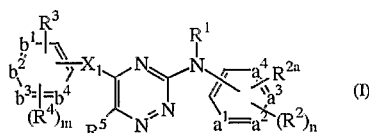


HIV INHIBITING 1,2,4-TRIAZINES

- The present invention is concerned with 1,2,4-triazine derivatives having HIV (Human Immunodeficiency Virus) replication inhibiting properties. The invention further relates to methods for their preparation and pharmaceutical compositions comprising them. The invention also relates to the use of said compounds for the manufacture of a medicament for the prevention or the treatment of HIV infection.
- Compounds structurally related to the present compounds are disclosed in the prior art. In Huaxue Xuebao (1987), 45(2), 185-190, and J.Chem. Soc., Perkin Transactions 1. Organic and Bio-organic Chemistry (1972-1999) (1982), 5, 1251-1254 the synthesis of 1,2,4-triazine derivatives is disclosed.
- The compounds of the invention differ from prior art compounds in structure, pharmacological activity and/or pharmacological potency. The compounds of the invention are highly active to inhibit the replication of Human Immunodeficiency Virus (HIV), and in particular they are highly active to inhibit the replication of mutant strains, in particular drug or multidrug resistant HIV strains, i.e. strains which have become resistant to one or more art-known NNRTI drug(s) (Non Nucleoside Reverse Transcriptase Inhibitor drugs).

The present invention concerns a compound of formula



- a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine or a stereochemically isomeric form thereof, wherein
- a¹=a²-a³=a⁴- represents a bivalent radical of formula
- CH=CH-CH=CH- (a-1);
- N=CH-CH=CH- (a-2);
- N=CH-N=CH- (a-3);
- N=CH-CH=N- (a-4);
- N=N-CH=CH- (a-5);
- b¹=b²-b³=b⁴- represents a bivalent radical of formula
- CH=CH-CH=CH- (b-1);

- -N=CH-CH=CH- (b-2);
 -N=CH-N=CH- (b-3);
 -N=CH-CH=N- (b-4);
 -N=N-CH=CH- (b-5);
- 5 n is 0, 1, 2, 3 and in case $\text{-a}^1=\text{a}^2=\text{a}^3=\text{a}^4$ is (a-1), then n may also be 4;
 m is 0, 1, 2, 3 and in case $\text{-b}^1=\text{b}^2=\text{b}^3=\text{b}^4$ is (b-1), then m may also be 4;
 R^1 is hydrogen; aryl; formyl; C_{1-6} alkylcarbonyl; C_{1-6} alkyl; C_{1-6} alkyloxycarbonyl;
 C_{1-6} alkyl substituted with formyl, C_{1-6} alkylcarbonyl, C_{1-6} alkyloxycarbonyl,
 C_{1-6} alkylcarbonyloxy; C_{1-6} alkyloxy C_{1-6} alkylcarbonyl substituted with
 10 C_{1-6} alkyloxycarbonyl;
 each R^2 independently is hydroxy; halo; C_{1-6} alkyl optionally substituted with one or
 more substituents each independently selected from halo, cyano or -C(=O)R^6 ;
 C_{3-7} cycloalkyl; C_{2-6} alkenyl optionally substituted with one or more substituents each
 independently selected from halo, cyano or -C(=O)R^6 ; C_{2-6} alkynyl optionally
 15 substituted with one or more substituents each independently selected from halo,
 cyano or -C(=O)R^6 ; C_{1-6} alkyloxycarbonyl; carboxyl; cyano; nitro; amino; mono- or
 di(C_{1-6} alkyl)amino; polyhalomethyl; polyhalomethylthio; $\text{-S(=O)}_p\text{R}^6$;
 $\text{-NH-S(=O)}_p\text{R}^6$; -C(=O)R^6 ; -NHC(=O)H ; -C(=O)NHNH_2 ; NHC(=O)R^6 ; C(=NH)R^6 ;
 R^{2a} is cyano; aminocarbonyl; amino; C_{1-6} alkyl; halo; C_{1-6} alkyloxy wherein C_{1-6} alkyl
 20 may optionally be substituted with cyano; NHR^{13} ; $\text{NR}^{13}\text{R}^{14}$; -C(=O)-NHR^{13} ;
 $\text{-C(=O)-NR}^{13}\text{R}^{14}$; -C(=O)-R^{15} ; $\text{-CH=N-NH-C(=O)-R}^{16}$; C_{1-6} alkyl substituted with
 one or more substituents each independently selected from halo, cyano, NR^9R^{10} ,
 $\text{-C(=O)-NR}^9\text{R}^{10}$, $\text{-C(=O)-C}_{1-6}\text{alkyl}$ or R^7 ; C_{1-6} alkyl substituted with hydroxy and a
 second substituent selected from halo, cyano, NR^9R^{10} , $\text{-C(=O)-NR}^9\text{R}^{10}$,
 25 $\text{-C(=O)-C}_{1-6}\text{alkyl}$ or R^7 ; C_{1-6} alkyloxy C_{1-6} alkyl optionally substituted with one or more
 substituents each independently selected from halo, cyano, NR^9R^{10} , $\text{-C(=O)-NR}^9\text{R}^{10}$,
 $\text{-C(=O)-C}_{1-6}\text{alkyl}$ or R^7 ; C_{2-6} alkenyl substituted with one or more substituents each
 independently selected from halo, cyano, NR^9R^{10} , $\text{-C(=O)-NR}^9\text{R}^{10}$, $\text{-C(=O)-C}_{1-6}\text{alkyl}$
 or R^7 ; C_{2-6} alkynyl substituted with one or more substituents each independently
 30 selected from halo, cyano, NR^9R^{10} , $\text{-C(=O)-NR}^9\text{R}^{10}$, $\text{-C(=O)-C}_{1-6}\text{alkyl}$ or R^7 ;
 $\text{-C(=N-O-R}^8\text{)-C}_{1-4}\text{alkyl}$; R^7 or $\text{-X}_3\text{-R}^7$;
 X_1 is -NR^1 -, -NH-NH- , -N=N- , -O- , -C(=O)- , C_{1-4} alkanediyl, -CHOH- , -S- , -S(=O)_p -,
 $\text{-X}_2\text{-C}_{1-4}\text{alkanediyl-}$ or $\text{-C}_{1-4}\text{alkanediyl-X}_2$;
 X_2 is -NR^1 -, -NH-NH- , -N=N- , -O- , -C(=O)- , -CHOH- , -S- , -S(=O)_p ;
 35 R^3 is cyano; aminocarbonyl; amino; C_{1-6} alkyl; halo; C_{1-6} alkyloxy wherein C_{1-6} alkyl
 may optionally be substituted with cyano; NHR^{13} ; $\text{NR}^{13}\text{R}^{14}$; -C(=O)-NHR^{13} ;
 $\text{-C(=O)-NR}^{13}\text{R}^{14}$; -C(=O)-R^{15} ; $\text{-CH=N-NH-C(=O)-R}^{16}$; C_{1-6} alkyl substituted

with one or more substituents each independently selected from halo, cyano, NR⁹R¹⁰, -C(=O)-NR⁹R¹⁰, -C(=O)-C₁₋₆alkyl or R⁷; C₁₋₆alkyl substituted with hydroxy and a second substituent selected from halo, cyano, NR⁹R¹⁰, -C(=O)-NR⁹R¹⁰, -C(=O)-C₁₋₆alkyl or R⁷; C₁₋₆alkyloxyC₁₋₆alkyl optionally substituted with one or more substituents each independently selected from halo, cyano, NR⁹R¹⁰, -C(=O)-NR⁹R¹⁰, -C(=O)-C₁₋₆alkyl or R⁷; C₂₋₆alkenyl substituted with one or more substituents each independently selected from halo, cyano, NR⁹R¹⁰, -C(=O)-NR⁹R¹⁰, -C(=O)-C₁₋₆alkyl or R⁷; C₂₋₆alkynyl substituted with one or more substituents each independently selected from halo, cyano, NR⁹R¹⁰, -C(=O)-NR⁹R¹⁰, -C(=O)-C₁₋₆alkyl or R⁷; -C(=N-O-R⁸)-C₁₋₄alkyl; R⁷ or -X₃-R⁷; X₃ is -NR¹-, -NH-NH-, -N=N-, -O-, -C(=O)-, -S-, -S(=O)_p-, -X₂-C₁₋₄alkanediyl-, -C₁₋₄alkanediyl-X_{2a}-, -C₁₋₄alkanediyl-X_{2b}-C₁₋₄alkanediyl, -C(=N-OR⁸)-C₁₋₄alkanediyl-; with X_{2a} being -NH-NH-, -N=N-, -O-, -C(=O)-, -S-, -S(=O)_p-; and with X_{2b} being -NH-NH-, -N=N-, -C(=O)-, -S-, -S(=O)_p-; R⁴ is halo; hydroxy; C₁₋₆alkyl optionally substituted with one or more substituents each independently selected from halo, cyano or -C(=O)R⁶; C₂₋₆alkenyl optionally substituted with one or more substituents each independently selected from halo, cyano or -C(=O)R⁶; C₂₋₆alkynyl optionally substituted with one or more substituents each independently selected from halo, cyano or -C(=O)R⁶; C₃₋₇cycloalkyl; C₁₋₆alkyloxy; cyano; nitro; polyhaloC₁₋₆alkyl; polyhaloC₁₋₆alkyloxy; aminocarbonyl; mono- or di(C₁₋₄alkyl)aminocarbonyl; C₁₋₆alkyloxycarbonyl; C₁₋₆alkylcarbonyl; formyl; amino; mono- or di(C₁₋₄alkyl)amino or R⁷; R⁵ is hydrogen; halo; aminocarbonyl; mono- or di(C₁₋₄alkyl)aminocarbonyl; amino; C₁₋₆alkyloxycarbonyl; C₁₋₆alkyloxycarbonylamino; polyhaloC₁₋₆alkyl; C₁₋₆alkyl optionally substituted with cyano, hydroxy, halo, C₁₋₆alkyloxy, C₁₋₆alkylthio or S(=O)_p-C₁₋₆alkyl; C₂₋₆alkenyl optionally substituted with cyano, hydroxy, halo, C₁₋₆alkyloxy, C₁₋₆alkylthio or S(=O)_p-C₁₋₆alkyl; C₂₋₆alkynyl optionally substituted with cyano, hydroxy, halo, C₁₋₆alkyloxy, C₁₋₆alkylthio or S(=O)_p-C₁₋₆alkyl; R⁶ is C₁₋₄alkyl, amino, mono- or di(C₁₋₄alkyl)amino or polyhaloC₁₋₄alkyl; R⁷ is a monocyclic, bicyclic or tricyclic saturated, partially saturated or aromatic carbocycle or a monocyclic, bicyclic or tricyclic saturated, partially saturated or aromatic heterocycle, wherein each of said carbocyclic or heterocyclic ring systems may optionally be substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, mercapto, C₁₋₆alkyl, hydroxyC₁₋₆alkyl, aminoC₁₋₆alkyl, mono or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, formyl,

C₁₋₆alkylcarbonyl, C₃₋₇cycloalkyl, C₁₋₆alkyloxy, C₁₋₆alkyloxy carbonyl, C₁₋₆alkylthio, cyano, nitro, polyhaloC₁₋₆alkyl, polyhaloC₁₋₆alkyloxy, aminocarbonyl, -CH(=N-O-R⁸), R^{7a}, -X₃-R^{7a} or R^{7a}-C₁₋₄alkyl;

R^{7a} is a monocyclic, bicyclic or tricyclic saturated, partially saturated or aromatic carbocycle or a monocyclic, bicyclic or tricyclic saturated, partially saturated or aromatic heterocycle, wherein each of said carbocyclic or heterocyclic ring systems may optionally be substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, mercapto, C₁₋₆alkyl, hydroxyC₁₋₆alkyl, aminoC₁₋₆alkyl, mono or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, formyl, C₁₋₆alkylcarbonyl, C₃₋₇cycloalkyl, C₁₋₆alkyloxy, C₁₋₆alkyloxy carbonyl, C₁₋₆alkylthio, cyano, nitro, polyhaloC₁₋₆alkyl, polyhaloC₁₋₆alkyloxy, aminocarbonyl, -CH(=N-O-R⁸);

R⁸ is hydrogen, C₁₋₄alkyl, aryl or arylC₁₋₄alkyl;

R⁹ and R¹⁰ each independently are hydrogen; hydroxy; C₁₋₆alkyl; C₁₋₆alkyloxy; C₁₋₆alkylcarbonyl; C₁₋₆alkyloxy carbonyl; amino; mono- or di(C₁₋₆alkyl)amino; mono- or di(C₁₋₆alkyl)aminocarbonyl; -CH(=NR¹¹) or R⁷, wherein each of the aforementioned C₁₋₆alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C₁₋₆alkyloxy, hydroxyC₁₋₆alkyloxy, carboxyl, C₁₋₆alkyloxy carbonyl, cyano, amino, imino, mono- or di(C₁₋₄alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, -S(=O)_pR⁶, -NH-S(=O)_pR⁶, -C(=O)R⁶, -NHC(=O)H, -C(=O)NHNH₂, -NHC(=O)R⁶, -C(=NH)R⁶, R⁷; or

R⁹ and R¹⁰ may be taken together to form a bivalent or trivalent radical of formula

- | | | |
|----|---|-------|
| | -CH ₂ -CH ₂ -CH ₂ -CH ₂ - | (d-1) |
| 25 | -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ - | (d-2) |
| | -CH ₂ -CH ₂ -O-CH ₂ -CH ₂ - | (d-3) |
| | -CH ₂ -CH ₂ -S-CH ₂ -CH ₂ - | (d-4) |
| | -CH ₂ -CH ₂ -NR ¹² -CH ₂ -CH ₂ - | (d-5) |
| | -CH ₂ -CH=CH-CH ₂ - | (d-6) |
| 30 | =CH-CH=CH-CH=CH- | (d-7) |

R¹¹ is cyano; C₁₋₄alkyl optionally substituted with C₁₋₄alkyloxy, cyano, amino, mono- or di(C₁₋₄alkyl)amino or aminocarbonyl; C₁₋₄alkylcarbonyl; C₁₋₄alkyloxy carbonyl; aminocarbonyl; mono- or di(C₁₋₄alkyl)aminocarbonyl;

R¹² is hydrogen or C₁₋₄alkyl;

R¹³ and R¹⁴ each independently are C₁₋₆alkyl optionally substituted with cyano or aminocarbonyl, C₂₋₆alkenyl optionally substituted with cyano or aminocarbonyl, C₂₋₆alkynyl optionally substituted with cyano or aminocarbonyl;

R^{15} is C_{1-6} alkyl substituted with cyano or aminocarbonyl;

R^{16} is C_{1-6} alkyl optionally substituted with cyano or aminocarbonyl, or R^7 ;

p is 1 or 2;

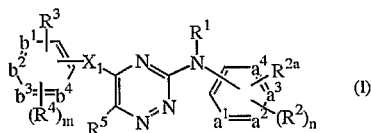
aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each

- 5 independently selected from halo, hydroxy, mercapto, C_{1-6} alkyl, hydroxy C_{1-6} alkyl, amino C_{1-6} alkyl, mono or di(C_{1-6} alkyl)amino C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{3-7} cycloalkyl, C_{1-6} alkyloxy, C_{1-6} alkyloxycarbonyl, C_{1-6} alkylthio, cyano, nitro, polyhalo C_{1-6} alkyl, polyhalo C_{1-6} alkyloxy, aminocarbonyl, R^7 or $-X_3-R^7$

provided the following compounds

- 10 1,2,4-triazine-6-carboxylic acid, 3,5-bis[(4-methylphenyl)amino]-, ethyl ester;
1,2,4-triazine-6-carboxylic acid, 3,5-bis[(4-nitrophenyl)amino]-, ethyl ester;
 N,N' -bis(4-chlorophenyl)-6-fluoro-1,2,4-triazine-3,5-diamine;
are not included.

- 15 The present invention also relates to the use of a compound for the manufacture of a medicament for the treatment or prevention of HIV infection, wherein the compound has the formula



a N -oxide, a pharmaceutically acceptable addition salt, a quaternary amine or a

- 20 stereochemically isomeric form thereof, wherein

$-a^1=a^2-a^3=a^4-$ represents a bivalent radical of formula

$-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$ (a-1);

$-\text{N}=\text{CH}-\text{CH}=\text{CH}-$ (a-2);

$-\text{N}=\text{CH}-\text{N}=\text{CH}-$ (a-3);

- 25 $-\text{N}=\text{CH}-\text{CH}=\text{N}-$ (a-4);

$-\text{N}=\text{N}-\text{CH}=\text{CH}-$ (a-5);

$-b^1=b^2-b^3=b^4-$ represents a bivalent radical of formula

$-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$ (b-1);

$-\text{N}=\text{CH}-\text{CH}=\text{CH}-$ (b-2);

- 30 $-\text{N}=\text{CH}-\text{N}=\text{CH}-$ (b-3);

$-\text{N}=\text{CH}-\text{CH}=\text{N}-$ (b-4);

$-\text{N}=\text{N}-\text{CH}=\text{CH}-$ (b-5);

n is 0, 1, 2, 3 and in case $-a^1=a^2-a^3=a^4-$ is (a-1), then n may also be 4;

m is 0, 1, 2, 3 and in case $-b^1=b^2-b^3=b^4-$ is (b-1), then m may also be 4;

- R^1 is hydrogen; aryl; formyl; C₁₋₆alkylcarbonyl; C₁₋₆alkyl; C₁₋₆alkyloxycarbonyl; C₁₋₆alkyl substituted with formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylcarbonyloxy; C₁₋₆alkyloxyC₁₋₆alkylcarbonyl substituted with C₁₋₆alkyloxycarbonyl;
- 5 each R^2 independently is hydroxy; halo; C₁₋₆alkyl optionally substituted with one or more substituents each independently selected from halo, cyano or $-C(=O)R^6$; C₃₋₇cycloalkyl; C₂₋₆alkenyl optionally substituted with one or more substituents each independently selected from halo, cyano or $-C(=O)R^6$; C₂₋₆alkynyl optionally substituted with one or more substituents each independently selected from halo, cyano or $-C(=O)R^6$; C₁₋₆alkyloxycarbonyl; carboxyl; cyano; nitro; amino; mono- or di(C₁₋₆alkyl)amino; polyhalomethyl; polyhalomethylthio; $-S(=O)_pR^6$; $-NH-S(=O)_pR^6$; $-C(=O)R^6$; $-NHC(=O)H$; $-C(=O)NHNH_2$; $NHC(=O)R^6$; $C(=NH)R^6$;
- 10 R^{2a} is cyano; aminocarbonyl; amino; C₁₋₆alkyl; halo; C₁₋₆alkyloxy wherein C₁₋₆alkyl may optionally be substituted with cyano; NHR^{13} ; $NR^{13}R^{14}$; $-C(=O)-NHR^{13}$; $-C(=O)-NR^{13}R^{14}$; $-C(=O)-R^{15}$; $-CH=N-NH-C(=O)-R^{16}$; C₁₋₆alkyl substituted with one or more substituents each independently selected from halo, cyano, NR^9R^{10} , $-C(=O)-NR^9R^{10}$, $-C(=O)-C_{1-6}alkyl$ or R^7 ; C₁₋₆alkyl substituted with hydroxy and a second substituent selected from halo, cyano, NR^9R^{10} , $-C(=O)-NR^9R^{10}$, $-C(=O)-C_{1-6}alkyl$ or R^7 ; C₁₋₆alkyloxyC₁₋₆alkyl optionally substituted with one or more substituents each independently selected from halo, cyano, NR^9R^{10} , $-C(=O)-NR^9R^{10}$, $-C(=O)-C_{1-6}alkyl$ or R^7 ; C₂₋₆alkenyl substituted with one or more substituents each independently selected from halo, cyano, NR^9R^{10} , $-C(=O)-NR^9R^{10}$, $-C(=O)-C_{1-6}alkyl$ or R^7 ; C₂₋₆alkynyl substituted with one or more substituents each independently selected from halo, cyano, NR^9R^{10} , $-C(=O)-NR^9R^{10}$, $-C(=O)-C_{1-6}alkyl$ or R^7 ;
- 15 $-C(=N-O-R^8)-C_{1-4}alkyl$; R^7 or $-X_3-R^7$;
- 20 X_1 is $-NR^1$ -, $-NH-NH$ -, $-N=N$ -, $-O$ -, $-C(=O)$ -, C₁₋₄alkanediyl, $-CHOH$ -, $-S$ -, $-S(=O)_p$ -, $-X_2-C_{1-4}alkanediyl$ or $-C_{1-4}alkanediyl-X_2$;
- X_2 is $-NR^1$ -, $-NH-NH$ -, $-N=N$ -, $-O$ -, $-C(=O)$ -, $-CHOH$ -, $-S$ -, $-S(=O)_p$;
- 25 R^3 is cyano; aminocarbonyl; amino; C₁₋₆alkyl; halo; C₁₋₆alkyloxy wherein C₁₋₆alkyl may optionally be substituted with cyano; NHR^{13} ; $NR^{13}R^{14}$; $-C(=O)-NHR^{13}$; $-C(=O)-NR^{13}R^{14}$; $-C(=O)-R^{15}$; $-CH=N-NH-C(=O)-R^{16}$; C₁₋₆alkyl substituted with one or more substituents each independently selected from halo, cyano, NR^9R^{10} , $-C(=O)-NR^9R^{10}$, $-C(=O)-C_{1-6}alkyl$ or R^7 ; C₁₋₆alkyl substituted with hydroxy and a second substituent selected from halo, cyano, NR^9R^{10} , $-C(=O)-NR^9R^{10}$, $-C(=O)-C_{1-6}alkyl$ or R^7 ; C₁₋₆alkyloxyC₁₋₆alkyl optionally substituted with one or more substituents each independently selected from halo, cyano, NR^9R^{10} , $-C(=O)-NR^9R^{10}$, $-C(=O)-C_{1-6}alkyl$ or R^7 ; C₂₋₆alkenyl substituted with one or
- 30
- 35

