, Br, C₁-₄-alkyl, cyano, hydroxy, carboxy, COO-C₁-₄-alkyl, CO-C₁-₄-alkyl, NH₂, NHC₁-₄-alkyl, N(C₁-₄-alkyl)₂, CONH₂, CONHC₁-₄-alkyl, or CON(C₁-₄-alkyl)₂, or benzyloxy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C₁-₄-alkyl, cyano, hydroxy, carboxy, COO-C₁-₄-alkyl, CO-C₁-₄-alkyl, NH₂, NHC₁-₄-alkyl, N(C₁-₄-alkyl)₂, CONH₂, CONHC₁-₄-alkyl, or CON(C₁-₄-alkyl)₂.

Icc A is a single bond;

R², R¹₂, R³, and R¹₃ are each H; and
$R_4$ is an $-$O-C$_{1-4}$-alkyl-heterocycle wherein the heterocycle group has 5-10 members, $-$O-C$_{1-4}$-alkyl-heteroaryl wherein the heteroaryl group has 5-10 members (e.g., morpholinylethoxy, tetrahydropyranylethoxy, 1,3-dioxanylmethoxy, dimethyl-1,3-dioxanylmethoxy, 1,3-dioxolanylmethoxy, piperidinylethoxy, thiénylmethoxy, pyridinylmethoxy, and oxo-tetrahydrofuranylmethoxy) optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C$_{1-4}$-alkyl, CO-C$_{1-4}$-alkyl, NH$_2$, NHC$_{1-4}$-alkyl, or N(C$_{1-4}$-alkyl)$_2$, phenoxy optionally substituted by F, Cl, Br, C$_{1-4}$-alkyl, cyano, hydroxy, carboxy, COO-C$_{1-4}$-alkyl, CO-C$_{1-4}$-alkyl, NH$_2$, NHC$_{1-4}$-alkyl, N(C$_{1-4}$-alkyl)$_2$, CONH$_2$, CONHC$_{1-4}$-alkyl, or CON(C$_{1-4}$-alkyl)$_2$, or benzyloxy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C$_{1-4}$-alkyl, cyano, hydroxy, carboxy, COO-C$_{1-4}$-alkyl, CO-C$_{1-4}$-alkyl, NH$_2$, NHC$_{1-4}$-alkyl, N(C$_{1-4}$-alkyl)$_2$, CONH$_2$, CONHC$_{1-4}$-alkyl, or CON(C$_{1-4}$-alkyl)$_2$.

$Id$: A is a single bond;

$R^2$, $R'^2$, $R^3$, and $R'^3$ are each H;
\( R^1 \) is benzyl, phenethyl, phenpropyl, or naphthylmethyl, in each case optionally substituted by F, Cl, Br, C<sub>1-4</sub>-alkyl, cyano, hydroxy, carboxy, COO-C<sub>1-4</sub>-alkyl, CO-C<sub>1-4</sub>-alkyl, NH<sub>2</sub>, NHC<sub>1-4</sub>-alkyl, N(C<sub>1-4</sub>-alkyl)<sub>2</sub>, CONH<sub>2</sub>, CONHC<sub>1-4</sub>-alkyl, or CON(C<sub>1-4</sub>-alkyl)<sub>2</sub>; and

\( R_4 \) is an \(-O-C_1-4-alkyl\)-heterocycle wherein the heterocycle group has 5-10 members, \(-O-C_1-4-alkyl\)-heteroaryl wherein the heteroaryl group has 5-10 members (e.g., morpholinylethoxy, tetrahydropyranylethoxy, 1,3-dioxanylthoxy, dimethyl-1,3-dioxanylethoxy, 1,3-dioxolanylmethoxy, piperidinylenethoxy, thienylethoxy, pyridinylethoxy, and oxo-tetrahydrofuranylmethoxy) optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C<sub>1-4</sub>-alkyl, CO-C<sub>1-4</sub>-alkyl, NH<sub>2</sub>, NHC<sub>1-4</sub>-alkyl, or N(C<sub>1-4</sub>-alkyl)<sub>2</sub>, phenoxy optionally substituted by F, Cl, Br, C<sub>1-4</sub>-alkyl, cyano, hydroxy, carboxy, COO-C<sub>1-4</sub>-alkyl, CO-C<sub>1-4</sub>-alkyl, NH<sub>2</sub>, NHC<sub>1-4</sub>-alkyl, N(C<sub>1-4</sub>-alkyl)<sub>2</sub>, CONH<sub>2</sub>, CONHC<sub>1-4</sub>-alkyl, or CON(C<sub>1-4</sub>-alkyl)<sub>2</sub>, or benzyloxy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C<sub>1-4</sub>-alkyl, cyano, hydroxy, carboxy, COO-C<sub>1-4</sub>-alkyl, CO-C<sub>1-4</sub>-alkyl, NH<sub>2</sub>, NHC<sub>1-4</sub>-alkyl, N(C<sub>1-4</sub>-alkyl)<sub>2</sub>, CONH<sub>2</sub>, CONHC<sub>1-4</sub>-alkyl, or CON(C<sub>1-4</sub>-alkyl)<sub>2</sub>.
Iee  A is a single bond;

R², R'², R³, and R'³ are each H;

5  R¹ is benzyl optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-
    C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or
    CON(C₁₋₄-alkyl)₂; and
10  R₄ is an -O-C₁₋₄-alkyl-heterocycle wherein the heterocycle group has 5-10 members, -O-C₁₋₄-alkyl-
heteroaryl wherein the heteroaryl group has 5-10 members (e.g., morpholinylethoxy,
15  tetrahydropyranylethoxy; 1,3-dioxanylmethoxy, dimethyl-1,3-dioxanylmethoxy, 1,3-
dioxolanylethoxy, piperidinylethoxy, thienylethoxy, pyridinylethoxy, and oxo-
tetrahydrofuranylethoxy) optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy,
20  carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, or N(C₁₋₄-alkyl)₂, phenoxy optionally
    substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl,
    NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂, or benzyloxy,
25  phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C₁₋₄-alkyl,
    cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂,
    CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂.
Iff A is a single bond;

\[ R^2, R'^2, R^3, \text{ and } R'^3 \text{ are each } H; \]

5

\[ R^5 \text{ is hydrogen, halogen, cyano, hydroxy, } C_{1-4}-\text{alkyl, hydroxyalkyl having 1 to 4 carbon atoms, } C_{2-4}-\text{alkenyl, COOH, COO-C}_{1-4}-\text{alkyl, } NH_2, \]

\[ \text{NHC}_{1-4}-\text{alkyl, or } N(C_{1-4}-\text{alkyl})_2; \text{ and } \]

10

\[ R_4 \text{ is an } -O-C_{1-4}-\text{alkyl-heterocycle wherein the heterocycle group has 5-10 members, } -O-C_{1-4}-\text{alkyl-heteroaryl wherein the heteroaryl group has 5-10 members (e.g., morpholinylethoxy, tetrahydropyranylethoxy, 1,3-dioxanylethoxy, dimethyl-1,3-dioxanylethoxy, 1,3-dioxa-}

15

diolamylethoxy, piperidinylethoxy, thienylethoxy, pyridinylethoxy, and oxo-tetrahydrofuranylmethoxy) optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C_{1-4}-\text{alkyl, CO-C}_{1-4}-\text{alkyl, } NH_2, \text{ NHC}_{1-4}-\text{alkyl, or } N(C_{1-4}-\text{alkyl})_2, \text{ phenoxy optionally substituted by F, Cl, Br, C}_{1-4}-\text{alkyl, cyano, hydroxy, carboxy, COO-C}_{1-4}-\text{alkyl, CO-C}_{1-4}-\text{alkyl, } NH_2, \text{ NHC}_{1-4}-\text{alkyl, } N(C_{1-4}-\text{alkyl})_2, \text{ CONH}_2, \text{ CONHC}_{1-4}-\text{alkyl, or CON}(C_{1-4}-\text{alkyl})_2, \text{ or benzyloxy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C}_{1-4}-\text{alkyl, cyano, hydroxy, carboxy, COO-C}_{1-4}-\text{alkyl, CO-C}_{1-4}-\text{alkyl, NH}_2, \text{ NHC}_{1-4}-\text{alkyl, } N(C_{1-4}-\text{alkyl})_2, \text{ CONH}_2, \]

25

\[ \text{CONHC}_{1-4}-\text{alkyl, or } CON(C_{1-4}-\text{alkyl})_2. \]
Igg A is a single bond;

R², R'², R³, and R'³ are each H;

R⁵ is hydrogen, halogen, cyano, hydroxy, C₁-₄-alkyl, hydroxyalkyl having 1 to 4 carbon atoms, C₂-₄-alkenyl, COOH, COO-C₁-₄-alkyl, NH₂, NHC₁-₄-alkyl, or N(C₁-₄-alkyl)₂;

R¹ is benzyl, phenethyl, phenpropyl, or naphthylmethyl, in each case optionally substituted by F, Cl, Br, C₁-₄-alkyl, cyano, hydroxy, carboxy, COO-C₁-₄-alkyl, CO-C₁-₄-alkyl, NH₂, NHC₁-₄-alkyl, N(C₁-₄-alkyl)₂, CONH₂, CONHC₁-₄-alkyl, or CON(C₁-₄-alkyl)₂; and
R₄ is an -O-C₁₋₄-alkyl-heterocycle wherein the heterocycle group has 5-10 members, -O-C₁₋₄-alkyl-heteroaryl wherein the heteroaryl group has 5-10 members (e.g., morpholinylethoxy, tetrahydropyranylethoxy, 1,3-dioxanylmethoxy, dimethyl-1,3-dioxanylmethoxy, 1,3-dioxolanylmethoxy, piperidinylethoxy, thienylethoxy, pyridinylethoxy, and oxo-tetrahydrofuranylmethoxy) optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, or N(C₁₋₄-alkyl)₂, phenoxy optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂, or benzyloxy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂.

Ihh A is a single bond;

R², R¹², R³, and R¹³ are each H;

R⁵ is hydrogen; and
R₄ is an -O-C₁₋₄-alkyl-heterocycle wherein the heterocycle group has 5-10 members, -O-C₁₋₄-alkyl-heteroaryl wherein the heteroaryl group has 5-10 members (e.g., morpholinylethoxy, tetrahydropropyranylethoxy, 1,3-dioxanylmethoxy, dimethyl-1,3-dioxanylmethoxy, 1,3-dioxolanylmethoxy, piperidinylethoxy, thiénylmethoxy, pyridinylmethoxy, and oxo-tetrahydrofuranylethoxy) optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, or N(C₁₋₄-alkyl)₂, phenoxy optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONH₂-C₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂, or benzyloxy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONH₂-C₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂.

Iii A is a single bond;

R², R¹₂, R³, and R¹³ are each H;

R⁵ is hydrogen;
R₁ is benzyl, phenethyl, phenpropyl, or naphthylethyl, in each case optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂; and

R₄ is an -O-C₁₋₄-alkyl-heterocycle wherein the heterocycle group has 5-10 members, -O-C₁₋₄-alkyl-heteroaeryl wherein the heteroaeryl group has 5-10 members (e.g., morpholinylethoxy, tetrahydropyranylmethoxy, 1,3-dioxanylethoxy, dimethyl-1,3-dioxanylethoxy, 1,3-dioxolanylmethoxy, piperidinylethoxy, thiénylthoxy, pyridinylethoxy, and oxo-tetrahydrofuranylthoxy) optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, or N(C₁₋₄-alkyl)₂, phenoxy optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂, or benzyloxy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂.
A is a single bond;
\[ R^2, R'^2, R^3, \text{ and } R'^3 \text{ are each H; } \]
\[ R^5 \text{ is hydrogen; } \]
\[ R^1 \text{ is benzyl optionally substituted by } F, \text{ Cl, Br, C}_{1-4}-\text{alkyl, } \text{cyano, hydroxy, carboxy, COO-} \]
\[ \text{C}_{1-4}-\text{alkyl, CO-C}_{1-4}-\text{alkyl, NH}_2, \text{NHC}_{1-4}-\text{alkyl, } \text{N(C}_{1-4}-\text{alkyl)}_2, \text{CONH}_2, \text{CONHC}_{1-4}-\text{alkyl, or } \]
\[ \text{CON(C}_{1-4}-\text{alkyl)}_2; \text{ and } \]

SUBSTITUTE SHEET (RULE 26)
R₄ is an -O-C₄₋₄-alkyl-heterocycle wherein the heterocycle group has 5-10 members, -O-C₄₋₄-alkyl-heteroaryl wherein the heteroaryl group has 5-10 members (e.g., morpholinylethoxy, tetrahydropropyranylethoxy, 1,3-dioxanylmethoxy, dimethyl-1,3-dioxanylmethoxy, 1,3-dioxolanylethoxy, piperidinylethoxy, thienylethoxy, pyridinylethoxy, and oxo-tetrahydrofuranylethoxy) optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C₄₋₄-alkyl, CO-C₄₋₄-alkyl, NH₂, NHC₄₋₄-alkyl, or N(C₄₋₄-alkyl)₂, phenoxy optionally substituted by F, Cl, Br, C₄₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₄₋₄-alkyl, CO-C₄₋₄-alkyl, NH₂, NHC₄₋₄-alkyl, N(C₄₋₄-alkyl)₂, CONH₂, CONHC₄₋₄-alkyl, or CON(C₄₋₄-alkyl)₂, or benzyloxy, phenethoxy, or phenproproxy, in each case optionally substituted by F, Cl, Br, C₄₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₄₋₄-alkyl, CO-C₄₋₄-alkyl, NH₂, NHC₄₋₄-alkyl, N(C₄₋₄-alkyl)₂, CONH₂, CONHC₄₋₄-alkyl, or CON(C₄₋₄-alkyl)₂.

In one aspect, the present invention provides novel compounds including:

6-Bromo-2-(4-fluoro-benzyl)-9-hydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione;
6-\{1,1\text{-Dioxo}-[1,2\text{-}thiazinan-2-yl]\}-2-(4-
fluoro-benzyl)-9-hydroxy-3,4-dihydro-2H-
pyrido[1,2-a]pyrazine-1,8-dione;

2-(4-Fluoro-benzyl)-9-hydroxy-6-
(tetrahydro-furan-2-yl)-3,4-dihydro-2H-
pyrido[1,2-a]pyrazine-1,8-dione;

2-(4-Fluoro-benzyl)-6-furan-2-yl-9-
hydroxy-3,4-dihydro-2H-pyrido[1,2-
a]pyrazine-1,8-dione;

2-(4-Fluoro-benzyl)-9-hydroxy-6-thiazol-
2-yl-3,4-dihydro-2H-pyrido[1,2-
a]pyrazine-1,8-dione;

2-(4-Fluoro-benzyl)-9-hydroxy-6-phenyl-
3,4-dihydro-2H-pyrido[1,2-a]pyrazine-
1,8-dione;

2-(4-Fluoro-benzyl)-9-hydroxy-6-
methanesulfonyl-3,4-dihydro-2H-
pyrido[1,2-a]pyrazine-1,8-dione;

6-Azido-2-(4-Fluoro-benzyl)-9-hydroxy-
xy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione;
36 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-PIPERIDIN-1-YL-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

37 6-CYCLOHEXYL-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

38 4-FLUORO-N-(4-FLUORO-BENZOYL)-N-[2-(4-FLUORO-BENZYL)-9-HYDROXY-1,8-DIOXO-1,3,4,8-TETRAHYDRO-2H-PYRIDO[1,2-A]PYRAZIN-6-YL]-BENZAMIDE;

39 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-MORPHOLIN-4-YL-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

40 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-PYRROLIDIN-1-YL-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

41 FURAN-2-CARBOXYLIC ACID [2-(4-FLUORO-BENZYL)-9-HYDROXY-1,8-DIOXO-1,3,4,8-TETRAHYDRO-2H-PYRIDO[1,2-A]PYRAZIN-6-YL]- (FURAN-2-CARBONYL)-AMIDE;

42 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-(TETRAHYDRO-FURAN-3-YL)-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;
and pharmaceutically acceptable salts thereof, pharmaceutically solvates thereof, and solvates of pharmaceutically acceptable salts thereof.

According to a further embodiment, the present invention provides novel compounds including:

2-(4-FLUORO-BENZYL)-9-HYDROXY-6-METHOXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;
48 6-ETHOXY-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

49 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-ISOPROPOXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

50 6-(2,2-DIFLUORO-ETHOXY)-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

51 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-PROPOXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

52 2-(4-FLUORO-BENZYL)-6-(2-FLUORO-ETHOXY)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

53 6-CYCLOPROPYL METHOXY-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

54 6-CYCLOHEXYLMETHOXY-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;
2-(4-FLUORO-BENZYL)-9-HYDROXY-6-(2,2,2-
TRIFLUORO-ETHOXY)-3,4-DIHYDRO-2H-
PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

2-(4-FLUORO-BENZYL)-9-HYDROXY-6-(2-
MORPHOLIN-4-YL-ETHOXY)-3,4-DIHYDRO-2H-
PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

2-(4-FLUORO-BENZYL)-9-HYDROXY-6-
PHENOXY-3,4-DIHYDRO-2H-PYRIDO[1,2-
A]PYRAZINE-1,8-DIONE;

2-(4-FLUORO-BENZYL)-9-HYDROXY-6-
ISOBUTOXY-3,4-DIHYDRO-2H-PYRIDO[1,2-
A]PYRAZINE-1,8-DIONE;

2-(4-FLUORO-BENZYL)-6-(4-FLUORO-PHENOXY)-
9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-
A]PYRAZINE-1,8-DIONE;

2-(4-FLUORO-BENZYL)-9-HYDROXY-6-
(TETRAHYDRO-PYRAN-4-YLMETHOXY)-3,4-
DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-
DIONE;

7-FLUORO-2-(4-FLUORO-BENZYL)-9-HYDROXY-
6-METHOXY-3,4-DIHYDRO-2H-PYRIDO[1,2-
A]PYRAZINE-1,8-DIONE;
62 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-(2-METHOXY-ETHOXY)-3,4-DIHYDRO-2H PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

63 6-(2,2-DIMETHYL-[1,3]DIOXOLAN-4-YLMETHOXY)-2-(4-FLUORO-BENZYL)-9 HYDROXY-3,4-DIHYDRO-2H PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

64 6-(2-DIMETHYLAMINO-ETHOXY)-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

65 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-(2-METHANESULFONYL-ETHOXY)-3,4-DIHYDRO 2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

66 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-[2-(4-METHOXY-PHENYL)-ETHOXY]-3,4-DIHYDRO-2H PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

67 2-(4-FLUORO-BENZYL)-6-(3-FLUORO-PROPoxy)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

68 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-(PYRIDIN-2-YLMETHOXY)-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;
69  2-(4-FLUORO-BENZYL)-9-HYDROXY-6-PHENETHYLOXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

70  6-([1,3]DIOXOLAN-4-YLMETHOXY)-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

71  6-([1,3]DIOXAN-5-YLOXY)-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

72  2-(4-FLUORO-BENZYL)-9-HYDROXY-6-(2-PIPERIDIN-1-YL-ETHOXY)-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

73  6-CYCLOPENTYL METHOXY-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

74  6-CYCLOBUTYL METHOXY-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

75  2-[2-(4-FLUORO-BENZYL)-9-HYDROXY-1,8-DIOXO-1,3,4,8-TETRAHYDRO-2H-PYRIDO[1,2-A]PYRAZIN-6-YLOXY]-N,N-DIMETHYL-ACETAMIDE
76 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-(PYRIDIN-3-YLOXY)-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

77 6-(2-CYCLOPROPYL-ETHOXY)-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

78 6-BROMO-2-(3,4-DICHLORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO(1,2-A)PYRAZINE-1,8-DIONE;

79 6-BROMO-2-(3-CHLORO-4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO(1,2-A)PYRAZINE-1,8-DIONE;

80 6-(4,4-DIFLUORO-CYCLOHEXYL-METHOXY)-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

81 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-(2-HYDROXY-ETHOXY)-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

82 6-(2,2-DIMETHOXY-ETHOXY)-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;
83 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-((R)-5-OXO-TETRAHYDRO-FURAN-2-YLMETHOXY)-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

84 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-((S)-5-OXO-TETRAHYDRO-FURAN-2-YLMETHOXY)-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

85 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-(2-THIOPHEN-2-YL-ETHOXY)-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

86 2-BENZYL-9-HYDROXY-6-METHOXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

87 2-(3,4-Dichloro-benzyl)-9-hydroxy-6-methoxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione;

88 2-BENZYL-6-(2-FLUORO-ETHOXY)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

89 2-(3,4-DICHLORO-BENZYL)-6-(2-FLUORO-ETHOXY)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO-(1,2-A)PYRAZINE-1,8-DIONE;
6-(2-CYCLOPENTYL-ETHOXY)-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

2-(3,4-Dichloro-benzyl)-9-hydroxy-6-(pyridin-3-yloxy)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione;

2-(3-Chloro-4-fluoro-benzyl)-9-hydroxy-6-(pyridin-3-yloxy)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione; and

2-(3-Chloro-4-fluoro-benzyl)-9-hydroxy-6-(2-methoxy-ethoxy)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione;

and pharmaceutically acceptable salts thereof, pharmaceutically solvates thereof, and solvates of pharmaceutically acceptable salts thereof.