- more substituents each independently selected from halo, cyano, NR^9R^{10} , $-\text{C}(=\text{O})-\text{NR}^9\text{R}^{10}$, $-\text{C}(=\text{O})-\text{C}_{1-6}\text{alkyl}$ or R^7 ; $\text{C}_{2-6}\text{alkynyl}$ substituted with one or more substituents each independently selected from halo, cyano, NR^9R^{10} , $-\text{C}(=\text{O})-\text{NR}^9\text{R}^{10}$, $-\text{C}(=\text{O})-\text{C}_{1-6}\text{alkyl}$ or R^7 ; $-\text{C}(=\text{N}-\text{O}-\text{R}^8)-\text{C}_{1-4}\text{alkyl}$; R^7 or $-\text{X}_3-\text{R}^7$;
- 5 X_3 is $-\text{NR}^1-$, $-\text{NH}-\text{NH}-$, $-\text{N}=\text{N}-$, $-\text{O}-$, $-\text{C}(=\text{O})-$, $-\text{S}-$, $-\text{S}(=\text{O})_p-$, $-\text{X}_2-\text{C}_{1-4}\text{alkanediyl}$, $-\text{C}_{1-4}\text{alkanediyl}-\text{X}_{2a}-$, $-\text{C}_{1-4}\text{alkanediyl}-\text{X}_{2b}-\text{C}_{1-4}\text{alkanediyl}$, $-\text{C}(=\text{N}-\text{OR}^8)-\text{C}_{1-4}\text{alkanediyl}$;
- with X_{2a} being $-\text{NH}-\text{NH}-$, $-\text{N}=\text{N}-$, $-\text{O}-$, $-\text{C}(=\text{O})-$, $-\text{S}-$, $-\text{S}(=\text{O})_p-$; and
with X_{2b} being $-\text{NH}-\text{NH}-$, $-\text{N}=\text{N}-$, $-\text{C}(=\text{O})-$, $-\text{S}-$, $-\text{S}(=\text{O})_p-$;
- 10 R^4 is halo; hydroxy; $\text{C}_{1-6}\text{alkyl}$ optionally substituted with one or more substituents each independently selected from halo, cyano or $-\text{C}(=\text{O})\text{R}^6$; $\text{C}_{2-6}\text{alkenyl}$ optionally substituted with one or more substituents each independently selected from halo, cyano or $-\text{C}(=\text{O})\text{R}^6$; $\text{C}_{2-6}\text{alkynyl}$ optionally substituted with one or more substituents each independently selected from halo, cyano or $-\text{C}(=\text{O})\text{R}^6$;
- 15 $\text{C}_{3-7}\text{cycloalkyl}$; $\text{C}_{1-6}\text{alkyloxy}$; cyano; nitro; polyhalo $\text{C}_{1-6}\text{alkyl}$; polyhalo $\text{C}_{1-6}\text{alkyloxy}$; aminocarbonyl; mono- or di($\text{C}_{1-4}\text{alkyl}$)aminocarbonyl; $\text{C}_{1-6}\text{alkyloxycarbonyl}$; $\text{C}_{1-6}\text{alkylcarbonyl}$; formyl; amino; mono- or di($\text{C}_{1-4}\text{alkyl}$)amino or R^7 ;
- R^5 is hydrogen; halo; aminocarbonyl; mono- or di($\text{C}_{1-4}\text{alkyl}$)aminocarbonyl; amino;
- 20 $\text{C}_{1-6}\text{alkyloxycarbonyl}$; $\text{C}_{1-6}\text{alkyloxycarbonylamino}$; polyhalo $\text{C}_{1-6}\text{alkyl}$; $\text{C}_{1-6}\text{alkyl}$ optionally substituted with cyano, hydroxy, halo, $\text{C}_{1-6}\text{alkyloxy}$, $\text{C}_{1-6}\text{alkylthio}$ or $\text{S}(=\text{O})_p-\text{C}_{1-6}\text{alkyl}$; $\text{C}_{2-6}\text{alkenyl}$ optionally substituted with cyano, hydroxy, halo, $\text{C}_{1-6}\text{alkyloxy}$, $\text{C}_{1-6}\text{alkylthio}$ or $\text{S}(=\text{O})_p-\text{C}_{1-6}\text{alkyl}$; $\text{C}_{2-6}\text{alkynyl}$ optionally substituted with cyano, hydroxy, halo, $\text{C}_{1-6}\text{alkyloxy}$, $\text{C}_{1-6}\text{alkylthio}$ or $\text{S}(=\text{O})_p-\text{C}_{1-6}\text{alkyl}$;
- 25 R^6 is $\text{C}_{1-4}\text{alkyl}$, amino, mono- or di($\text{C}_{1-4}\text{alkyl}$)amino or polyhalo $\text{C}_{1-4}\text{alkyl}$;
- R^7 is a monocyclic, bicyclic or tricyclic saturated, partially saturated or aromatic carbocycle or a monocyclic, bicyclic or tricyclic saturated, partially saturated or aromatic heterocycle, wherein each of said carbocyclic or heterocyclic ring systems may optionally be substituted with one, two, three, four or five substituents each
- 30 independently selected from halo, hydroxy, mercapto, $\text{C}_{1-6}\text{alkyl}$, hydroxy $\text{C}_{1-6}\text{alkyl}$, amino $\text{C}_{1-6}\text{alkyl}$, mono or di($\text{C}_{1-6}\text{alkyl}$)amino $\text{C}_{1-6}\text{alkyl}$, formyl, $\text{C}_{1-6}\text{alkylcarbonyl}$, $\text{C}_{3-7}\text{cycloalkyl}$, $\text{C}_{1-6}\text{alkyloxy}$, $\text{C}_{1-6}\text{alkyloxycarbonyl}$, $\text{C}_{1-6}\text{alkylthio}$, cyano, nitro, polyhalo $\text{C}_{1-6}\text{alkyl}$, polyhalo $\text{C}_{1-6}\text{alkyloxy}$, aminocarbonyl, $-\text{CH}(=\text{N}-\text{O}-\text{R}^8)$, R^{7a} , $-\text{X}_3-\text{R}^{7a}$ or $\text{R}^{7a}-\text{C}_{1-4}\text{alkyl}$;
- 35 R^{7a} is a monocyclic, bicyclic or tricyclic saturated, partially saturated or aromatic carbocycle or a monocyclic, bicyclic or tricyclic saturated, partially saturated or aromatic heterocycle, wherein each of said carbocyclic or heterocyclic ring systems

- may optionally be substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, mercapto, C₁₋₆alkyl, hydroxyC₁₋₆alkyl, aminoC₁₋₆alkyl, mono or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, formyl, C₁₋₆alkylcarbonyl, C₃₋₇cycloalkyl, C₁₋₆alkyloxy, C₁₋₆alkyloxycarbonyl,
- 5 C₁₋₆alkylthio, cyano, nitro, polyhaloC₁₋₆alkyl, polyhaloC₁₋₆alkyloxy, aminocarbonyl, -CH(=N-O-R⁸);
- R⁸ is hydrogen, C₁₋₄alkyl, aryl or arylC₁₋₄alkyl;
- R⁹ and R¹⁰ each independently are hydrogen; hydroxy; C₁₋₆alkyl; C₁₋₆alkyloxy; C₁₋₆alkylcarbonyl; C₁₋₆alkyloxycarbonyl; amino; mono- or di(C₁₋₆alkyl)amino; mono- or di(C₁₋₆alkyl)aminocarbonyl; -CH(=NR¹¹) or R⁷, wherein each of the
- 10 aforementioned C₁₋₆alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C₁₋₆alkyloxy, hydroxyC₁₋₆alkyloxy, carboxyl, C₁₋₆alkyloxycarbonyl, cyano, amino, imino, mono- or di(C₁₋₄alkyl)amino, polyhalomethyl, polyhalomethyloxy,
- 15 polyhalomethylthio, -S(=O)_pR⁶, -NH-S(=O)_pR⁶, -C(=O)R⁶, -NHC(=O)H, -C(=O)NHNH₂, -NHC(=O)R⁶, -C(=NH)R⁶, R⁷; or
- R⁹ and R¹⁰ may be taken together to form a bivalent or trivalent radical of formula
- | | | |
|----|---|-------|
| | -CH ₂ -CH ₂ -CH ₂ -CH ₂ - | (d-1) |
| | -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ - | (d-2) |
| 20 | -CH ₂ -CH ₂ -O-CH ₂ -CH ₂ - | (d-3) |
| | -CH ₂ -CH ₂ -S-CH ₂ -CH ₂ - | (d-4) |
| | -CH ₂ -CH ₂ -NR ¹² -CH ₂ -CH ₂ - | (d-5) |
| | -CH ₂ -CH=CH-CH ₂ - | (d-6) |
| | =CH-CH=CH-CH=CH- | (d-7) |
- 25 R¹¹ is cyano; C₁₋₄alkyl optionally substituted with C₁₋₄alkyloxy, cyano, amino, mono- or di(C₁₋₄alkyl)amino or aminocarbonyl; C₁₋₄alkylcarbonyl; C₁₋₄alkyloxycarbonyl; aminocarbonyl; mono- or di(C₁₋₄alkyl)aminocarbonyl;
- R¹² is hydrogen or C₁₋₄alkyl;
- R¹³ and R¹⁴ each independently are C₁₋₆alkyl optionally substituted with cyano or aminocarbonyl, C₂₋₆alkenyl optionally substituted with cyano or aminocarbonyl,
- 30 C₂₋₆alkynyl optionally substituted with cyano or aminocarbonyl;
- R¹⁵ is C₁₋₆alkyl substituted with cyano or aminocarbonyl;
- R¹⁶ is C₁₋₆alkyl optionally substituted with cyano or aminocarbonyl, or R⁷;
- p is 1 or 2;
- 35 aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, mercapto, C₁₋₆alkyl, hydroxyC₁₋₆alkyl, aminoC₁₋₆alkyl, mono or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, C₁₋₆alkylcarbonyl,

C₃₋₇cycloalkyl, C₁₋₆alkyloxy, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylthio, cyano, nitro, polyhaloC₁₋₆alkyl, polyhaloC₁₋₆alkyloxy, aminocarbonyl, R⁷ or -X₃-R⁷.

As used hereinbefore or hereinafter C₁₋₄alkyl as a group or part of a group defines
 5 straight or branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as methyl, ethyl, propyl, 1-methylethyl, butyl; C₁₋₆alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as the group defined for C₁₋₄alkyl and pentyl, hexyl, 2-methylbutyl and the like; C₂₋₆alkyl as a group or part of a group defines straight or
 10 branched chain saturated hydrocarbon radicals having from 2 to 6 carbon atoms such as ethyl, propyl, 1-methylethyl, butyl, pentyl, hexyl, 2-methylbutyl and the like; C₁₋₄alkanediyl defines straight or branched chain saturated bivalent hydrocarbon radicals having from 1 to 4 carbon atoms such as methylene, 1,2-ethanediyl or 1,2-ethylidene, 1,3-propanediyl or 1,3-propylidene, 1,4-butanediyl or
 15 1,4-butyldiene and the like; C₃₋₇cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; C₂₋₆alkenyl defines straight and branched chain hydrocarbon radicals having from 2 to 6 carbon atoms containing a double bond such as ethenyl, propenyl, butenyl, pentenyl, hexenyl and the like; C₂₋₆alkynyl defines straight and branched chain hydrocarbon radicals having from 2 to 6 carbon atoms
 20 containing a triple bond such as ethynyl, propynyl, butynyl, pentynyl, hexynyl and the like; a monocyclic, bicyclic or tricyclic saturated carbocycle represents a ring system consisting of 1, 2 or 3 rings, said ring system being composed of only carbon atoms and said ring system containing only single bonds; a monocyclic, bicyclic or tricyclic partially saturated carbocycle represents a ring system consisting of 1, 2 or 3 rings, said
 25 ring system being composed of only carbon atoms and comprising at least one double bond provided that the ring system is not an aromatic ring system; a monocyclic, bicyclic or tricyclic aromatic carbocycle represents an aromatic ring system consisting of 1, 2 or 3 rings, said ring system being composed of only carbon atoms; the term aromatic is well known to a person skilled in the art and designates cyclically
 30 conjugated systems of 4n + 2 electrons, that is with 6, 10, 14 etc. π -electrons (rule of Hückel); a monocyclic, bicyclic or tricyclic saturated heterocycle represents a ring system consisting of 1, 2 or 3 rings and comprising at least one heteroatom selected from O, N or S, said ring system containing only single bonds; a monocyclic, bicyclic or tricyclic partially saturated heterocycle represents a ring system consisting of 1, 2 or
 35 3 rings and comprising at least one heteroatom selected from O, N or S, and at least one double bond provided that the ring system is not an aromatic ring system; a monocyclic, bicyclic or tricyclic aromatic heterocycle represents an aromatic ring

system consisting of 1, 2 or 3 rings and comprising at least one heteroatom selected from O, N or S.

Particular examples of monocyclic, bicyclic or tricyclic saturated carbocycles are
5 cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl,
bicyclo[4,2,0]octanyl, cyclononanyl, cyclodecanyl, decahydronaphthalenyl,
tetradecahydroanthracenyl and the like.

Particular examples of monocyclic, bicyclic or tricyclic partially saturated carbocycles
10 are cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclo-
octenyl, bicyclo[4,2,0]octenyl, cyclononenyl, cyclodecenyl, octahydronaphthalenyl,
1,2,3,4-tetrahydronaphthalenyl, 1,2,3,4,4a,9,9a,10-octahydro-anthracenyl and the like.

Particular examples of monocyclic, bicyclic or tricyclic aromatic carbocycles are
15 phenyl, naphthalenyl, anthracenyl.

Particular examples of monocyclic, bicyclic or tricyclic saturated heterocycles are
tetrahydrofuranlyl, pyrrolidinyl, dioxolanyl, imidazolidinyl, thiazolidinyl,
tetrahydrothienyl, dihydrooxazolyl, isothiazolidinyl, isoxazolidinyl, oxadiazolidinyl,
20 triazolidinyl, thiadiazolidinyl, pyrazolidinyl, piperidinyl, hexahydropyrimidinyl,
hexahydropyrazinyl, dioxanyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl,
trithianyl, decahydroquinolinyl, octahydroindolyl and the like.

Particular examples of monocyclic, bicyclic or tricyclic partially saturated heterocycles
25 are pyrrolinyl, imidazolinyl, pyrazolinyl, 2,3-dihydrobenzofuranlyl, 1,3-benzodioxolyl,
2,3-dihydro-1,4-benzodioxinyl, indolinyl and the like.

Particular examples of monocyclic, bicyclic or tricyclic aromatic heterocycles are
azetyl, oxetylidenyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl,
30 isothiazolyl, pyrazolyl, triazolyl, thiadiazolyl, oxadiazolyl, tetrazolyl, pyridyl,
pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, pyranlyl, benzofuryl, isobenzofuryl,
benzothienyl, isobenzothienyl, indolizinyll, indolyl, isoindolyl, benzoxazolyl,
benzimidazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, benzopyrazolyl,
benzoxadiazolyl, benzothiadiazolyl, benzotriazolyl, purinyl, quinolinyl, isoquinolinyl,
35 cinnolinyl, quinolizinyll, phthalazinyl, quinoxalinyll, quinazolinyl, naphthiridinyl,
pteridinyl, benzopyranlyl, pyrrolopyridyl, thienopyridyl, furopyridyl, isothiazolopyridyl,
thiazolopyridyl, isoxazolopyridyl, oxazolopyridyl, pyrazolopyridyl, imidazopyridyl,

pyrrolopyrazinyl, thienopyrazinyl, furopyrazinyl, isothiazolopyrazinyl, thiazolopyrazinyl, isoxazolopyrazinyl, oxazolopyrazinyl, pyrazolopyrazinyl, imidazopyrazinyl, pyrrolopyrimidinyl, thienopyrimidinyl, furopyrimidinyl, isothiazolopyrimidinyl, thiazolopyrimidinyl, isoxazolopyrimidinyl, 5 oxazolopyrimidinyl, pyrazolopyrimidinyl, imidazopyrimidinyl, pyrrolopyridazinyl, thienopyridazinyl, furopyridazinyl, isothiazolopyridazinyl, thiazolopyridazinyl, isoxazolopyridazinyl, oxazolopyridazinyl, pyrazolopyridazinyl, imidazopyridazinyl, oxadiazolopyridyl, thiadiazolopyridyl, triazolopyridyl, oxadiazolopyrazinyl, thiadiazolopyrazinyl, triazolopyrazinyl, oxadiazolopyrimidinyl, thiadiazolopyrimidinyl, 10 triazolopyrimidinyl, oxadiazolopyridazinyl, thiadiazolopyridazinyl, triazolopyridazinyl, imidazooxazolyl, imidazothiazolyl, imidazoimidazolyl, isoxazolotriazinyl, isothiazolotriazinyl, pyrazolotriazinyl, oxazolotriazinyl, thiazolotriazinyl, imidazotriazinyl, oxadiazolotriazinyl, thiadiazolotriazinyl, triazolotriazinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl and the like.

15

As used herein before, the term (=O) forms a carbonyl moiety when attached to a carbon atom, a sulfoxide moiety when attached to a sulfur atom and a sulfonyl moiety when two of said terms are attached to a sulfur atom.

20

The term halo is generic to fluoro, chloro, bromo and iodo. As used in the foregoing and hereinafter, polyhalomethyl as a group or part of a group is defined as mono- or polyhalosubstituted methyl, in particular methyl with one or more fluoro atoms, for example, difluoromethyl or trifluoromethyl; polyhaloC₁₋₄alkyl or polyhaloC₁₋₆alkyl as a group or part of a group is defined as mono- or polyhalosubstituted C₁₋₄alkyl or 25 C₁₋₆alkyl, for example, the groups defined in halomethyl, 1,1-difluoro-ethyl and the like. In case more than one halogen atoms are attached to an alkyl group within the definition of polyhalomethyl, polyhaloC₁₋₄alkyl or polyhaloC₁₋₆alkyl, they may be the same or different.

30

The term heterocycle in the definition of R⁷ or R^{7a} is meant to include all the possible isomeric forms of the heterocycles, for instance, pyrrolyl comprises 1*H*-pyrrolyl and 2*H*-pyrrolyl.

35

The carbocycle or heterocycle in the definition of R⁷ or R^{7a} may be attached to the remainder of the molecule of formula (I) through any ring carbon or heteroatom as appropriate, if not otherwise specified. Thus, for example, when the heterocycle is

imidazolyl, it may be 1-imidazolyl, 2-imidazolyl, 4-imidazolyl and the like, or when the carbocycle is naphthalenyl, it may be 1-naphthalenyl, 2-naphthalenyl and the like.

When any variable (eg. R^7 , X_2) occurs more than one time in any constituent, each
5 definition is independent.

Lines drawn from substituents into ring systems indicate that the bond may be attached to any of the suitable ring atoms.

10 For therapeutic use, salts of the compounds of formula (I) are those wherein the counterion is pharmaceutically acceptable. However, salts of acids and bases which are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether
15 pharmaceutically acceptable or not are included within the ambit of the present invention.

The pharmaceutically acceptable addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. The latter can conveniently be obtained by
20 treating the base form with such appropriate acids as inorganic acids, for example, hydrohalic acids, e.g. hydrochloric, hydrobromic and the like; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic,
25 ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted by treatment with alkali into the free base form.

The compounds of formula (I) containing acidic protons may be converted into their
30 therapeutically active non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. primary, secondary and tertiary aliphatic and aromatic amines such as methylamine,
35 ethylamine, propylamine, isopropylamine, the four butylamine isomers, dimethylamine, diethylamine, diethanolamine, dipropylamine, diisopropylamine, di-n-butylamine, pyrrolidine, piperidine, morpholine, trimethylamine, triethylamine,

tripropylamine, quinuclidine, pyridine, quinoline and isoquinoline, the benzathine, *N*-methyl-D-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like. Conversely the salt form can be converted by treatment with acid into the free acid form.

The term addition salt also comprises the hydrates and solvent addition forms which the compounds of formula (I) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

The term "quaternary amine" as used hereinbefore defines the quaternary ammonium salts which the compounds of formula (I) are able to form by reaction between a basic nitrogen of a compound of formula (I) and an appropriate quaternizing agent, such as, for example, an optionally substituted alkylhalide, arylhalide or arylalkylhalide, e.g. methyl iodide or benzyl iodide. Other reactants with good leaving groups may also be used, such as alkyl trifluoromethanesulfonates, alkyl methanesulfonates, and alkyl *p*-toluenesulfonates. A quaternary amine has a positively charged nitrogen. Pharmaceutically acceptable counterions include chloro, bromo, iodo, trifluoroacetate and acetate. The counterion of choice can be introduced using ion exchange resins.

The *N*-oxide forms of the present compounds are meant to comprise the compounds of formula (I) wherein one or several tertiary nitrogen atoms are oxidized to the so-called *N*-oxide.

It will be appreciated that some of the compounds of formula (I) and their *N*-oxides, addition salts, quaternary amines and stereochemically isomeric forms may contain one or more centers of chirality and exist as stereochemically isomeric forms.

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible stereoisomeric forms which the compounds of formula (I), and their *N*-oxides, addition salts, quaternary amines or physiologically functional derivatives may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure as well as each of the individual isomeric forms of formula (I) and their *N*-oxides, salts, solvates or quaternary amines substantially free, *i.e.* associated with less than 10%, preferably less than 5%, in particular less than 2% and most preferably less than 1% of the other

isomers. Thus, when a compound of formula (I) is for instance specified as (E), this means that the compound is substantially free of the (Z) isomer.

In particular, stereogenic centers may have the R- or S-configuration; substituents on bivalent cyclic (partially) saturated radicals may have either the *cis*- or *trans*-

5 configuration. Compounds encompassing double bonds can have an E (entgegen) or Z (zusammen) -stereochemistry at said double bond. The terms *cis*, *trans*, R, S, E and Z are well known to a person skilled in the art.

Stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be embraced within the scope of this invention.

10

Some of the compounds of formula (I) may also exist in their tautomeric form. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

15

Whenever used hereinafter, the term "compounds of formula (I)" is meant to also include their *N*-oxide forms, their salts, their quaternary amines and their stereochemically isomeric forms. Of special interest are those compounds of formula (I) which are stereochemically pure.

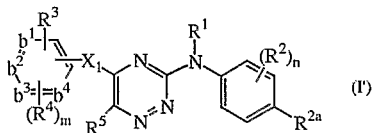
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Whenever used hereinbefore or hereinafter that substituents can be selected each independently out of a list of numerous definitions, such as for example for R⁹ and R¹⁰, all possible combinations are intended which are chemically possible or which lead to chemically stable molecules.

25

An interesting group of compounds are those compounds of formula (I) wherein -a¹=a²-a³=a⁴- represents a bivalent radical of formula -CH=CH-CH=CH- (a-1).

Also an interesting group of compounds are those compounds of formula (I) having the formula



30

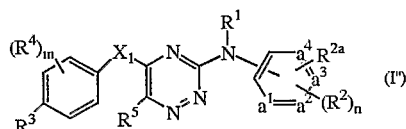
the *N*-oxides, the pharmaceutically acceptable addition salts, the quaternary amines or the stereochemically isomeric forms thereof, wherein

-b¹=b²-b³=b⁴-, R¹, R², R^{2a}, R³, R⁴, R⁵, m, n and X₁ are as defined hereinabove.

Preferably R^{2a} is cyano, aminocarbonyl, C_{1-6} alkyl optionally substituted with cyano or aminocarbonyl, C_{2-6} alkenyl optionally substituted with cyano or aminocarbonyl.

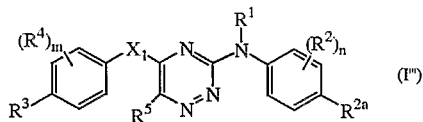
Another interesting group of compounds are those compounds of formula (I) or (I')
 5 wherein $-b^1=b^2-b^3=b^4-$ represents a bivalent radical of formula (b-1).

Yet a further interesting group of compounds are those compounds of formula (I) having the formula



10 the *N*-oxides, the pharmaceutically acceptable addition salts, the quaternary amines or the stereochemically isomeric forms thereof, wherein
 $-a^1=a^2-a^3=a^4-$, R^1 , R^2 , R^{2a} , R^3 , R^4 , R^5 , m , n and X_1 are as defined hereinabove.

Another interesting group of compounds are those compounds of formula (I) having the
 15 formula



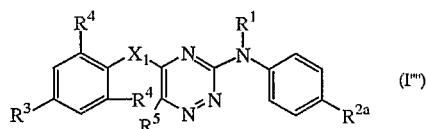
the *N*-oxides, the pharmaceutically acceptable addition salts, the quaternary amines or the stereochemically isomeric forms thereof, wherein
 R^1 , R^2 , R^{2a} , R^3 , R^4 , R^5 , m , n and X_1 are as defined hereinabove.

20 Preferably R^{2a} is cyano, aminocarbonyl, C_{1-6} alkyl substituted with cyano or aminocarbonyl, C_{2-6} alkenyl substituted with cyano or aminocarbonyl.

An interesting embodiment are those compounds of formula (I), (I'), (I'') or (I''') wherein at least one of m or n is other than 0.

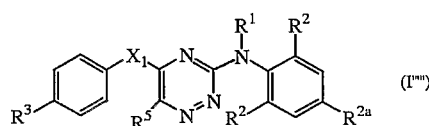
25

Another interesting embodiment encompasses those compounds of formula (I) having the formula



the *N*-oxides, the pharmaceutically acceptable addition salts, the quaternary amines or the stereochemically isomeric forms thereof, wherein R^1 , R^{2a} , R^3 , R^4 , R^5 and X_1 are as defined hereinabove.

- 5 Also an interesting embodiment encompasses those compounds of formula (I) having the formula



the *N*-oxides, the pharmaceutically acceptable addition salts, the quaternary amines or the stereochemically isomeric forms thereof, wherein

- 10 R^1 , R^2 , R^{2a} , R^3 , R^5 and X_1 are as defined hereinabove.

Also particular compounds are those compounds of formula (I), (I'), (I''), (I'''), (I''') or (I''') wherein one or wherever possible more of the following conditions apply :

- a) m is 1, 2 or 3, in particular 2 or 3, more in particular 2, even more in particular m is 2
 15 and said two R^4 substituents are placed in position 2 and 6 (ortho position) in respect of the X_1 moiety;
 b) m is 0;
 c) m is 0 and R^3 is cyano or aminocarbonyl;
 d) X_1 is $-NR^1$ -, $-O$ -, $-C(=O)$ -, C_{1-4} alkanediyl, $-CHOH$ -, $-S(=O)_p$ - or S ; in particular
 20 $-NR^1$ -, O or S ;
 e) n is 0;
 f) n is 1, 2 or 3, in particular 2 or 3, more in particular 2, even more in particular n is 2
 and said two R^2 substituents are placed in position 2 and 6 (ortho position) in respect of the NR^1 -linker;
 25 g) n is 2 and R^{2a} is cyano, aminocarbonyl, C_{1-6} alkyl optionally substituted with cyano or aminocarbonyl, or C_{2-6} alkenyl optionally substituted with cyano or aminocarbonyl;
 h) R^{2a} is cyano, aminocarbonyl, C_{1-6} alkyl substituted with cyano or aminocarbonyl, or C_{2-6} alkenyl substituted with cyano or aminocarbonyl; in particular cyano;
 i) R^3 is NHR^{13} ; $NR^{13}R^{14}$; $-C(=O)-NHR^{13}$; $-C(=O)-NR^{13}R^{14}$; $-C(=O)-R^{15}$;
 30 $-CH=N-NH-C(=O)-R^{16}$; C_{1-6} alkyl substituted with one or more substituents each independently selected from cyano, NR^9R^{10} , $-C(=O)-NR^9R^{10}$, $-C(=O)-C_{1-6}$ alkyl or R^7 ; C_{1-6} alkyl substituted with hydroxy and a second substituent selected from cyano, NR^9R^{10} , $-C(=O)-NR^9R^{10}$, $-C(=O)-C_{1-6}$ alkyl or R^7 ; C_{1-6} alkyloxy C_{1-6} alkyl optionally substituted with one or more substituents each independently selected from cyano,

NR⁹R¹⁰, -C(=O)-NR⁹R¹⁰, -C(=O)-C₁₋₆alkyl or R⁷; C₂₋₆alkenyl substituted with one or more substituents each independently selected from halo, cyano, NR⁹R¹⁰,
 -C(=O)-NR⁹R¹⁰, -C(=O)-C₁₋₆alkyl or R⁷; C₂₋₆alkynyl substituted with one or more
 substituents each independently selected from halo, cyano, NR⁹R¹⁰, -C(=O)-NR⁹R¹⁰,
 5 -C(=O)-C₁₋₆alkyl or R⁷; -C(=N-O-R⁸)-C₁₋₄alkyl; R⁷ or -X₃-R⁷.

Another embodiment encompasses those compounds of formula (I), (I'), (I''), (I'''),
 (I''') or (I''') wherein R³ is NHR¹³, NR¹³R¹⁴, -C(=O)-NHR¹³, -C(=O)-NR¹³R¹⁴,
 -C(=O)-R¹⁵, -CH=N-NH-C(=O)-R¹⁶; C₂₋₆alkyl substituted with cyano or
 10 aminocarbonyl; C₁₋₆alkyl substituted with halo, NR⁹R¹⁰, -C(=O)-NR^{9a}R¹⁰,
 -C(=O)-C₁₋₆alkyl or R⁷; C₁₋₆alkyl substituted with two or more substituents each
 independently selected from halo, cyano, NR⁹R¹⁰, -C(=O)-NR⁹R¹⁰, -C(=O)-C₁₋₆alkyl or
 R⁷; C₁₋₆alkyl substituted with hydroxy and a second substituent selected from halo,
 cyano, NR⁹R¹⁰, -C(=O)-NR⁹R¹⁰, -C(=O)-C₁₋₆alkyl or R⁷; C₁₋₆alkyloxyC₁₋₆alkyl
 15 optionally substituted with one or more substituents each independently selected from
 halo, cyano, NR⁹R¹⁰, -C(=O)-NR⁹R¹⁰, -C(=O)-C₁₋₆alkyl or R⁷; C₂₋₆alkenyl substituted
 with one or more substituents each independently selected from halo, cyano, NR⁹R¹⁰,
 -C(=O)-NR⁹R¹⁰, -C(=O)-C₁₋₆alkyl or R⁷; C₂₋₆alkynyl substituted with one or more
 substituents each independently selected from halo, cyano, NR⁹R¹⁰, -C(=O)-NR⁹R¹⁰,
 20 -C(=O)-C₁₋₆alkyl or R⁷; -C(=N-O-R⁸)-C₁₋₄alkyl; R⁷ or -X₃-R⁷; with R^{9a} representing
 hydroxy; C₁₋₆alkyl; C₁₋₆alkyloxy; C₁₋₆alkylcarbonyl; C₁₋₆alkyloxycarbonyl; amino;
 mono- or di(C₁₋₆alkyl)amino; mono- or di(C₁₋₆alkyl)aminocarbonyl, -CH(=NR¹¹) or R⁷,
 wherein each of the aforementioned C₁₋₆alkyl groups in the definition of R^{9a} may
 optionally and each individually be substituted with one or two substituents each
 25 independently selected from hydroxy,
 C₁₋₆alkyloxy, hydroxyC₁₋₆alkyloxy, carboxyl, C₁₋₆alkyloxycarbonyl, cyano, amino,
 imino, mono- or di(C₁₋₄alkyl)amino, polyhalomethyl, polyhalomethyloxy,
 polyhalomethylthio, -S(=O)_pR⁶, -NH-S(=O)_pR⁶, -C(=O)R⁶, -NHC(=O)H,
 -C(=O)NHNH₂, -NHC(=O)R⁶, -C(=NH)R⁶, R⁷; R^{9a} may also be taken together with R¹⁰
 30 to form a bivalent or trivalent radical of formula (d-1), (d-2), (d-3), (d-4), (d-5), (d-6) or
 (d-7) as defined hereinabove.

Also a preferred embodiment of the present invention encompasses those compounds
 of formula (I), (I'), (I''), (I'''), (I''') or (I''') wherein R¹ is hydrogen.

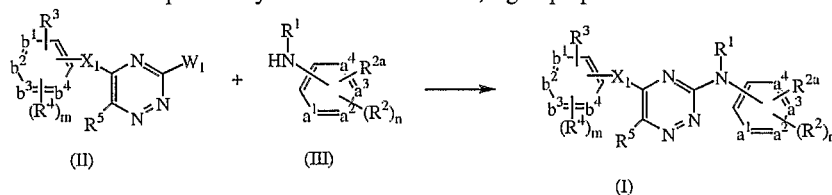
35 Also an interesting group of compounds are those compounds of formula (I), (I'), (I''),
 (I'''), (I''') or (I''') wherein one or more of the following restrictions apply :

- a) R^1 is hydrogen;
 b) X_1 is NH, S or O;
 c) R^5 is hydrogen, C_{1-6} alkyl or halo;
 d) R^{2a} or R^2 is halo, cyano, aminocarbonyl, C_{1-6} alkyloxy, C_{1-6} alkyl, C_{1-6} alkyl
 5 substituted with cyano or C_{2-6} alkenyl substituted with cyano;
 e) n is 0 or 2;
 f) R^3 is C_{1-6} alkyl; cyano; aminocarbonyl; mono or di(C_{1-4} alkyl)aminocarbonyl; C_{1-6} alkyl substituted with cyano or aminocarbonyl; C_{2-6} alkenyl substituted with cyano or aminocarbonyl or mono- or di(C_{1-4} alkyl)aminocarbonyl or $C(=O)NR^9R^{10}$ wherein R^9
 10 and R^{10} are taken together; halo; C_{1-6} alkyloxy optionally substituted with cyano;
 g) m is 0 and R^3 is cyano or aminocarbonyl;
 h) m is 2 and R^4 is C_{1-6} alkyl, halo, C_{1-6} alkyloxy, C_{1-6} alkyl substituted with cyano; in particular said R^4 substituents are placed in position 2 and 6 compared to the X_1 linker.

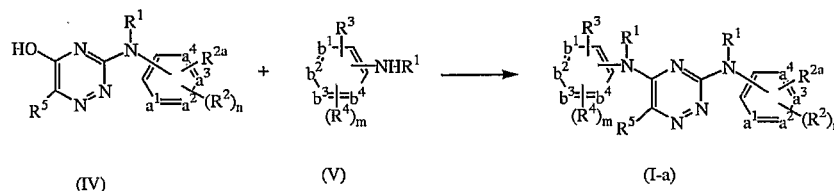
- 15 Also an interesting embodiment of the present invention are those compounds of formula (I), (I'), (I''), (I'''), (I''') or (I''') wherein n is 0, R^{2a} is cyano, m is 2 and R^3 is C_{2-6} alkenyl substituted with cyano.

- Also an interesting embodiment of the present invention are those compounds of
 20 formula (I), (I'), (I''), (I'''), (I''') or (I''') wherein n is 2, R^3 is cyano, m is 0 and R^{2a} is C_{2-6} alkenyl substituted with cyano.

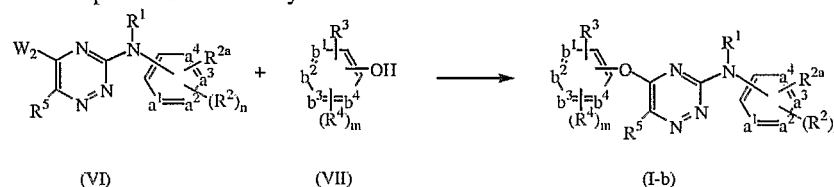
- In general, compounds of formula (I) can be prepared by reacting an intermediate of
 formula (II) wherein W_1 represents a suitable leaving group, such as for example
 25 halogen, e.g. chloro and the like, with an intermediate of formula (III) in the presence of a suitable acid, such as for example camphor sulfonic acid, and a suitable solvent, such as for example tetrahydrofuran or an alcohol, e.g. 2-propanol.



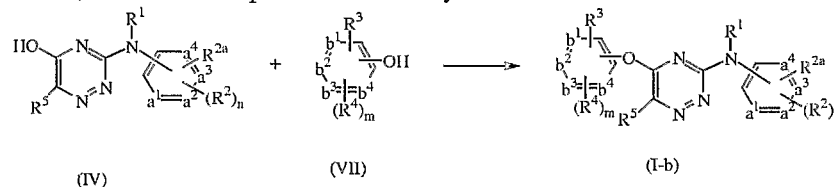
- Compounds of formula (I) wherein X_1 represents NR^1 , said compounds being
 30 represented by formula (I-a), can be prepared by reacting an intermediate of formula (IV) with an intermediate of formula (V) in the presence of $POCl_3$ and optionally in the presence of a suitable base, such as for example *N,N*-di-*n*-propylpropanamine.



Compounds of formula (I) wherein X_1 represents O, said compounds being represented by formula (I-b), can be prepared by reacting an intermediate of formula (VI) wherein W_2 represents a suitable leaving group, such as for example halo, e.g. chloro and the like, with an intermediate of formula (VII) in the presence of a suitable base, such as for example K_2CO_3 or potassium *t*-butoxide (KO *t*-Bu), and a suitable solvent, such as for example acetone or tetrahydrofuran.



Compounds of formula (I-b) can also be prepared by reacting an intermediate of formula (IV) with an intermediate of formula (VII) in the presence of $POCl_3$, a suitable base, such as for example K_2CO_3 or potassium *t*-butoxide (KO *t*-Bu), and a suitable solvent, such as for example acetone or tetrahydrofuran.



The compounds of formula (I) may further be prepared by converting compounds of formula (I) into each other according to art-known group transformation reactions.

The compounds of formula (I) may be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboxylic acid or halo substituted benzenecarboxylic acid, e.g. 3-chlorobenzenecarboxylic acid.

peroxoic acid, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. tert.butyl hydro-peroxide. Suitable solvents are, for example, water, lower alcohols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

5

Compounds of formula (I) wherein R^2 , R^{2a} , R^3 or R^4 is C_{2-6} alkenyl substituted with aminocarbonyl, can be converted into a compound of formula (I) wherein R^2 , R^{2a} , R^3 or R^4 is C_{2-6} alkenyl substituted with cyano by reaction with $POCl_3$.

- 10 Compounds of formula (I) wherein m is zero, can be converted into a compound of formula (I) wherein m is other than zero and R^4 represents halo, by reaction with a suitable halo-introducing agent, such as for example *N*-chlorosuccinimide or *N*-borosuccinimide, or a combination thereof, in the presence of a suitable solvent, such as for example acetic acid.

15

Compounds of formula (I) wherein R^3 represents halo, may be converted into a compound of formula (I) wherein R^3 represents C_{2-6} alkenyl substituted with one or more substituents each independently selected from halo, cyano, NR^9R^{10} , $-C(=O)-NR^9R^{10}$, $-C(=O)-C_{1-6}$ alkyl or R^7 , by reaction with the corresponding

20 C_{2-6} alkene substituted with one or more substituents each independently selected from halo, cyano, NR^9R^{10} , $-C(=O)-NR^9R^{10}$, $-C(=O)-C_{1-6}$ alkyl or R^7 in the presence of a suitable base, such as for example *N,N*-diethyl-ethanamine, a suitable catalyst, such as for example palladium acetate in the presence of triphenylphosphine, and a suitable solvent, such as for example *N,N*-dimethylformamide.

25

Compounds of formula (I) wherein R^{2a} represents halo, may be converted into a compound of formula (I) wherein R^{2a} represents C_{2-6} alkenyl substituted with one or more substituents each independently selected from halo, cyano, NR^9R^{10} , $-C(=O)-NR^9R^{10}$, $-C(=O)-C_{1-6}$ alkyl or R^7 , by reaction with the corresponding

30 C_{2-6} alkene substituted with one or more substituents each independently selected from halo, cyano, NR^9R^{10} , $-C(=O)-NR^9R^{10}$, $-C(=O)-C_{1-6}$ alkyl or R^7 in the presence of a suitable base, such as for example *N,N*-diethyl-ethanamine, a suitable catalyst, such as for example palladium acetate in the presence of triphenylphosphine, and a suitable solvent, such as for example *N,N*-dimethylformamide.

35

Compounds of formula (I) wherein R^1 represents C_{1-6} alkyloxycarbonyl, can be converted into a compound of formula (I) wherein R^1 represents hydrogen, by reaction with a suitable acid, such as for example trifluoroacetic acid.

- 5 Some of the compounds of formula (I) and some of the intermediates in the present invention may contain an asymmetric carbon atom. Pure stereochemically isomeric forms of said compounds and said intermediates can be obtained by the application of art-known procedures. For example, diastereoisomers can be separated by physical methods such as selective crystallization or chromatographic techniques, e.g. counter
- 10 current distribution, liquid chromatography and the like methods. Enantiomers can be obtained from racemic mixtures by first converting said racemic mixtures with suitable resolving agents such as, for example, chiral acids, to mixtures of diastereomeric salts or compounds; then physically separating said mixtures of diastereomeric salts or compounds by, for example, selective crystallization or chromatographic techniques,
- 15 e.g. liquid chromatography and the like methods; and finally converting said separated diastereomeric salts or compounds into the corresponding enantiomers. Pure stereochemically isomeric forms may also be obtained from the pure stereochemically isomeric forms of the appropriate intermediates and starting materials, provided that the intervening reactions occur stereospecifically.

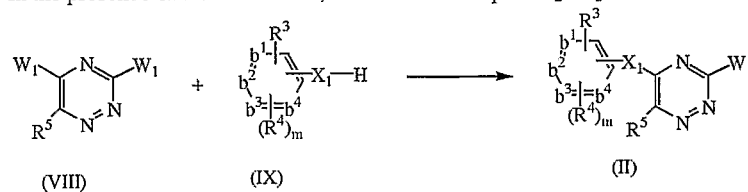
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An alternative manner of separating the enantiomeric forms of the compounds of formula (I) and intermediates involves liquid chromatography, in particular liquid chromatography using a chiral stationary phase.

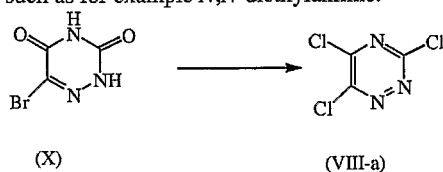
- 25 Some of the intermediates and starting materials are known compounds and may be commercially available or may be prepared according to art-known procedures.

Intermediates of formula (II) can be prepared by reacting an intermediate of formula (VIII) wherein W_1 is defined as hereinabove, with an intermediate of formula (IX) in

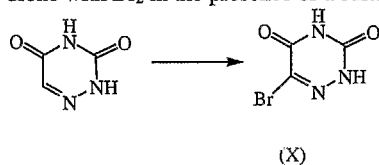
30 the presence of a suitable solvent, such as for example tetrahydrofuran, and optionally in the presence of a suitable base, such as for example Na_2CO_3 .



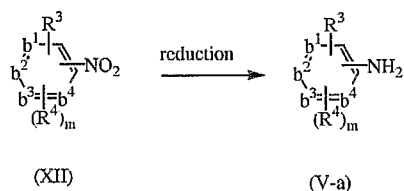
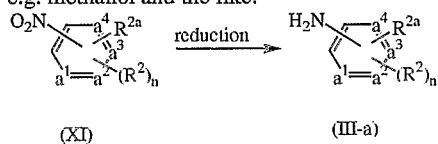
Intermediates of formula (VIII) wherein W_1 is chloro and R^5 is chloro, said intermediates being represented by formula (VIII-a), can be prepared by reacting an intermediate of formula (X) with $POCl_3$ and PCl_5 in the presence of a suitable base, such as for example *N,N*-diethylaniline.



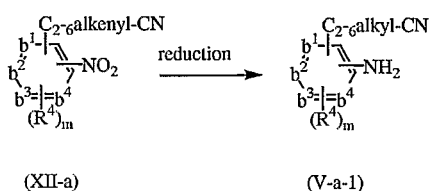
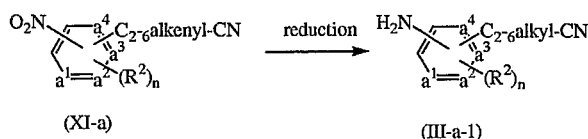
Intermediates of formula (X) can be prepared by reacting 1,2,4-triazine-3,5 (2*H*,4*H*) dione with Br_2 in the presence of a suitable solvent, such as for example H_2O .



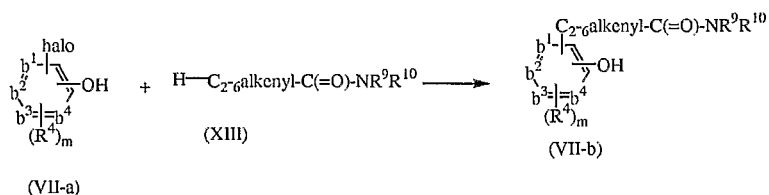
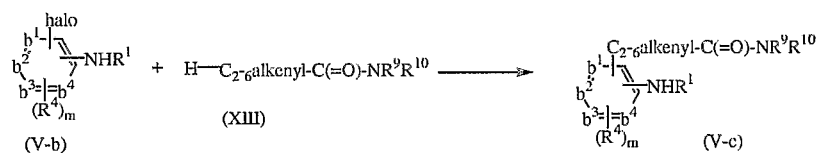
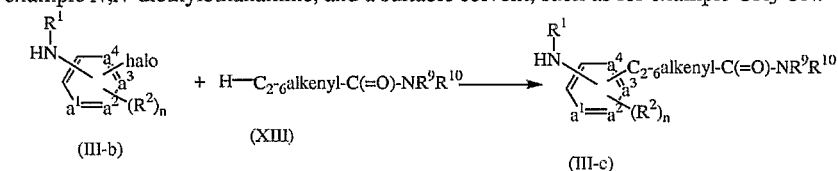
- 10 Intermediates of formula (III) or (V) wherein R^1 is hydrogen, said intermediates being represented by formula (III-a) and (V-a), can be prepared by reacting an intermediate of formula (XI) or (XII) with a suitable reducing agent, such as Fe, in the presence of NH_4Cl and a suitable solvent, such as for example tetrahydrofuran, H_2O and an alcohol, e.g. methanol and the like.



- 15 Intermediates of formula (III-a) or (V-a) wherein R^{2a} respectively R^3 represents C_{2-6} alkyl substituted with cyano, said intermediates being represented by formula (III-a-1) and (V-a-1), can be prepared by reacting an intermediate of formula (XI-a) respectively (XII-a) with Pd/C in the presence of a suitable solvent, such as for example an alcohol, e.g. ethanol and the like.

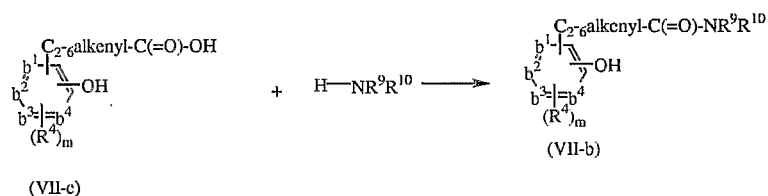
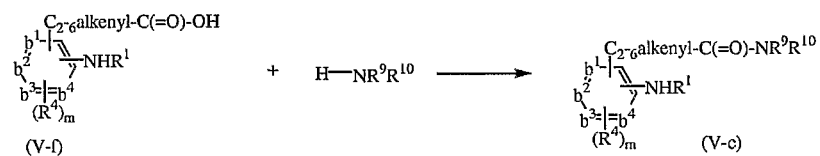
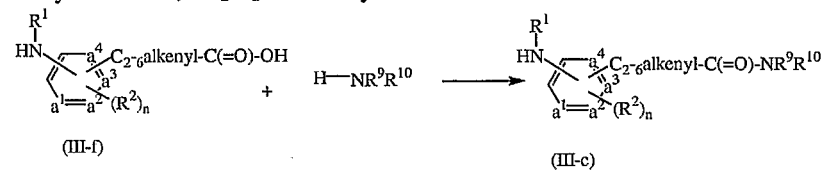


Intermediates of formula (III), (V) or (VII) wherein R^{2a} respectively R^3 is halo, said intermediates being represented by formula (III-b), (V-b) and (VII-a), may be converted into an intermediate of formula (III) respectively (V) or (VII) wherein R^{2a} respectively R^3 is $\text{C}_{2-6}\text{alkenyl}$ substituted with $\text{C}(=\text{O})\text{NR}^9\text{R}^{10}$, said intermediates being represented by formula (III-c), (V-c) and (VII-b) by reaction with an intermediate of formula (XIII) in the presence of $\text{Pd}(\text{OAc})_2$, $\text{P}(o\text{-Tol})_3$, a suitable base, such as for example N,N -diethylethanamine, and a suitable solvent, such as for example $\text{CH}_3\text{-CN}$.

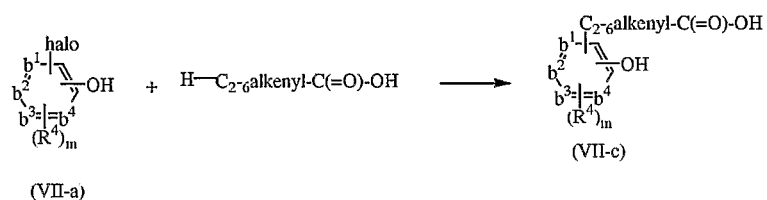
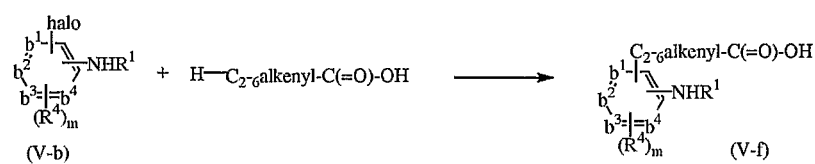
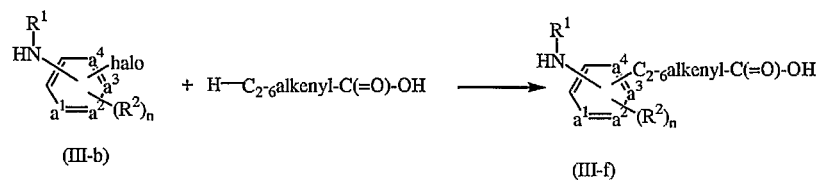


Intermediates of formula (III-c), (V-c) and (VII-b) can also be prepared by reacting an intermediate of formula (III-f), (V-f) and (VII-c) with $\text{H-NR}^9\text{R}^{10}$ in the presence of

oxalyl chloride and in the presence of a suitable solvent, such as for example *N,N*-dimethylformamide, CH_2Cl_2 and tetrahydrofuran.

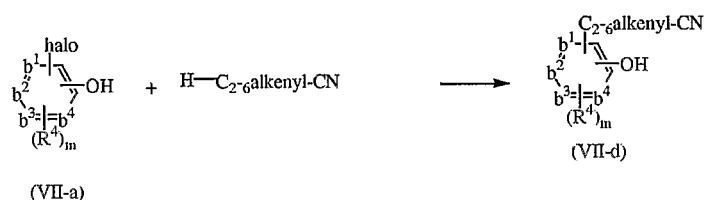
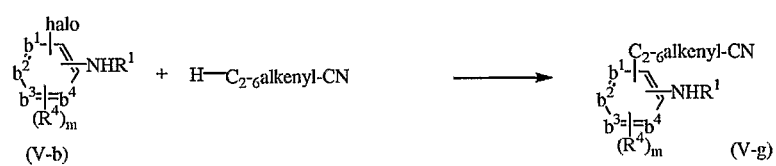
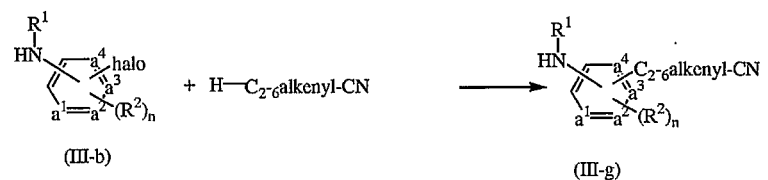


- Intermediates of formula (III-f), (V-f) and (VII-c) can be prepared by reacting an
 5 intermediate of formula (III-b), (V-b) and (VII-a), with $\text{H} - \text{C}_2-6\text{alkenyl} - \text{C}(=\text{O}) - \text{OH}$ in the presence of $\text{Pd}(\text{OAc})_2$, $\text{P}(o\text{-Tol})_3$, a suitable base, such as for example *N,N*-diethylethanamine, and a suitable solvent, such as for example $\text{CH}_3\text{-CN}$.