Reference hereinafter to a compound according to the invention includes compounds of the general formula (I) and their pharmaceutically acceptable salts, hydrates and solvates.
In one embodiment, the compounds of the present invention are the (+) enantiomer having an enantiomeric excess of 99%.

In one embodiment, the compounds of the present invention are the (+) enantiomer having an enantiomeric excess of 95%.

In one embodiment, the compounds of the present invention are the (+) enantiomer having an enantiomeric excess of 90%.

In one embodiment, the compounds of the present invention are the (-) enantiomer having an enantiomeric excess of 99%.

In one embodiment, the compounds of the present invention are the (-) enantiomer having an enantiomeric excess of 95%.

In one embodiment, the compounds of the present invention are the (-) enantiomer having an enantiomeric excess of 90%.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification,
including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

The term "alkyl" represents a linear, branched or cyclic hydrocarbon moiety having 1 to 10 carbon atoms, which may have one or more double bonds or triple bonds in the chain, and is optionally substituted. Examples include but are not limited to methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, hexyl, isohexyl, neo-hexyl, allyl, vinyl, acetylenyl, ethylenyl, propenyl, isopropenyl, butenyl, isobutenyl, hexenyl, butadienyl, pentenyl, pentadienyl, hexenyl, hexadienyl, hexatrienyl, heptenyl, heptadienyl, heptatrienyl, octenyl, octadienyl, octatrienyl, octatetraenyl, propynyl, butynyl, pentynyl, hexynyl, cyclopropyl, cyclobutyl, cyclohexenyl, cyclohexadienyl and cyclohexyl. The term alkyl is also meant to include haloalkyls in which one or more hydrogen atom is replaced by a halogen, i.e. an alkylhalide. Examples include but are not limited to trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, dichloromethyl, chloromethyl, trifluoroethyl, difluoroethyl, fluoroethyl, trichloroethyl, dichloroethyl, chloroethyl, chlorofluoromethyl, chlorodifluoromethyl, dichlorofluoroethyl. Aside from halogens, the alkyl groups can also be optionally substituted by, for example, hydroxy, amino, amido, and/or carboxy.
The term "cycloalkyl" represents a cyclic alkyl moiety having 3 to 10 carbon atoms, which is optionally substituted (e.g., cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl). Suitable substituents are, for example, halogens, hydroxy, amino, amido, and/or carboxy.

The term "alkoxy" represents an alkyl which is covalently bonded to the adjacent atom through an oxygen atom. Like the alkyl groups, the alkoxy groups can also be optionally substituted. Examples include but are not limited to methoxy, ethoxy, propoxy, isoproxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, isopentyloxy, neopentyloxy, tert-pentyloxy, hexyloxy, isohexyloxy, trifluoromethoxy and neohexyloxy. The alkoxy groups can be optionally substituted by, for example, halogens, hydroxy, amino, amido, and/or carboxy.

The term "aryl" represents a carbocyclic moiety containing at least one benzenoid-type ring (i.e. may be monocyclic or polycyclic), and which may be optionally substituted with one or more substituents. Examples include but are not limited to phenyl, tolyl, dimethylphenyl, aminophenyl, anilinyl, naphthyl, anthryl, phenanthryl or biphenyl. The aryl groups can be optionally substituted by, for example, halogens, hydroxy, amino, amido, and/or carboxy.

The term "aralkyl" represents an aryl group attached to the adjacent atom by a C1-10 alkyl. Like the aryl
groups, the aralkyl groups can also be optionally substituted. Examples include but are not limited to benzyl, benzhydryl, trityl, phenethyl, 3-phenylpropyl, 2-phenylpropyl, 4-phenylbutyl and naphthylmethyl. The aralkyl groups can be optionally substituted by, for example, halogens, hydroxy, amino, amido, and/or carboxy.

"Aralkyloxy" represents an aralkyl which is covalently bonded to the adjacent atom through an oxygen atom. Like the aryl groups, the aralkyloxy groups can also be optionally substituted. Examples include but are not limited to benzyloxy, benzhydryloxy, trityloxy, phenethyloxy, 3-phenylpropyloxy, 2-phenylpropyloxy, 4-phenylbutyloxy and naphthylmethoxy. The aralkyloxy groups can be optionally substituted by, for example, halogens, hydroxy, amino, amido, and/or carboxy.

The term "acceptable" means that it must not be deleterious to the recipient thereof.

"Halogen atom" is specifically a fluorine atom, chlorine atom, bromine atom or iodine atom.

The term "independently" means that a substituent can be the same or a different definition for each item.

The term "amidino" represents $-\text{C(=NR}_d\text{NR}_e\text{R}_f$ wherein $R_d$, $R_e$ and $R_f$ are each independently selected from H, C$_{1-10}$ alkyl, C$_{6-12}$ aryl or C$_{7-12}$ aralkyl, or $R_e$ and $R_f$ are taken
together with the nitrogen to which they are attached
to form a 4 to 10 member heterocycle.

The term "guanidino" represents \(-N(R_d)C(=NR_e)NR_g\)
wherein \(R_d, R_e, R_f\) and \(R_g\) are each independently
selected from \(H, C_{1-10} alkyl, C_{6-12} aryl\) or \(C_{7-12} aralkyl,\)
or \(R_f\) and \(R_g\) are taken together with the nitrogen to
which they are attached to form a 4 to 10 member
heterocycle.

The term "amido" represents \(-CONH_2, -CONHR_d, -CONR_dR_e, -NHCOR_d, -NR_dCOR_e,\)
wherein \(R_d\) and \(R_e\) are each independently
selected from \(C_{1-10} alkyl, C_{6-12} aryl\) or \(C_{7-12} aralkyl,\)
or \(R_d\) and \(R_e\) are taken together with the
nitrogen to which they are attached to form a 4 to 10 member
heterocycle.

The term "amino" represents a derivative of ammonia
obtained by substituting one or more hydrogen atom and
include \(-NH_2, -NHR_d\) and \(-NR_dR_e,\) wherein \(R_d\) and \(R_e\) are
each independently selected from \(C_{1-10} alkyl, C_{6-12} aryl\)
or \(C_{7-12} aralkyl,\) or \(R_d\) and \(R_e\) are taken together with the
nitrogen to which they are attached to form a 4 to
10 member heterocycle.

The term "sulfonamido" represents \(-SO_2NH_2, -SO_2NHR_d, -SO_2NR_dR_e,\)
and \(-NR_dSO_2R_e,\) wherein \(R_d\) and \(R_e\) are each independently
selected from \(C_{1-10} alkyl, C_{6-12} aryl\) or \(C_{7-12} aralkyl,\) or \(R_d\) and \(R_e\) are taken together with the
nitrogen to which they are attached to form a 5 to 10 member heterocycle.
The term "urea" represents $-N(R_d)\text{CONR}_eR_f$ wherein $R_d$ is H or C$_{1-10}$ alkyl and wherein $R_d$ and $R_e$ are each independently selected from the group consisting of H, C$_{1-10}$ alkyl, C$_{6-10}$ aryl, 3-10 member heterocycle, and C$_{7-12}$ aralkyl, or $R_e$ and $R_f$ are taken together with the nitrogen to which they are attached to form a C$_{3-10}$ heterocycle.

The term "heterocycle" represents an optionally substituted, saturated, partially saturated, or aromatic cyclic moiety wherein said cyclic moiety is interrupted by at least one heteroatom selected from oxygen (O), sulfur (S) or nitrogen (N). Heterocycles may be monocyclic or polycyclic rings. Examples include but are not limited to azepinyl, aziridinyl, azetyl, azetidinyl, diazepinyl, dithiadiazinyl, dioxaepinyl, dioxolany, dithiazolyl, furanyl, isooxazolyl, isothiazolyl, imidazolyl, morpholinyl, morpholino, oxetanyl, oxadiazolyl, oxirany, oxazinyl, oxazolyl, piperazinyl, pyrazinyl, pyridazinyl, pyrimidinyl, piperidyl, piperidino, pyridyl, pyrany, pyrazolyl, pyrrol, pyrrolidinyl, thiatriazolyl, tetrazolyl, thiaazolyl, triazolyl, thiazolyl, thienyl, tetrazinyl, thiaazinyl, triazinyl, thiazinyl, thiopyranyl, furoisoxazolyl, imidazothiazolyl, thienoisothiazolyl, thienothiazolyl, imidazopyrazolyl, cyclopentapryrazolyl, pyrrolepyrrolyl, thienothienyl, thiaazolopyrimidinyl, thiazolothiazinyl, thiaazolopyrimidinyl,
thiazolopyridinyl, oxazolopyrimidinyl, oxazolopyridyl, benzoazolyl, benzothiazolyl, benzothiazolyl, imidazopyrazinyl, purinyl, pyrazolopyrimidinyl, imidazopyridinyl, benzimidazolyl, indazolyl, benzoxathioliyl, benzodioxolyl, benzodithioliyl, indolizinyl, indolinyl, isoindolinyl, furopyrimidinyl, furopyridyl, benzofuranyl, isobenzofurany1, thienopyrimidinyl, thienopyridyl, benzothienyl, cyclopentaazoxazinyl, cyclopentafuranyl, benzoxazinyl, benzothiazinyl, quinazolinyl, naphthyridinyl, quinolinyl, isoquinolinyl, benzopyranyl, pyridopyrazinyl and pyridopyrimidinyl. The heterocyclic groups can be optionally substituted by, for example, halogens, hydroxy, amino, amido, and/or carboxy.

The term "heteroaryl" represents an optionally substituted aromatic cyclic moiety wherein said cyclic moiety is interrupted by at least one heteroatom selected from oxygen (O), sulfur (S) or nitrogen (N). Heteroaryls may be monocyclic or polycyclic rings. Examples include but are not limited to azepinyl, aziridinyl, azetyl, diazepinyl, dithiadiazinyl, dioxazepinyl, dithiazolyl, furanyl, isoaxazolyl, isothiazolyl, imidazolyl, oxadiazolyl, oxiranyl, oxazinyl, oxazolyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyridyl, pyranyl, pyrazolyl, pyrrolyl, pyrrolidinyl, thiatriazolyl, tetrazolyl, thiazipolyl, triazolyl, thiazolyl, thienyl, tetrazinyl, thiadiazinyl, triazinyl, thiazinyl, thiopyranyl, furoisoaxazolyl, imidazothiazolyl, thienoisothiazolyl,
thienothiazolyl, imidazopyrazolyl, pyrrolopyrrolyl, thienothienyl, thiazolothiazinyl, thiazolopyrimidinyl, thiazolopyridinyl, oxazolo pyrimidinyl, oxazolopyridyl, benzoxazolyl, benzisothiazolyl, benzothiazolyl, imidazopyrazinyl, purinyl, pyrazolo pyrimidinyl, imidazopyridinyl, benzimidazolyl, indazolyl, benzoxathiyl, benzodioxolyl, benzodithiolyl, indoliziny l, indolinyl, isoindolinyl, furopyrimidinyl, fur pyridyl, benzofuranyl, isobenzofuran yl, thienopyrimidinyl, thienopyridyl, benzothienyl, benzoxazinyl, benzothiazinyl, quinazolinyl, naphthyridinyl, quinolinyl, isoquino linyl, benzopyranyl, pyridopyridazinyl and pyridopyrimidinyl.

The heteroaryl groups can be optionally substituted by, for example, halogens, hydroxy, amino, amido, and/or carboxy.

The term "heteroaralkyl" represents an optionally substituted heteroaryl group attached to the adjacent atom by a C\(_{1-10}\) alkyl. The heteroaralkyl groups can be optionally substituted by, for example, halogens, hydroxy, amino, amido, and/or carboxy.

The term "optionally substituted" represents a group which is substituted by one or more substituents selected from:
halogen,
amino,
amidino,
amido,
azido,
cyano,
guanidino,
5 hydroxyl,
nitro,
nitroso,
urea,
\(S(O)_{0-2}R_a\) (wherein \(R_a\) is H, C\(_{1-10}\) alkyl, C\(_{6-10}\) aryl or 3-10
10 member heterocycle),
C\(_{1-10}\) alkyl,
C\(_{7-12}\) aralkyl,
C\(_{6-10}\) aryl,
5-10 member heteroaryl,
15 C\(_{1-10}\) alkoxy,
C\(_{6-10}\) aryl-C\(_{1-10}\) alkoxy,
C\(_{6-10}\) arlyloxy,
3-10 member heterocycle,
C(O)R\(_b\) (wherein \(R_b\) is H, C\(_{1-10}\) alkyl, C\(_{6-10}\) aryl, C\(_{7-12}\)
aralkyl or 3-10 member heterocycle),
20 C(O)OR\(_b\) (wherein \(R_b\) is H, C\(_{1-10}\) alkyl, C\(_{6-10}\) aryl, C\(_{7-12}\)
aralkyl or 3-10 member heterocycle),
NR\(_b\)C(O)R'\(_b\) (wherein \(R_b\) and \(R'_b\) are each independently H, C\(_{1-10}\) alkyl, C\(_{6-10}\) aryl, C\(_{7-12}\) aralkyl or 3-10 member
25 heterocycle, or \(R_b\) and \(R'_b\) are taken together with the
atoms to which they are attached to form a 5-10 member
heterocycle),
SO\(_2\)NR\(_b\)R'\(_b\) (wherein \(R_b\) and \(R'_b\) are each independently H, C\(_{1-10}\) alkyl, C\(_{6-10}\) aryl, C\(_{7-12}\) aralkyl or 3-10 member
30 heterocycle, or \(R_b\) and \(R'_b\) are taken together with the
atoms to which they are attached to form a 5-10 member heterocycle),

\[ NR_bSO_2\text{R'}_b \] (wherein \( R_b \) and \( R_b' \) are each independently \( H, \) C\(_{1-10}\) alkyl, C\(_{6-10}\) aryl, C\(_{7-12}\) aralkyl or 3-10 member heterocycle, or \( R_b \) and \( R_b' \) are taken together with the atoms to which they are attached to form a 5-10 member heterocycle),

\[ NR_bSO_2NR_bR_c \] (wherein \( R_b \), \( R_b' \) and \( R_c \) are each independently \( H, \) C\(_{1-10}\) alkyl, C\(_{6-10}\) aryl, C\(_{7-12}\) aralkyl or 3-10 member heterocycle, or \( R_b' \) and \( R_c \) are taken together with the atoms to which they are attached to form a 5-10 member heterocycle),

\[ CR_bN=\text{OR}'_b \] (wherein \( R_b \) and \( R_b' \) are each independently \( H, \) C\(_{1-10}\) alkyl, C\(_{6-10}\) aryl, 3-10 member heterocycle or C\(_{7-12}\) aralkyl), and

\[ NR_b\text{COOR}'_b \] (wherein \( R_b \) and \( R_b' \) are each independently \( H, \) C\(_{1-10}\) alkyl, C\(_{6-10}\) aryl, C\(_{7-12}\) aralkyl or 3-10 member heterocycle).

There is also provided "enantiomers" of the present invention. It will be appreciated that the compounds in accordance with the present invention can contain a chiral center. The compounds in accordance with the present invention may thus exist in the form of two different optical isomers, that is (+) or (−) enantiomers. All such enantiomers and mixtures thereof, including racemic or other ratio mixtures of individual enantiomers, are included within the scope of the invention. The single enantiomer can be obtained by methods well known to those of ordinary skill in the
art, such as chiral HPLC, enzymatic resolution and chiral auxiliary derivatization.

It will also be appreciated that the compounds in accordance with the present invention can contain more than one chiral centers. The compounds of the present invention may thus exist in the form of different diastereomers. All such diastereomers and mixtures thereof are included within the scope of the invention.

The single diastereomer can be obtained by method well known in the art, such as HPLC, crystallization and chromatography.

The optical purity is numerically equivalent to the "enantiomeric excess". The term "enantiomeric excess" is defined in percentage (%) value as follows: [mole fraction (major enantiomer) - mole fraction (minor enantiomer)] x 100. An example of ee of 99% represents a ratio of 99.5% of one enantiomer and 0.5% of the opposite enantiomer.

There is also provided "pharmaceutically acceptable salts" of the compounds of the present invention. The salt(s) must be "acceptable" in the sense of not being deleterious to the recipient thereof. By the term pharmaceutically acceptable salts of compounds are meant those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include but are not limited to hydrochloric, hydrobromic, sulphuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic,
lactic, salicylic, succinic, toluene-p-sulphonic, tartaric, acetic, trifluoroacetic, citric, methanesulphonic, formic, benzoic, malonic, naphthalene-2-sulphonic and benzenesulphonic acids. Other acids such as oxalic, while not in themselves pharmaceutically acceptable, may be useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

Also meant by "pharmaceutically acceptable salts" are salts derived from appropriate bases include alkali metal, alkaline earth metal or ammonium salts. Non-limiting examples of such salts known by those of ordinary skill include without limitation calcium, potassium, sodium, choline, ethylenediamine, tromethamine, arginine, glycine, lysine, magnesium and meglumine.