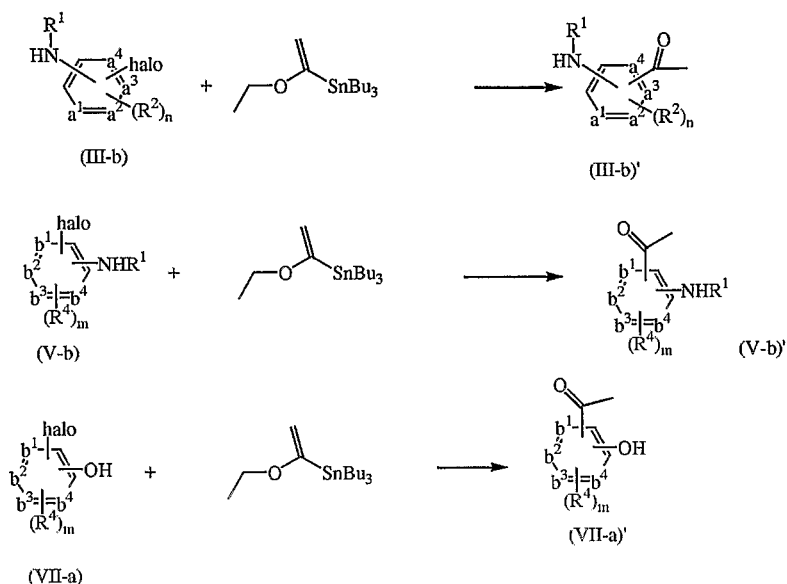
Intermediates of formula (III-b), (V-b) and (VII-a), may also be converted into an intermediate of formula (III) respectively (V) or (VII) wherein R^{2a} respectively R³ is C₂₋₆alkenyl substituted with CN, said intermediates being represented by formula

- 5 (III-g), (V-g) and (VII-d) by reaction with H-C₂₋₆alkenyl-CN in the presence of Pd(OAc)₂, P(*o*-Tol)₃, a suitable base, such as for example *N,N*-diethylethanamine, and a suitable solvent, such as for example CH₃-CN.



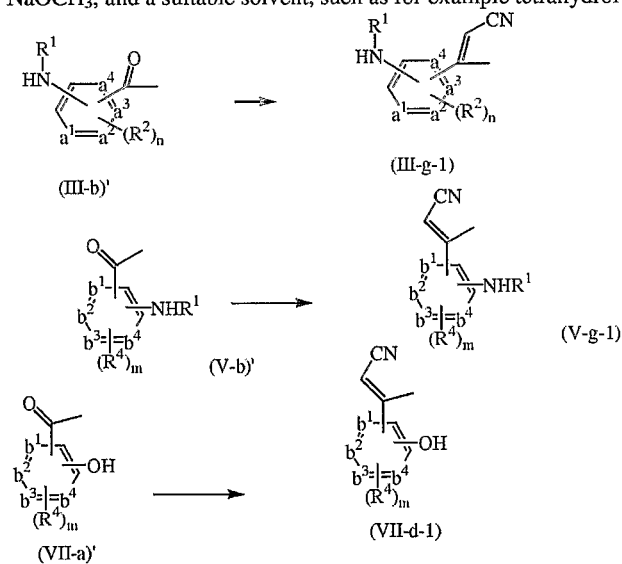
Intermediates of formula (III-b), (V-b) and (VII-a) can also be converted into an intermediate of formula (III-b)', (V-b)' and (VII-a)' by reaction with tributyl(1-ethoxyethenyl)stannane in the presence of Pd(OAc)₂, P(*o*-Tol)₃, a suitable base, such as

5 for example *N,N*-diethylethanamine, and a suitable solvent, such as for example CH₃-CN.

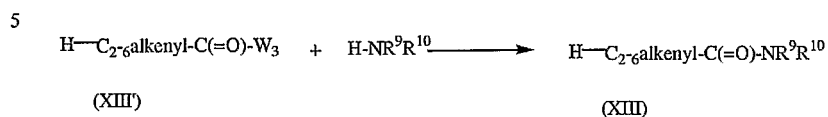


The intermediates of formula (III-b)', (V-b)' and (VII-a)' can be converted into an intermediate of formula (III-g-1), (V-g-1) and (VII-d-1) by reaction with diethylcyanomethylphosphonate in the presence of a suitable base, such as for example

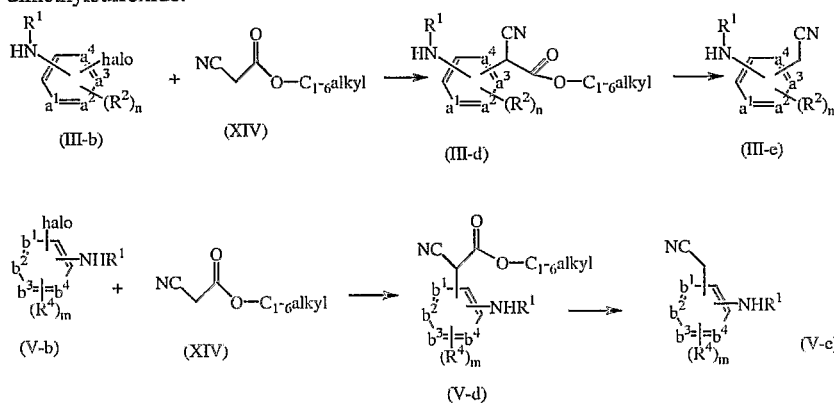
- 5 NaOCH₃, and a suitable solvent, such as for example tetrahydrofuran.



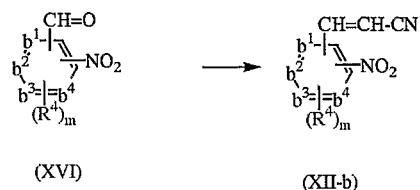
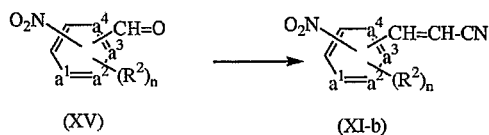
Intermediates of formula (XIII) can be prepared by reacting an intermediate of formula (XIII') wherein W_3 represents a suitable leaving group, such as for example halogen, e.g. chloro, with $H-NR^9R^{10}$ in the presence of a suitable solvent, such as for example diethylether and tetrahydrofuran.



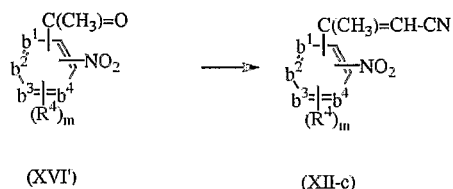
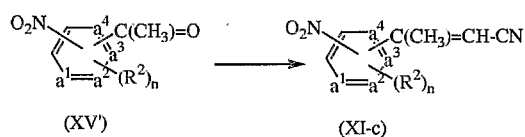
Intermediates of formula (III-b) and (V-b) may also be converted into an intermediate of formula (III-d) respectively (V-d) by reaction with an intermediate of formula (XIV) in the presence of $Pd_2(dba)_3$, $P(t-Bu)_3$, Na_3PO_4 and a suitable solvent, such as for example toluene. The intermediates of formula (III-d) respectively (V-d) may further be converted into an intermediate of formula (III-e) respectively (V-e) by reaction with NaCl in the presence of a suitable solvent, such as for example H_2O and dimethylsulfoxide.



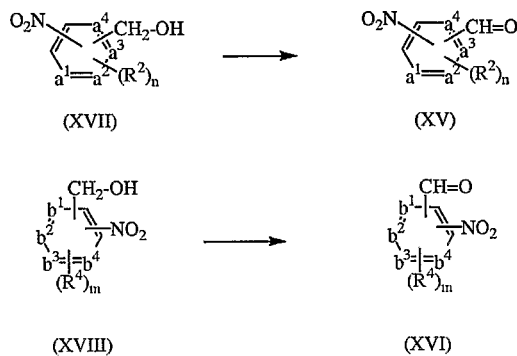
15 Intermediates of formula (XI) or (XII) wherein R^{2a} respectively R^3 represents cyanovinyl, said intermediates being represented by formula (XI-b) and (XII-b), can be prepared by reacting an intermediate of formula (XV) respectively (XVI) with diethylcyanomethylphosphonate in the presence of a suitable base, such as for example $NaOCH_3$, and a suitable solvent, such as for example tetrahydrofuran.



- Intermediates of formula (XI) or (XII) wherein R^{2a} respectively R^3 represents $-\text{C}(\text{CH}_3)=\text{CH}-\text{CN}$, said intermediates being represented by formula (XI-c) and (XII-c), can be prepared by reacting an intermediate of formula (XV') respectively (XVI') with
- 5 diethylcyanomethylphosphonate in the presence of a suitable base, such as for example NaOCH_3 , and a suitable solvent, such as for example tetrahydrofuran.

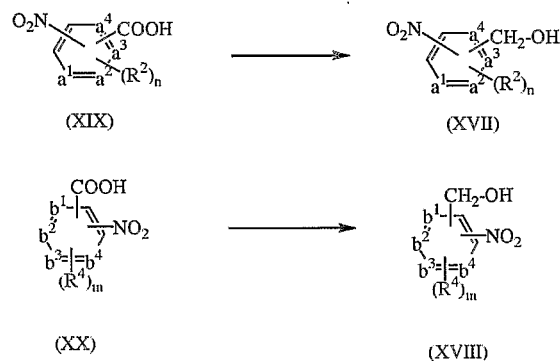


- Intermediates of formula (XV) and (XVI) can be prepared by reacting an intermediate
- 10 of formula (XVII) respectively (XVIII) with a suitable oxidizing agent, such as for example MnO_2 , in the presence of a suitable solvent, such as for example acetone.



Intermediates of formula (XVII) and (XVIII) can be prepared by reacting an intermediate of formula (XIX) respectively (XX) with NaBH₄ in the presence of ethylchloroformate, a suitable base, such as for example *N,N*-diethylethanamine, and a suitable solvent, such as for example tetrahydrofuran.

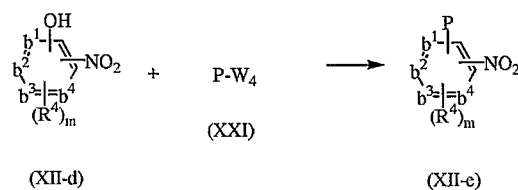
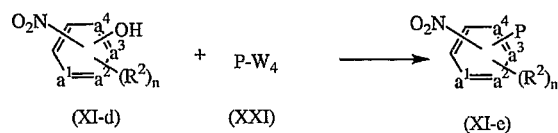
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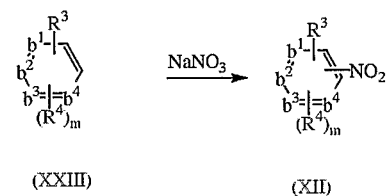
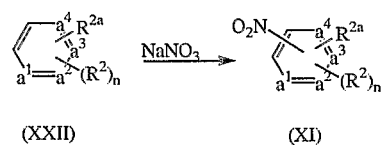
Intermediates of formula (XI) and (XII) wherein R^{2a} respectively R³ represent hydroxy, said intermediates being represented by formula (XI-d) respectively (XII-d), can be converted into an intermediate of formula (XI) respectively (XII) wherein R^{2a} respectively R³ represent C₁₋₆alkyloxy wherein the C₁₋₆alkyl may optionally be substituted with cyano, said R^{2a} respectively R³ being represented by P and said intermediates being represented by formula (XI-e) respectively (XII-e), by reaction with an intermediate of formula (XXI) wherein W₄ represents a suitable leaving group, such as for example halogen, e.g. chloro and the like, in the presence of NaI, a suitable base, such as for example K₂CO₃, and a suitable solvent, such as for example acetone.

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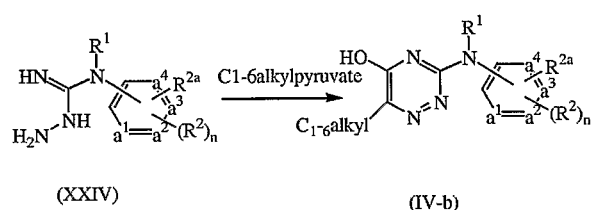
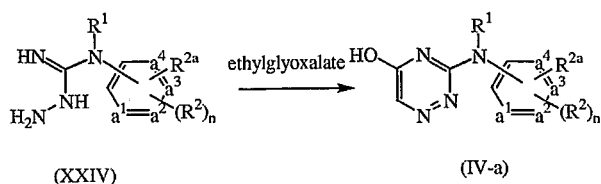
Intermediates of formula (XI) and (XII) can be prepared by reacting an intermediate of formula (XXII) respectively (XXIII) with NaNO₃ in the presence of CH₃SO₃H.



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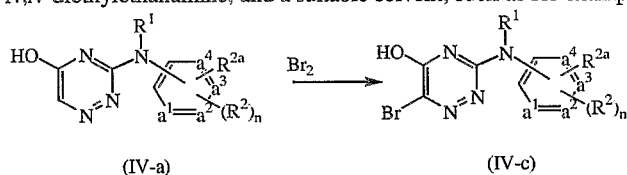
Intermediates of formula (IV) wherein R⁵ is hydrogen respectively C₁₋₆alkyl, said intermediates being represented by formula (IV-a) respectively (IV-b), can be prepared by reacting an intermediate of formula (XXIV) with ethylglyoxalate respectively C₁₋₆alkylpyruvate in the presence of a suitable solvent, such as for example an alcohol,

10 e.g. methanol.

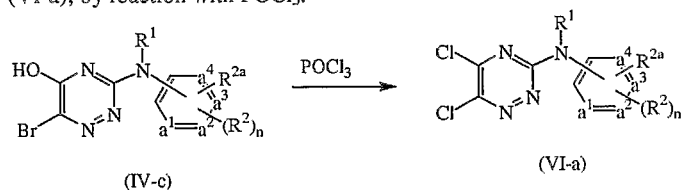


Intermediates of formula (IV-a) can be converted into an intermediate of formula (IV) wherein R⁵ represents bromo, said intermediate being represented by formula (IV-c), by reaction with Br₂ in the presence of a suitable base, such as for example

5 *N,N*-diethylethanamine, and a suitable solvent, such as for example dimethylsulfoxide.

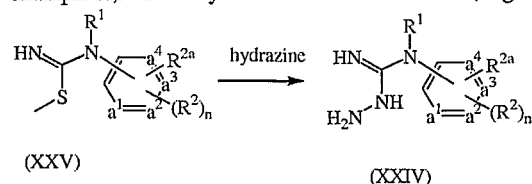


Intermediates of formula (IV-c) can be converted into an intermediate of formula (VI) wherein R⁵ and W₂ represent chloro, said intermediate being represented by formula (VI-a), by reaction with POCl₃.

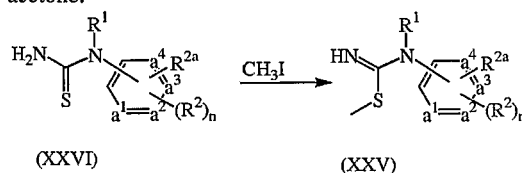


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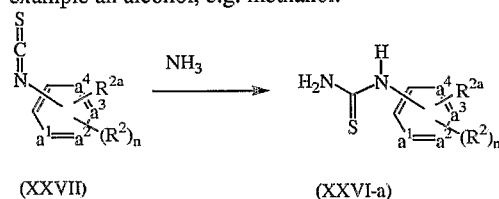
Intermediates of formula (XXIV) can be prepared by reacting an intermediate of formula (XXV) with hydrazine in the presence of a suitable solvent, such as for example *N,N*-dimethylformamide and an alcohol, e.g. methanol.



Intermediates of formula (XXV) can be prepared by reacting an intermediate of formula (XXVI) with CH_3I in the presence of a suitable solvent, such as for example acetone.



- 5 Intermediates of formula (XXVI) wherein R^1 represents hydrogen, said intermediates being represented by formula (XXVI-a), can be prepared by reacting an intermediate of formula (XXVII) with ammonia in the presence of a suitable solvent, such as for example an alcohol, e.g. methanol.



10

- The compounds of formula (I), (I'), (I''), (I'''), (I''') and (I''') show antiretroviral properties (reverse transcriptase inhibiting properties), in particular against Human Immunodeficiency Virus (HIV), which is the aetiological agent of Acquired Immune Deficiency Syndrome (AIDS) in humans. The HIV virus preferentially infects human T-4 cells and destroys them or changes their normal function, particularly the coordination of the immune system. As a result, an infected patient has an ever decreasing number of T-4 cells, which moreover behave abnormally. Hence, the immunological defense system is unable to combat infections and neoplasms and the HIV infected subject usually dies by opportunistic infections such as pneumonia, or by cancers. Other conditions associated with HIV infection include thrombocytopenia, Kaposi's sarcoma and infection of the central nervous system characterized by progressive demyelination, resulting in dementia and symptoms such as, progressive dysarthria, ataxia and disorientation. HIV infection further has also been associated with peripheral neuropathy, progressive generalized lymphadenopathy (PGL) and AIDS-related complex (ARC).
- 25

The present compounds also show activity against (multi) drug resistant HIV strains, in particular (multi) drug resistant HIV-1 strains, more in particular the present

compounds show activity against HIV strains, especially HIV-1 strains, that have acquired resistance to one or more art-known non-nucleoside reverse transcriptase inhibitors. Art-known non-nucleoside reverse transcriptase inhibitors are those non-nucleoside reverse transcriptase inhibitors other than the present compounds and
5 known to the person skilled in the art, in particular commercial non-nucleoside reverse transcriptase inhibitors. The present compounds also have little or no binding affinity to human α -1 acid glycoprotein; human α -1 acid glycoprotein does not or only weakly affect the anti HIV activity of the present compounds.

10 Due to their antiretroviral properties, particularly their anti-HIV properties, especially their anti-HIV-1-activity, the compounds of formula (I), their *N*-oxides, pharmaceutically acceptable addition salts, quaternary amines and stereochemically isomeric forms thereof, are useful in the treatment of individuals infected by HIV and for the prophylaxis of these infections. In general, the compounds of the present
15 invention may be useful in the treatment of warm-blooded animals infected with viruses whose existence is mediated by, or depends upon, the enzyme reverse transcriptase. Conditions which may be prevented or treated with the compounds of the present invention, especially conditions associated with HIV and other pathogenic retroviruses, include AIDS, AIDS-related complex (ARC), progressive generalized
20 lymphadenopathy (PGL), as well as chronic Central Nervous System diseases caused by retroviruses, such as, for example HIV mediated dementia and multiple sclerosis.

The compounds of the present invention or any subgroup thereof may therefore be used as medicines against above-mentioned conditions. Said use as a medicine or method of
25 treatment comprises the administration to HIV-infected subjects of an amount effective to combat the conditions associated with HIV and other pathogenic retroviruses, especially HIV-1. In particular, the compounds of formula (I) may be used in the manufacture of a medicament for the treatment or the prevention of HIV infections.

30 In view of the utility of the compounds of formula (I), there is provided a method of treating warm-blooded animals, including humans, suffering from or a method of preventing warm-blooded animals, including humans, to suffer from viral infections, especially HIV infections. Said method comprises the administration, preferably oral administration, of an effective amount of a compound of formula (I), a *N*-oxide form, a
35 pharmaceutically acceptable addition salt, a quaternary amine or a possible stereoisomeric form thereof, to warm-blooded animals, including humans.

The present invention also provides compositions for treating viral infections comprising a therapeutically effective amount of a compound of formula (I) and a pharmaceutically acceptable carrier or diluent.

- 5 The compounds of the present invention or any subgroup thereof may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form, as the
- 10 active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, particularly, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the
- 15 compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules, and tablets.
- 20 Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in
- 25 which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous
- 30 administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be
- 35 administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment. The compounds of the present invention may also be administered via inhalation or insufflation by means of methods and formulations employed in the art for

administration via this way. Thus, in general the compounds of the present invention may be administered to the lungs in the form of a solution, a suspension or a dry powder. Any system developed for the delivery of solutions, suspensions or dry powders via oral or nasal inhalation or insufflation are suitable for the administration of the present compounds.

To aid solubility of the compounds of formula (I), suitable ingredients, e.g. cyclodextrins, may be included in the compositions. Appropriate cyclodextrins are α -, β -, γ -cyclodextrins or ethers and mixed ethers thereof wherein one or more of the hydroxy groups of the anhydroglucose units of the cyclodextrin are substituted with C₁-alkyl, particularly methyl, ethyl or isopropyl, e.g. randomly methylated β -CD; hydroxyC₁-alkyl, particularly hydroxyethyl, hydroxy-propyl or hydroxybutyl; carboxyC₁-alkyl, particularly carboxymethyl or carboxy-ethyl; C₁-alkylcarbonyl, particularly acetyl. Especially noteworthy as complexants and/or solubilizers are β -CD, randomly methylated β -CD, 2,6-dimethyl- β -CD, 2-hydroxyethyl- β -CD, 2-hydroxyethyl- β -CD, 2-hydroxypropyl- β -CD and (2-carboxymethoxy)propyl- β -CD, and in particular 2-hydroxypropyl- β -CD (2-HP- β -CD).

The term mixed ether denotes cyclodextrin derivatives wherein at least two cyclodextrin hydroxy groups are etherified with different groups such as, for example, hydroxy-propyl and hydroxyethyl.

The average molar substitution (M.S.) is used as a measure of the average number of moles of alkoxy units per mole of anhydroglucose. The average substitution degree (D.S.) refers to the average number of substituted hydroxyls per anhydroglucose unit. The M.S. and D.S. value can be determined by various analytical techniques such as nuclear magnetic resonance (NMR), mass spectrometry (MS) and infrared spectroscopy (IR). Depending on the technique used, slightly different values may be obtained for one given cyclodextrin derivative. Preferably, as measured by mass spectrometry, the M.S. ranges from 0.125 to 10 and the D.S. ranges from 0.125 to 3.

Other suitable compositions for oral or rectal administration comprise particles consisting of a solid dispersion comprising a compound of formula (I) and one or more appropriate pharmaceutically acceptable water-soluble polymers.

The term "a solid dispersion" used hereinafter defines a system in a solid state (as opposed to a liquid or gaseous state) comprising at least two components, in casu the

compound of formula (I) and the water-soluble polymer, wherein one component is dispersed more or less evenly throughout the other component or components (in case additional pharmaceutically acceptable formulating agents, generally known in the art, are included, such as plasticizers, preservatives and the like). When said dispersion of
5 the components is such that the system is chemically and physically uniform or homogenous throughout or consists of one phase as defined in thermo-dynamics, such a solid dispersion will be called "a solid solution". Solid solutions are preferred physical systems because the components therein are usually readily bioavailable to the organisms to which they are administered. This advantage can probably be explained
10 by the ease with which said solid solutions can form liquid solutions when contacted with a liquid medium such as the gastro-intestinal juices. The ease of dissolution may be attributed at least in part to the fact that the energy required for dissolution of the components from a solid solution is less than that required for the dissolution of components from a crystalline or microcrystalline solid phase.

15 The term "a solid dispersion" also comprises dispersions which are less homogenous throughout than solid solutions. Such dispersions are not chemically and physically uniform throughout or comprise more than one phase. For example, the term "a solid dispersion" also relates to a system having domains or small regions wherein
20 amorphous, microcrystalline or crystalline compound of formula (I), or amorphous, microcrystalline or crystalline water-soluble polymer, or both, are dispersed more or less evenly in another phase comprising water-soluble polymer, or compound of formula (I), or a solid solution comprising compound of formula (I) and water-soluble polymer. Said domains are regions within the solid dispersion distinctively marked by
25 some physical feature, small in size, and evenly and randomly distributed throughout the solid dispersion.

Various techniques exist for preparing solid dispersions including melt-extrusion, spray-drying and solution-evaporation.