There is also provided pharmaceutically acceptable hydrates of the compounds of the present invention. The hydrate(s) must be "acceptable" in the sense of not being deleterious to the recipient thereof. "Hydrates" exist when the compound of the invention incorporates water. The hydrate may contain one or more molecule of water per molecule of compound of the invention. Illustrative non-limiting examples include monohydrate, dihydrate, trihydrate and tetrahydrate. The hydrate may contain one or more molecule of compound of the invention per molecule of water. An illustrative non-limiting example includes semi-hydrate. In one
embodiment, the water may be held in the crystal in various ways and thus, the water molecules may occupy lattice positions in the crystal, or they may form bonds with salts of the compounds as described herein. The hydrate must be "acceptable" in the sense of not being deleterious to the recipient thereof. The hydration may be assessed by methods known in the art such as Loss on Drying techniques (LOD) and Karl Fisher titration.

The term "Solvate" means that compound of the invention incorporates one or more pharmaceutically acceptable solvent (e.g., when the solvent is water the solvate is a hydrate). The solvate(s) must be "acceptable" in the sense of not being deleterious to the recipient thereof. The solvate may contain one or more molecule of solvent per molecule of compound of the invention or may contain one or more molecule of compound of the invention per molecule of solvent. In one embodiment, the solvent may be held in the crystal in various ways and thus, the solvent molecule may occupy lattice positions in the crystal, or they may form bonds with salts of the compounds as described herein. The solvate(s) must be "acceptable" in the sense of not being deleterious to the recipient thereof. The solvation may be assessed by methods known in the art such as Loss on Drying techniques (LOD) Polymorphs & pseudopolymorphs: It will be appreciated by those skilled in the art that the compounds in accordance with the present invention can exist in
several different crystalline forms due to a different arrangement of molecules in the crystal lattice. This may include solvate or hydrate (also known as pseudopolymorphs) and amorphous forms. All such crystalline forms and polymorphs are included within the scope of the invention. The polymorphs may be characterized by methods well known in the art. Examples of analytical procedures that may be used to determine whether polymorphism occurs include: melting point (including hot-stage microscopy), infrared (not in solution), X-ray powder diffraction, thermal analysis methods (e.g. differential scanning calorimetry (DSC) differential thermal analysis (DTA), thermogravimetric analysis (TGA)), Raman spectroscopy, comparative intrinsic dissolution rate, scanning electron microscopy (SEM).

When there is a sulfur atom present, the sulfur atom can be at different oxidation levels, i.e. S, SO, or SO₂. All such oxidation levels are within the scope of the present invention.

When there is a nitrogen atom present, the nitrogen atom can be at different oxidation levels, i.e. N or NO. All such oxidation levels are within the scope of the present invention.

The following Table lists compounds in accordance with the invention.
<table>
<thead>
<tr>
<th></th>
<th>Chemical Structure</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><img src="image1" alt="Structure 1" /></td>
<td>2-((4-Fluoro-benzyl)-9-hydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione</td>
</tr>
<tr>
<td>2.</td>
<td><img src="image2" alt="Structure 2" /></td>
<td>6-Bromo-2-((4-fluoro-benzyl)-9-hydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione</td>
</tr>
<tr>
<td>3.</td>
<td><img src="image3" alt="Structure 3" /></td>
<td>7-Bromo-2-((4-fluoro-benzyl)-9-hydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione</td>
</tr>
<tr>
<td>4.</td>
<td><img src="image4" alt="Structure 4" /></td>
<td>9-Hydroxy-6-hydroxymethyl-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione</td>
</tr>
<tr>
<td>5.</td>
<td><img src="image5" alt="Structure 5" /></td>
<td>2-((4-Fluoro-benzyl)-9-hydroxy-6-hydroxymethyl-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione</td>
</tr>
<tr>
<td>6.</td>
<td><img src="image6" alt="Structure 6" /></td>
<td>5-(1,1-Dioxo-[1,2]thiazinan-2-yl)-2-((4-fluoro-benzyl)-9-hydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione</td>
</tr>
<tr>
<td>7.</td>
<td><img src="image7" alt="Structure 7" /></td>
<td>2-((4-Fluoro-benzyl)-9-hydroxy-6-((tetrahydro-furan-2-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione</td>
</tr>
<tr>
<td></td>
<td>![Molecule 8]</td>
<td>2-((4-Fluoro-benzyl)-6-furan-2-yl-9-hydroxy-3,4-dihydro-2H-pyrido(1,2-a)pyrazine-1,8-dione</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>9</td>
<td>![Molecule 9]</td>
<td>2-((4-Fluoro-benzyl)-9-hydroxy-6-thiazol-2-yl-3,4-dihydro-2H-pyrido(1,2-a)pyrazine-1,8-dione</td>
</tr>
<tr>
<td>10</td>
<td>![Molecule 10]</td>
<td>2-((4-Fluoro-benzyl)-9-hydroxy-6-phenyl-3,4-dihydro-2H-pyrido(1,2-a)pyrazine-1,8-dione</td>
</tr>
<tr>
<td>11</td>
<td>![Molecule 11]</td>
<td>2-((4-Fluoro-benzyl)-9-hydroxy-6-methyl-3,4-dihydro-2H-pyrido(1,2-a)pyrazine-1,8-dione</td>
</tr>
<tr>
<td>12</td>
<td>![Molecule 12]</td>
<td>6-Ethyl-2-((4-Fluoro-benzyl)-9-hydroxy-3,4-dihydro-2H-pyrido(1,2-a)pyrazine-1,8-dione</td>
</tr>
<tr>
<td>13</td>
<td>![Molecule 13]</td>
<td>2-((4-Fluoro-benzyl)-9-hydroxy-6-vinyl-3,4-dihydro-2H-pyrido(1,2-a)pyrazine-1,8-dione</td>
</tr>
<tr>
<td>14</td>
<td>![Molecule 14]</td>
<td>6-(1,2-Dihydroxy-ethyl)-2-((4-Fluoro-benzyl)-9-hydroxy-3,4-dihydro-2H-pyrido(1,2-a)pyrazine-1,8-dione</td>
</tr>
<tr>
<td>No.</td>
<td>Chemical Structure</td>
<td>Chemical Name</td>
</tr>
<tr>
<td>-----</td>
<td>-------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>15</td>
<td><img src="image" alt="Structure 15" /></td>
<td>2-(4-Fluoro-benzyl)-9-hydroxy-1,8-dioxo-1,3,4,8-tetrahydro-2H-pyrido[1,2-a]pyrazine-6-carboxylic acid</td>
</tr>
<tr>
<td>16</td>
<td><img src="image" alt="Structure 16" /></td>
<td>2-(4-Fluoro-benzyl)-9-hydroxy-6-methanesulfonyl-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione</td>
</tr>
<tr>
<td>17</td>
<td><img src="image" alt="Structure 17" /></td>
<td>2-(4-fluoro-benzyl)-7,9-dihydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione,</td>
</tr>
<tr>
<td>18</td>
<td><img src="image" alt="Structure 18" /></td>
<td>7-Amino-2-(4-fluoro-benzyl)-9-hydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione,</td>
</tr>
<tr>
<td>19</td>
<td><img src="image" alt="Structure 19" /></td>
<td>2-(4-fluoro-benzyl)-9-hydroxy-7-methyl-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione,</td>
</tr>
<tr>
<td>20</td>
<td><img src="image" alt="Structure 20" /></td>
<td>2-(4-fluoro-benzyl)-9-hydroxy-7-hydroxymethyl-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione,</td>
</tr>
<tr>
<td>21</td>
<td><img src="image" alt="Structure 21" /></td>
<td>2-(4-fluoro-benzyl)-9-hydroxy-1,8-dioxo-1,3,4,8-tetrahydro-2H-pyrido[1,2-a]pyrazine-7-carboxylic acid,</td>
</tr>
<tr>
<td></td>
<td>Molecular Structure</td>
<td>Chemical Formula</td>
</tr>
<tr>
<td>---</td>
<td>-------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>22</td>
<td><img src="image" alt="Molecule 22" /></td>
<td>2-(4-fluoro-benzyl)-9-hydroxy-1,8-dioxo-1,3,4,8-tetrahydro-2H-pyrido[1,2-a]pyrazine-7-carbonitrile,</td>
</tr>
<tr>
<td>23</td>
<td><img src="image" alt="Molecule 23" /></td>
<td>2-(4-fluoro-benzyl)-9-hydroxy-1,8-dioxo-1,3,4,8-tetrahydro-2H-pyrido[1,2-a]pyrazine-7-carboxylic acid 4-fluoro-benzylamide</td>
</tr>
<tr>
<td>24</td>
<td><img src="image" alt="Molecule 24" /></td>
<td>7-(1,2-Dihydroxy-ethyl)-2-(4-fluoro-benzyl)-9-hydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione,</td>
</tr>
<tr>
<td>25</td>
<td><img src="image" alt="Molecule 25" /></td>
<td>2-(4-fluoro-benzyl)-9-hydroxy-7-vinyl-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione,</td>
</tr>
<tr>
<td>26</td>
<td><img src="image" alt="Molecule 26" /></td>
<td>2-(4-FLUORO-BENZYL)-9-HYDROXY-1,8-DIOXO-1,3,4,8-TETRAHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-6-XYLIC ACID 4-FLUOROBENZYLAMIDE</td>
</tr>
<tr>
<td>27</td>
<td><img src="image" alt="Molecule 27" /></td>
<td>2-(4-FLUORO-BENZYL)-9-HYDROXY-1,8-DIOXO-1,3,4,8-TETRAHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-6-CLIC ACID METHYL ESTER</td>
</tr>
</tbody>
</table>

**SUBSTITUTE SHEET (RULE 26)**
<table>
<thead>
<tr>
<th></th>
<th>Chemical Structure</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td><img src="image1" alt="Image" /></td>
<td>7-ethyl-2-(4-fluoro-benzyl)-9-hydroxy-3,4-dihydro-2h-pyrido[1,2-a]pyrazine-1,8-dione hydrochloride salt</td>
</tr>
<tr>
<td>29</td>
<td><img src="image2" alt="Image" /></td>
<td>2-(4-fluoro-benzyl)-9-hydroxy-7-vinyl-3,4-dihydro-2h-pyrido[1,2-a]pyrazine-1,8-dione hydrochloride salt</td>
</tr>
<tr>
<td>30</td>
<td><img src="image3" alt="Image" /></td>
<td>6-(4-acetyl-piperazin-1-yl)-2-(4-fluoro-benzyl)-9-hydroxy-3,4-dihydro-2h-pyrido[1,2-a]pyrazine-1,8-dione</td>
</tr>
<tr>
<td>31</td>
<td><img src="image4" alt="Image" /></td>
<td>2-(4-fluoro-benzyl)-9-methoxy-6-methoxymethyl-3,4-dihydro-2h-pyrido[1,2-a]pyrazine-1,8-dione</td>
</tr>
<tr>
<td>32</td>
<td><img src="image5" alt="Image" /></td>
<td>2-(4-fluoro-benzyl)-9-hydroxy-6-methoxymethyl-3,4-dihydro-2h-pyrido[1,2-a]pyrazine-1,8-dione</td>
</tr>
</tbody>
</table>
33

2-(4-FLUORO-BENZYL)-9-HYDROXY-1,8-DIOXO-1,3,4,8-TETRAHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-6-CARBOXYLIC ACID AMIDE

34

8-AMINO-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE HYDROCHLORIDE

35

6-azido-2-(4-fluoro-benzyl)-9-hydroxy-3,4-dihydro-2h-pyrido[1,2-a]pyrazine-1,8-dione
<table>
<thead>
<tr>
<th>No.</th>
<th>Structure</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>36</td>
<td><img src="image" alt="Structure 36" /></td>
<td>2-(4-FLUORO-BENZYL)-9-HYDROXY-6-PIPERIDIN-1-YL-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE</td>
</tr>
<tr>
<td>37</td>
<td><img src="image" alt="Structure 37" /></td>
<td>6-CYCLOHEXYL-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE</td>
</tr>
<tr>
<td>38</td>
<td><img src="image" alt="Structure 38" /></td>
<td>4-FLUORO-N-(4-FLUORO-BENZOXYL)-N-[2-(4-FLUORO-BENZYL)-9-HYDROXY-1,8-DIOXO-1,3,4,8-TETRAYDRO-2H-PYRIDO[1,2-A]PYRAZIN-6-YL]BENZAMIDE</td>
</tr>
<tr>
<td>39</td>
<td><img src="image" alt="Structure 39" /></td>
<td>2-(4-FLUORO-BENZYL)-9-HYDROXY-6-MORPHOLIN-4-YL-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE</td>
</tr>
<tr>
<td></td>
<td>Chemical Structure</td>
<td>Chemical Name</td>
</tr>
<tr>
<td>---</td>
<td>--------------------</td>
<td>-------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>40</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td>2-(4-FLUORO-BENZYL)-9-HYDROXY-6-PYRROLIDIN-1-YL-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE</td>
</tr>
<tr>
<td>41</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td>FURAN-2-CARBOXYLIC ACID [2-(4-FLUORO-BENZYL)-9-HYDROXY-1,8-DIOXO-1,3,4,8-TETRAHYDRO-2H-PYRIDO[1,2-A]PYRAZIN-6-YL]- (FURAN-2-CARBONYL)-AMIDE</td>
</tr>
<tr>
<td>42</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td>2-(4-FLUORO-BENZYL)-9-HYDROXY-6-(TETRAHYDRO-FURAN-3-YL)-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE</td>
</tr>
<tr>
<td>43</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td>2-(4-FLUORO-BENZYL)-6-(4-FLUORO-PHENYLAMINO)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE; HYDROCHLORIDE</td>
</tr>
<tr>
<td>44</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td>6-DIMETHYLAMINO-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE; HYDROCHLORIDE</td>
</tr>
<tr>
<td>45</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td>2-(4-FLUORO-BENZYL)-9-HYDROXY-6-METHOXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE</td>
</tr>
<tr>
<td>No.</td>
<td>Chemical Structure</td>
<td>Description</td>
</tr>
<tr>
<td>-----</td>
<td>-------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>46</td>
<td><img src="image" alt="Chemical Structure 46" /></td>
<td>2-(4-FLUORO-BENZYL)-9-HYDROXY-6-[1,2,3]TRIAZOL-1-YL-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE; HYDROCHLORIDE</td>
</tr>
<tr>
<td>47</td>
<td><img src="image" alt="Chemical Structure 47" /></td>
<td>1-[2-(4-FLUORO-BENZYL)-9-HYDROXY-1,8-DIOXO-1,3,4,8-TETRAHYDRO-2H-PYRIDO[1,2-A]PYRAZIN-6-L]-1H-[1,2,3]TRIAZOLE-4-CARBOXYLIC ACID METHYL ESTER; HYDROCHLORIDE</td>
</tr>
<tr>
<td>48</td>
<td><img src="image" alt="Chemical Structure 48" /></td>
<td>6-ETHOXY-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE</td>
</tr>
<tr>
<td>49</td>
<td><img src="image" alt="Chemical Structure 49" /></td>
<td>2-(4-FLUORO-BENZYL)-9-HYDROXY-6-ISOPROPOXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE</td>
</tr>
<tr>
<td>50</td>
<td><img src="image" alt="Chemical Structure 50" /></td>
<td>6-(2,2-DIFLUORO-ETHOXY)-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE</td>
</tr>
<tr>
<td>51</td>
<td><img src="image" alt="Chemical Structure 51" /></td>
<td>2-(4-FLUORO-BENZYL)-9-HYDROXY-6-PROPOXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE</td>
</tr>
<tr>
<td>52</td>
<td><img src="image" alt="Chemical Structure 52" /></td>
<td>2-(4-FLUORO-BENZYL)-6-(2-FLUORO-ETHOXY)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE</td>
</tr>
<tr>
<td><strong>53</strong></td>
<td>8-CYCLOPROPYLMETHOXY-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE</td>
<td></td>
</tr>
<tr>
<td><strong>54</strong></td>
<td>8-CYCLOHEXYLMETHOXY-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE</td>
<td></td>
</tr>
<tr>
<td><strong>55</strong></td>
<td>2-(4-FLUORO-BENZYL)-9-HYDROXY-6-(2,2,2-TRIFLUORO-ETHOXY)-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE</td>
<td></td>
</tr>
<tr>
<td><strong>56</strong></td>
<td>2-(4-FLUORO-BENZYL)-9-HYDROXY-6-(2-MORPHOLIN-4-YL-ETHOXY)-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE</td>
<td></td>
</tr>
<tr>
<td><strong>57</strong></td>
<td>2-(4-FLUORO-BENZYL)-9-HYDROXY-6-PHENOXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE</td>
<td></td>
</tr>
<tr>
<td><strong>58</strong></td>
<td>2-(4-FLUORO-BENZYL)-9-HYDROXY-6-ISOBUTOXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE</td>
<td></td>
</tr>
<tr>
<td><strong>59</strong></td>
<td>2-(4-FLUORO-BENZYL)-6-(4-FLUORO-PHENOXY)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE</td>
<td></td>
</tr>
</tbody>
</table>
60. 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-(TETRAHYDRO-PYRAN-4-YLMETHOXY)-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE

61. 7-FLUORO-2-(4-FLUORO-BENZYL)-9-HYDROXY-6-METHOXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE

62. 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-(2-METHOXY-ETHOXY)-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE

63. 6-(2,2-DIMETHYL-[1,3]DIOXOLAN-4-YLMETHOXY)-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE

64. 6-(2-DIMETHYLAMINO-ETHOXY)-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE

65. 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-(2-METHANESULFONYL-ETHOXY)-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE

66. 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-[2-(4-METHOXY-PHENYL)-ETHOXY]-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE
<p>| 67 | <img src="image1" alt="Chemical Structure" /> | 2-(4-FLUORO-BENZYL)-6-(3-FLUORO-PROPOXY)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZONE-1,8-DIONE |
| 68 | <img src="image2" alt="Chemical Structure" /> | 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-(PYRIDIN-2-YLMETHOXY)-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZONE-1,8-DIONE |
| 69 | <img src="image3" alt="Chemical Structure" /> | 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-PHENETHYLOXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZONE-1,8-DIONE |
| 70 | <img src="image4" alt="Chemical Structure" /> | 8-([1,3]DIOXOLAN-4-YLMETHOXY)-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZONE-1,8-DIONE |
| 71 | <img src="image5" alt="Chemical Structure" /> | 8-([1,3]DIOXAN-5-YLOXY)-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZONE-1,8-DIONE |
| 72 | <img src="image6" alt="Chemical Structure" /> | 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-(2-PIPERIDIN-1-YL-ETHOXY)-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZONE-1,8-DIONE |
| 73 | <img src="image7" alt="Chemical Structure" /> | 8-CYCLOPENTYLMETHOXY-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZONE-1,8-DIONE |</p>
<table>
<thead>
<tr>
<th></th>
<th>Molecular Structure</th>
<th>Chemical Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>74</td>
<td><img src="image_url" alt="Molecular Structure" /></td>
<td>6-CYCLOBUTYL METHOXY-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE</td>
</tr>
<tr>
<td>75</td>
<td><img src="image_url" alt="Molecular Structure" /></td>
<td>2-{2-(4-FLUORO-BENZYL)-9-HYDROXY-1,8-DIOXO-1,3,4,8-TETRAHYDRO-2H-PYRIDO[1,2-A]PYRAZIN-6-YLOXY]-N,N-DIMETHYL-ACETAMIDE</td>
</tr>
<tr>
<td>76</td>
<td><img src="image_url" alt="Molecular Structure" /></td>
<td>2-(4-FLUORO-BENZYL)-9-HYDROXY-6-(PYRIDIN-3-YLOXY)-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE</td>
</tr>
<tr>
<td>77</td>
<td><img src="image_url" alt="Molecular Structure" /></td>
<td>6-(2-CYCLOPROPYL-ETHOXY)-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE</td>
</tr>
<tr>
<td>78</td>
<td><img src="image_url" alt="Molecular Structure" /></td>
<td>6-BROMO-2-(3,4-DICHLORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO(1,2-A)-PYRAZINE-1,8-DIONE</td>
</tr>
<tr>
<td>79</td>
<td><img src="image_url" alt="Molecular Structure" /></td>
<td>6-BROMO-2-(3-CHLORO-4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO-(1,2-A)-PYRAZINE-1,8-DIONE</td>
</tr>
<tr>
<td>80</td>
<td><img src="image_url" alt="Molecular Structure" /></td>
<td>6-(4,4-DIFLUORO-CYCLOHEXYL-METHOXY)-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO-[1,2-A]PYRAZINE-1,8-DIONE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td><strong>81</strong></td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>2-(4-FLUORO-BENZYL)-9-HYDROXY-6-(2-HYDROXY-ETHOXY)-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE</td>
</tr>
<tr>
<td><strong>82</strong></td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>6-(2,2-DIMETHOXY-ETHOXY)-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE</td>
</tr>
<tr>
<td><strong>83</strong></td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Chiral 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-(R)-5-OXO-TETRAHYDROFURAN-2-YLMETHOXY)-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE</td>
</tr>
<tr>
<td><strong>84</strong></td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Chiral 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-(S)-5-OXO-TETRAHYDROFURAN-2-YLMETHOXY)-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE</td>
</tr>
<tr>
<td><strong>85</strong></td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>2-(4-FLUORO-BENZYL)-9-HYDROXY-6-(2-THIOPHEN-2-YL-ETHOXY)-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE</td>
</tr>
<tr>
<td><strong>86</strong></td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>2-BENZYL-9-HYDROXY-6-METHOXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE</td>
</tr>
<tr>
<td><strong>87</strong></td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>2-(3,4-Dichloro-benzyl)-9-hydroxy-6-methoxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione</td>
</tr>
<tr>
<td>No.</td>
<td>Molecular Structure</td>
<td>Chemical Formula</td>
</tr>
<tr>
<td>-----</td>
<td>--------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>88</td>
<td><img src="image" alt="Molecule 88" /></td>
<td>2-BENZYL-6-(2-FLUORO-ETHOXY)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO(1,2-A)-PYRAZINE-1,8-DIONE</td>
</tr>
<tr>
<td>89</td>
<td><img src="image" alt="Molecule 89" /></td>
<td>2-(3,4-DICHLORO-BENZYL)-6-(2-FLUORO-ETHOXY)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO(1,2-A)-PYRAZINE-1,8-DIONE</td>
</tr>
<tr>
<td>90</td>
<td><img src="image" alt="Molecule 90" /></td>
<td>6-(2-CYCLOPENTYL-ETHOXY)-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE</td>
</tr>
<tr>
<td>91</td>
<td><img src="image" alt="Molecule 91" /></td>
<td>2-(3,4-Dichloro-benzyl)-9-hydroxy-6-(pyridin-3-yl-oxo)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione</td>
</tr>
<tr>
<td>92</td>
<td><img src="image" alt="Molecule 92" /></td>
<td>2-(3-Chloro-4-fluoro-benzyl)-9-hydroxy-6-(pyridin-3-yl-oxo)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione</td>
</tr>
<tr>
<td>93</td>
<td><img src="image" alt="Molecule 93" /></td>
<td>2-(3,4-Dichloro-benzyl)-9-hydroxy-6-(2-methoxy-ethoxy)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione</td>
</tr>
<tr>
<td>94</td>
<td><img src="image" alt="Molecule 94" /></td>
<td>2-(3-Chloro-4-fluoro-benzyl)-9-hydroxy-6-(2-methoxy-ethoxy)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione</td>
</tr>
</tbody>
</table>
In one embodiment, there is provided a method of preventing or treating HIV infection in a subject which comprises administering to the subject a therapeutically effective amount of a compound of the present invention.

In one embodiment, there is provided a method of preventing or treating HIV infection in a subject which comprises administering to the subject a therapeutically effective amount of a combination or pharmaceutical composition of the present invention.

In one embodiment, there is provided a method of preventing, delaying or treating AIDS in a subject which comprises administering to the subject a therapeutically effective amount of a compound of the present invention.

In one embodiment, there is provided a method of preventing, delaying or treating AIDS in a subject which comprises administering to the subject a therapeutically effective amount of a combination or a pharmaceutical composition of the present invention.

In one embodiment, there is provided a method of preventing HIV replication in a subject which comprises administering to the subject a therapeutically effective amount of a compound of the present invention.
In one embodiment, there is provided a method of preventing HIV replication in a subject which comprises administering to the subject a therapeutically effective amount of a combination or a pharmaceutical composition of the present invention.

In one embodiment, there is provided a method of inhibiting HIV integrase in a subject which comprises administering to the subject a therapeutically effective amount of a compound of the present invention.

In one embodiment, there is provided a method of inhibiting HIV integrase in a subject which comprises administering to the subject a therapeutically effective amount of a combination or a pharmaceutical composition of the present invention.

In one embodiment, there is provided a method of preventing integration of HIV DNA into host cell DNA in a subject which comprises administering to the subject a therapeutically effective amount of a compound of the present invention.

In one embodiment, there is provided a method of preventing integration of HIV DNA into host cell DNA in a subject which comprises administering to the subject a therapeutically effective amount of a combination or a pharmaceutical composition of the present invention.
In one embodiment, there is provided a method of preventing the 3′-end processing of HIV DNA in a subject, the method comprising administering to the subject a therapeutically effective amount of a compound of the present invention.

In one embodiment, there is provided a method of preventing the 3′-end processing of HIV DNA in a subject which comprises administering to the subject a combination or a pharmaceutical composition of the present invention.

In one embodiment, there is provided a method of preventing the HIV DNA strand transfer to the host cell DNA in a subject which comprises administering to the subject a therapeutically effective amount of a compound of the present invention.

In one embodiment, there is provided a method of preventing the HIV DNA strand transfer to the host cell DNA in a subject which comprises administering to the subject a therapeutically effective amount of a combination or a pharmaceutical composition of the present invention.

In one embodiment, combinations of the present invention comprise those wherein the following embodiments are present, either independently or in combination.
In a further embodiment, the pharmaceutical combinations of this invention may contain at least one further therapeutic agent chosen from an agent used in inflammatory diseases, immunoregulatory diseases and in organ transplantation reactions.

In another embodiment, the pharmaceutical combination of this invention may contain at least one further therapeutic agent which is an antiviral agent.

In one embodiment, the pharmaceutical combination of this invention may contain at least one further antiviral agent which is chosen from nucleoside and nucleotide analog reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors attachment and fusion inhibitors, entry inhibitors or maturation inhibitors.

In one embodiment, the pharmaceutical combinations of this invention may contain at least one other antiviral agent which is a nucleoside and nucleotide analog reverse transcriptase inhibitors chosen from 3TC (lamivudine, Epivir®), AZT (zidovudine, Retrovir®), Emtricitabine (Coviracil®, formerly FTC), d4T (2',3'-dideoxy-2',3'-didehydro-thymidine, stavudine and Zerit®), tenofovir (Viread®), 2',3'-dideoxyinosine (ddI, didanosine, Videx®), 2',3'-dideoxycytidine (ddC, zalcitabine, Hivid®), Combivir® (AZT/3TC or zidovudine/lamivudine combination), Trivizir® (AZT/3TC/abacavir or zidovudine/lamivudine/abacavir
combination), abacavir (1592089, Ziagen®), SPD-754, ACH-126,443 (Beta-L-Fd4C), Alovudine (MIV-310), DAPD (amdoxovir), Racivir, 9-[(2-hydroxymethyl)-1,3-
dioxolan-4-yl]guanine or 2-amino-9-[(2-hydroxymethyl)-
1,3-dioxolan-4-yl]adenine.

In another embodiment, the pharmaceutical combination
of this invention may contain at least one other
antiviral agent which is a non-nucleoside reverse
transcriptase inhibitor chosen from Nevirapine
(Viramune®, NV®, BI-RG-587), delavirdine (Rescriptor®,
DLV), efavirenz (DMP 266, Sustiva®), (+)-Calanolide A,
Capravirine (AG1549, formerly S-1153), DPC083, MIV-150,
TMC120, TMC125 or BHAP (delavirdine), calanolides or L-
697,661 (2-Pyridinone 3benzoazolMeNH derivative).

In another embodiment, the pharmaceutical combination
of this invention may contain at least one other
antiviral agent which is a protease inhibitor chosen
from nelfinavir (Viracept®, NFV), amprenavir (141W94,
Agenerase®), indinavir (MK-639, IDV, Crixivan®), saquinavir
(Invirase®, Fortovase®, SQV), ritonavir
(Norvir®, RTV), lopinavir (ABT-378, Kaletra®),
Atazanavir (BMS232632), mozenavir (DMP-450),
fosamprenavir (GW433908), RO033-4649, Tipranavir (PNU-
140690), TMC114 or VX-385.

In another embodiment, the pharmaceutical combination
of this invention may contain at least one other
antiviral agent which is an attachment and fusion
inhibitor chosen from T-20 (enfuvirtide, Fuzeon®), T-
1249, Schering C (SCH-C), Schering D (SCH-D), FP21399, PRO-140, PRO 542, PRO 452, TNX-355, GW873140 (AK602), TAK-220, TAK-652, UK-427,857 or soluble CD4, CD4 fragments, CD4-hybrid molecules, BMS-806, BMS-488043, AMD3100, AMD070 or KRH-2731.

In another embodiment, the pharmaceutical combination of this invention may contain at least one other antiviral agent which is an integrase inhibitor chosen from S-1360, JKT 303, L-870,810, L-870,812 or C-2507.

In another embodiment, the pharmaceutical combination of this invention may contain at least one other antiviral agent which is a maturation inhibitor and is PA-457.

In another embodiment, the pharmaceutical combination of this invention may contain at least one other antiviral agent which is a zinc finger inhibitor and is azodicarbonamide (ADA).

In another embodiment, the pharmaceutical combination of this invention may contain at least one other antiviral agent which is an antisense drug and is HGT43.

In another embodiment, the pharmaceutical combination of this invention may contain at least one other antiviral agent which is an immunomodulator, immune stimulator or cytokine chosen from interleukin-2 (IL-2, Aldesleukin, Proleukin), granulocyte macrophage colony...
stimulating factor (GM-CSF), erythropoietin, Multikine, Ampligen, thymomodulin, thymopentin, foscarnet, HE2000, Reticulose, Murabutide, Resveratrol, HRG214, HIV-1 Immunogen (Remune) or EP HIV-1090.

In another embodiment, the pharmaceutical combination of this invention may contain at least one other antiviral agent chosen from 2',3'-dideoxyadenosine, 3'-deoxythymidine, 2',3'-dideoxy-2',3'-didehydrocytidine and ribavirin; acyclic nucleosides such as acyclovir, ganciclovir; interferons such as alpha-, beta-and gamma-interferon; glucuronation inhibitors such as probenecid; or TIBO drugs, HEPT, TSAO derivatives.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier thereof comprises a further aspect of the invention.

The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

In a further embodiment, the said compound of formula (I) and said therapeutic agent are administered sequentially.
In a further embodiment, the said compound of formula (I) and said therapeutic agent are administered simultaneously.

5 The subject to which the compounds are administered can be, for example, a mammal or a human. Preferably, the subject is a human.

In one embodiment, the present invention further provides a pharmaceutical composition comprising at least one compound having the formula (I) or pharmaceutically acceptable salts or pharmaceutically acceptable hydrates or pharmaceutically acceptable solvates thereof and at least one pharmaceutically acceptable carrier or excipient.

In one embodiment, there is provided a method of preventing, or delaying opportunistic infections in HIV-infected subject which comprises administering to the subject a therapeutically effective amount of a compound of the present invention.

In one embodiment, the opportunistic infection is selected from CMV retinitis, Pneumocystis carinii pneumonia, Mycobacterium avium complex, cryptococcal meningitis, or herpes simplex.

In another embodiment, the invention provides the use of a compound of the present invention for the
manufacture of a medicament for preventing or treating HIV infection or preventing, delaying or treating AIDS.

In another embodiment, the invention provides the use of a compound of the present invention for the manufacture of a medicament for preventing or treating HIV infection or preventing, delaying or treating AIDS.

In another embodiment, the invention provides the use of a combination of the invention for the manufacture of a medicament for preventing or treating HIV infection or preventing, delaying or treating AIDS.

In another embodiment, the invention provides the use of a compound of the present invention for the manufacture of a medicament for preventing anyone of HIV replication, integration of HIV DNA into host cell DNA, 3'-end processing of HIV DNA or HIV DNA strand transfer to the host cell DNA.

In another embodiment, the invention provides the use of a combination of the invention for the manufacture of a medicament for preventing anyone of HIV replication, integration of HIV DNA into host cell DNA, 3'-end processing of HIV DNA or HIV DNA strand transfer to the host cell DNA.

In another embodiment, the invention provides the use of a compound of the present invention for the manufacture of a medicament for inhibiting HIV integrase.
In another embodiment, the invention provides the use of a combination of the invention for the manufacture of a medicament for inhibiting HIV integrase.

According to a further embodiment, the subject in the above-mentioned methods and uses is a human.

In another embodiment, the present invention provides a combination comprising a therapeutically effective amount of a compound of the present invention, and a therapeutically effective amount of at least one further antiviral agent wherein said compound and said antiviral agent are present in a synergistic ratio.

It will be clear to a person of ordinary skill that if a further additional therapeutic agent is required or desired, ratios will be readily adjusted. It will be understood that the scope of combinations described herein is not limited to the antiviral agents listed above, but includes in principles any therapeutic agent useful for the prevention and treatment of HIV infection and AIDS.

The compound and combinations referred to above as well as individual components of such combinations may be administered as pharmaceutical compositions.

A further aspect of the invention is therefore presented as a pharmaceutical composition comprising a
compound of the present invention together with at least one pharmaceutically acceptable carrier or excipient thereof.

In another embodiment, the present invention provides a pharmaceutical composition comprising a compound of the present invention or a pharmaceutically acceptable salts, hydrates or solvates thereof or combination as defined herein together with one or more pharmaceutically acceptable carrier or excipient thereof.

The carrier(s) or excipient(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not being deleterious to the recipient thereof.

It will be appreciated that the amount of a compound of the invention required for use in treatment will vary not only with the particular compound selected but also with the route of administration, the nature of the condition for which treatment is required and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. In general however a suitable dose will be in the range of from about 0.1 to about 750 mg/kg of body weight per day, alternatively in the range of 0.5 to 60 mg/kg/day, in a further alternative in the range of 1 to 20 mg/kg/day.
The desired dose may conveniently be presented in a single dose or as divided dose administered at appropriate intervals, for example as two, three, four or more doses per day.

The compound is conveniently administered in unit dosage form; for example containing 1 to 1500 mg, as a further example the unit dosage form is containing 10 to 1000 mg, as a further example the unit dosage form is containing 50 to 750 mg of active ingredient per unit dosage form.

Ideally the active ingredient should be administered to achieve peak plasma concentrations of the active compound of from about 1 to about 75µM, preferably about 2 to 50 µM, most preferably about 3 to about 30 µM. This may be achieved, for example, by the intravenous injection of a 0.1 to 5% solution of the active ingredient, optionally in saline, or orally administered as a bolus containing about 1 to about 500 mg of the active ingredient. Desirable blood levels may be maintained by a continuous infusion to provide about 0.01 to about 5.0 mg/kg/hour or by intermittent infusions containing about 0.4 to about 15 mg/kg of the active ingredient.

While it is possible that, for use in therapy, a compound or combination of the invention may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical composition.
Pharmaceutical compositions include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), transdermal, vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the active compound with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Pharmaceutical compositions suitable for oral administration may conveniently be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution, a suspension or as an emulsion. The active ingredient may also be presented as a bolus, electuary or paste. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, or wetting agents. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid
preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), or preservatives.

The compounds and combinations according to the invention may also be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

For topical administration to the epidermis, the compounds and combinations according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Such transdermal patches may contain penetration enhancers such as linalool, carvacrol, thymol, citral, menthol and t-anethole. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in
general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents.

Compositions suitable for topical administration in the mouth include lozenges comprising active ingredient in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Pharmaceutical compositions suitable for rectal administration wherein the carrier is a solid are most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art, and the suppositories may be conveniently formed by admixture of the active compound with the softened or melted carrier(s) followed by chilling and shaping in moulds.

Compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

For intra-nasal administration the compounds of the invention may be used as a liquid spray or dispersible powder or in the form of drops. Drops may be formulated with an aqueous or non-aqueous base also comprising one
more dispersing agents, solubilising agents or suspending agents. Liquid sprays are conveniently delivered from pressurized packs.

For administration by inhalation the compounds and combinations according to the invention are conveniently delivered from an insufflator, nebulizer or a pressurized pack or other convenient means of delivering an aerosol spray. Pressurized packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount.

Alternatively, for administration by inhalation or insufflation, the compounds and combinations according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form in, for example, capsules or cartridges or e.g. gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

When desired the above described formulations adapted to give sustained release of the active ingredient may be employed.
The compounds of the invention have been found to have activity in the inhibition of HIV integrase, as described in example 30, generally with an observed inhibitory activity at 50 μM.

Certain compounds of the present invention have also been tested in an assay for HIV activity, as described in Example 31, and generally having an IC$_{50}$ value of less than 10 μM.