30 The solution-evaporation process comprises the following steps :
a) dissolving the compound of formula (I) and the water-soluble polymer in an appropriate solvent, optionally at elevated temperatures;
b) heating the solution resulting under point a), optionally under vacuum, until the
35 solvent is evaporated. The solution may also be poured onto a large surface so as to form a thin film, and evaporating the solvent therefrom.

In the spray-drying technique, the two components are also dissolved in an appropriate solvent and the resulting solution is then sprayed through the nozzle of a spray dryer followed by evaporating the solvent from the resulting droplets at elevated temperatures.

5

The preferred technique for preparing solid dispersions is the melt-extrusion process comprising the following steps :

- a) mixing a compound of formula (I) and an appropriate water-soluble polymer,
- b) optionally blending additives with the thus obtained mixture,
- 10 c) heating and compounding the thus obtained blend until one obtains a homogenous melt,
- d) forcing the thus obtained melt through one or more nozzles; and
- e) cooling the melt till it solidifies.

15

The terms "melt" and "melting" should be interpreted broadly. These terms not only mean the alteration from a solid state to a liquid state, but can also refer to a transition to a glassy state or a rubbery state, and in which it is possible for one component of the mixture to get embedded more or less homogeneously into the other. In particular cases, one component will melt and the other component(s) will dissolve in the melt
20 thus forming a solution, which upon cooling may form a solid solution having advantageous dissolution properties.

25

After preparing the solid dispersions as described hereinabove, the obtained products can be optionally milled and sieved.

The solid dispersion product may be milled or ground to particles having a particle size of less than 600 μm , preferably less than 400 μm and most preferably less than 125 μm .

30

The particles prepared as described hereinabove can then be formulated by conventional techniques into pharmaceutical dosage forms such as tablets and capsules.

35

It will be appreciated that a person of skill in the art will be able to optimize the parameters of the solid dispersion preparation techniques described above, such as the most appropriate solvent, the working temperature, the kind of apparatus being used, the rate of spray-drying, the throughput rate in the melt-extruder

The water-soluble polymers in the particles are polymers that have an apparent viscosity, when dissolved at 20°C in an aqueous solution at 2 % (w/v), of 1 to 5000 mPa.s more preferably of 1 to 700 mPa.s, and most preferred of 1 to 100 mPa.s. For example, suitable water-soluble polymers include alkylcelluloses, hydroxyalkyl-
5 celluloses, hydroxyalkyl alkylcelluloses, carboxyalkylcelluloses, alkali metal salts of carboxyalkylcelluloses, carboxyalkylalkylcelluloses, carboxyalkylcellulose esters, starches, pectines, chitin derivates, di-, oligo- and polysaccharides such as trehalose, alginic acid or alkali metal and ammonium salts thereof, carrageenans, galactomannans, tragacanth, agar-agar, gummi arabicum, guar gummi and xanthan gummi, polyacrylic
10 acids and the salts thereof, polymethacrylic acids and the salts thereof, methacrylate copolymers, polyvinylalcohol, polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone with vinyl acetate, combinations of polyvinylalcohol and polyvinylpyrrolidone, polyalkylene oxides and copolymers of ethylene oxide and propylene oxide. Preferred water-soluble polymers are hydroxypropyl
15 methylcelluloses.

Also one or more cyclodextrins can be used as water soluble polymer in the preparation of the above-mentioned particles as is disclosed in WO 97/18839. Said cyclodextrins include the pharmaceutically acceptable unsubstituted and substituted cyclodextrins
20 known in the art, more particularly α , β or γ cyclodextrins or the pharmaceutically acceptable derivatives thereof.

Substituted cyclodextrins which can be used to prepare the above described particles include polyethers described in U.S. Patent 3,459,731. Further substituted
25 cyclodextrins are ethers wherein the hydrogen of one or more cyclodextrin hydroxy groups is replaced by C₁₋₆alkyl, hydroxyC₁₋₆alkyl, carboxy-C₁₋₆alkyl or C₁₋₆alkyloxycarbonylC₁₋₆alkyl or mixed ethers thereof. In particular such substituted cyclodextrins are ethers wherein the hydrogen of one or more cyclodextrin hydroxy groups is replaced by C₁₋₃alkyl, hydroxyC₂₋₄alkyl or carboxyC₁₋₂alkyl or more in
30 particular by methyl, ethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, carboxy-methyl or carboxyethyl.

Of particular utility are the β -cyclodextrin ethers, e.g. dimethyl- β -cyclodextrin as described in Drugs of the Future, Vol. 9, No. 8, p. 577-578 by M. Nogradi (1984) and
35 polyethers, e.g. hydroxypropyl β -cyclodextrin and hydroxyethyl β -cyclodextrin, being examples. Such an alkyl ether may be a methyl ether with a degree of substitution of about 0.125 to 3, e.g. about 0.3 to 2. Such a hydroxypropyl cyclodextrin may for

example be formed from the reaction between β -cyclodextrin and propylene oxide and may have a MS value of about 0.125 to 10, e.g. about 0.3 to 3.

Another type of substituted cyclodextrins is sulfobutylcyclodextrines.

5

The ratio of the compound of formula (I) over the water soluble polymer may vary widely. For example ratios of 1/100 to 100/1 may be applied. Interesting ratios of the compound of formula (I) over cyclodextrin range from about 1/10 to 10/1. More interesting ratios range from about 1/5 to 5/1.

10

It may further be convenient to formulate the compounds of formula (I) in the form of nanoparticles which have a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than 1000 nm. Useful surface modifiers are believed to include those which physically adhere to the surface of the compound of formula (I) but do not chemically bond to said compound.

15

Suitable surface modifiers can preferably be selected from known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products and surfactants. Preferred surface modifiers include nonionic and anionic surfactants.

20

Yet another interesting way of formulating the compounds of formula (I) involves a pharmaceutical composition whereby the compounds of formula (I) are incorporated in hydrophilic polymers and applying this mixture as a coat film over many small beads, thus yielding a composition which can conveniently be manufactured and which is suitable for preparing pharmaceutical dosage forms for oral administration.

25

Said beads comprise a central, rounded or spherical core, a coating film of a hydrophilic polymer and a compound of formula (I) and optionally a seal-coating layer.

30

Materials suitable for use as cores in the beads are manifold, provided that said materials are pharmaceutically acceptable and have appropriate dimensions and firmness. Examples of such materials are polymers, inorganic substances, organic substances, and saccharides and derivatives thereof.

35

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage.

Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including
5 scored or coated tablets), capsules, pills, powder packets, wafers, suppositories, injectable solutions or suspensions and the like, and segregated multiples thereof.

Those of skill in the treatment of HIV-infection could determine the effective daily amount from the test results presented here. In general it is contemplated that an
10 effective daily amount would be from 0.01 mg/kg to 50 mg/kg body weight, more preferably from 0.1 mg/kg to 10 mg/kg body weight. It may be appropriate to administer the required dose as two, three, four or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms, for example, containing 1 to 1000 mg, and in particular 5 to 200 mg of active
15 ingredient per unit dosage form.

The exact dosage and frequency of administration depends on the particular compound of formula (I) used, the particular condition being treated, the severity of the condition being treated, the age, weight and general physical condition of the particular patient as
20 well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention. The effective daily amount ranges mentioned hereinabove are therefore only guidelines and
25 are not intended to limit the scope or use of the invention to any extent.

The present compounds of formula (I) can be used alone or in combination with other therapeutic agents, such as anti-virals, antibiotics, immunomodulators or vaccines for the treatment of viral infections. They may also be used alone or in combination with
30 other prophylactic agents for the prevention of viral infections. The present compounds may be used in vaccines and methods for protecting individuals against viral infections over an extended period of time. The compounds may be employed in such vaccines either alone or together with other compounds of this invention or together with other anti-viral agents in a manner consistent with the conventional utilization of reverse
35 transcriptase inhibitors in vaccines. Thus, the present compounds may be combined with pharmaceutically acceptable adjuvants conventionally employed in vaccines and

administered in prophylactically effective amounts to protect individuals over an extended period of time against HIV infection.

Also, the combination of one or more additional antiretroviral compounds and a
 5 compound of formula (I) can be used as a medicine. Thus, the present invention also relates to a product containing (a) a compound of formula (I), and (b) one or more additional antiretroviral compounds, as a combined preparation for simultaneous, separate or sequential use in anti-HIV treatment. The different drugs may be combined in a single preparation together with pharmaceutically acceptable carriers. Said other
 10 antiretroviral compounds may be known antiretroviral compounds such as suramine, pentamidine, thymopentin, castanospermine, dextran (dextran sulfate), foscarnet-sodium (trisodium phosphono formate); nucleoside reverse transcriptase inhibitors, e.g. zidovudine (3'-azido-3'-deoxythymidine, AZT), didanosine (2',3'-dideoxyinosine; ddI), zalcitabine (dideoxycytidine, ddC) or lamivudine (2'-3'-dideoxy-3'-thiacytidine, 3TC), stavudine (2',3'-didehydro-3'-deoxythymidine, d4T), abacavir and the like; non-
 15 nucleoside reverse transcriptase inhibitors such as nevirapine (11-cyclopropyl-5,11-dihydro-4-methyl-6*H*-dipyrido-[3,2-*b*:2',3'-*c*][1,4]diazepin-6-one), efavirenz, delavirdine, TMC-120, TMC-125 and the like; phosphonate reverse transcriptase inhibitors, e.g. tenofovir and the like; compounds of the TIBO (tetrahydro-
 20 imidazo[4,5,1-*jk*][1,4]-benzodiazepine-2(1*H*)-one and thione)-type e.g. (S)-8-chloro-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)imidazo-
 [4,5,1-*jk*][1,4]benzodiazepine-2(1*H*)-thione; compounds of the α -APA (α -anilino phenyl acetamide) type e.g. α -[(2-nitrophenyl)amino]-2,6-dichlorobenzene-acetamide and the like; inhibitors of trans-activating proteins, such as
 25 TAT-inhibitors, e.g. RO-5-3335, or REV inhibitors, and the like; protease inhibitors e.g. indinavir, ritonavir, saquinavir, lopinavir (ABT-378), nelfinavir, amprenavir, TMC-126, BMS-232632, VX-175 and the like; fusion inhibitors, e.g. T-20, T-1249 and the like; CXCR4 receptor antagonists, e.g. AMD-3100 and the like; inhibitors of the viral integrase; nucleotide-like reverse transcriptase inhibitors, e.g. tenofovir and the
 30 like; ribonucleotide reductase inhibitors, e.g. hydroxyurea and the like.

By administering the compounds of the present invention with other anti-viral agents which target different events in the viral life cycle, the therapeutic effect of these compounds can be potentiated. Combination therapies as described above exert a
 35 synergistic effect in inhibiting HIV replication because each component of the combination acts on a different site of HIV replication. The use of such combinations may reduce the dosage of a given conventional anti-retroviral agent which would be

required for a desired therapeutic or prophylactic effect as compared to when that agent is administered as a monotherapy. These combinations may reduce or eliminate the side effects of conventional single anti-retroviral therapy while not interfering with the anti-viral activity of the agents. These combinations reduce potential of resistance to single agent therapies, while minimizing any associated toxicity. These combinations may also increase the efficacy of the conventional agent without increasing the associated toxicity.

The compounds of the present invention may also be administered in combination with immunomodulating agents, e.g. levamisole, bropiramine, anti-human alpha interferon antibody, interferon alpha, interleukin 2, methionine enkephalin, diethyldithiocarbamate, tumor necrosis factor, naltrexone and the like; antibiotics, e.g. pentamidine isethionate and the like; cholinergic agents, e.g. tacrine, rivastigmine, donepezil, galantamine and the like; NMDA channel blockers, e.g. memantine to prevent or combat infection and diseases or symptoms of diseases associated with HIV infections, such as AIDS and ARC, e.g. dementia. A compound of formula (I) can also be combined with another compound of formula (I).

Although the present invention focuses on the use of the present compounds for preventing or treating HIV infections, the present compounds may also be used as inhibitory agents for other viruses which depend on similar reverse transcriptases for obligatory events in their life cycle.

The following examples are intended to illustrate the present invention.

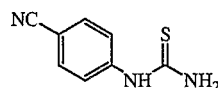
Experimental Part

Hereinafter, "DMSO" is defined as dimethylsulfoxide, "TFA" is defined as trifluoroacetic acid, "DMF" is defined as *N,N*-dimethylformamide and "THF" is defined as tetrahydrofuran.

A. Preparation of the intermediate compounds

Example A1

a) Preparation of intermediate 1

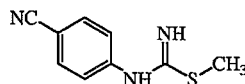


4-Isothiocyanatobenzonitrile (9.95 g) was suspended in methanol (100 ml) and NH_3 , 26% aqueous (50 ml) was added. The reaction mixture was put in a cooler and filtered

off, washed with methanol and Et₂O (2x) and dried at 35°C under reduced pressure.

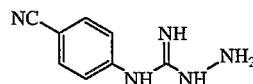
Yield : 9.99 g (90.9%) of intermediate 1.

b) Preparation of intermediate 2



To intermediate 1 (9.99 g), CH₃I (3.87 ml) and acetone (150 ml) were added. The reaction mixture was stirred for 3 days. The reaction mixture was put in a cooler for 2 hours and then filtered off. The filtrate was washed with acetone and dried. Yield : 17.03 g (95.3%) of intermediate 2.

c) Preparation of intermediate 3

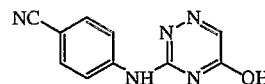


To intermediate 2 (17.03 g) was added hydrazine hydrate (3.11 ml) and methanol (150 ml). The reaction mixture was stirred for 3 days at 20°C with a gas outlet.

Yield : intermediate 3. The reaction mixture was used for the next reaction steps described in A2.a) and b).

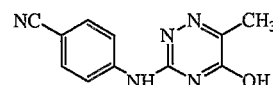
Example A2

a) Preparation of intermediate 4

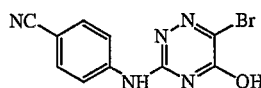


To two thirds (2/3) of the reaction mixture obtained in A1.c) was added ethyl glyoxalate 50% in toluene (14.11 ml) and the reaction mixture was stirred at 20°C overnight. The solvent was evaporated and the residue was dried under high vacuum. DMF (150 ml) was added and the mixture was heated at 80°C overnight. DMF was evaporated and the residue was dried under high vacuum. The residue was stirred in methanol (150 ml) and put in a cooler overnight. The precipitate was filtered off. Yield : 1.80 g (23.7%) of intermediate 4.

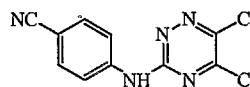
b) Preparation of intermediate 5



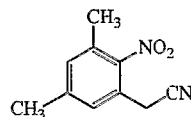
To one third (1/3) of the reaction mixture obtained in A1.c), was added methyl pyruvate (3.22 ml) and the reaction mixture was stirred at 20°C overnight. The solvent was evaporated and the residue was dried under high vacuum. DMF (150 ml) was added and the mixture was heated at 80°C overnight. DMF was evaporated and the residue was dried under high vacuum. The residue was stirred in methanol (75 ml) and put in a cooler overnight. The precipitate was filtered off. Yield : 1.60 g (39.6%) of intermediate 5.

Example A3a) Preparation of intermediate 6

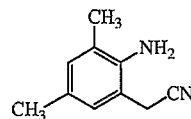
- 5 To a flask under Argon was added intermediate 4 (0.00469 mol), DMSO (25 ml), Br₂ (0.00704 mol), and Et₃N (0.00704 mol). The mixture was stirred at room temperature overnight. Water was added, and the mixture was stirred for 20 minutes. The reaction mixture was worked up to yield 0.30 g of intermediate 6. The solid was dried at 75°C for 16 hours at 200 mm Hg.

b) Preparation of intermediate 7

- 10 To a pressure vessel under Argon were added intermediate 6 (0.000616 mol) and POCl₃ (6 ml). The mixture was heated in an oil bath at 110°C for 30 minutes, cooled, poured onto ice, stirred for 5 minutes, and filtered. Yield: 0.14 g of intermediate 7. The solid was dried at 200 mm Hg for 3 days at room temperature.

Example A4a) Preparation of intermediate 8

- 20 3,5-Dimethylbenzeneacetonitrile (3.0 g) was dissolved in MeSO₃H (10 ml) and cooled to 0°C. NaNO₃ (1.76 g) was added at once at 0°C. After 2 hours, the reaction mixture was poured into ice-H₂O under vigorous stirring. The product was extracted with EtOAc. The extract was washed with saturated aqueous NaHCO₃ (2x), dried with brine and Na₂SO₄ and purified using a mixture of EtOAc and n-heptane on silicagel. Yield : 2.00 g (51%) of intermediate 8.

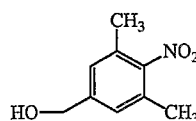
b) Preparation of intermediate 9

- 25 NH₄Cl (2.53 g) was dissolved in H₂O (20 ml) and Fe (1.59 g) was added. Intermediate 8 (1.80 g) dissolved in methanol (40 ml) and THF (20 ml) was added to the aqueous solution. The reaction mixture was stirred at 70°C for 2 to 4 hours. The organic

solvents were removed. The residue was stirred in EtOAc and the EtOAc was decanted; this procedure was repeated twice. The combined organic extracts were dried with brine and Na₂SO₄ and evaporated. Yield : 1.35 g of intermediate 9 (89%).

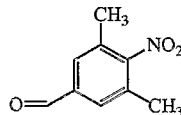
5 Example A5

a) Preparation of intermediate 10



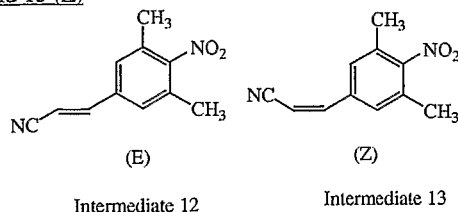
- 10.0 g of 3,5-dimethyl-4-nitrobenzoic acid and 7.10 ml (1 eq.) of Et₃N were dissolved in 40 ml of dry THF and cooled to -5°C. A solution of 5.14 ml of ethyl chloroformate in 10 ml of dry THF was added in the course of 10 minutes. The mixture was stirred for 0.5 hours at 20°C. The Et₃N-HCl was filtered off and the THF solution was added drop wise (30 minutes) to an aqueous solution (50 ml) of 4.07 g NaBH₄. This mixture was stirred for 4 hours at 20°C and quenched with 1 N HCl until pH=2. The THF was evaporated and the residue was dissolved in EtOAc and washed with saturated aqueous NaHCO₃ and with brine and dried over Na₂SO₄. After evaporation, the residue was purified by silica column chromatography using heptane/EtOAc : 3/1. Yield : intermediate 10 (68%).

b) Preparation of intermediate 11



- 4.3 g of intermediate 10 was dissolved in 100 ml of acetone and 8.25 g (4 eq.) of MnO₂ were added. After 3 days stirring at 20°C, 2.06 g extra MnO₂ was added. Stirring was continued for 2 days. Then MnO₂ was filtered off, 100 ml heptane was added and the solution was again filtered and evaporated. The residue was dissolved in CH₂Cl₂ and filtered. The solvent was evaporated. Yield : 3.18 g (75%) of intermediate 11.

c) Preparation of intermediate 12 (E) and 13 (Z)



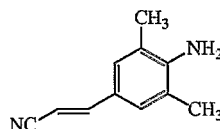
Intermediate 12

Intermediate 13

2.68 g of intermediate 11 and 2.65 g of diethyl cyanomethyl phosphonate were dissolved in 50 ml of dry THF and added to a suspension of 5.99 g of NaOMe in 30 ml of dry THF at 0°C. The reaction mixture was stirred for 1 hour at 0°C. The reaction mixture was quenched with 0.1 N HCl and the solvent was evaporated. EtOAc was added. The resulting solution was washed with saturated aqueous NaHCO₃ and dried with brine and Na₂SO₄ successively and evaporated. The residue was purified by silica column chromatography using heptane/EtOAc : 5/1 as the eluent. Total yield of intermediate 12 (E) and 13 (Z) was 62%; the ratio of the intermediates 12 and 13 = 89/11.

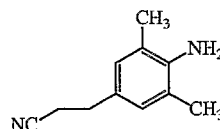
Example A6-1

a) Preparation of intermediate 14

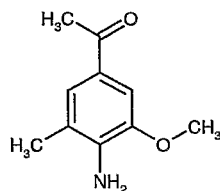


2.00 g of intermediate 12 was dissolved in 20 ml of THF and added to a solution of 2.65 g of NH₄Cl in 20 ml of H₂O. 40 ml of MeOH and 1.66 g of Fe were added. The reaction was stirred at 50°C for 4 hours and after that cooled to ambient temperature. The solid material was filtered off and the filtrate was diluted with EtOAc and washed with saturated aqueous NaHCO₃ and dried with brine and with Na₂SO₄. The EtOAc was evaporated. Yield : 99% of intermediate 14.

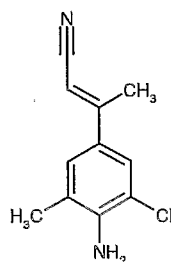
b) Preparation of intermediate 15



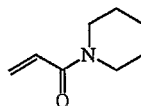
- 1) 1.68 g of intermediate 12 was hydrogenated using 0.88 g of 5% Pd/C in 200 ml of EtOH. After 4 hours, the Pd/C was filtered off and the filtrate was evaporated and stripped with CH₂Cl₂ to furnish intermediate 15 in 93% yield.
- 2) Intermediate 14 (3.44 g, 20 mmoles) was dissolved in EtOH (20 ml). 10% Pd/C (0.300 g) was added and the mixture was hydrogenated for 24 hours at room temperature after which period it was filtered on celite. The solvent was evaporated. Yield: 3.21 g of intermediate 15 (92%).

Example A6-2a) Preparation of intermediate 30

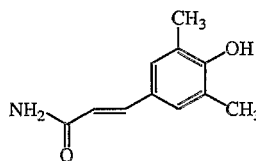
- Pd(OAc)₂ (0.1 eq.), P(*o*-Tol)₃ (0.2 eq), Et₃N (1.5 eq), 4-bromo-2-methoxy-6-methylbenzenamine (1.0 g; 4.63 mmol) and tributyl(1-ethoxyethenyl)stannane (1.0 eq.; 1.37 ml) were dissolved in dry MeCN (15 ml). N₂ was bubbled through the suspension for at least 20 minutes. Then a cooler was mounted strictly under nitrogen atmosphere. The reaction mixture was heated at 70°C overnight. The reaction mixture was allowed to cool to 20°C and was diluted with CH₂Cl₂ and washed with saturated aqueous NaHCO₃ (2x) and dried with brine and Na₂SO₄. The residue was sonicated in diisopropyl ether and filtered off. Yield: 0.22 g of intermediate 30 (26%).

b) Preparation of intermediate 29

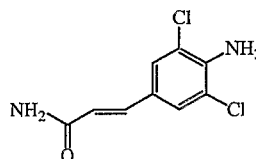
- 1-(4-amino-3-chloro-5-methylphenyl)ethanone (181 mg) (prepared according to A6-2a)) was added to NaOMe (133 mg) in dry THF (3 ml; 2.5 eq). Then diethyl cyanomethyl phosphonate (0.193 ml; 1.2 eq) were added. The mixture was stirred at room temperature. Extra phosphonate reagent (0.075 ml; 0.47 eq) was added and extra NaOMe (53 mg; 1.0 eq). The next day the same amounts extra reagent were added. The reaction mixture was diluted with EtOAc and washed with saturated aqueous NaHCO₃ and brine. The organic fraction was dried over Na₂SO₄ and evaporated. The residue was stirred and sonicated in diisopropyl ether/heptane 1/1 and filtered off. Yield: 0.11 g of intermediate 29 (54%).

Example A7Preparation of intermediate 16

- Acryloyl chloride (2.0 ml) was dissolved in dry Et₂O (20 ml) and cooled to 0°C. Two equivalents of piperidine in Et₂O (20 ml) was added dropwise. The reaction was stirred for 1 hour. The precipitate was filtered off and washed with ether. The organic fraction was washed with 0.5% KHSO₄ and with saturated aqueous NaHCO₃ and dried with brine and Na₂SO₄. The solvent was removed. Yield : 2.02 g (59%) of intermediate 16.

10 Example A8a) Preparation of intermediate 17

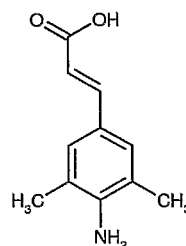
- Pd(OAc)₂ (222 mg), P(*o*-Tol)₃ (604 mg), Et₃N (2.07 ml), 4-bromo-2,6-dimethylphenol (2.0 g) and acrylamide (1.06 g) were dissolved in MeCN (15 ml) and N₂ was bubbled through the reaction mixture for at least 20 minutes. Then a cooler was mounted strictly under nitrogen atmosphere. The reaction mixture was heated at 70°C overnight. The reaction mixture was allowed to cool to 20°C and was diluted with CH₂Cl₂ and washed with saturated aqueous NaHCO₃ (2x) and dried with brine and Na₂SO₄. The residue was sonicated in diisopropyl ether and filtered off. Yield: 0.76 g of intermediate 17 (40%).