In the foregoing and in the following examples, all temperatures are set forth uncorrected in degrees Celsius; and, unless otherwise indicated, all parts and percentages are by weight.

The entire disclosures of all applications, patents and publications, cited above and below, are hereby incorporated by reference.

The following general schemes and examples are provided to illustrate various embodiments of the present invention and shall not be considered as limiting in scope.
EXAMPLES

Scheme 1:

5-Bromo-3-methoxy-2-methyl-1H-pyridin-4-one.

To a solution of 3-methoxy-2-methyl-1H-pyridone (7g, 50.3 mmol) in chloroform (100 ml) was added N-bromosuccinimide (NBS, 9.9 g, 1.1 eq.) portionwise.

119

SUBSTITUTE SHEET (RULE 26)
reaction mixture was stirred at rt for 1h and the precipitate was removed by filtration. The filtrate was concentrated under reduced pressure and was purified on silica gel using CH₂Cl₂: MeOH 9:1 as eluent to give 9.7 g of desired product in 89% yield.

$^1$H NMR (400 MHz, CDCl₃): $\delta$ [ppm] 8.0 (s, 1H), 3.82 (s, 3H), 2.43 (s, 3H).

**Example 2**

4-Benzylxoy-3-methoxy-2-methyl-pyridine.

\[
\begin{array}{c}
\text{OBn} \\
\end{array}
\]

To a stirring solution of 3-methoxy-2-methyl-1H-pyridone (3g, 21.5 mmol), triphenyl phosphine (6.8 g, 1.2 eq), benzyl alcohol (2.6 g, 1.1 eq) in THF (40 ml) was added dropwise diisopropyl azodicarboxylate ( 5g, 1.1eq). The mixture was stirred at rt for 1h and refluxed for 18 hrs. After cooling to rt, the solvent was removed under reduced pressure. The residue was suspended in water, acidified with 6N-HCl solution to pH 1 and washed with diethyl ether. The pH of the aqueous solution was then increased to 8 with sodium hydroxide and extracted with ethyl acetate (3x100 ml). The organic phase was washed with water, dried with Na₂SO₄ and evaporated under reduced pressure to give 3.8 g (77%) of desired product as oil which was used in the next step without further purification.
\[ \text{Example 3} \]

**4-Benzyl-3-methoxy-5-bromo-2-methyl-pyridine.**

\[
\begin{array}{c}
\text{Br} \\
\text{O} \\
\text{Bn}
\end{array}
\]

The compound was prepared starting from 5-bromo-3-methoxy-2-methyl-1H-pyridin-4-one in a similar manner as described above.

\[ ^1H \text{ NMR (400 MHz, CDCl}_3\text{): } \delta \text{ [ppm] 8.32 (s, 1H), 7.50 (m, 2H), 7.40 (m, 3H), 5.18 (s, 2H), 3.80 (s, 3H), 2.40 (s, 3H).} \]

\[ \text{Example 4} \]

**4-Benzyl-3-methoxy-2-methyl-pyridine N-oxide.**

\[
\begin{array}{c}
\text{O} \\
\text{Bn}
\end{array}
\]

To a solution of 4-benzyl-3-methoxy-2-methyl-pyridine (3.8 g, 16.6 mmol) in dichloromethane (50 ml) was added portionwise m-chloroperoxybenzoic acid (75% MCPBA, 4.6 g, 1.2 eq.). The reaction mixture was stirred at rt for overnight, washed with 5% sodium carbonate solution (3x50 ml), water and dried over
Na₂SO₄. The solvent was removed under reduced pressure to give 4.2 g of product as oil which was used in the next step without further purification.

\[ ^1H \text{ NMR (400 MHz, CDCl}_3\text{): } \delta [\text{ppm}] 8.22 (d, 1\text{H}), 7.40 (m, 5\text{H}), 6.70 (d, 1\text{H}), 5.18 (s, 2\text{H}), 3.82 (s, 3\text{H}), 2.48 (s, 3\text{H}). \]

**Example 5**

Acetic acid 4-benzylxyloxy-3-methoxy-pyridin-2-ylmethyl ester.

A solution of 4-benzylxyloxy-3-methoxy-2-methyl-pyridine N-oxide (4.2 g, 17.1 mmol) in acetic anhydride (35 ml) was stirred at 100°C for 2h and cooled to rt. The reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in methylene chloride (150 ml), washed with saturated NaHCO₃ solution, water and dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified on silica gel using hexane:EtOAc 7:3, 3:2 and 1:1 as eluent to give 3.9 g of pure product in 80% yield.

\[ ^1H \text{ NMR (400 MHz, CDCl}_3\text{): } \delta [\text{ppm}] 8.22 (d, 1\text{H}), 7.40 (m, 5\text{H}), 6.84 (d, 1\text{H}), 5.22 (s, 2\text{H}), 5.18 (s, 2\text{H}), 3.82 (s, 3\text{H}), 2.12 (s, 3\text{H}). \]
Example 6

Acetic acid 4-benzyloxy-5-bromo-3-methoxy-pyridin-2-ylmethyl ester.

\[
\begin{array}{c}
\text{O} \\
\text{Bn} \\
\text{Br} \\
\text{O} \\
\text{N} \\
\text{CH}_2\text{OAc}
\end{array}
\]

The compound was prepared starting from 4-benzyloxy-3-methoxy-5-bromo-2-methyl-pyridine in a similar manner as described above.

\(^1\text{H NMR (400 MHz, CDCl}_3\text{): }\delta [\text{ppm}] 8.44 (s, 1H), 7.50 (m, 2H), 7.40 (m, 3H), 5.22 (s, 2H), 5.19 (s, 2H), 3.92 (s, 3H), 2.14 (s, 3H).

Example 7

(4-Benzylxoy-3-methoxy-pyridin-2-yl)-methanol.

\[
\begin{array}{c}
\text{O} \\
\text{Bn} \\
\text{O} \\
\text{N} \\
\text{CH}_2\text{OH}
\end{array}
\]

To a solution of acetic acid 4-benzyloxy-3-methoxy-pyridin-2-ylmethyl ester (1.8 g, 6.27 mmol) in dioxane (15 ml)-water (5 ml) was added a solution of lithium hydroxide (300mg, 1.2 eq.) in water (3 ml). The reaction mixture was stirred as rt for 3 h and evaporated under reduced pressure. The residue was dissolved in methylene chloride (100 ml), washed with water, brine
solution and dried over Na₂SO₄. The solvent was removed under reduced pressure to give 1.56 g of desired product in 100% yield. The $^1$H-NMR indicated pure product which was used in the next step without further purification.

$^1$H NMR (400 MHz, CDCl₃): $\delta$ [ppm] 8.20 (d, 1H), 7.40 (m, 5H), 6.84 (d, 1H), 5.20 (s, 2H), 4.78 (s, 2H), 3.90 (s, 3H).

10. **Example 8**

4-Benzylxoy-3-methoxy-5-bromo-pyridin-2-yl)-methanol.

![Chemical Structure](image)

The compound was prepared starting from acetic acid 4-benzyloxy-5-bromo-3-methoxy-pyridin-2-ylmethyl ester in a similar manner using the procedure described above.

$^1$H NMR (400 MHz, CDCl₃): $\delta$ [ppm] 8.39 (s, 1H), 7.50 (m, 2H), 7.40 (m, 3H), 5.20 (s, 2H), 4.73 (s, 2H), 3.89 (s, 3H).

15. **Example 9**

4-Benzylxoy-3-methoxy-pyridine-2-carbaldehyde.

![Chemical Structure](image)
MnO₂ (85%, 2.5 g, 5 eq.) was added to a solution of 4-benzzyloxy-3-methoxy-pyridin-2-yl)-methanol (1.23 g, 5 mmol) in methylene chloride (40 ml). The mixture was stirred at rt for 3 h and an additional portion of MnO₂ was added. The mixture was stirred for overnight and filtered through celite. The residue was washed with methylene chloride-methanol 4:1 mixture (20 ml). The combined organic solution was evaporated to dryness under reduced pressure. The residue was purified on silica gel using hexane:EtOAc 1:1 as eluent to give 970 mg of product in 79% yield.

¹H NMR (400 MHz, CDCl₃): δ [ppm] 10.36 (s, 1H), 8.39 (d, 1H), 7.40 (m, 5H), 7.05 (d, 1H), 5.22 (s, 2H), 4.02 (s, 3H).

Example 10

4-Benzzyloxy-3-methoxy-5-bromo-pyridine-2-carbaldehyde.

The compound was prepared starting from 4-benzzyloxy-3-methoxy-5-bromo-pyridin-2-yl)-methanol in a similar manner using the procedure described above.

¹H NMR (400 MHz, CDCl₃): δ [ppm] 10.22 (s, 1H), 8.60 (s, 1H), 7.50 (m, 2H), 7.40 (m, 3H), 5.28 (s, 2H), 4.01 (s, 3H).
Example 11

4-Benzylxoy-3-methoxy-pyridine-2-carboxylic acid.

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{OH}
\end{align*}
\]

To a solution of 4-benzylxoy-3-methoxy-pyridine-2-carbaldehyde (970 mg, 4 mmol) in a 1:1 mixture of acetonitrile (20 ml) and water (20 ml) was added sodium dihydrogen phosphate \( \text{NaH}_{2}\text{PO}_{4} \) (720 mg, 1.3 eq.), followed by sodium chlorite \( \text{NaClO}_{2} \) (80%, 1.1 g, 3 eq.). The mixture was stirred for 3 hrs and evaporated to dryness under reduced pressure. The solid residue was triturated with methanol and filtered. The filtrate was evaporated to dryness to give 725 mg of product in 70% yield. The \(^1\text{H}-\text{NMR} \) indicated pure product which used in the next step without purification.

\(^1\text{H} \text{ NMR} \) (400 MHz, DMSO-\( \text{d}_6 \)): \( \delta \) [ppm] 8.37 (d, 1H), 7.52 (m, 3H), 7.43 (m, 3H), 5.37 (s, 2H), 3.83 (s, 3H).

Example 12

4-Benzylxoy-3-methoxy-5-brobo-pyridine-2-carboxylic acid.
The compound was prepared in a similar manner using the procedure described above.

$^1$H NMR (400 MHz, CDCl$_3$): δ [ppm] 8.43 (s, 1H), 7.50 (m, 2H), 7.40 (m, 3H), 5.34 (s, 2H), 4.01(s, 3H).

**Example 13**

[2-(tert-Butyl-dimethyl-silyloxy-ethyl)-(4-fluoro-benzyl)-amine]

To a solution of (tert-butyl-dimethyl-silyloxy)-acetaldehyde (90%, 195mg, 1 mmol) and 4-fluorobenzylamine (137 mg, 1.1eq.) in 1,2-dichloroethane (15 ml) was added sodium triacetoxyborohydride (300 mg, 1.4eq.) under stirring. The solution became cloudy and stirring was continued at rt for overnight. The reaction mixture was then poured in saturated NaHCO$_3$ solution and the product was extracted with methylene chloride, dried over Na$_2$SO$_4$ and evaporated. The residue was purified on silica gel using hexane:EtOAc 7:3 as eluent to give 240 mg of product in 85% yield.

$^1$H NMR (400 MHz, CDCl$_3$): δ [ppm] 7.25 (m, 2H), 6.95 (m, 2H), 3.75 (s, 3H), 3.70 (tt, 2H), 2.67 (tt, 2H).
Example 14

4-Benzyloxy-3-methoxy-pyridine-2-carboxylic acid [2-5 (tert-butyl-dimethyl-silanyloxy)-ethyl]-(4-fluoro-benzyl)-amide.

To a solution of 4-benzyloxy-3-methoxy-pyridine-2-carboxylic acid (259 mg, 1mmol) in anhydrous DMF (5 ml) were added N,N-diisopropylethylamine (260 µl, 1.5eq.) and [2-(tert-Butyl-dimethyl-silanyloxy-ethyl]-(4-fluoro-benzyl)-amine (312 mg, 1.1eq). The mixture was stirred for 5 min. and O-(7-azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluoro-phosphate (HATU, 418 mg, 1.1eq.) was added. The mixture was stirred at rt for overnight and DMF was removed under reduced pressure. The residue was dissolved in methylene chloride (50 ml), washed with water (2x20 ml), brine and dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified on silica gel using hexane-EtOAc 9:1, 4:1, 7:3, 3:2, 1:1 and 2:3 each 50 ml as eluent. It gave 242 mg of pure product in 46% yield. The ¹H-NMR indicated the presence of two rotamers in a 45:55 ratio.

¹H NMR (400 MHz, CDCl₃): δ [ppm] 8.28 (t) 7.5 (m), 7.35 (m), 7.08 (m), 6.95 (m), 5.27 (s), 5.24 (s), 4.95(s),
4.52 (s), 4.03 (s), 4.00 (s), 3.93 (t), 3.70 (t), 3.58 (t), 3.22 (t), 0.98 (s), 0.88 (s), 0.15 (s), 0.00 (s).

**Example 15**

4-Benzylxoy-3-methoxy-5-bromo-pyridine-2-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-[4-fluoro-benzyl]-amide.

The compound was prepared starting from 4-benzylxoy-3-methoxy-5-bromo-pyridine-2-carboxylic acid in a similar manner using the procedure described above.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ [ppm] 8.45 (s), 8.40 (s), 7.5 (m), 7.35 (m), 7.08 (m), 6.95 (m), 5.27 (s), 5.24 (s), 4.95(s), 4.52 (s), 4.03 (s), 4.00(s), 3.93 (t), 3.70 (t), 3.58 (t), 3.22 (t), 0.98 (s), 0.88 (s), 0.15 (s), 0.00 (s).

**Example 16**

3-Benzylxoy-4-methoxy-6-bromo-pyridine-2-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-[4-fluoro-benzyl]-amide.
The compound was prepared starting from 3-benzylxoy-4-methoxy-6-bromo-pyridine-2-carboxylic acid (WO0105769) in a similar manner using the procedure described above.

$^1$H NMR (400 MHz, CDCl$_3$): δ [ppm] 7.5 (m), 7.30 (m), 7.10 (s), 7.06 (s), 6.95 (m), 6.82 (m), 5.15 (s), 5.11 (s), 4.85(s), 4.42 (s), 4.00 (s), 3.98(s), 3.83 (t), 3.70 (t), 3.50 (t), 3.12 (t), 0.98 (s), 0.88 (s), 0.15 (s), 0.00 (s).

**Example 17**

4-Benzylxoy-3-methoxy-pyridine-2-carboxylic acid (4-fluoro-benzyl)-(2-hydroxy-ethyl)-amide.

To a solution of 4-benzylxoy-3-methoxy-pyridine-2-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-(4-fluoro-benzyl)-amide (240 mg, 0.46 mmol) in THF (5ml) was added a THF solution of tetrabutylammonium fluoride (TBAF, 1M, 0.5ml, 1.1eq.).
The mixture was stirred at rt for 3 hrs and solvent was removed under reduced pressure. The residue was dissolved in methylene chloride (50 ml), washed with water (3x20ml), brine and dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified on silica gel using CH₂Cl₂:MeOH 95:5, 9:1 as eluent to give 180 mg of desired product in 96% yield. The ¹H-NMR indicated the presence of two rotamers in a 35:65 ratio.

¹H NMR (400 MHz, CDCl₃): δ [ppm] 8.20 (d), 8.16 (d), 7.45 (m), 7.35 (m), 7.27 (m), 7.03 (m), 6.95 (m), 5.2 (s), 5.17 (s), 4.80 (bs), 3.97 (s), 3.95 (s), 3.80 (t), 3.67 (t), 3.55 (t), 3.25 (t).

Example 18

4-Benzylolxy-3-methoxy-5-bromo-pyridine-2-carboxylic acid (4-fluoro-benzyl)-(2-hydroxy-ethyl)-amide.

![Chemical Structure](image)

The compound was prepared starting from 4-benzyloxy-3-methoxy-5-bromo-pyridine-2-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-(4-fluoro-benzyl)-amide in a similar manner using the procedure described above.
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ [ppm] 8.40 (s), 7.5 (m), 7.35 (m), 7.08 (m), 6.95 (m), 5.27 (s), 4.80 (s), 4.30 (s), 3.97 (s), 3.80 (t), 3.65 (t), 3.58 (t), 3.22 (t).

**Example 19**

3-Benzyloxy-4-methoxy-6-bromo-pyridine-2-carboxylic acid (4-fluoro-benzyl)-(2-hydroxy-ethyl)-amide.

![Chemical Structure]

The compound was prepared starting from 3-benzyloxy-4-methoxy-6-bromo-pyridine-2-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-4-fluoro-benzyl)-amide in a similar manner using the procedure described above.

$^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ [ppm] 7.45 (m), 7.40 (m), 7.13 (m), 7.05 (m), 5.07 (s), 4.78 (s), 4.33 (s), 4.03 (s), 4.00 (s), 3.50 (t), 3.40 (t), 3.38 (t), 3.02 (t).

**Example 20**

2-(4-Fluoro-benzyl)-9-hydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione.
To a suspension of polystyryldiphenylphosphine (1 mmol/g, 634 mg, 1.3 eq) in methylene chloride (10 ml) were added imidazole (43 mg, 1.3 eq) and iodine (161 mg, 1.3eq.). The mixture was stirred for 5 min. and a solution of 4-benzyloxy-3-methoxy-pyridine-2-carboxylic acid (4-fluoro-benzyl)-(2-hydroxy-ethyl)-amide (200 mg, 0.48 mmol) in methylene chloride (5 ml) was added. The reaction mixture was stirred at rt for overnight, filtered and the residue was washed with methylene chloride (20 ml). The combined methylene chloride solution was washed with 5% sodium thiosulfate solution, water, brine and dried over Na₂SO₄. The solvent was removed under reduced pressure to give 189 mg of a foam residue. The ¹H-NMR indicated that the residue is a quaternary cyclic product.

¹H NMR (400 MHz, CDCl₃): 8 [ppm] 9.40 (d, 1H), 7.93 (d, 1H), 7.45 (m, 2H), 7.40 (m, 3H), 7.33 (m, 2H), 7.03 (m, 2H), 5.50 (s, 2H), 5.03 (m, 2H), 4.73 (s, 2H), 4.07 (s, 3H), 3.87 (m, 2H).

The above residue was dissolved in HBr-AcOH solution (38%, 5 ml). The mixture was heated at 100°C for overnight and cooled to rt. A precipitate was formed and collected by filtration giving 80 mg of desired product as a white solid.
^2^H NMR (400 MHz, DMSO-d$_6$): δ [ppm] 8.20 (d, 1H), 7.45 (m, 2H), 7.24 (m, 2H), 7.13 (d, 1H), 4.75 (s, 2H), 4.53 (m, 2H), 3.80 (m, 2H).

Example 21

7-Bromo-2-(4-fluoro-benzyl)-9-methoxy-3,4-dihydro-2H-pyrido[1,2]pyrazine-1,8-dione.

To a suspension of polystyryldiphenylphosphine (1 mmol/g, 722 mg, 1.3eq) in methylene chloride (15 ml) were added imidazole (50 mg, 1.3eq) and iodine (183 mg, 1.3eq.). The mixture was stirred for 5 min. and a solution of 4-benzyloxy-3-methoxy-5-bromo-pyridine-2-carboxylic acid (4-fluoro-benzyl)-(2-hydroxy-ethyl)-amide (250 mg, 0.51 mmol) in methylene chloride (5 ml) was added. The reaction mixture was stirred at rt for overnight, filtered and the residue was washed with methylene chloride (20 ml). The combined methylene chloride solution was washed with 5% sodium thiosulfate solution, water, and brine and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure and the residue was purified on silica gel using CH$_2$Cl$_2$:MeOH 95:5 as eluent to give 140 mg of a solid product in 72% yield. The ^2^H-NMR indicated the cyclic product.
Example 22

7-Bromo-2-(4-fluoro-benzyl)-9-hydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione.

\[ \text{Br} \]
\[ \text{O} \]
\[ \text{HO} \]
\[ \text{Br} \]
\[ \text{O} \]
\[ \text{Br} \]
\[ \text{F} \]

7-Bromo-2-(4-fluoro-benzyl)-9-methoxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione (37 mg) was dissolved in HBr-ACOH solution (38%, 2 ml) and heated at 100°C for 3 hrs. After cooling to rt the mixture was evaporated to dryness. The residue was titrated with methylene chloride and filtered to give 15 mg of desired product as a white solid.

\[ \text{H NMR (400 MHz, DMSO-d}_6\text{): } \delta \text{ [ppm]} \]
\[ 8.20 \text{ (s, 1H) }, \]
\[ 7.40 \text{ (m, 2H) }, \]
\[ 7.20 \text{ (m, 2H) }, \]
\[ 4.63 \text{ (s, 2H) }, \]
\[ 4.20 \text{ (m, 2H) }, \]
\[ 3.63 \text{ (m, 2H) }. \]
Example 23

6-Bromo-2-(4-fluoro-benzyl)-9-hydroxy-3,4-dihydro-2H-
pyrido[1,2-a]pyrazine-1,8-dione.

![Chemical Structure]

3-Benzyl oxy-4-methoxy-6-bromo-pyridine-2-carboxylic acid (4-fluoro-benzyl)-(2-hydroxy-ethyl)-amide (35 mg) was dissolved in HBr-AcOH solution (38%, 2 mL) and heated at 100°C for overnight. After cooling to rt the mixture was evaporated to dryness. The residue was titurated with methylene chloride: MeOH and filtered to give 13 mg of a white solid. $^1$H-NMR spectrum indicated the desired cyclic product.

$^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ [ppm] 7.40 (m, 2H), 7.20 (m, 2H), 6.80 (s, 1H), 4.70 (s, 2H), 4.40 (m, 2H), 3.68 (m, 2H).

136
SUBSTITUTE SHEET (RULE 26)
Scheme 2

Example 24

3-Benzylxoy-6-(tert-butyl-dimethyl-silylloxy)methyl)-4-oxo-4H-pyran-2-carboxylic acid.

Starting from the known kojic acid, compound 3-benzylxoy-6-(tert-butyl-dimethyl-silylloxy)methyl)-4-oxo-4H-pyran-2-carbaldehyde was prepared using the procedure described in Kiyama, R. WO 03/016275 A1.
To a solution of this aldehyde (774 mg, 2.15 mmol) in acetonitrile/water (10 mL/10 mL) were added NaH₂PO₄ (516 mg, 4.3 mmol) and NaClO₂ (80%, 850 mg, 7.25 mmol). The reaction mixture was stirred at rt for 12 h. After removal of the solvent under reduced pressure, the residue was suspended into 30 mL of water and the pH was adjusted to 3. The mixture was extracted with methylene chloride (3 x 15 mL). The combined organic phases were washed with brine, dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure afforded a white solid of 730 mg, which was used in the next step without further purification.

**Example 25**

(2-((3-Benzyloxy-6-(tert-butyl-dimethyl-silanyloxymethyl)-4-oxo-4H-pyran-2-carbonyl)-(4-fluorobenzyl)-amino)-ethyl)-carbamic acid tert-butyl ester

![Chemical Structure](image)

To the solution of the above-mentioned acid (753 g, 2 mmol) in DMF (20 mL) were added (2-(4-fluorobenzylamino)-ethyl)-carbamic acid tert-butyl ester (644, 2.4 mmol), DIPEA (0.66 mL, 4 mmol), DCC (619 mg, 3 mmol), and HOBT.H₂O (405 mg, 3 mmol). The
reaction mixture was stirred at rt for 12 h. After removal of the solvent under reduced pressure, the residue was suspended into 50 mL of water and the mixture was extracted with chloroform (3 x 50 ml). The combined organic phases were washed with brine, dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure gave a residue, which was purified using silica gel chromatography with hexane and ethyl acetate (4:1) to provide the title compound as a white solid in the form of two rotamers (610 mg).

**Example 26**

\[
(2-((3-Benzzyloxy-6-(tert-butyl-dimethyl-silanyloxy)methyl)-4-oxo-4H-pyran-2-carbonyl)-amino)-ethyl)-carbamic acid tert-butyl ester
\]

![Chemical Structure](image)

This compound was prepared starting from 3-Benzzyloxy-6-(tert-butyl-dimethyl-silanyloxy)methyl)-4-oxo-4H-pyran-2-carboxylic acid in a similar manner using the procedure described above.

\[^1\text{H} \text{NMR (400 MHz, CDCl}_3\text{): } \delta \text{ [ppm]} 7.81 \text{ (bs, 1H ), 7.19 (m, 5H), 6.48 (s, 1H), 5.27 (s, 2H), 4.56(bs, 1H), 4.45}]

SUBSTITUTE SHEET (RULE 26)
(s, 2H), 3.22 (m, 2H), 3.15 (m, 2H), 1.33 (s, 9H), 0.82 (s, 9H), 0.00 (s, 6H).

**Example 27**

9-Benzylxoy-2-(4-fluoro-benzyl)-6-hydroxymethyl-3,4-dihydro-2H-pyrido(1,2-a)pyrazine-1,8-dione

![Chemical Structure](image)

The above-mentioned rotameric mixture of (2-{(3-Benzyloxy-6-(tert-butyl-dimethyl-silyloxymethyl)-4-oxo-4H-pyran-2-carbonyl)-(4-fluoro-benzyl)-amino)-ethyl}-carbamic acid tert-butyl ester (50 mg) was added to a solution of ethyl acetate saturated with HCl (~3M). The mixture was stirred at rt for 1h. Slowly the solution became cloudy when the reaction proceeded. Then the solvent was evaporated under reduced pressure to provide a yellowish solid. NMR showed that both TBDMS and Boc protective groups were removed. The mixture was used directly in the next step without purification.

The mixture was then dissolved into methanol (5 ml) and the solution was neutralized with N,N'-diisopropylethyl amine (DIPEA). The mixture was heated to 70°C for 2 h. After removal of the solvent under reduced pressure, the residue was purified on a silica gel column using
5% methanol in dichloromethane to give a white solid (20 mg).

¹H NMR (400 MHz, CD₃OD): δ [ppm] 7.45 (m, 2H), 7.36 (m, 2H), 7.27 (m, 3H), 7.08 (m, 2H), 6.67 (s, 1H), 5.18 (s, 2H), 4.66 (s, 2H), 4.53 (s, 2H), 4.13 (m, 2H), 3.47 (m, 2H).

**Example 28**

2-(4-Fluoro-benzyl)-9-hydroxy-6-hydroxymethyl-3,4-dihydro-2H-pyrido(1,2-a)pyrazine-1,8-dione

![Chemical Structure Image]

To a solution of 9-benzyloxy-2-(4-fluoro-benzyl)-6-hydroxymethyl-3,4-dihydro-2H-pyrido(1,2-a)pyrazine-1,8-dione (20 mg) in methanol (5 ml) was added 10% Pd-C (5 mg). The hydrogenation reaction was run at rt for 1h. To the suspension was added one drop of diluted HCl to dissolve the precipitate and the mixture was filtered. The filtrate was concentrated to dryness under reduced pressure to afford a yellowish solid (10 mg).

¹H NMR (400 MHz, CD₃OD): δ [ppm] 7.45 (m, 2H), 7.10 (m, 3H), 4.80 - 4.60 (m, 6H), 3.84 (m, 2H).

**Example 29**

**SUBSTITUTE SHEET (RULE 26)**
9-Hydroxy-6-hydroxymethyl-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione

The compound was prepared starting from (2-((3-Benzzyloxy-6-(tert-butyl-dimethyl-silyloxy)methyl)-4-oxo-4H-pyran-2-carbonyl)-amino)-ethyl)-carbamic acid tert-butyl ester in a similar manner using the procedure described above.

$^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ [ppm] 10.72 (bs, 1H), 6.13 (s, 1H), 5.54 (bs, 1H), 4.23 (s, 2H), 3.46 (m, 2H), 3.34 (m, 2H).

LC/MS: m/z 210.19 (M + H$^+$).

Compounds 6-16 can be prepared by Scheme 3

Scheme 3:
Compounds 17-25 can be made by Scheme 4

Scheme 4:

Example 30

6-Cyclohexylmethoxy-2-(4-fluoro-benzyl)-9-hydroxy-3,4-dihydro-2H-pyrido[1,2-a] pyrazine-1,8-dione
Step 1
To a solution of 9-benzyloxy-6-bromo-2-(4-fluorobenzyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione (100 mg, 0.22 mmol) in DMF (3 mL) were added cesium carbonate (181 mg, 0.56 mmol) and cyclohexanemethylmethanol (135 µL, 1.1 mmol) in a sealed tube. The mixture was stirred at 60 °C for 24 h. After removal of the solvent under reduced pressure, the residue was dissolved into water (10 mL) and extracted with dichloromethane (3 x 10 mL); the combined organic layers were dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure provided a residue which was purified by preparative silica gel TLC eluting with 5% methanol in dichloromethane to afford 9-benzyloxy-6-cyclohexylmethoxy-2-(4-fluorobenzyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione as a white solid (73 mg).

Step 2
The product from step 1 (73 mg) was dissolved into a mixture of 10 ml of methanol and 10 ml of ethyl
acetate. To the solution was added 7 mg of 10% Pd/C and the mixture was stirred was stirred under hydrogen at atmospheric pressure. After stirring for 1 h at rt, the mixture was filtered to remove the catalyst. The filtrate was concentrated to dryness under reduced pressure to afford 6-cyclohexylmethoxy-2-(4-fluorobenzyl)-9-hydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione as a white solid (60 mg).

Example 31

2-(4-Fluoro-benzyl)-9-hydroxy-6-phenoxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione

Step 1

To a solution of 9-benzyloxy-6-bromo-2-(4-fluoro-benzyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione (140 mg, 0.31 mmol) in DMF (3 mL) were added cesium carbonate (204 mg, 0.62 mmol), and phenol (59 mg, 0.62 mmol) in a sealed tube. The mixture was stirred at 50 °C for 12 h. After removal of the solvent under reduced pressure, the residue was taken into water (10 mL) and extracted with dichloromethane (3 x 10 mL); the
combined organic layers were dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure provided a residue which was purified by silica gel chromatography eluting with 3% methanol in dichloromethane to afford 9-benzyloxy-2-(4-fluoro-benzyl)-6-phenoxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione as a white solid (130 mg).

Step 2
The product (130 mg) from Step 1 was deprotected by hydrogenolysis as described for Example XXX to provide 2-(4-fluoro-benzyl)-9-hydroxy-6-phenoxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione (105 mg) as a white solid.

Example 32

7-Fluoro-2-(4-fluoro-benzyl)-9-hydroxy-6-methoxy-3,4-dihydro-2H-pyrido[1,2-a] pyrazine-1,8-dione

![Chemical structure diagram]
Step 1
To a solution of 9-benzyloxy-2-(4-fluoro-benzyl)-6-methoxy-3,4-dihydro-2H-quinolizine-1,8-dione (127 mg, 0.31 mmol) in acetonitrile (3 ml) were added cesium carbonate (201 mg, 0.62 mmol) and Selectfluor® (219 mg, 0.62 mmol). The mixture was stirred at rt for 6 h. After removal of the solvent under reduced pressure, the residue was taken into water (10 mL) and extracted with dichloromethane (3 x 10 mL); the combined organic layers were dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure provided a residue which was purified on preparative silica gel TLC using 5% methanol in dichloromethane to afford 9-benzyloxy-7-fluoro-2-(4-fluoro-benzyl)-6-methoxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione as a white solid (43 mg).

Step 2
The product (44 mg) from Step 1 was deprotected by hydrogenolysis as described for Example XXX to provide 7-fluoro-2-(4-fluoro-benzyl)-9-hydroxy-6-methoxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione as a white solid (36 mg).
Example 33

9-Benzzyloxy-6-cyclopropylmethoxy-2-(4-fluoro-benzyl)-3,4-dihydro-2H-pyrido[1,2-a] pyrazine-1,8-dione

Step 1
To a solution of 9-benzzyloxy-6-bromo-2-(4-fluoro-benzyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione (150 mg, 0.33 mmol) in cyclopropylmethanol (5 ml) was added cesium carbonate (217 mg, 0.66 mmol) in a sealed tube. After stirred at rt for 12 h, the reaction mixture was filtered and the solid was further washed with dichloromethane. The filtrate was concentrated to dryness under reduced pressure and the residue was purified by silica gel chromatography using 4% methanol in dichloromethane to provide the title compound 9-benzzyloxy-6-cyclopropylmethoxy-2-(4-fluoro-benzyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione as a white solid (138 mg).

Step 2
The product (148 mg) from Step 1 was deprotected by hydrogenolysis as described for Example XXX to provide 9-benzyloxy-6-cyclopropylmethoxy-2-(4-fluoro-benzyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione as a white solid (110 mg).

Example 34
HIV Integrase Strand Transfer inhibition assay

Example 35
Anti-HIV-1 replication Assay in H9 cells for anti-HIV-1 integrase compounds.

The anti-HIV-1 activities of the compounds were tested by employing HIV-1IIIIB in H9 cells. The prepared cells were suspended at 5X106/ml in complete medium (RPML 1640, 10%FBS, 2mM glutamine, 100 units penicillin/ml, 100 µg streptomycin/ml), incubated with virus at a multiplicity of infection of 0.1 for 2h in an atmosphere of 5% CO2 and 37°C. The infected cells were washed twice with PBS to remove residual virus and cultured at presence of inhibitors at serial concentrations for 7-8 days. The anti-HIV-1 efficacy was determined by testing for HIV-1 RT activity in the cell culture supernatants. All assays were performed in duplicate with Merck compound L-731988 and Shionogi
compound S-1360 as control. The 50% effective concentrations (IC50s) were calculated from the linear portion of the dose-response curve.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention and, without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.
We Claim:

1. A compound according to Formula I:

\[
\begin{align*}
\text{I}
\end{align*}
\]

wherein

A is a single or double bond, and when A is a double bond \( R_2 \) or \( R_2' \) and \( R_3 \) or \( R_3' \) are absent;

\( R_1 \) is \( \text{H}, \text{OH}, \) optionally substituted \( C_{6-10} \) aryl, optionally substituted 5-10 member heteroaryl, optionally substituted 4-10 member heterocycle, or \( C_{1-10} \) alkyl optionally substituted with one or more substituents selected from optionally substituted \( C_{3-10} \) cycloalkyl, optionally substituted \( C_{6-10} \) aryl, optionally substituted 5-10 member heteroaryl, or optionally substituted 4-10 member heterocycle;

\( R_2, R_2', R_3 \) and \( R_3' \) are each, independently, hydrogen, optionally substituted \( C_{1-10} \) alkyl, optionally substituted \( C_{3-10} \) cycloalkyl, optionally substituted \( C_{6-10} \) aryl, optionally substituted 5-10 member heteroaryl, optionally substituted 4-10 member heterocycle, \( \text{COOR}_6, \text{CONR}_7R_7' \), or \( \text{CR}_6=\text{NOR}_6' \);
R₂ or R₂' can also be taken together with R₃ or R₃', and the atoms to which they are attached, to form an optionally substituted C₃-10 cycloalkyl, an optionally substituted 4-10 member heterocycle, an optionally substituted C₆-10 aryl or an optionally substituted 5-10 member heteroaryl;

R₂ and R₂' or R₃ and R₃' can also be joined together, with the atoms to which they are attached, to form an optionally substituted C₃-10 cycloalkyl or an optionally substituted 5-10 member heterocycle;

R₂ and R₂' or R₃ and R₃' can also be joined together to form a carbonyl (C=O);

R₄ is optionally substituted C₁-10 alkoxy, optionally substituted C₆-10 aryloxy, or optionally substituted C₆aryl-C₁-10 alkoxy;

n is 0, 1, or 2;

R₅ is hydrogen, halogen, OH, CN, azido, NO₂, COOR₆, C₁-10 alkyl, amino, amido, sulfonamido, urea, guanidino, amidino, SO₅R₆, OCONR₇R₇', NR₅SO₂NR₇R₇', NR₅COOR₇, CR₅=NOR₇', C₁-10 alkoxy, optionally substituted C₆-10 aryl, optionally substituted 5-10 member heterocycle, or optionally substituted 5-10 member heteroaryl;
$R_6$, $R_7$, $R'_7$ are each independently hydrogen, optionally substituted $C_{1-10}$ alkyl, optionally substituted $C_{6-10}$ aryl, or optionally substituted $C_{7-12}$ aralkyl;

$R_6$ can also be taken together with $R_7$ or $R'_7$, with the atoms to which they are attached, to form a 5-10 member heterocycle; and

$R_7$ and $R'_7$ can be taken together, with the atom to which they are attached, to form a 4-10 member heterocycle;

or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable solvate thereof, or a solvate of a pharmaceutically acceptable salt thereof, wherein alkyl groups can optionally contain one or more double bonds or triple bonds in their chain, and

optionally substituted means that the radical can be unsubstituted or substituted by one or more substituents selected from:

halogen,
amino,
amidino,
amido,
azido,
cyano,
guanidino,
hydroxyl,
nitro,
nitroso,
urea,
S(O)\textsubscript{0-2}Ra wherein R\textsubscript{a} is H, C\textsubscript{1-10} alkyl, C\textsubscript{6-10} aryl or 3-10 member heterocycle,
5 C\textsubscript{1-10} alkyl,
C\textsubscript{7-12} aralkyl,
C\textsubscript{6-10} aryl,
5-10 member heteroaryl,
C\textsubscript{1-10} alkoxy,
10 C\textsubscript{6-10} aryl-C\textsubscript{1-10} alkoxy,
C\textsubscript{6-10} arlyloxy,
3-10 member heterocycle,
C(O)R\textsubscript{b} wherein R\textsubscript{b} is H, C\textsubscript{1-10} alkyl, C\textsubscript{6-10} aryl, C\textsubscript{7-12} aralkyl or 3-10 member heterocycle,
15 C(O)OR\textsubscript{b} wherein R\textsubscript{b} is H, C\textsubscript{1-10} alkyl, C\textsubscript{6-10} aryl, C\textsubscript{7-12} aralkyl or 3-10 member heterocycle,
NR\textsubscript{b}C(O)R_'b wherein R\textsubscript{b} and R_'b are each independently H, C\textsubscript{1-10} alkyl, C\textsubscript{6-10} aryl, C\textsubscript{7-12} aralkyl or 3-10 member heterocycle, or R\textsubscript{b} and R_'b are taken together with the atoms to which they are attached to form a 5-10 member heterocycle,
20 SO\textsubscript{2}NR\textsubscript{b}R_'b wherein R\textsubscript{b} and R_'b are each independently H, C\textsubscript{1-10} alkyl, C\textsubscript{6-10} aryl, C\textsubscript{7-12} aralkyl or 3-10 member heterocycle, or R\textsubscript{b} and R_'b are taken together with the atoms to which they are attached to form a 5-10 member heterocycle,
NR\textsubscript{b}SO\textsubscript{2}R_'b wherein R\textsubscript{b} and R_'b are each independently H, C\textsubscript{1-10} alkyl, C\textsubscript{6-10} aryl, C\textsubscript{7-12} aralkyl or 3-10 member heterocycle, or R\textsubscript{b} and R_'b are taken together with the atoms to which they are attached to form a 5-10 member heterocycle,
NR_{b}SO_{2}NR'_{b}R_{c} wherein R_{b}, R'_{b} and R_{c} are each independently H, C_{1-10} alkyl, C_{6-10} aryl, C_{7-12} aralkyl or 3-10 member heterocycle, or R'_{b} and R_{c} are taken together with the atoms to which they are attached to form a 5-10 member heterocycle,

CR_{b}N=OR'_{b} wherein R_{b} and R'_{b} are each independently H, C_{1-10} alkyl, C_{6-10} aryl, 3-10 member heterocycle or C_{7-12} aralkyl, and

NR_{b}COOR'_{b} wherein R_{b} and R'_{b} are each independently H, C_{1-10} alkyl, C_{6-10} aryl, C_{7-12} aralkyl or 3-10 member heterocycle.