20 b) Preparation of intermediate 18

- Pd(OAc)₂ (186 mg), P(*o*-Tol)₃ (505 mg), Et₃N (1.73 ml), 4-bromo-2,6-dichlorobenzeneamine (2.0 g) and acrylamide (885 mg) were dissolved in MeCN (15 ml) and N₂ was bubbled through the reaction mixture for at least 20 minutes. Then a cooler was mounted strictly under nitrogen atmosphere. The reaction mixture was heated at 70°C overnight. The reaction mixture was allowed to cool to 20°C and was

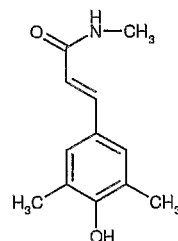
diluted with CH_2Cl_2 and washed with saturated aqueous NaHCO_3 (2x) and dried with brine and Na_2SO_4 . The residue was sonicated in diisopropyl ether and filtered off. Yield: 0.55 g of intermediate 18 (30%).

c-1) Preparation of intermediate 31



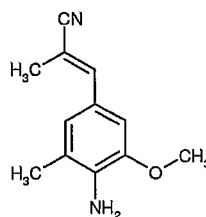
- 5 Pd(OAc)₂ (0.1 eq.), P(*o*-Tol)₃ (0.2 eq.), Et₃N (1.5 eq.), 4-bromo-2,6-dimethylbenzenamine (3.0 g; 14.99 mmol) and 2-propenoic acid (2.06 ml) were dissolved in dry MeCN (25 ml) and N₂ was bubbled through the reaction mixture for at least 20 minutes. Then a cooler was mounted strictly under nitrogen atmosphere. The reaction mixture was heated at 70°C overnight. The reaction mixture was allowed to
10 cool to 20°C and was diluted with CH_2Cl_2 and washed with saturated aqueous NaHCO_3 (2x) and dried with brine and Na_2SO_4 . The residue was sonicated in diisopropyl ether and filtered off. Yield: 0.76 g of intermediate 31 (40%) (E+Z).

c-2) Preparation of intermediate 28



- 3-(4-hydroxy-3,5-dimethylphenyl)-2-propenoic acid (1.0 g) was suspended in CH_2Cl_2
15 (10 ml) and 1.2 equivalents oxalylchloride were added followed by three drops of DMF. The mixture was stirred overnight at room temperature, split into two equal batches and the solvent was evaporated. The oily residue was stripped with toluene. The residue was redissolved in dry THF (6 ml) and dropped onto methylamine in THF (2 M, 3.9 ml, 3 eq) and stirred overnight at ambient temperature. The reaction mixture
20 was diluted with EtOAc and washed with saturated aqueous NaHCO_3 and dried (brine, Na_2SO_4). The EtOAc was evaporated and the residue was sonicated in diisopropyl ether containing a few ml of EtOAc. The residue was filtered off and dried. Yield: 0.24 g of intermediate 28 (44%).

d) Preparation of intermediate 32



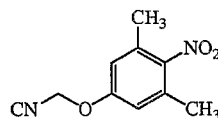
The reaction takes place in a closed vessel in a microwave oven. Pd(OAc)₂ (0.1 eq.), P(*o*-Tol)₃ (0.2 eq), Et₃N (1.5 eq), 4-bromo-2-methoxy-6-methylbenzenamine (2.16 g; 10 mmol) and 2-methyl-2-propenenitrile (1.5 eq.) were dissolved in MeCN (20 ml).

- 5 N₂ was bubbled through the suspension for at least 20 minutes. The reaction mixture was heated at 150°C for 10 minutes. The reaction mixture was allowed to cool to 20°C and was diluted with EtOAc and washed with saturated aqueous NaHCO₃ (2x) and dried with brine and Na₂SO₄. The residue was used for flash chromatography (eluent: H/EA 4:1). Yield: 0.46 g of intermediate 32 (23%) (Z-isomer).

10

Example A9

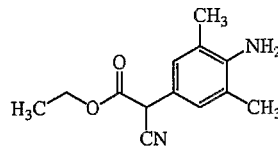
Preparation of intermediate 20



- 15 ClCH₂CN (0.80 ml), K₂CO₃ (2.31 g), NaI (126 mg) and 3,5-dimethyl-4-nitrophenol (prepared according to A4.a)(1.4 g) were dissolved in acetone (40 ml). The mixture was stirred overnight at 50°C. The residue was filtered off and the acetone was evaporated. The residue was dissolved in EtOAc and washed with saturated aqueous NaHCO₃ and dried with brine and Na₂SO₄. The EtOAc was evaporated. Yield : 1.91 g of intermediate 20 (99%)

20 Example A10

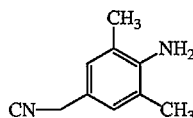
a) Preparation of intermediate 21



4-Bromo-2,6-dimethylbenzenamine (1.0 g), ethylcyanoacetate (0.59 ml), Pd₂(dba)₃ (0.058 mg), P(*t*-Bu)₃ (0.049 ml) and Na₃PO₄ (2.46 g) were dissolved in dry toluene (25

ml) and flushed 30 minutes with N₂. The reaction mixture was stirred overnight at 70°C. The reaction mixture was allowed to cool to 20°C and filtered off. The toluene was purified on silica using 5% EtOAc in toluene. The product was sonicated in diisopropyl ether/*n*-heptane and filtered off. Yield : 0.45 g of intermediate 21 (65%).

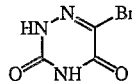
5 b) Preparation of intermediate 22



Intermediate 21 (450 mg) was dissolved in DMSO (16 ml) and H₂O (1 ml). NaCl (0.74 g) was added. The reaction mixture was heated for 3 hours at 140°C. The reaction mixture was then cooled to 20°C and diluted with Et₂O. The organic solution was washed with brine (4x) and dried over Na₂SO₄. The combined brine extracts were
10 extracted with Et₂O and this was combined with the first Et₂O fraction. The Et₂O was evaporated. Yield : 0.26 g of intermediate 22 (84%)

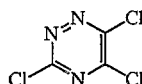
Example A11

a) preparation of intermediate 23

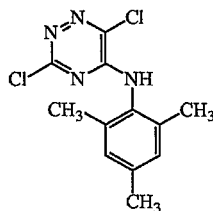


15 A mixture of 25 g of 6-azauracil, bromine (25 ml) and water (250 ml) was stirred at room temperature for 30 hours. The precipitate was filtered off. The filtrate was concentrated and the second precipitate was collected by filtration. The two precipitate fractions were combined and dried. Yield : 38.3 g of intermediate 23 (92%) (mp. 231-234°C).

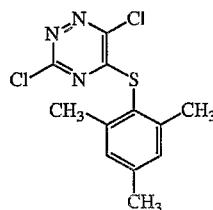
20 b) Preparation of intermediate 24



To 18 g of intermediate 23 in 150 ml of phosphorus oxychloride were added 39.2 g of phosphorus pentachloride and 38 ml of *N,N*-diethylaniline. The mixture was stirred at 120°C for 5 hours after which period the excess of solvent was evaporated. The residue was several times extracted with carbon tetrachloride. After evaporation of the
25 solvent, the remaining residue was put in the refrigerator where it solidified. Yield: 13 g of intermediate 24 (m.p. 57-60°C).

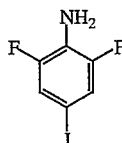
Example A12a) Preparation of intermediate 25

To a solution of intermediate 24 (0.560 g) in dry THF (30 ml) at -78°C under nitrogen atmosphere was added 2,4,6-trimethylaniline (0.418 g). The reaction mixture was
5 allowed to reach room temperature and was further stirred overnight at this temperature. The solvent was evaporated. The resulting residue was suspended in an aqueous solution of Na_2CO_3 and extracted with methylene chloride. The methylene chloride solution was dried over MgSO_4 and evaporated. The residue was chromatographed on a silica gel column using methylene chloride as eluent. Yield :
10 0.467 g of intermediate 25 (55%).

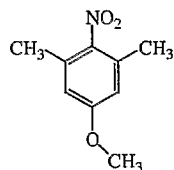
b) Preparation of intermediate 26

To a solution of intermediate 24 (0.560 g) in dry THF (30 ml) at -78°C under nitrogen atmosphere was added 2,4,6-trimethylbenzenethiol (0.457 g) and sodium carbonate (0.318 g). The reaction mixture was allowed to reach room temperature and was
15 further stirred overnight at this temperature. The solvent was evaporated. The resulting residue was suspended in water and extracted with methylene chloride. The methylene chloride solution was dried over MgSO_4 and evaporated. The residue was chromatographed on a silica gel column using methylene chloride as eluent. Yield :
0.612 g of intermediate 26 (68%).

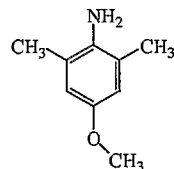
20

Example A13Preparation of intermediate 33

- 2,6-Difluorobenzaniline (3.0g, 22.56 mmol) was dissolved in acetic acid (10 ml). Iodine monochloride (3.581g, 22.56 mmol) was added to the solution. The mixture was stirred for 15 minutes at room temperature. After evaporation of the solvent, the residue was treated with an aqueous solution of sodium carbonate. The aqueous solution was extracted with dichloromethane. The organic extract was dried over MgSO_4 and was evaporated. Yield: 95% of intermediate 33.

10 Example A14a) Preparation of intermediate 34

- 1-Methoxy-3,5-dimethylbenzene (4.12 g, 30 mmol) was dissolved in acetic acid (20 ml). To this solution was added dropwise a mixture of nitric acid (1.26 ml, 30 mmol) and concentrated sulfuric acid (1.9 ml, 35 mmol). The mixture was heated at 70 °C for 15 minutes. After cooling, water was added and the mixture was extracted with dichloromethane. The organic extract was dried and evaporated. The resulting residue was purified by column chromatography (30% heptane in CH_2Cl_2). Yield: 1.91 g of intermediate 34 (35%).

20 b) Preparation of intermediate 35

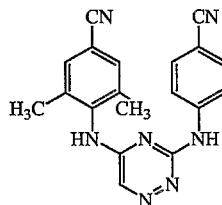
To a solution of intermediate 34 (1.81 g, 10 mmol) in ethanol (20 ml) was added tin (II) chloride dihydrate (11.51 g, 50 mmol) and the mixture was refluxed overnight. Upon cooling, ice was added to the reaction mixture followed by basification with 2N

NaOH. The mixture was filtered and the filtrate was concentrated under reduced pressure. The aqueous solution was extracted with dichloromethane (4 x 30 ml). The organic layers were combined and dried over anhydrous MgSO_4 and the solvent was removed under reduced pressure. The residue was purified on a silica gel column chromatography (CH_2Cl_2 as eluent). Yield: 1.18 g of intermediate 35 (78%).

B. Preparation of the final compounds

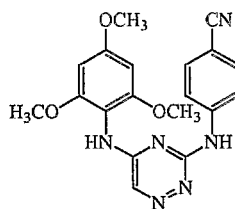
Example B1

a) Preparation of compound 1



To intermediate 4 (prepared according to A2.a) (0.0019 mol) under Argon in POCl_3 (4 ml) was added $\text{N}(n\text{-Pr})_3$ (0.39 ml). The reaction mixture was stirred at room temperature for one hour. 4-amino-3,5-dimethylbenzonitrile (0.0028 mol) was added and stirring at room temperature was continued for 16 hours. The reaction mixture was poured onto ice, then extracted with CH_2Cl_2 and evaporated. The residue was purified by flash column chromatography, eluting with 0.5% MeOH: CH_2Cl_2 to afford 0.27 g of residue. The residue was purified by reversed-phase HPLC (gradient of 0.1% TFA in water and 0.1% TFA in CH_3CN). Yield: 0.030 g of compound 1.

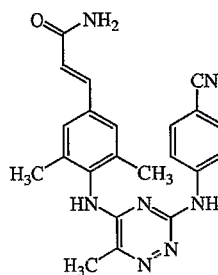
b) Preparation of compound 36



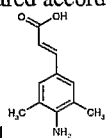
Intermediate 4 (100 mg) was added to 3 ml of POCl_3 at 0°C . 2,4,6-trimethoxybenzenamine (0.13 g) was added and the reaction mixture was stirred for 3 to 5 days. The ice bath was allowed to melt during the first couple of hours. After that, the POCl_3 suspension was dropped to 200 ml of vigorously stirred diisopropyl ether. The solid material was filtered off and washed with diisopropyl ether. The residue was immediately stirred in EtOAc/saturated aqueous NaHCO_3 (1/1) (200 ml) for 1 hour. The EtOAc was dried using brine and Na_2SO_4 successively and evaporated. The

residue was purified by preparative TLC using CH₂Cl₂/MeOH (95/5) as the eluent or by precipitation in CH₂Cl₂/MeOH. Yield: 0.01 g of compound 36 (8%).

c) Preparation of compound 58



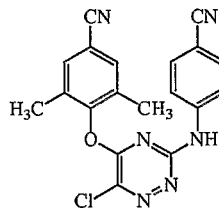
Intermediate 5 (prepared according to A2.b) (100 mg) was added to 3 ml of POCl₃ at



- 5 0°C. Intermediate 31 (prepared according to A8.c-1) (0.17 g) was added and the reaction mixture was stirred for 3 to 5 days. The ice bath was allowed to melt during the first couple of hours. The reaction mixture was poured onto heptane. The heptane was decanted. The residue was added at once to a large excess of 0.5 N NH₃ in dioxane containing 10 eq. DIPEA (diisopropylethylamine). The mixture was stirred
- 10 overnight. The residue was filtered off and stirred in EtOAc / saturated aqueous NaHCO₃. The organic fraction was dried (brine, Na₂SO₄) and evaporated. The product was purified by preparative-TLC using CH₂Cl₂/MeOH 9/1 as the eluent. Yield: 0.01 g of compound 58 (3%).

15 Example B2

a) Preparation of compound 3

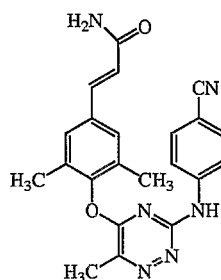


- To a flask under Argon were added intermediate 7 (prepared according to A3.b) (0.000489 mol), K₂CO₃ (0.00244 mol), acetone (2 ml), and 4-hydroxy-3,5-dimethylbenzonitrile (0.000733 mol). The mixture was stirred at room temperature
- 20 overnight. The reaction mixture was evaporated, and water was added. The mixture

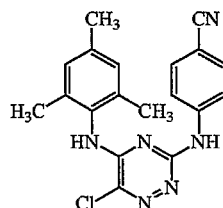
was extracted with CH_2Cl_2 , dried over Na_2SO_4 , and evaporated. The aqueous phase was extracted again, dried, and evaporated. The two fractions were combined, and purified by flash column chromatography (0,2% methanol: CH_2Cl_2). The sample was recrystallized in CH_3CN , and filtered. Yield: 0.05 g of compound 3. The solid was

5 dried at 0.2 mm Hg for 16 hours at room temperature.

b) Preparation of compound 48



- First step : Intermediate 5 (prepared according to A2.b) (100 mg) was added to 3 ml of POCl_3 at 0°C . The reaction mixture was stirred overnight. The ice bath was allowed to melt during the first couple of hours. After that, the POCl_3 suspension was dropped to
- 10 200 ml of vigorously stirred *n*-heptane. The solid material was filtered off and washed with heptane (2x). The residue was immediately stirred in EtOAc with crushed ice for 5 minutes. The EtOAc was dried using brine and Na_2SO_4 successively and evaporated. The residue was sonicated in *n*-heptane and filtered off. The triazine chloride prepared in this way was used in the next step.
- 15 Second step : $\text{KO-}t\text{Bu}$ (27 mg) was dissolved in THF (6 ml) and added to a solution of intermediate 17 (1.5 eq.; ratio to the triazine chloride prepared above) (prepared according to A8a). After 1 hour, a solution of 60 mg of the triazine-chloride prepared above in THF was added to the deprotonated phenol and the mixture was stirred for 3 days. After that, the reaction mixture was poured onto EtOAc/ H_2O /brine:2/1/1 (200
- 20 ml). The organic fraction was dried (brine and Na_2SO_4) and evaporated. The product was precipitated in acetone and filtered off. The residue was purified by preparative TLC using CH_2Cl_2 /*n*-heptane/EtOAc/MeOH: 50/30/20/2 as the eluent. Yield: 0.05 g of compound 48 (41%).

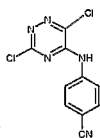
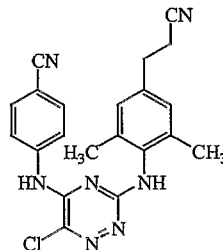
Example B3a) Preparation of compound 44

A mixture of intermediate 25 (prepared according to A12.a) (0.425 g),

4-aminobenzonitrile (0.272 g) and camphorsulfonic acid (CSA) (0.249 g) was refluxed

- 5 for 48 hours in THF. After evaporation of the solvent, the residue was suspended in an aqueous solution of Na_2CO_3 and extracted with CH_2Cl_2 . The dichloromethane solution was dried over MgSO_4 and evaporated. The resulting residue was purified by column chromatography using 10% ethyl acetate in dichloromethane as eluent. Yield : 0.454 g of compound 44.

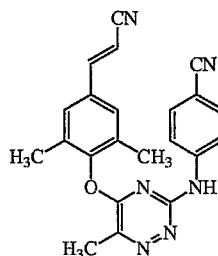
10 b) Preparation of compound 79



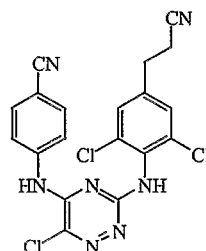
A mixture of (prepared according to A12.b) (1 equiv.), intermediate 15 (prepared according to A6-1.b) (1.5 equiv.), and camphor sulfonic acid (0.7 equiv.)

was refluxed overnight in THF (oil bath 120°C). After evaporation the residue was

- 15 suspended in an aqueous solution of Na_2CO_3 , and was extracted (3 times) with dichloromethane. After drying over MgSO_4 and evaporation of the dichloromethane extract, the residue was purified by column chromatography using 10% ethyl acetate in dichloromethane as eluent. Yield: 33% of final compound 79 (m.p. 266-267°C).

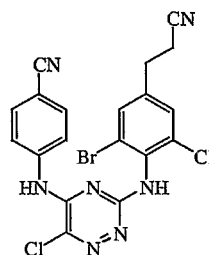
Example B4Preparation of compound 49

Compound 48 (prepared according B2.b) (40 mg) was dissolved in 2 ml of POCl₃ and stirred for 2 days. Then, the mixture was dropped into diisopropyl ether and filtered off and washed. Yield : 0.04 g of compound 49 (95%).

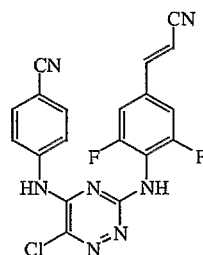
Example B5a) Preparation of compound 74

In a two necked flask protected with an aluminium foil and equipped with a condenser was dissolved compound 83 (prepared according to B3.b) (0.200 g; 0.53 mmol) in acetic acid (5 ml). *N*-chlorosuccinimide (0.212 g, 1.60 mmol) was added. The mixture was degassed, and was heated at 120°C. After evaporation, the residue was dissolved in ethyl acetate. The solution was washed with an aqueous solution of Na₂CO₃ and water, dried over MgSO₄ and evaporated. The residue was chromatographed on a silica gel column (10% EtOAc in CH₂Cl₂). Yield: 24 % of final compound 74 (m.p. 256-257°C).

b) Preparation of compound 75



In a two necked flask protected with an aluminium foil and equipped with a condenser was dissolved compound 83 (prepared according to B3.b) (0.207 g, 0.55 mmole) in acetic acid. *N*-Bromosuccinimide (0.198 g, 1.1 mmole) was added. The mixture was
 5 degassed, and was heated at 110°C for 15 minutes. After evaporation, the residue was dissolved in ethyl acetate. The solution was washed successively with an aqueous solution of Na₂CO₃, and water before drying over MgSO₄ and evaporation. The residue was dissolved in acetic acid in a two necked flask protected with an aluminium foil and equipped with a condenser as above. *N*-chlorosuccinimide (0.111 g, 0.83 mmole) was
 10 added. The mixture was degassed, and was heated at 110°C for 15 minutes. After evaporation, the residue was dissolved in ethyl acetate. The solution was washed successively with an aqueous solution of Na₂CO₃ and water before drying over MgSO₄ and evaporation followed by purification of the residue by chromatography on a silica gel column (10% EtOAc in CH₂Cl₂). Yield: Final compound 75 (0.110 g, 41% yield)
 15 (m.p. 252-254°C).

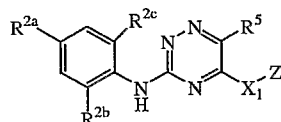
Example B6Preparation of compound 62

To a DMF solution of final compound 82 (prepared according to B3.b) (0.450 g, 0.928
 20 mmole) were added acrylonitrile (0.12 ml, 1.856 mmole), triethylamine (0.26 ml, 1.856 mmole), palladium acetate (0.0111 g, 0.023 mmole) and triphenylphosphine (0.0123 g, 0.046 mmole). After degassing the reaction mixture, it was flushed with nitrogen and the flask was stopped with a septum. It was then stirred overnight at 100°C.

After cooling, the reaction mixture was diluted with dichloromethane. The CH_2Cl_2 solution was washed with water (3 times) and was dried over MgSO_4 before evaporation. After evaporation, the residue was purified by column chromatography on a silica gel column (10% EtOAc in CH_2Cl_2 . Yield: Final compound 62 (0.207 g, 54% yield) (m.p. 276-277°C).

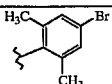
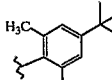
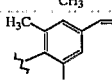
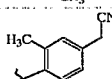
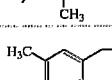
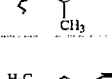
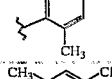
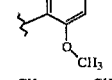
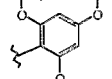
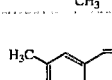
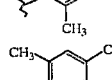
Table 1 lists the compounds that were prepared according to one of the above Examples (Ex.No.).