2. A compound according to claim 1, wherein R_{1} is hydrogen.

3. A compound according to claim 1, wherein R_{1} is hydroxy.

4. A compound according to claim 1, wherein R_{1} is C_{1-4} alkyl substituted by an optionally substituted aryl group.

5. A compound according to claim 1, wherein R_{1} is (CH_{2})_{1-4} phenyl where phenyl is unsubstituted or substituted with one or more substituents independently selected from: halogen, amino, amidino, amido, azido.
cyano,
guanidino,
hydroxyl,
nitro,
5 nitroso,
urea,
$S(\text{O})_{\text{0-2}}R_\text{a}$ (wherein $R_\text{a}$ is $H$, $C_{1-10}$ alkyl, $C_{6-10}$ aryl or 3-10 member heterocycle),
$C_{1-10}$alkyl,
10 $C_{7-10}$ aralkyl,
$C_{6-10}$ aryl,
5-10 member heteroaryl
$C_{1-10}$alkoxy,
$C_{6-10}$aryl-$C_{1-10}$alkyloxy,
15 $C_{6-10}$ arlyloxy,
3-10 member heterocycle,
$C(\text{O})R_\text{b}$ wherein $R_\text{b}$ is $H$, $C_{1-10}$ alkyl, $C_{6-10}$ aryl, $C_{7-12}$ aralkyl or 3-10 member heterocycle,
$C(\text{O})\text{OR}_\text{b}$ wherein $R_\text{b}$ is $H$, $C_{1-10}$ alkyl, $C_{6-10}$ aryl, $C_{7-12}$ aralkyl or 3-10 member heterocycle,
20 aralkyl—or 3-10 member heterocycle,
$N_{R_\text{b}}C(\text{O})R_\text{b}'$ wherein $R_\text{b}$ and $R_\text{b}'$ are each independently $H$, $C_{1-10}$ alkyl, $C_{6-10}$ aryl, $C_{7-12}$ aralkyl or 3-10 member heterocycle, or $R_\text{b}$ and $R_\text{b}'$ are taken together with the atoms to which they are attached to form a 5-10 member heterocycle,
$SO_{2}NR_{b}R_{b}'$ wherein $R_{b}$ and $R_{b}'$ are each independently $H$, $C_{1-10}$ alkyl, $C_{6-10}$ aryl, $C_{7-12}$ aralkyl or 3-10 member heterocycle, or $R_{b}$ and $R_{b}'$ are taken together with the atoms to which they are attached to form a 5-10 member heterocycle,
NR₆SO₂R₆' wherein R₆ and R₆' are each independently H, C₁₋₁₀ alkyl, C₆₋₁₀ aryl, C₇₋₁₂ aralkyl or 3₋₁₀ member heterocycle, or R₆ and R₆' are taken together with the atoms to which they are attached to form a 5₋₁₀ member heterocycle,
NR₆SO₂NR₆'R₆ wherein R₆, R₆' and R₆ are each independently H, C₁₋₁₀ alkyl, C₆₋₁₀ aryl, C₇₋₁₂ aralkyl or 3₋₁₀ member heterocycle, or R₆' and R₆ are taken together with the atoms to which they are attached to form a 5₋₁₀ member heterocycle,
CR₆N=OR₆' wherein R₆ and R₆' are each independently H, C₁₋₁₀ alkyl, C₆₋₁₀ aryl, C₇₋₁₂ aralkyl or 3₋₁₀ member heterocycle, and
NR₆COO R₆' (wherein R₆ and R₆' are each independently H, C₁₋₁₀ alkyl, C₆₋₁₀ aryl, C₇₋₁₂ aralkyl or 3₋₁₀ member heterocycle.

6. A compound according to claim 1, wherein R₁ is (CH₂)₁₋₄phenyl where phenyl is unsubstituted or substituted with one or more substituents independently selected from:
halogen,
aminos,
amido,
cyano,
hydroxyl,
urea,
OC₁₋₁₀ alkyl,
S(O)₀₋₂R₄ (wherein R₄ is H, C₁₋₁₀ alkyl, C₆₋₁₀ aryl or 3₋₁₀ member heterocycle),
C₁₋₁₀ alkyl,
C_{5-10} aryl,
5-10 member heteroaryl
3-10 member heterocycle,
C(O)OR\_b wherein R\_b is H, C\_1-10 alkyl, C\_7-12 aralkyl or 3-10
member heterocycle,
NR\_bC(O)R\_b' wherein R\_b and R\_b' are each independently H, 
C\_1-10 alkyl, C\_7-12 aralkyl or 3-10 member heterocycle, or 
R\_b and R\_b' are taken together with the atoms to which 
you are attached to form a 5-10 member heterocycle,
NR\_bSO\_2R\_b' wherein R\_b and R\_b' are each independently H, 
C\_1-10 alkyl, C\_7-12 aralkyl or 3-10 member heterocycle, or 
R\_b and R\_b' are taken together with the atoms to which 
you are attached to form a 5-10 member heterocycle,
CR\_bN=OR\_b wherein R\_b and R\_b' are each independently H, 
C\_1-10 alkyl, C\_6-10 aryl, C\_7-12 aralkyl or 3-10 member 
heterocycle, and
NR\_bCOOR\_b' wherein R\_b and R\_b' are each independently H, 
C\_1-10 alkyl, C\_6-10 aryl, C\_7-12 aralkyl or 3-10 member 
heterocycle.

7. A compound according to claim 1, wherein R\_1 
is (CH\_2)\_1-4-phenyl where phenyl is substituted with one 
or more substituents independently selected from:
fluoro, bromo, chloro, CONHCH\_3, CON(CH\_3)\_2, CF\_3, NHCOCH\_3,
NHCONHCH\_3, and SO\_2NHCH\_3.

8. A compound according to claim 1, wherein R\_1 
is CH\_2(4-fluorophenyl).

9. A compound according to claim 1, wherein R\_2 
and R\_2' are each independently selected from:
H,

optionally substituted phenyl,
optionally substituted C_{1-6}alkyl,
COOC_{1-6}alkyl,
CONR_{7}R'_{7}, and
CR_{6}=NOR'_{6}.

10. A compound according to claim 1, wherein R_{2} and R'_{2} are each independently chosen from:

H;

unsubstituted phenyl or phenyl substituted by one or more substituents independently selected from halogens, hydroxy, -NH_{2}, -NHR_{d} and -NR_{d}R_{e}, -CONH_{2}, -CONHR_{d}, -CONR_{d}R_{e}, -NHCOR_{d}, -NR_{d}COR_{e}, carboxy, CF_{3}, NR_{d}COR_{e}, NR_{d}CONR_{d}R_{e}, and SO_{2}NR_{d}R_{e} wherein R_{d} and R_{e} are each independently selected from C_{1-10} alkyl;

unsubstituted C_{1-6}alkyl or C_{1-6}alkyl substituted by one or more substituents independently selected from halogens, hydroxy, -NH_{2}, -NHR_{d} and -NR_{d}R_{e}, wherein R_{d} and R_{e} are each independently selected from C_{1-10} alkyl, -CONH_{2}, -CONHR_{d}, -CONR_{d}R_{e}, -NHCOR_{d}, -NR_{d}COR_{e}, and carboxy, wherein R_{d} and R_{e} are each independently selected from C_{1-10} alkyl;

COOC_{1-6}alkyl;

CONR_{7}R'_{7}; and

CR_{6}=NOR'_{6}.
11. A compound according to claim 1, wherein R₂ and R'₂ are each independently chosen from:
H, phenyl, C₁₋₆alkyl, COOC₁₋₆alkyl, CONR₃R'₇, and
CR₆=NOR’₆.

12. A compound according to claim 1, wherein R₃ and R’₃ are each independently chosen from:
H,
optionally substituted phenyl,
optionally substituted C₁₋₆alkyl,
COOC₁₋₆alkyl,
CONR₃R’₇, and
CR₆=NOR’₆.

13. A compound according to claim 1, wherein R₃ and R’₃ are each independently chosen from:
H;
unsubstituted phenyl or phenyl substituted by one or more substituents independently selected from halogens, hydroxy, −NH₂, −NHRd and −NRdRₑ, −CONH₂, −CONHRd, −CONRdRₑ, −NHCORd, −NRdCORₑ, carboxy, CF₃, NRdCORₑ, NRdCONRdRₑ, and SO₂NRdRₑ wherein Rd and Rₑ are each independently selected from C₁₋₁₀ alkyl;
unsubstituted C₁₋₆alkyl or C₁₋₆alkyl substituted by one or more substituents independently selected from halogens, hydroxy, −NH₂, −NHRd and −NRdRₑ, wherein Rd and Rₑ are each independently selected from C₁₋₁₀ alkyl, −CONH₂, −CONHRd, −CONRdRₑ, −NHCORd, −NRdCORₑ, and carboxy,
wherein R₄ and R₆ are each independently selected from
C₁₋₁₀ alkyl;

COOC₁₋₆alkyl;

CONR₇R’₇; and

CR₆=NOR’₆.

14. A compound according to claim 1, wherein R₃
and R’₃ are each independently chosen from:
H, phenyl, C₁₋₆alkyl, COOC₁₋₆alkyl, CONR₇R’₇, and
CR₆=NOR’₆.

15. A compound according to claim 1, wherein R₄
is optionally substituted C₁₋₁₀ alkoxy.

16. A compound according to claim 1, wherein R₄
is optionally substituted C₁₋₆alkoxy.

17. A compound according to claim 1, wherein R₄
is optionally substituted C₆₋₁₀ aryloxy.

18. A compound according to claim 1, wherein R₄
is optionally substituted C₆aryl-C₁₋₁₀alkyloxy.

19. A compound according to claim 1, wherein R₄
is optionally halogenated C₁₋₁₀ alkoxy.

20. A compound according to claim 1, wherein R₄
is optionally halogenated C₆₋₁₀ aryloxy.
21. A compound according to claim 1, wherein $R_4$ is optionally halogenated C$_6$aryl-C$_{1-10}$alkyloxy.

22. A compound according to claim 1, wherein $R_5$ is halogen, amino, hydroxy, C$_{1-6}$ alkyl, 5-10 member heteroaryl, C$_{6-10}$ aryl, or CONR$_6$R'$_6$.

23. A compound according to claim 1, wherein:
A is a single bond; and
$R^4$ is C$_{1-10}$ alkoxy optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C$_{1-4}$-alkyl, CO-C$_{1-4}$-alkyl, NH$_2$, NHC$_{1-4}$-alkyl, or N(C$_{1-4}$-alkyl)$_2$,
phenoxo optionally substituted by F, Cl, Br, C$_{1-4}$-alkyl, cyano, hydroxy, carboxy, COO-C$_{1-4}$-alkyl, CO-C$_{1-4}$-alkyl, NH$_2$, NHC$_{1-4}$-alkyl, N(C$_{1-4}$-alkyl)$_2$, CONH$_2$,
CONHC$_{1-4}$-alkyl, or CON(C$_{1-4}$-alkyl)$_2$, or benzylxoy, phenethoxy, or phenpropxo, in each case optionally substituted by F, Cl, Br, C$_{1-4}$-alkyl, cyano, hydroxy, carboxy, COO-C$_{1-4}$-alkyl, CO-C$_{1-4}$-alkyl, NH$_2$, NHC$_{1-4}$-alkyl, N(C$_{1-4}$-alkyl)$_2$, CONH$_2$,
CONHC$_{1-4}$-alkyl, or CON(C$_{1-4}$-alkyl)$_2$.

24. A compound according to claim 1, wherein:
A is a single bond;
$R^2$, $R'^2$, $R^3$, and $R'^3$ are each H; and
R^4 is C_{1-10} alkoxy optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C_{1-4}-alkyl, CO-C_{1-4}-alkyl, NH_2, NHC_{1-4}-alkyl, or N(C_{1-4}-alkyl)_2,

phenoxycarbonyl optionally substituted by F, Cl, Br, C_{1-4}-alkyl, cyano, hydroxy, carboxy, COO-C_{1-4}-alkyl, CO-C_{1-4}-alkyl, NH_2, NHC_{1-4}-alkyl, N(C_{1-4}-alkyl)_2, CONH_2, CONHC_{1-4}-alkyl, or CON(C_{1-4}-alkyl)_2, or phenyl, phenoxy, or phenylpropoxy, in each case optionally substituted by F, Cl, Br, C_{1-4}-alkyl, cyano, hydroxy, carboxy, COO-C_{1-4}-alkyl, CO-C_{1-4}-alkyl, NH_2, NHC_{1-4}-alkyl, N(C_{1-4}-alkyl)_2, CONH_2, CONHC_{1-4}-alkyl, or CON(C_{1-4}-alkyl)_2.

25. A compound according to claim 1, wherein:
A is a single bond;
R^2, R^1^2, R^3, and R^3^ are each H;
R^4 is benzyl, phenethyl, phenpropyl, or naphthylmethyl, in each case optionally substituted by F, Cl, Br, C_{1-4}-alkyl, cyano, hydroxy, carboxy, COO-C_{1-4}-alkyl, CO-C_{1-4}-alkyl, NH_2, NHC_{1-4}-alkyl, N(C_{1-4}-alkyl)_2, CONH_2, CONHC_{1-4}-alkyl, or CON(C_{1-4}-alkyl)_2; and
R^4 is C_{1-10} alkoxy optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C_{1-4}-alkyl, CO-C_{1-4}-alkyl, NH_2, NHC_{1-4}-alkyl, or N(C_{1-4}-alkyl)_2,

phenoxycarbonyl optionally substituted by F, Cl, Br, C_{1-4}-alkyl, cyano, hydroxy, carboxy, COO-C_{1-4}-alkyl, CO-C_{1-4}-alkyl, NH_2, NHC_{1-4}-alkyl, N(C_{1-4}-alkyl)_2, CONH_2, CONHC_{1-4}-alkyl, or CON(C_{1-4}-alkyl)_2, or
benzyloxy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C1-4-alkyl, cyano, hydroxy, carboxy, COO-C1-4-alkyl, CO-C1-4-alkyl, NH2, NHC1-4-alkyl, N(C1-4-alkyl)2, CONH2, CONHC1-4-alkyl, or CON(C1-4-alkyl)2.

26. A compound according to claim 1, wherein:
A is a single bond;
R2, R'2, R3, and R'3 are each H;
R1 is benzyl optionally substituted by F, Cl, Br, C1-4-alkyl, cyano, hydroxy, carboxy, COO-C1-4-alkyl, CO-C1-4-alkyl, NH2, NHC1-4-alkyl, N(C1-4-alkyl)2, CONH2, CONHC1-4-alkyl, or CON(C1-4-alkyl)2; and
R4 is C1-10 alkoxy optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C1-4-alkyl, CO-C1-4-alkyl, NH2, NHC1-4-alkyl, N(C1-4-alkyl)2, phenoxy optionally substituted by F, Cl, Br, C1-4-alkyl, cyano, hydroxy, carboxy, COO-C1-4-alkyl, CO-C1-4-alkyl, NH2, NHC1-4-alkyl, N(C1-4-alkyl)2, CONH2, CONHC1-4-alkyl, or CON(C1-4-alkyl)2, or benzyloxy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C1-4-alkyl, cyano, hydroxy, carboxy, COO-C1-4-alkyl, CO-C1-4-alkyl, NH2, NHC1-4-alkyl, N(C1-4-alkyl)2, CONH2, CONHC1-4-alkyl, or CON(C1-4-alkyl)2.

27. A compound according to claim 1, wherein:
A is a single bond;
R2, R'2, R3, and R'3 are each H;
R⁵ is hydrogen, halogen, cyano, hydroxy, C₁₋₄-alkyl, hydroxyalkyl having 1 to 4 carbon atoms, C₂₋₄-alkenyl, COOH, COO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, or N(C₁₋₄-alkyl)₂; and

R⁴ is C₁₋₁₀ alkoxy optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, or N(C₁₋₄-alkyl)₂, phenoxy optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂, or benzyloxy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂.