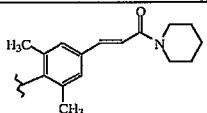
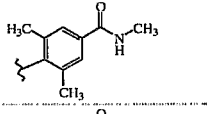
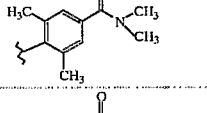
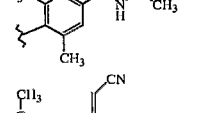
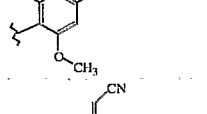
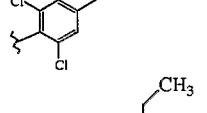
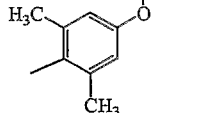
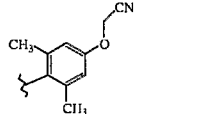
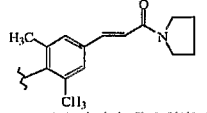
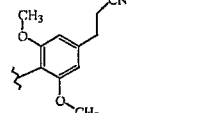
10 Table 1

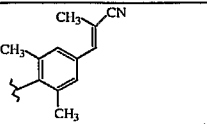
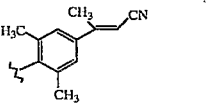
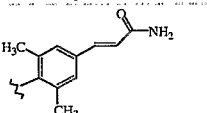
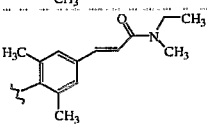
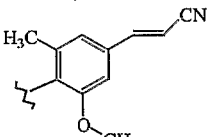
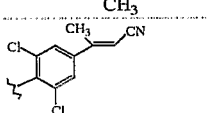
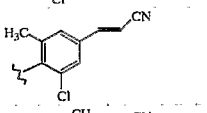
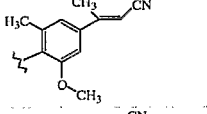
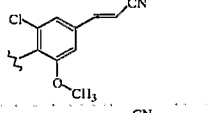
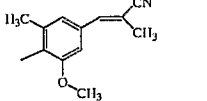


Co. no.	Exp. no.	R ^{2a}	R ^{2b}	R ^{2c}	X ₁	R ⁵	Z	Phys. data
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7	B1.b	CN	H	H	NH	H		
8	B1.b	CN	H	H	NH	H		
9	B1.b	CN	H	H	NH	H		
10	B1.b	CN	H	H	NH	H		
14	B1.b	CN	H	H	NH	H		
15	B1.b	CN	H	H	NH	H		
24	B1.b	CN	H	H	NH	H		

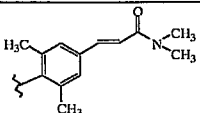
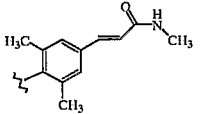
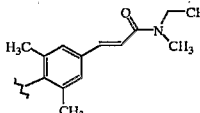
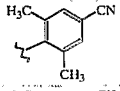
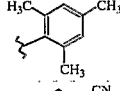
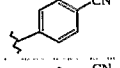
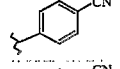
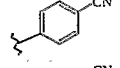
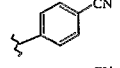
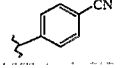
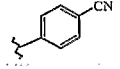
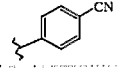
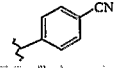
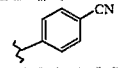
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36	B1.b	CN	H	H	NH	H		
37	B1.b	CN	H	H	NH	H		
41	B1.b	CN	H	H	NH	H		
43	B1.b	CN	H	H	NH	H		
52	B1.b	CN	H	H	NH	H		
51	B1.b	CN	H	H	NH	H		
2	B1.b	CN	H	H	NH	CH ₃		
5	B1.b	CN	H	H	NH	CH ₃		
11	B1.b	CN	H	H	NH	CH ₃		
12	B1.b	CN	H	H	NH	CH ₃		
13	B1.b	CN	H	H	NH	CH ₃		(E)

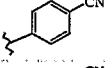
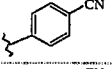
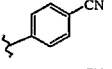
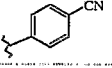
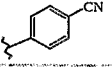
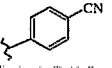
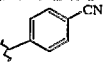
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18	B1.b	CN	H	H	NH	CH ₃		
19	B1.b	CN	H	H	NH	CH ₃		(Z)
20	B1.b	CN	H	H	NH	CH ₃		
21	B1.b	CN	H	H	NH	CH ₃		
22	B1.b	CN	H	H	NH	CH ₃		
23	B1.b	CN	H	H	NH	CH ₃		
25	B1.b	CN	H	H	NH	CH ₃		
26	B1.b	CN	H	H	NH	CH ₃		
27	B1.b	CN	H	H	NH	CH ₃		
28	B1.b	CN	H	H	NH	CH ₃		

Co. no.	Exp. no.	R ^{2a}	R ^{2b}	R ^{2c}	X ₁	R ⁵	Z	Phys. data
29	B1.b	CN	H	H	NH	CH ₃		
30	B1.b	CN	H	H	NH	CH ₃		
31	B1.b	CN	H	H	NH	CH ₃		
32	B1.b	CN	H	H	NH	CH ₃		
33	B1.b	CN	H	H	NH	CH ₃		
34	B1.b	CN	H	H	NH	CH ₃		
35	B1.b	CN	H	H	NH	CH ₃		
38	B1.b	CN	H	H	NH	CH ₃		
39	B1.b	CN	H	H	NH	CH ₃		
40	B1.b	CN	H	H	NH	CH ₃		

Co. no.	Exp. no.	R ^{2a}	R ^{2b}	R ^{2c}	X ₁	R ⁵	Z	Phys. data
42	B1.b	CN	H	H	NH	CH ₃		
55	B1.b	CN	H	H	NH	CH ₃		(RS)
58	B1.c	CN	H	H	NH	CH ₃		
59	B1.b	CN	H	H	NH	CH ₃		
60	B1.b	CN	H	H	NH	CH ₃		(E)
61	B1.b	CN	H	H	NH	CH ₃		(E)
65	B1.b	CN	H	H	NH	CH ₃		(E)
66	B1.b	CN	H	H	NH	CH ₃		
70	B1.b	CN	H	H	NH	CH ₃		
81	B1.b	CN	H	H	NH	CH ₃		

Co. no.	Exp. no.	R ^{2a}	R ^{2b}	R ^{2c}	X ₁	R ⁵	Z	Phys. data
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67	B1.b	CN	H	H	NH	CH ₃		(E)
71	B1.b	CN	H	H	NH	CH ₃		
69	B1.b	CN	H	H	NH	CH ₃		(E)
6	B1.b		H	H	NH	CH ₃		
54	B3.a	CN	H	H	NH	Cl		
44	B3.a	CN	H	H	NH	Cl		
4	B2.b	CN	H	H	O	CH ₃		
47	B2.b	CN	H	H	O	CH ₃		
48	B2.b	CN	H	H	O	CH ₃		
49	B4	CN	H	H	O	CH ₃		

Co. no.	Exp. no.	R ^{2a}	R ^{2b}	R ^{2c}	X ₁	R ⁵	Z	Phys. data
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57	B2.b	CN	H	H	O	CH ₃		
3	B2.a	CN	H	H	O	Cl		
46	B3.a	CN	H	H	S	Cl		
72	B3.b	CN	CH ₃	CH ₃	NH	Cl		
45	B3.b	CH ₃	CH ₃	CH ₃	NH	Cl		
64	B3.b	-OCH ₃	CH ₃	CH ₃	NH	Cl		
83	B3.b	-CH ₂ -CH ₂ -CN	H	H	NH	Cl		
79	B3.b	-CH ₂ -CH ₂ -CN	CH ₃	CH ₃	NH	Cl		(E+Z)
74	B5.a	-CH ₂ -CH ₂ -CN	Cl	Cl	NH	Cl		
73	B5.a	-CH ₂ -CH ₂ -CN	Br	Br	NH	Cl		
75	B5.b	-CH ₂ -CH ₂ -CN	Cl	Br	NH	Cl		
62	B6	-CH=CH-CN	F	F	NH	Cl		(E)

Co. no.	Exp. no.	R ^{2a}	R ^{2b}	R ^{2c}	X ₁	R ⁵	Z	Phys. data
76	B6	-CH=CH-CN	Cl	Cl	NH	Cl		(E)
78	B6	-CH=CH-CN	Br	Br	NH	Cl		(E+Z)
77	B6	-CH=CH-CN	Cl	Br	NH	Cl		(E)
53	B3.b	-CH=CH-CN	CH ₃	CH ₃	NH	Cl		
80	B6	-CH=CH-CN	OCH ₃	CH ₃	NH	Cl		
63	B3.b	I	F	F	NH	H		
82	B3.b	I	F	F	NH	Cl		

C. Analytical Part

1. Melting points

5 Table 2 : Melting points of compounds of the present invention.

Compound no.	Result (°C)
3	>300
44	272-273
46	295-296
53	274-276
54	281-282
62	276-277
63	305-306
72	260-261
73	256-257
74	254-257
75	252-254
80	>338
79	266-267

2. [MH⁺] results

[MH⁺] is the mass of the protonated compound (Chemical Ionisation Mass Spectrum)

Table 3:

5

Compound no.	[MH ⁺]
45	365
64	381
76	442
77	486
78	512

D. Pharmacological example

The pharmacological activity of the present compounds was examined using one of the following tests (indicated in Table 4 in the most right column).

10 Test A

A rapid, sensitive and automated assay procedure was used for the *in vitro* evaluation of anti-HIV agents. An HIV-1 transformed T4-cell line, MT-4, which was previously shown (Koyanagi et al., *Int. J. Cancer*, 36, 445-451, 1985) to be highly susceptible to and permissive for HIV infection, served as the target cell line. Inhibition of the HIV-
 15 induced cytopathic effect was used as the end point. The viability of both HIV- and mock-infected cells was assessed spectrophotometrically via the *in situ* reduction of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT). The 50% cytotoxic concentration (CC₅₀ in M) was defined as the concentration of compound that reduced the absorbance of the mock-infected control sample by 50%. The percent
 20 protection achieved by the compound in HIV-infected cells was calculated by the following formula :

$$\frac{(\text{OD}_T)_{\text{HIV}} - (\text{OD}_C)_{\text{HIV}}}{(\text{OD}_C)_{\text{MOCK}} - (\text{OD}_C)_{\text{HIV}}} \quad \text{expressed in \%},$$

whereby (OD_T)_{HIV} is the optical density measured with a given concentration of the test compound in HIV-infected cells; (OD_C)_{HIV} is the optical density measured for the
 25 control untreated HIV-infected cells; (OD_C)_{MOCK} is the optical density measured for the control untreated mock-infected cells; all optical density values were determined at 540 nm. The dose achieving 50% protection according to the above formula was defined as the 50% inhibitory concentration (IC₅₀ in M). The ratio of CC₅₀ to IC₅₀ was defined as the selectivity index (SI).

Test B

An HIV-1 transformed T4-cell line, MT-4, which was previously shown (Koyanagi et al., *Int. J. Cancer*, 36, 445-451, 1985) to be highly susceptible to and permissive for HIV infection, served as the target cell line. In these cells, engineered with GFP (and an HIV-specific promotor), ongoing HIV-infection was measured fluorometrically. Cytotoxicity is measured in the same cells, but engineered with GFP under a constitutional promotor. The infection (or inhibition thereof) of HIV infected cells and the fluorescence of mock-infected cells is assessed by the fluorescent GFP signal generated by the two above mentioned cell lines.

The 50% effective concentration (EC₅₀ in μM) was defined as the concentration of compound that reduced the fluorescence of HIV-infected cells by 50%. The 50% cytotoxic concentration (CC₅₀ in μM) was defined as the concentration of compound that reduced fluorescence of the mock-infected cells by 50%.

Table 4 lists the pIC₅₀ (-logIC₅₀), values for the compounds of formula (I). For example, a compound with a IC₅₀ value of 10^{-9}M has a pIC₅₀ value of 9.

20 Table 4

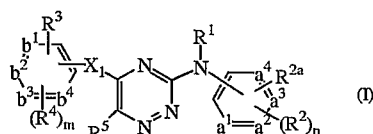
Co. No.	pIC ₅₀ (M)	pCC ₅₀	pSI	Test
1	8.7	<4.0	<-4.7	A
2	9.0	<4.0	<-5.0	A
3	8.3	<4.0	<-4.3	A
5	8.7	<4.0	<-4.7	A
7	9.3	5.5	<-3.8	A
8	7.3	<4.0	<-3.3	A
9	7.8	<4.0	<-3.8	A
10	7.6	<4.5	<-3.1	A
11	9.2	5.5	<-3.7	A
12	8.9	4.0	<-4.9	A
13	8.2	<4.0	<-4.2	A
14	8.8	<4.0	<-4.8	A
15	8.8	<4.0	<-4.8	A
16	8.7	4.2	-4.5	A

Co. No.	pIC ₅₀ (M)	pCC ₅₀	pSI	Test
17	8.0	<4.0	<-4.0	A
18	8.1	<4.0	<-4.1	A
19	9.0	4.6	-4.4	A
20	8.6	<4.6	<-4.0	A
22	7.1	<4.6	<-2.5	A
23	8.9	6.4	-2.5	A
24	8.8	<4.6	<-4.2	A
25	8.6	4.4	-4.3	A
27	8.3	<4.0	<-4.3	A
31	7.5	<4.0	<-3.5	A
33	8.6	5.4	-3.2	A
34	8.6	5.0	-3.6	A
35	8.2	<4.6	<-3.6	A
36	9.3	<4.0	<-5.3	A
37	7.0	4.3	-2.7	A
38	8.9	4.7	-4.2	A
39	7.2	<4.0	<-3.2	A
40	8.6	5.0	-3.6	A
41	7.6	<4.6	<-3.0	A
42	9.1	4.8	-4.3	A
43	8.1	<4.6	<-3.5	A
44	8.6	<4.6	<-4.0	A
45	7.6	<4.6	<-3.0	A
46	7.9	<4.6	<-3.3	A
47	8.1	<4.6	<-3.5	A
48	9.2	4.6	-4.6	B
50	8.9	4.7	-4.2	B
51	7.2	5.1	-2.1	B
52	8.6	<4.6	<-4.0	B
53	8.5	4.9	-3.6	B
54	9.2	4.9	-4.3	B
55	9.2	5.2	-4.0	B
56	9.2	4.8	-4.4	B
57	9.1	4.7	-4.4	B
58	6.6	5.0	-1.6	B

Co. No.	pIC ₅₀ (M)	pCC ₅₀	pSI	Test
60	8.9	6.0	-2.9	B
61	8.6	5.4	-3.2	B
62	8.5	4.6	-3.9	B
63	8.2	4.9	-3.3	B
64	8.6	4.7	-3.9	B
65	9.2	5.3	-3.9	B
66	9.2	5.7	-3.5	B
67	8.5	4.9	-3.6	B
68	8.6	5.2	-3.4	B
69	8.7	5.7	-3.0	B
70	9.0	6.2	-2.8	B
71	8.5	5.1	-3.4	B
72	7.1	<4.6	<-2.5	B
73	8.5	<4.6	<-3.9	B
74	8.3	<4.6	<-3.7	B
75	8.5	<4.6	<-3.9	B
76	8.6	<4.6	<-4.0	B
77	8.5	5.0	-3.5	B
78	8.6	5.1	-3.5	B

Claims

1. A compound of formula



a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine or a stereochemically isomeric form thereof, wherein

-a¹=a²-a³=a⁴- represents a bivalent radical of formula

-CH=CH-CH=CH- (a-1);

-N=CH-CH=CH- (a-2);

-N=CH-N=CH- (a-3);

-N=CH-CH=N- (a-4);

-N=N-CH=CH- (a-5);

-b¹=b²-b³=b⁴- represents a bivalent radical of formula

-CH=CH-CH=CH- (b-1);

-N=CH-CH=CH- (b-2);

-N=CH-N=CH- (b-3);

-N=CH-CH=N- (b-4);

-N=N-CH=CH- (b-5);

n is 0, 1, 2, 3 and in case -a¹=a²-a³=a⁴- is (a-1), then n may also be 4;

m is 0, 1, 2, 3 and in case -b¹=b²-b³=b⁴- is (b-1), then m may also be 4;

R¹ is hydrogen; aryl; formyl; C₁₋₆alkylcarbonyl; C₁₋₆alkyl; C₁₋₆alkyloxycarbonyl;

C₁₋₆alkyl substituted with formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl,

C₁₋₆alkylcarbonyloxy; C₁₋₆alkyloxyC₁₋₆alkylcarbonyl substituted with

C₁₋₆alkyloxycarbonyl;

each R² independently is hydroxy; halo; C₁₋₆alkyl optionally substituted with one or

more substituents each independently selected from halo, cyano or -C(=O)R⁶;

C₃₋₇cycloalkyl; C₂₋₆alkenyl optionally substituted with one or more substituents each

independently selected from halo, cyano or -C(=O)R⁶; C₂₋₆alkynyl optionally

substituted with one or more substituents each independently selected from halo,

cyano or -C(=O)R⁶; C₁₋₆alkyloxycarbonyl; carboxyl; cyano; nitro; amino; mono- or

di(C₁₋₆alkyl)amino; polyhalomethyl; polyhalomethylthio; -S(=O)_pR⁶;

-NH-S(=O)_pR⁶; -C(=O)R⁶; -NHC(=O)H; -C(=O)NHNH₂; NHC(=O)R⁶; C(=NH)R⁶;

R^{2a} is cyano; aminocarbonyl; amino; C₁₋₆alkyl; halo; C₁₋₆alkyloxy wherein C₁₋₆alkyl

may optionally be substituted with cyano; NHR¹³; NR¹³R¹⁴; -C(=O)-NHR¹³;

-C(=O)-NR¹³R¹⁴; -C(=O)-R¹⁵; -CH=N-NH-C(=O)-R¹⁶; C₁₋₆alkyl substituted with

one or more substituents each independently selected from halo, cyano, NR^9R^{10} , $-\text{C}(=\text{O})-\text{NR}^9\text{R}^{10}$, $-\text{C}(=\text{O})-\text{C}_{1-6}\text{alkyl}$ or R^7 ; $\text{C}_{1-6}\text{alkyl}$ substituted with hydroxy and a second substituent selected from halo, cyano, NR^9R^{10} , $-\text{C}(=\text{O})-\text{NR}^9\text{R}^{10}$, $-\text{C}(=\text{O})-\text{C}_{1-6}\text{alkyl}$ or R^7 ; $\text{C}_{1-6}\text{alkyloxyC}_{1-6}\text{alkyl}$ optionally substituted with one or more substituents each independently selected from halo, cyano, NR^9R^{10} , $-\text{C}(=\text{O})-\text{NR}^9\text{R}^{10}$, $-\text{C}(=\text{O})-\text{C}_{1-6}\text{alkyl}$ or R^7 ; $\text{C}_{2-6}\text{alkenyl}$ substituted with one or more substituents each independently selected from halo, cyano, NR^9R^{10} , $-\text{C}(=\text{O})-\text{NR}^9\text{R}^{10}$, $-\text{C}(=\text{O})-\text{C}_{1-6}\text{alkyl}$ or R^7 ; $\text{C}_{2-6}\text{alkynyl}$ substituted with one or more substituents each independently selected from halo, cyano, NR^9R^{10} , $-\text{C}(=\text{O})-\text{NR}^9\text{R}^{10}$, $-\text{C}(=\text{O})-\text{C}_{1-6}\text{alkyl}$ or R^7 ; $-\text{C}(=\text{N}-\text{O}-\text{R}^8)-\text{C}_{1-4}\text{alkyl}$; R^7 or $-\text{X}_3-\text{R}^7$;

X_1 is $-\text{NR}^1-$, $-\text{NH}-\text{NH}-$, $-\text{N}=\text{N}-$, $-\text{O}-$, $-\text{C}(=\text{O})-$, $\text{C}_{1-4}\text{alkanediyl}$, $-\text{CHOH}-$, $-\text{S}-$, $-\text{S}(=\text{O})_{\text{p}}-$, $-\text{X}_2-\text{C}_{1-4}\text{alkanediyl}-$ or $-\text{C}_{1-4}\text{alkanediyl}-\text{X}_2-$;

X_2 is $-\text{NR}^1-$, $-\text{NH}-\text{NH}-$, $-\text{N}=\text{N}-$, $-\text{O}-$, $-\text{C}(=\text{O})-$, $-\text{CHOH}-$, $-\text{S}-$, $-\text{S}(=\text{O})_{\text{p}}-$;

R^3 is cyano; aminocarbonyl; amino; $\text{C}_{1-6}\text{alkyl}$; halo; $\text{C}_{1-6}\text{alkyloxy}$ wherein $\text{C}_{1-6}\text{alkyl}$ may optionally be substituted with cyano; NHR^{13} , $\text{NR}^{13}\text{R}^{14}$, $-\text{C}(=\text{O})-\text{NHR}^{13}$, $-\text{C}(=\text{O})-\text{NR}^{13}\text{R}^{14}$, $-\text{C}(=\text{O})-\text{R}^{15}$, $-\text{CH}=\text{N}-\text{NH}-\text{C}(=\text{O})-\text{R}^{16}$; $\text{C}_{1-6}\text{alkyl}$ substituted with one or more substituents each independently selected from halo, cyano, NR^9R^{10} , $-\text{C}(=\text{O})-\text{NR}^9\text{R}^{10}$, $-\text{C}(=\text{O})-\text{C}_{1-6}\text{alkyl}$ or R^7 ; $\text{C}_{1-6}\text{alkyl}$ substituted with hydroxy and a second substituent selected from halo, cyano, NR^9R^{10} , $-\text{C}(=\text{O})-\text{NR}^9\text{R}^{10}$, $-\text{C}(=\text{O})-\text{C}_{1-6}\text{alkyl}$ or R^7 ; $\text{C}_{1-6}\text{alkyloxyC}_{1-6}\text{alkyl}$ optionally substituted with one or more substituents each independently selected from halo, cyano, NR^9R^{10} , $-\text{C}(=\text{O})-\text{NR}^9\text{R}^{10}$, $-\text{C}(=\text{O})-\text{C}_{1-6}\text{alkyl}$ or R^7 ; $\text{C}_{2-6}\text{alkenyl}$ substituted with one or more substituents each independently selected from halo, cyano, NR^9R^{10} , $-\text{C}(=\text{O})-\text{NR}^9\text{R}^{10}$, $-\text{C}(=\text{O})-\text{C}_{1-6}\text{alkyl}$ or R^7 ; $\text{C}_{2-6}\text{alkynyl}$ substituted with one or more substituents each independently selected from halo, cyano, NR^9R^{10} , $-\text{C}(=\text{O})-\text{NR}^9\text{R}^{10}$, $-\text{C}(=\text{O})-\text{C}_{1-6}\text{alkyl}$ or R^7 ; $-\text{C}(=\text{N}-\text{O}-\text{R}^8)-\text{C}_{1-4}\text{alkyl}$; R^7 or $-\text{X}_3-\text{R}^7$;

X_3 is $-\text{NR}^1-$, $-\text{NH}-\text{NH}-$, $-\text{N}=\text{N}-$, $-\text{O}-$, $-\text{C}(=\text{O})-$, $-\text{S}-$, $-\text{S}(=\text{O})_{\text{p}}-$, $-\text{X}_2-\text{C}_{1-4}\text{alkanediyl}-$, $-\text{C}_{1-4}\text{alkanediyl}-\text{X}_{2\text{a}}-$, $-\text{C}_{1-4}\text{alkanediyl}-\text{X}_{2\text{b}}-\text{C}_{1-4}\text{alkanediyl}$, $-\text{C}(=\text{N}-\text{OR}^8)-\text{C}_{1-4}\text{alkanediyl}-$;

with $\text{X}_{2\text{a}}$ being $-\text{NH}-\text{NH}-$, $-\text{N}=\text{N}-$, $-\text{O}-$, $-\text{C}(=\text{O})-$, $-\text{S}-$, $-\text{S}(=\text{O})_{\text{p}}-$; and with $\text{X}_{2\text{b}}$ being $-\text{NH}-\text{NH}-$, $-\text{N}=\text{N}-$, $-\text{C}(=\text{O})-$, $-\text{S}-$, $-\text{S}(=\text{O})_{\text{p}}-$;

R^4 is halo; hydroxy; $\text{C}_{1-6}\text{alkyl}$ optionally substituted with one or more substituents each independently selected from halo, cyano or $-\text{C}(=\text{O})\text{R}^6$; $\text{C}_{2-6}\text{alkenyl}$ optionally substituted with one or more substituents each independently selected from halo, cyano or $-\text{C}(=\text{O})\text{R}^6$; $\text{C}_{2-6}\text{alkynyl}$ optionally substituted with one or more substituents each independently selected from halo, cyano or $-\text{C}(=\text{O})\text{R}^6$; $\text{C}_{3-7}\text{cycloalkyl}$; $\text{C}_{1-6}\text{alkyloxy}$; cyano; nitro; polyhalo $\text{C}_{1-6}\text{alkyl}$;