28. A compound according to claim 1, wherein:

R², R'², R³, and R¹³ are each H;

R⁵ is hydrogen, halogen, cyano, hydroxy, C₁₋₄-alkyl, hydroxyalkyl having 1 to 4 carbon atoms, C₂₋₄-alkenyl, COOH, COO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, or N(C₁₋₄-alkyl)₂;

R¹ is benzyl, phenethyl, phenpropyl, or naphthylmethyl, in each case optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂; and
R⁴ is C₁⁻¹₀ alkoxy optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C₁⁻⁴-alkyl, CO-C₁⁻⁴-alkyl, NH₂, NHC₁⁻⁴-alkyl, or N(C₁⁻⁴-alkyl)₂,
phenoxy optionally substituted by F, Cl, Br, C₁⁻⁴-alkyl, cyano, hydroxy, carboxy, COO-C₁⁻⁴-alkyl, CO-C₁⁻⁴-alkyl, NH₂, NHC₁⁻⁴-alkyl, N(C₁⁻⁴-alkyl)₂, CONH₂,
CONHC₁⁻⁴-alkyl, or CON(C₁⁻⁴-alkyl)₂, or benzyl oxy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C₁⁻⁴-alkyl, cyano, hydroxy, carboxy, COO-C₁⁻⁴-alkyl, CO-C₁⁻⁴-alkyl, NH₂, NHC₁⁻⁴-alkyl, N(C₁⁻⁴-alkyl)₂, CONH₂,
CONHC₁⁻⁴-alkyl, or CON(C₁⁻⁴-alkyl)₂.

29. A compound according to claim 1, wherein:
A is a single bond;
R₂, R¹₂, R³, and R¹₃ are each H;
R⁵ is hydrogen; and
R⁴ is C₁⁻¹₀ alkoxy optionally substituted by F, Cl, Br,
methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C₁⁻⁴-alkyl, CO-C₁⁻⁴-alkyl, NH₂, NHC₁⁻⁴-alkyl, or N(C₁⁻⁴-alkyl)₂,
phenoxy optionally substituted by F, Cl, Br, C₁⁻⁴-alkyl, cyano, hydroxy, carboxy, COO-C₁⁻⁴-alkyl, CO-C₁⁻⁴-alkyl, NH₂, NHC₁⁻⁴-alkyl, N(C₁⁻⁴-alkyl)₂, CONH₂,
CONHC₁⁻⁴-alkyl, or CON(C₁⁻⁴-alkyl)₂, or benzyl oxy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C₁⁻⁴-alkyl, cyano, hydroxy, carboxy, COO-C₁⁻⁴-alkyl, CO-C₁⁻⁴-alkyl, NH₂, NHC₁⁻⁴-alkyl, N(C₁⁻⁴-alkyl)₂, CONH₂,
CONHC₁⁻⁴-alkyl, or CON(C₁⁻⁴-alkyl)₂.
30. A compound according to claim 1, wherein:
A is a single bond;
R², R¹², R³, and R¹³ are each H;
R⁵ is hydrogen;
R¹ is benzyl, phenethyl, phenpropyl, or naphthylmethyl,
in each case optionally substituted by F, Cl, Br, C₁₋₄-
alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-
alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-
alkyl, or CON(C₁₋₄-alkyl)₂; and
R⁴ is C₁₋₁₀ alkoxy optionally substituted by F, Cl, Br,
methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C₁₋₄-
alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, or N(C₁₋₄-
alkyl)₂,
phenoxy optionally substituted by F, Cl, Br, C₁₋₄-
alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-
C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂,
CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂, or
benzyloxy, phenethoxy, or phenpropoxy, in each

31. A compound according to claim 1, wherein:
A is a single bond;
R², R¹², R³, and R¹³ are each H;
R⁵ is hydrogen;
R¹ is benzyl optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂; and

R⁴ is C₁₋₁₀ alkoxy optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, or N(C₁₋₄-alkyl)₂,
phenoxy optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂, or benzyloxy, phenethoxy, or phenpropoxy, in each case optionally substituted by F, Cl, Br, C₁₋₄-alkyl, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, N(C₁₋₄-alkyl)₂, CONH₂, CONHC₁₋₄-alkyl, or CON(C₁₋₄-alkyl)₂.

32. A compound according to any one of claims 23 to 31, wherein R¹ is benzyl optionally substituted by F, Cl, or Br.

33. A compound according to any one of claims 23 to 32, wherein R⁴ is C₁₋₁₀ alkoxy optionally substituted by F, Cl, Br, methoxy, ethoxy, cyano, hydroxy, carboxy, COO-C₁₋₄-alkyl, CO-C₁₋₄-alkyl, NH₂, NHC₁₋₄-alkyl, or N(C₁₋₄-alkyl)₂.

34. A compound wherein said compound is selected from:
6-Bromo-2-(4-fluoro-benzyl)-9-hydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione;

6-(1,1-Dioxo-[1,2]thiazinan-2-yl)-2-(4-fluoro-benzyl)-9-hydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione;

2-(4-Fluoro-benzyl)-9-hydroxy-6-(tetrahydro-furan-2-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione;

2-(4-Fluoro-benzyl)-6-furan-2-yl-9-hydroxy-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione;

2-(4-Fluoro-benzyl)-9-hydroxy-6-thiazol-2-yl-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione;

2-(4-Fluoro-benzyl)-9-hydroxy-6-phenyl-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione;

2-(4-Fluoro-benzyl)-9-hydroxy-6-methanesulfonyl-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione;
35 6-AZIDO-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

36 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-PIPERIDIN-1-YL-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

37 6-CYCLOHEXYL-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

38 4-FLUORO-N-(4-FLUORO-BENZOYL)-N-[2-(4-FLUORO-BENZYL)-9-HYDROXY-1,8-DIOXO-1,3,4,8-TETRAHYDRO-2H-PYRIDO[1,2-A]PYRAZIN-6-YL]-BENZAMIDE;

39 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-MORPHOLIN-4-YL-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

40 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-PYRROLIDIN-1-YL-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

41 FURAN-2-CARBOXYLIC ACID [2-(4-FLUORO-BENZYL)-9-HYDROXY-1,8-DIOXO-1,3,4,8-TETRAHYDRO-2H-PYRIDO[1,2-A]PYRAZIN-6-YL]- (FURAN-2-CARBONYL)-AMIDE;
42 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-
(TETRAHYDRO-FURAN-3-YL)-3,4-DIHYDRO-2H-
PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

43 2-(4-FLUORO-BENZYL)-6-(4-FLUORO-
PHENYLAMINO)-9-HYDROXY-3,4-DIHYDRO-2H-
PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

44 6-DIMETHYLAMINO-2-(4-FLUORO-BENZYL)-9-
HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-
A]PYRAZINE-1,8-DIONE;

46 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-
[1,2,3]TRIAZOL-1-YL-3,4-DIHYDRO-2H-PYRIDO[1,2-
A]PYRAZINE-1,8-DIONE;

47 1-[2-(4-FLUORO-BENZYL)-9-HYDROXY-1,8-DIOXO-
1,3,4,8-TETRAHYDRO-2H-PYRIDO[1,2-A]PYRAZIN-
6-L]-1H-[1,2,3]TRIAZOLE-4-CARBOXYLIC ACID
METHYL ESTER;

and pharmaceutically acceptable salts thereof, 
pharmaceutically solvates thereof, and solvates of 
pharmaceutically acceptable salts thereof.

35. A compound wherein said compound is selected 
from:
45  2-(4-FLUORO-BENZYL)-9-HYDROXY-6-METHOXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

48  6-ETHOXY-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

49  2-(4-FLUORO-BENZYL)-9-HYDROXY-6-ISOPROPOXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

50  6-(2,2-DIFLUORO-ETHOXY)-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

51  2-(4-FLUORO-BENZYL)-9-HYDROXY-6-PROPANOXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

52  2-(4-FLUORO-BENZYL)-6-(2-FLUORO-ETHOXY)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

53  6-CYCLOPROPYLETHOXY-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;
6-CYCLOHEXYLMETHOXY-2-(4-FLUORO-
BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-
PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

2-(4-FLUORO-BENZYL)-9-HYDROXY-6-(2,2,2-
TRIFLUORO-ETHOXY)-3,4-DIHYDRO-2H-
PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

2-(4-FLUORO-BENZYL)-9-HYDROXY-6-(2-
MORPHOLIN-4-YL-ETHOXY)-3,4-DIHYDRO-2H-
PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

2-(4-FLUORO-BENZYL)-9-HYDROXY-6-
PHENOXY-3,4-DIHYDRO-2H-PYRIDO[1,2-
A]PYRAZINE-1,8-DIONE;

2-(4-FLUORO-BENZYL)-9-HYDROXY-6-
ISOBUTOXY-3,4-DIHYDRO-2H-PYRIDO[1,2-
A]PYRAZINE-1,8-DIONE;

2-(4-FLUORO-BENZYL)-6-(4-FLUORO-PHENOXY)-
9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-
A]PYRAZINE-1,8-DIONE;

2-(4-FLUORO-BENZYL)-9-HYDROXY-6-
(TETRAHYDRO-PYRAN-4-YLMETHOXY)-3,4-
DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-
DIONE;
61  7-FLUORO-2-(4-FLUORO-BENZYL)-9-HYDROXY-6-METHOXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

62  2-(4-FLUORO-BENZYL)-9-HYDROXY-6-(2-METHOXY-ETHOXY)-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

63  6-(2,2-DIMETHYL-[1,3]DIOX olan-4-YLMETHOXY)-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

64  6-(2-DIMETHYLAMINO-ETHOXY)-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

65  2-(4-FLUORO-BENZYL)-9-HYDROXY-6-(2-METHANESULFONYL-ETHOXY)-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

66  2-(4-FLUORO-BENZYL)-9-HYDROXY-6-[2-(4-METHOXY-PHENYL)-ETHOXY]-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

67  2-(4-FLUORO-BENZYL)-6-(3-FLUORO-PROPOXY)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;
68 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-(PYRIDIN-2-YLMETHOXY)-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

69 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-PHENETHYLOXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

70 6-{(1,3)DIOXOLAN-4-YLMETHOXY}-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

71 6-{(1,3)DIOXAN-5-YLOXY}-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

72 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-(2-PIPERIDIN-1-YL-ETHOXY)-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

73 6-CYCLOPENTYL METHOXY-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

74 6-CYCLOBUTYL METHOXY-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;
75 2-(2-(4-FLUORO-BENZYL)-9-HYDROXY-1,8-DIOXO-1,3,4,8- TETRAHYDRO-2H-PYRIDO[1,2-A]PYRAZIN-6-YLOXY)-N,N-DIMETHYL-ACETAMIDE

76 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-(PYRIDIN-3-YLOXY)-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

77 6-(2-CYCLOPROPYL-ETHOXY)-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

78 6-BROMO-2-(3,4-DICHLORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO(1,2-A)PYRAZINE-1,8-DIONE;

79 6-BROMO-2-(3-CHLORO-4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO(1,2-A)PYRAZINE-1,8-DIONE;

80 6-(4,4-DIFLUORO-CYCLOHEXYL-METHOXY)-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

81 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-(2- HYDROXY-ETHOXY)-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;
82 6-(2,2-DIMETHOXY-ETHOXY)-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-
PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

83 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-((R)-5-
OXO-TETRAHYDRO-FURAN-2-YLMETHOXY)-3,4-
DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-
DIONE;

84 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-((S)-5-
OXO-TETRAHYDRO-FURAN-2-YLMETHOXY)-3,4-
DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-
DIONE;

85 2-(4-FLUORO-BENZYL)-9-HYDROXY-6-(2-
THIOPHEN-2-YL-ETHOXY)-3,4-DIHYDRO-2H-
PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

86 2-BENZYL-9-HYDROXY-6-METHOXY-3,4-
DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-
DIONE;

87 2-(3,4-Dichloro-benzyl)-9-hydroxy-6-methoxy-3,4-
dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione;

88 2-BENZYL-6-(2-FLUORO-ETHOXY)-9-HYDROXY-
3,4-DIHYDRO-2H-PYRIDO-(1,2-A)PYRAZINE-1,8-
DIONE;
89 2-(3,4-DICHLORO-BENZYL)-6-(2-FLUORO-ETHOXY)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO(1,2-A)-PYRAZINE-1,8-DIONE;

90 6-(2-CYCLOPENTYL-ETHOXY)-2-(4-FLUORO-BENZYL)-9-HYDROXY-3,4-DIHYDRO-2H-PYRIDO[1,2-A]PYRAZINE-1,8-DIONE;

91 2-(3,4-Dichloro-benzyl)-9-hydroxy-6-(pyridin-3-yl oxy)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione;

92 2-(3-Chloro-4-fluoro-benzyl)-9-hydroxy-6-(pyridin-3-yl oxy)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione;

93 2-(3,4-Dichloro-benzyl)-9-hydroxy-6-(2-methoxy ethoxy)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione; and

94 2-(3-Chloro-4-fluoro-benzyl)-9-hydroxy-6-(2- methoxy-ethoxy)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,8-dione;

and pharmaceutically acceptable salts thereof, pharmaceutically solvates thereof, and solvates of pharmaceutically acceptable salts thereof.
36. A compound according to any one of claims 1 to 35, wherein said compound is in the form of the (+) enantiomer having an enantiomeric excess of 99%.

37. A compound according to any one of claims 1 to 35, wherein said compound is in the form of the (+) enantiomer having an enantiomeric excess of 95%.

38. A compound according to any one of claims 1 to 35, wherein said compound is in the form of the (+) enantiomer having an enantiomeric excess of 90%.

39. A compound according to any one of claims 1 to 35, wherein said compound is in the form of the (-) enantiomer having an enantiomeric excess of 99%.

40. A compound according to any one of claims 1 to 35, wherein said compound is in the form of the (-) enantiomer having an enantiomeric excess of 95%.

41. A compound according to any one of claims 1 to 35, wherein said compound is in the form of the (-) enantiomer having an enantiomeric excess of 90%.

42. A pharmaceutical composition comprising at least one compound according to any one of claims 1 to 42 and at least one pharmaceutically acceptable carrier or excipient.

43. A combination comprising at least one compound according to any one of claims 1 to 41 and at least one
further therapeutic agent chosen from an agent used in inflammatory diseases, immunoregulatory diseases and in organ transplantation reactions.

44. A combination comprising at least one compound according to any one of claims 1 to 41 and at least one further antiviral agent.

45. A combination according to claim 44, wherein said at least one further antiviral agent is selected from nucleoside and nucleotide analog reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors attachment and fusion inhibitors, entry inhibitors or maturation inhibitors.

46. A combination according to claim 44, wherein said at least one further antiviral agent is a nucleoside and nucleotide analog reverse transcriptase inhibitors selected from lamivudine, zidovudine, emtricitabine, 2',3'-dideoxy-2',3'-didehydro-thymidine, stavudine, tenofovir, 2',3'-dideoxyinosine, 2',3'-dideoxycytidine, zidovudine/lamivudine combination, zidovudine/lamivudine/abacavir combination, abacavir, SPD-754, ACH-126,443 (Beta-L-Fd4C), Alovudine (MIV-310), DAPD (amdoxovir), Racivir, 9-[(2-hydroxymethyl)-1,3-dioxolan-4-yl]guanine or 2-amino-9-[(2-hydroxymethyl)-1,3-dioxolan-4-yl]adenine.

47. A combination according to claim 44, wherein said at least one further antiviral agent is a non-
nucleoside reverse transcriptase inhibitor selected from Nevirapine, delavirdine, efavirenz, (+)-Calanolide A, Capravirine, DPC083, MIV-150, TMC120, TMC125, delavirdine, calanolides or L-697,661.

48. A combination according to claim 44, wherein said at least one further antiviral agent a protease inhibitor chosen from nelfinavir, amprenavir, indinavir, saquinavir, ritonavir, lopinavir, Atazanavir, mozenavir, fosamprenavir, RO033-4649, Tipranavir, TMC114 or VX-385.

49. A method of preventing or treating HIV infection in a subject, comprising administering to said subject a therapeutically effective amount of a compound according to any one of claims 1 to 41.

50. A method of preventing, delaying or treating AIDS in a subject, comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1 to 41.

51. A method of inhibiting HIV integrase in a subject, comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1 to 41.

52. A method of preventing integration of HIV DNA into host cell DNA in a subject, comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1 to 41.
53. A method of preventing HIV DNA strand transfer to the host cell DNA in a subject, comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1 to 41.

54. Use of a compound according to any one of claims 1 to 41 for the manufacture of a medicament for preventing or treating HIV infection or preventing, delaying or treating AIDS.

55. Use of a compound according to any one of claims 1 to 41 for the manufacture of a medicament for preventing any one of HIV replication, integration of HIV DNA into host cell DNA, 3'–end processing of HIV DNA or HIV DNA strand transfer to the host cell DNA.

56. A compound according to any one of claims 1 to 41, for use in medical therapy.

57. A compound according to any one of claims 1 to 41, for use in preventing or treating HIV infection or preventing, delaying or treating AIDS.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
   IPC: C07D 471/04 (2006.01), A61P 31/18 (2006.01), A61K 31/4985 (2006.01), A61K 31/7072 (2006.01), A61K 31/522 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC: C07D 471/04 (2006.01), A61P 31/18 (2006.01), A61K 31/4985 (2006.01), A61K 31/7072 (2006.01), A61K 31/522 (2006.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
Canadian Patent Database (pyrimidin*); STN (structure search); Delphinon (AIDS, HIV)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>CA 2,498.111 WAI et al. 25 March 2004, pages 3-6, 51, examples, claims</td>
<td>1-57, 1-57</td>
</tr>
</tbody>
</table>

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

[X] See patent family annex.

Date of the actual completion of the international search: 8 February 2006 (08-02-2006)

Date of mailing of the international search report: 28 February 2006 (28-02-2006)

Name and mailing address of the ISA/CA
Canadian Intellectual Property Office
Place du Portage I, C114 - 1st Floor, Box PCT
50 Victoria Street
Gatineau, Quebec K1A 0C9
Facsimile No.: 001(819)953-2476

Authorized officer
Sophie Beaudoin (819) 956-6128

Form PCT/ISA/210 (second sheet) (April 2005)
<table>
<thead>
<tr>
<th>Patent Document Cited in Search Report</th>
<th>Publication Date</th>
<th>Patent Family Member(s)</th>
<th>Publication Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA2498111</td>
<td>25-03-2004</td>
<td>AU2003267098 A1</td>
<td>30-04-2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP1549315 A2</td>
<td>06-07-2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO2004024078 A2</td>
<td>25-03-2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US20060024330 A1</td>
<td>02-02-2006</td>
</tr>
<tr>
<td>WO2005087766</td>
<td>22-09-2005</td>
<td>NONE</td>
<td></td>
</tr>
<tr>
<td>WO2005087767</td>
<td>22-09-2005</td>
<td>NONE</td>
<td></td>
</tr>
<tr>
<td>WO2005087768</td>
<td>22-09-2005</td>
<td>NONE</td>
<td></td>
</tr>
</tbody>
</table>
# INTERNATIONAL SEARCH REPORT

## Box No. II  Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claim Nos.: 49-53
   because they relate to subject matter not required to be searched by this Authority, namely:
   
   Although claims 49-53 are directed to a method of treatment of the human or animal body, the search has been carried out and based on the alleged effects or purposes of the compounds and composition thereof.

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

3. [ ] Claim Nos.:
   because they are dependant claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box No. III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

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

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

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

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

**Remark on Protest**

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

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

[ ] No protest accompanied the payment of additional search fees.