- polyhaloC₁₋₆alkyloxy; aminocarbonyl; mono- or di(C₁₋₄alkyl)aminocarbonyl; C₁₋₆alkyloxycarbonyl; C₁₋₆alkylcarbonyl; formyl; amino; mono- or di(C₁₋₄alkyl)amino or R⁷;
- 5 R⁵ is hydrogen; halo; aminocarbonyl; mono- or di(C₁₋₄alkyl)aminocarbonyl; amino; C₁₋₆alkyloxycarbonyl; C₁₋₆alkyloxycarbonylamino; polyhaloC₁₋₆alkyl; C₁₋₆alkyl optionally substituted with cyano, hydroxy, halo, C₁₋₆alkyloxy, C₁₋₆alkylthio or S(=O)_p-C₁₋₆alkyl; C₂₋₆alkenyl optionally substituted with cyano, hydroxy, halo, C₁₋₆alkyloxy, C₁₋₆alkylthio or S(=O)_p-C₁₋₆alkyl; C₂₋₆alkynyl optionally substituted with cyano, hydroxy, halo, C₁₋₆alkyloxy, C₁₋₆alkylthio or S(=O)_p-C₁₋₆alkyl;
- 10 R⁶ is C₁₋₄alkyl, amino, mono- or di(C₁₋₄alkyl)amino or polyhaloC₁₋₄alkyl; R⁷ is a monocyclic, bicyclic or tricyclic saturated, partially saturated or aromatic carbocycle or a monocyclic, bicyclic or tricyclic saturated, partially saturated or aromatic heterocycle, wherein each of said carbocyclic or heterocyclic ring systems may optionally be substituted with one, two, three, four or five substituents each
- 15 independently selected from halo, hydroxy, mercapto, C₁₋₆alkyl, hydroxyC₁₋₆alkyl, aminoC₁₋₆alkyl, mono or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, formyl, C₁₋₆alkylcarbonyl, C₃₋₇cycloalkyl, C₁₋₆alkyloxy, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylthio, cyano, nitro, polyhaloC₁₋₆alkyl, polyhaloC₁₋₆alkyloxy, aminocarbonyl, -CH(=N-O-R⁸), R^{7a}, -X₃-R^{7a} or R^{7a}-C₁₋₄alkyl;
- 20 R^{7a} is a monocyclic, bicyclic or tricyclic saturated, partially saturated or aromatic carbocycle or a monocyclic, bicyclic or tricyclic saturated, partially saturated or aromatic heterocycle, wherein each of said carbocyclic or heterocyclic ring systems may optionally be substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, mercapto, C₁₋₆alkyl, hydroxyC₁₋₆alkyl,
- 25 aminoC₁₋₆alkyl, mono or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, formyl, C₁₋₆alkylcarbonyl, C₃₋₇cycloalkyl, C₁₋₆alkyloxy, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylthio, cyano, nitro, polyhaloC₁₋₆alkyl, polyhaloC₁₋₆alkyloxy, aminocarbonyl, -CH(=N-O-R⁸);
- R⁸ is hydrogen, C₁₋₄alkyl, aryl or arylC₁₋₄alkyl;
- 30 R⁹ and R¹⁰ each independently are hydrogen; hydroxy; C₁₋₆alkyl; C₁₋₆alkyloxy; C₁₋₆alkylcarbonyl; C₁₋₆alkyloxycarbonyl; amino; mono- or di(C₁₋₆alkyl)amino; mono- or di(C₁₋₆alkyl)aminocarbonyl; -CH(=NR¹¹) or R⁷, wherein each of the aforementioned C₁₋₆alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy,
- 35 C₁₋₆alkyloxy, hydroxyC₁₋₆alkyloxy, carboxyl, C₁₋₆alkyloxycarbonyl, cyano, amino, imino, mono- or di(C₁₋₄alkyl)amino, polyhalomethyl, polyhalomethyloxy,

polyhalomethylthio, $-S(=O)_pR^6$, $-NH-S(=O)_pR^6$, $-C(=O)R^6$, $-NHC(=O)H$,
 $-C(=O)NHNH_2$, $-NHC(=O)R^6$, $-C(=NH)R^6$, R^7 ; or

R^9 and R^{10} may be taken together to form a bivalent or trivalent radical of formula

- 5 $-CH_2-CH_2-CH_2-CH_2-$ (d-1)
 $-CH_2-CH_2-CH_2-CH_2-CH_2-$ (d-2)
 $-CH_2-CH_2-O-CH_2-CH_2-$ (d-3)
 $-CH_2-CH_2-S-CH_2-CH_2-$ (d-4)
 $-CH_2-CH_2-NR^{12}-CH_2-CH_2-$ (d-5)
 $-CH_2-CH=CH-CH_2-$ (d-6)
 10 $=CH-CH=CH-CH=CH-$ (d-7)

R^{11} is cyano; C_{1-4} alkyl optionally substituted with C_{1-4} alkyloxy, cyano, amino, mono- or di(C_{1-4} alkyl)amino or aminocarbonyl; C_{1-4} alkylcarbonyl; C_{1-4} alkyloxycarbonyl; aminocarbonyl; mono- or di(C_{1-4} alkyl)aminocarbonyl;

R^{12} is hydrogen or C_{1-4} alkyl;

- 15 R^{13} and R^{14} each independently are C_{1-6} alkyl optionally substituted with cyano or aminocarbonyl, C_{2-6} alkenyl optionally substituted with cyano or aminocarbonyl, C_{2-6} alkynyl optionally substituted with cyano or aminocarbonyl;

R^{15} is C_{1-6} alkyl substituted with cyano or aminocarbonyl;

R^{16} is C_{1-6} alkyl optionally substituted with cyano or aminocarbonyl, or R^7 ;

- 20 p is 1 or 2;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, mercapto, C_{1-6} alkyl, hydroxy C_{1-6} alkyl, amino C_{1-6} alkyl, mono or di(C_{1-6} alkyl)amino C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{3-7} cycloalkyl, C_{1-6} alkyloxy, C_{1-6} alkyloxycarbonyl, C_{1-6} alkylthio, cyano, nitro,

- 25 polyhalo C_{1-6} alkyl, polyhalo C_{1-6} alkyloxy, aminocarbonyl, R^7 or $-X_3-R^7$

provided the following compounds

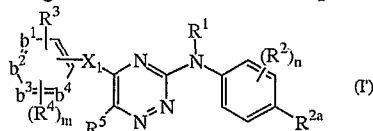
1,2,4-triazine-6-carboxylic acid, 3,5-bis[(4-methylphenyl)amino]-, ethyl ester;

1,2,4-triazine-6-carboxylic acid, 3,5-bis[(4-nitrophenyl)amino]-, ethyl ester;

N,N'-bis(4-chlorophenyl)-6-fluoro-1,2,4-triazine-3,5-diamine;

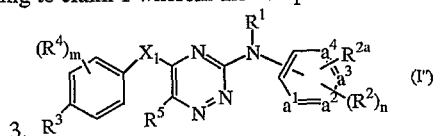
- 30 are not included.

2. A compound according to claim 1 wherein the compound has the formula



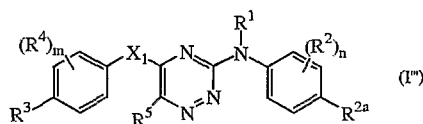
wherein $-b^1=b^2=b^3=b^4-$, R^1 , R^2 , R^{2a} , R^3 , R^4 , R^5 , m , n and X_1 are as defined in claim 1.

3. A compound according to claim 1 wherein the compound has the formula



wherein $-a^1=a^2-a^3=a^4-R^1$, R^2 , R^{2a} , R^3 , R^4 , R^5 , m , n and X_1 are as defined in claim 1.

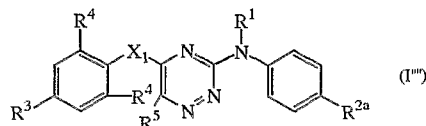
4. A compound according to any one of claims 1 to 3 wherein the compound has the formula



wherein R^1 , R^2 , R^{2a} , R^3 , R^4 , R^5 , m , n and X_1 are as defined in claim 1.

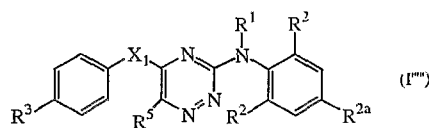
5. A compound according to any one of claims 1 to 4 wherein at least one of m or n is other than 0.

6. A compound according to any one of claims 1 to 5 wherein the compound has the formula



wherein R^1 , R^{2a} , R^3 , R^4 , R^5 and X_1 are as defined in claim 1.

7. A compound as claimed in any one of claims 1 to 5 wherein the compound has the formula

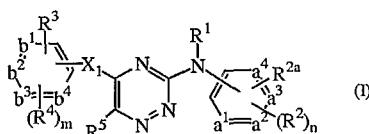


wherein R^1 , R^2 , R^{2a} , R^3 , R^5 and X_1 are as defined in claim 1.

8. A compound according to any one of claims 1 to 7 wherein R^{2a} is cyano, aminocarbonyl, C_{1-6} alkyl optionally substituted with cyano or aminocarbonyl, C_{2-6} alkenyl optionally substituted with cyano or aminocarbonyl.

9. A compound according to any one of claims 1 to 8 for use as a medicine.

10. Use of a compound for the manufacture of a medicament for the treatment or
5 prevention of HIV infection, wherein the compound has the formula



a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine or a stereochemically isomeric form thereof, wherein

-a¹=a²=a³=a⁴- represents a bivalent radical of formula

10 -CH=CH-CH=CH- (a-1);

-N=CH-CH=CH- (a-2);

-N=CH-N=CH- (a-3);

-N=CH-CH=N- (a-4);

-N=N-CH=CH- (a-5);

15 -b¹=b²=b³=b⁴- represents a bivalent radical of formula

-CH=CH-CH=CH- (b-1);

-N=CH-CH=CH- (b-2);

-N=CH-N=CH- (b-3);

-N=CH-CH=N- (b-4);

20 -N=N-CH=CH- (b-5);

n is 0, 1, 2, 3 and in case -a¹=a²=a³=a⁴- is (a-1), then *n* may also be 4;

m is 0, 1, 2, 3 and in case -b¹=b²=b³=b⁴- is (b-1), then *m* may also be 4;

R¹ is hydrogen; aryl; formyl; C₁-6alkylcarbonyl; C₁-6alkyl; C₁-6alkyloxycarbonyl;

C₁-6alkyl substituted with formyl, C₁-6alkylcarbonyl, C₁-6alkyloxycarbonyl,

25 C₁-6alkylcarbonyloxy; C₁-6alkyloxyC₁-6alkylcarbonyl substituted with

C₁-6alkyloxycarbonyl;

each R² independently is hydroxy; halo; C₁-6alkyl optionally substituted with one or

more substituents each independently selected from halo, cyano or -C(=O)R⁶;

C₃-7cycloalkyl; C₂-6alkenyl optionally substituted with one or more substituents each

30 independently selected from halo, cyano or -C(=O)R⁶; C₂-6alkynyl optionally

substituted with one or more substituents each independently selected from halo,

cyano or -C(=O)R⁶; C₁-6alkyloxycarbonyl; carboxyl; cyano; nitro; amino; mono- or

di(C₁-6alkyl)amino; polyhalomethyl; polyhalomethylthio; -S(=O)ₚR⁶;

-NH-S(=O)ₚR⁶; -C(=O)R⁶; -NHC(=O)H; -C(=O)NHNH₂; NHC(=O)R⁶; C(=NH)R⁶;

- R^{2a} is cyano; aminocarbonyl; amino; C₁₋₆alkyl; halo; C₁₋₆alkyloxy wherein C₁₋₆alkyl may optionally be substituted with cyano; NHR¹³; NR¹³R¹⁴; -C(=O)-NHR¹³; -C(=O)-NR¹³R¹⁴; -C(=O)-R¹⁵; -CH=N-NH-C(=O)-R¹⁶; C₁₋₆alkyl substituted with one or more substituents each independently selected from halo, cyano, NR⁹R¹⁰,
 5 -C(=O)-NR⁹R¹⁰, -C(=O)-C₁₋₆alkyl or R⁷; C₁₋₆alkyl substituted with hydroxy and a second substituent selected from halo, cyano, NR⁹R¹⁰, -C(=O)-NR⁹R¹⁰, -C(=O)-C₁₋₆alkyl or R⁷; C₁₋₆alkyloxyC₁₋₆alkyl optionally substituted with one or more substituents each independently selected from halo, cyano, NR⁹R¹⁰, -C(=O)-NR⁹R¹⁰, -C(=O)-C₁₋₆alkyl or R⁷; C₂₋₆alkenyl substituted with one or more substituents each
 10 independently selected from halo, cyano, NR⁹R¹⁰, -C(=O)-NR⁹R¹⁰, -C(=O)-C₁₋₆alkyl or R⁷; C₂₋₆alkynyl substituted with one or more substituents each independently selected from halo, cyano, NR⁹R¹⁰, -C(=O)-NR⁹R¹⁰, -C(=O)-C₁₋₆alkyl or R⁷; -C(=N-O-R⁸)-C₁₋₄alkyl; R⁷ or -X₃-R⁷;
- X₁ is -NR¹-, -NH-NH-, -N=N-, -O-, -C(=O)-, C₁₋₄alkanediyl, -CHOH-, -S-, -S(=O)_p-,
 15 -X₂-C₁₋₄alkanediyl- or -C₁₋₄alkanediyl-X₂-;
- X₂ is -NR¹-, -NH-NH-, -N=N-, -O-, -C(=O)-, -CHOH-, -S-, -S(=O)_p;
- R³ is cyano; aminocarbonyl; amino; C₁₋₆alkyl; halo; C₁₋₆alkyloxy wherein C₁₋₆alkyl may optionally be substituted with cyano; NHR¹³; NR¹³R¹⁴; -C(=O)-NHR¹³; -C(=O)-NR¹³R¹⁴; -C(=O)-R¹⁵; -CH=N-NH-C(=O)-R¹⁶; C₁₋₆alkyl substituted
 20 with one or more substituents each independently selected from halo, cyano, NR⁹R¹⁰, -C(=O)-NR⁹R¹⁰, -C(=O)-C₁₋₆alkyl or R⁷; C₁₋₆alkyl substituted with hydroxy and a second substituent selected from halo, cyano, NR⁹R¹⁰, -C(=O)-NR⁹R¹⁰, -C(=O)-C₁₋₆alkyl or R⁷; C₁₋₆alkyloxyC₁₋₆alkyl optionally substituted with one or more substituents each independently selected from halo,
 25 cyano, NR⁹R¹⁰, -C(=O)-NR⁹R¹⁰, -C(=O)-C₁₋₆alkyl or R⁷; C₂₋₆alkenyl substituted with one or more substituents each independently selected from halo, cyano, NR⁹R¹⁰, -C(=O)-NR⁹R¹⁰, -C(=O)-C₁₋₆alkyl or R⁷; C₂₋₆alkynyl substituted with one or more substituents each independently selected from halo, cyano, NR⁹R¹⁰, -C(=O)-NR⁹R¹⁰, -C(=O)-C₁₋₆alkyl or R⁷; -C(=N-O-R⁸)-C₁₋₄alkyl; R⁷ or -X₃-R⁷;
- 30 X₃ is -NR¹-, -NH-NH-, -N=N-, -O-, -C(=O)-, -S-, -S(=O)_p-, -X₂-C₁₋₄alkanediyl-, -C₁₋₄alkanediyl-X_{2a}-, -C₁₋₄alkanediyl-X_{2b}-C₁₋₄alkanediyl-, -C(=N-OR⁸)-C₁₋₄alkanediyl-;
- with X_{2a} being -NH-NH-, -N=N-, -O-, -C(=O)-, -S-, -S(=O)_p-; and
 with X_{2b} being -NH-NH-, -N=N-, -C(=O)-, -S-, -S(=O)_p-;
- 35 R⁴ is halo; hydroxy; C₁₋₆alkyl optionally substituted with one or more substituents each independently selected from halo, cyano or -C(=O)R⁶; C₂₋₆alkenyl optionally substituted with one or more substituents each independently selected

- from halo, cyano or $-C(=O)R^6$; C_{2-6} alkynyl optionally substituted with one or more substituents each independently selected from halo, cyano or $-C(=O)R^6$; C_{3-7} cycloalkyl; C_{1-6} alkyloxy; cyano; nitro; polyhalo C_{1-6} alkyl; polyhalo C_{1-6} alkyloxy; aminocarbonyl; mono- or di(C_{1-4} alkyl)aminocarbonyl; C_{1-6} alkyloxycarbonyl; C_{1-6} alkylcarbonyl; formyl; amino; mono- or di(C_{1-4} alkyl)amino or R^7 ;
- R^5 is hydrogen; halo; aminocarbonyl; mono- or di(C_{1-4} alkyl)aminocarbonyl; amino; C_{1-6} alkyloxycarbonyl; C_{1-6} alkyloxycarbonylamino; polyhalo C_{1-6} alkyl; C_{1-6} alkyl optionally substituted with cyano, hydroxy, halo, C_{1-6} alkyloxy, C_{1-6} alkylthio or $S(=O)_p-C_{1-6}$ alkyl; C_{2-6} alkenyl optionally substituted with cyano, hydroxy, halo, C_{1-6} alkyloxy, C_{1-6} alkylthio or $S(=O)_p-C_{1-6}$ alkyl; C_{2-6} alkynyl optionally substituted with cyano, hydroxy, halo, C_{1-6} alkyloxy, C_{1-6} alkylthio or $S(=O)_p-C_{1-6}$ alkyl;
- R^6 is C_{1-4} alkyl, amino, mono- or di(C_{1-4} alkyl)amino or polyhalo C_{1-4} alkyl;
- R^7 is a monocyclic, bicyclic or tricyclic saturated, partially saturated or aromatic carbocycle or a monocyclic, bicyclic or tricyclic saturated, partially saturated or aromatic heterocycle, wherein each of said carbocyclic or heterocyclic ring systems may optionally be substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, mercapto, C_{1-6} alkyl, hydroxy C_{1-6} alkyl, amino C_{1-6} alkyl, mono or di(C_{1-6} alkyl)amino C_{1-6} alkyl, formyl, C_{1-6} alkylcarbonyl, C_{3-7} cycloalkyl, C_{1-6} alkyloxy, C_{1-6} alkyloxycarbonyl, C_{1-6} alkylthio, cyano, nitro, polyhalo C_{1-6} alkyl, polyhalo C_{1-6} alkyloxy, aminocarbonyl, $-CH(=N-O-R^8)$, R^{7a} , $-X_3-R^{7a}$ or $R^{7a}-C_{1-4}$ alkyl;
- R^{7a} is a monocyclic, bicyclic or tricyclic saturated, partially saturated or aromatic carbocycle or a monocyclic, bicyclic or tricyclic saturated, partially saturated or aromatic heterocycle, wherein each of said carbocyclic or heterocyclic ring systems may optionally be substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, mercapto, C_{1-6} alkyl, hydroxy C_{1-6} alkyl, amino C_{1-6} alkyl, mono or di(C_{1-6} alkyl)amino C_{1-6} alkyl, formyl, C_{1-6} alkylcarbonyl, C_{3-7} cycloalkyl, C_{1-6} alkyloxy, C_{1-6} alkyloxycarbonyl, C_{1-6} alkylthio, cyano, nitro, polyhalo C_{1-6} alkyl, polyhalo C_{1-6} alkyloxy, aminocarbonyl, $-CH(=N-O-R^8)$;
- R^8 is hydrogen, C_{1-4} alkyl, aryl or aryl C_{1-4} alkyl;
- R^9 and R^{10} each independently are hydrogen; hydroxy; C_{1-6} alkyl; C_{1-6} alkyloxy; C_{1-6} alkylcarbonyl; C_{1-6} alkyloxycarbonyl; amino; mono- or di(C_{1-6} alkyl)amino; mono- or di(C_{1-6} alkyl)aminocarbonyl; $-CH(=NR^{11})$ or R^7 , wherein each of the aforementioned C_{1-6} alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy,

C₁₋₆alkyloxy, hydroxyC₁₋₆alkyloxy, carboxyl, C₁₋₆alkyloxycarbonyl, cyano, amino, imino, mono- or di(C₁₋₄alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, -S(=O)_pR⁶, -NH-S(=O)_pR⁶, -C(=O)R⁶, -NHC(=O)H, -C(=O)NHNH₂, -NHC(=O)R⁶, -C(=NH)R⁶, R⁷; or

5 R⁹ and R¹⁰ may be taken together to form a bivalent or trivalent radical of formula

-CH₂-CH₂-CH₂-CH₂- (d-1)

-CH₂-CH₂-CH₂-CH₂-CH₂- (d-2)

-CH₂-CH₂-O-CH₂-CH₂- (d-3)

-CH₂-CH₂-S-CH₂-CH₂- (d-4)

10 -CH₂-CH₂-NR¹²-CH₂-CH₂- (d-5)

-CH₂-CH=CH-CH₂- (d-6)

=CH-CH=CH-CH=CH- (d-7)

R¹¹ is cyano; C₁₋₄alkyl optionally substituted with C₁₋₄alkyloxy, cyano, amino, mono- or di(C₁₋₄alkyl)amino or aminocarbonyl; C₁₋₄alkylcarbonyl; C₁₋₄alkyloxycarbonyl; aminocarbonyl; mono- or di(C₁₋₄alkyl)aminocarbonyl;

R¹² is hydrogen or C₁₋₄alkyl;

R¹³ and R¹⁴ each independently are C₁₋₆alkyl optionally substituted with cyano or aminocarbonyl, C₂₋₆alkenyl optionally substituted with cyano or aminocarbonyl, C₂₋₆alkynyl optionally substituted with cyano or aminocarbonyl;

20 R¹⁵ is C₁₋₆alkyl substituted with cyano or aminocarbonyl;

R¹⁶ is C₁₋₆alkyl optionally substituted with cyano or aminocarbonyl, or R⁷;

p is 1 or 2;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, mercapto, C₁₋₆alkyl, hydroxyC₁₋₆alkyl, aminoC₁₋₆alkyl, mono or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, C₁₋₆alkylcarbonyl, C₃₋₇cycloalkyl, C₁₋₆alkyloxy, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylthio, cyano, nitro, polyhaloC₁₋₆alkyl, polyhaloC₁₋₆alkyloxy, aminocarbonyl, R⁷ or -X₃-R⁷.

11. Use according to claim 10 wherein the compound is a compound as defined in any one of claims 1 to 8.

12. The use of a compound according to claim 10 or 11 for the manufacture of a medicament for the treatment or prevention of (multi)drug resistant HIV infection.

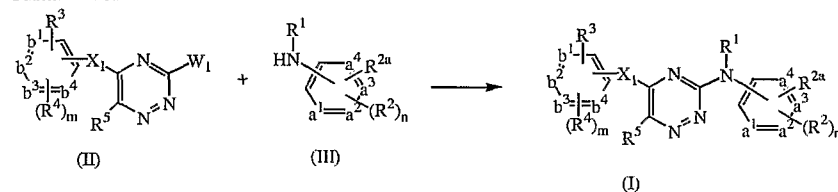
13. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredient a therapeutically effective amount of a compound as claimed in any one of claims 1 to 8.

14. A process for preparing a pharmaceutical composition according to claim 13 characterized in that a therapeutically effective amount of a compound as claimed in any one of claims 1 to 8 is intimately mixed with a pharmaceutically acceptable carrier.

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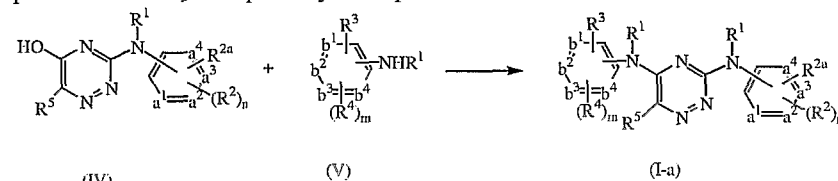
15. A process for preparing a compound as claimed in claim 1, characterized by a) reacting an intermediate of formula (II) wherein W_1 represents a suitable leaving group, with an intermediate of formula (III) in the presence of a suitable acid and a suitable solvent

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with $R^1, R^2, R^{2a}, R^3, R^4, R^5, m, n$ and X_1 as defined in claim 1;

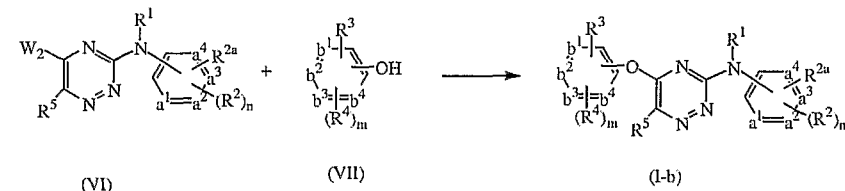
- b) reacting an intermediate of formula (IV) with an intermediate of formula (V) in the presence of $POCl_3$ and optionally in the presence of a suitable base



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with $R^1, R^2, R^{2a}, R^3, R^4, R^5, m$ and n as defined in claim 1;

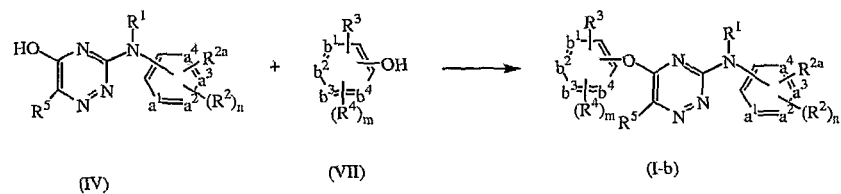
- c) reacting an intermediate of formula (VI) wherein W_2 represents a suitable leaving group with an intermediate of formula (VII) in the presence of a suitable base and a suitable solvent



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with $R^1, R^2, R^{2a}, R^3, R^4, R^5, m$ and n as defined in claim 1;

- d) reacting an intermediate of formula (IV) with an intermediate of formula (VII) in the presence of $POCl_3$, a suitable base and a suitable solvent



with $R^1, R^2, R^{2a}, R^3, R^4, R^5, m$ and n as defined in claim 1;

- or, if desired, converting compounds of formula (I) into each other following art-known transformations; and further, if desired, converting the compounds of formula (I), into a therapeutically active non-toxic acid addition salt by treatment with an acid, or conversely, converting the acid addition salt form into the free base by treatment with alkali; and, if desired, preparing stereochemically isomeric forms, *N*-oxide forms or quaternary amines thereof.