3-(Amino- or aminoalkyl)pyridinone derivatives and their use for the treatment of HIV related diseases

The present invention is concerned with 3-(amino- or aminoalkyl) pyridinone derivatives which inhibit the reverse transcriptase of the Human Immunodeficiency Virus (HIV).

It relates moreover to the use of such compounds for treating HIV-related diseases.

Furthermore it relates to a process for the preparation of these compounds.

It is known that some pyrimidinone and pyridinone derivatives inhibit HIV reverse transcriptase.

In particular, derivatives from 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT) are well known for their HIV1 reverse transcriptase inhibitory properties.

European Patent Application EP-0 462 800 (Merck and Company Inc.) discloses pyridinones being substituted on position 3 with an aryl or heterocyclic group, linked to the pyridinone ring through a chain.

Unfortunately, strains resistant to these compounds appeared . Thus, their use in therapeutical treatments is questionable.

4-aryl-thio-pyridinones have been more recently disclosed by **DOLLE et al.** (1995, J. Med. Chem., 38, 4679-4686), and in the corresponding PCT Patent Application WO 97/05 113.

However, their activities are still moderate and their use in human therapy also could lead to the emergence of resistant strains.

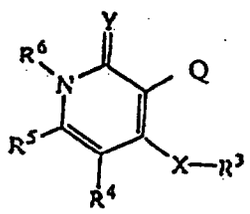
The most active thio pyridinones disclosed therein have a 50% inhibitory concentration of virus multiplication (IC_{50}) for nevirapine resistant strains of about 260 nM.

The inventors have found a new pyridinone derivative family which show better HIV inhibitory properties.

They have moreover found a new process for obtaining these compounds.

The present invention relates to compounds having the following general formula I.

FORMULA (I)



wherein

- Q represents $-NR_1R_2$ or $-R_0NR_1R_2$ wherein:

*R_o represents C_{1-6} alkanediyl;

* R_1 and R_2 each independently represent C_{1-6}alkyl or C_{3-6}alkenyl; said C_{1-6}alkyl and C_{3-6}alkenyl may be substituted with one, two or three substituents selected from hydroxy, C_{1-4}alkyloxy, C_{1-4}alkylthio, aryloxy, arylthio, amino, mono- or di(C_{1-4}alkyl)amino and aryl; or

* R_1 and R_2 taken together may form a bivalent radical $-R_1-R_2-$ wherein $-R_1-R_2$ - represents $-(CH_2)_2-O-(CH_2)_2-$, $-(CH_2)_2-NR_7-(CH_2)_2$, $-(CH_2)_2-CH(NHR_7)-(CH_2)_2-$ or $-(CH_2)_n$, wherein R_7 represents hydrogen or C_{1-4}alkyl and n represents 2, 3, 4, 5 or 6;

- R_3 represents aryl or a monocyclic or bicyclic heterocycle selected from pyridinyl, pyrimidinyl, thiazolinyl, furanyl, thienyl, imidazolyl, benzoxazolyl, benzothiazolyl, benzimidazolyl; said monocyclic or bicyclic heterocycle may optionally be substituted with one, two or three substituents each independently selected from hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, halo, trifluoromethyl, dimethylenoxy or phenyl,

- R_4 and R_5 each independently represent hydrogen, C_{1-6}alkyl, C_{3-6}alkenyl, C_{1-4}alkoxy, C_{1-4}alkyloxy, C_{1-4}alkyl, amino, mono- or di(C_{1-4}alkyl) amino, formyl, C_{1-4}alkylcarbonyl, carboxyl, C_{1-4} alkyloxycarbonyl, or C_{1-4}alkyl-

aminocarbonyl; wherein C_{1-6}alkyl and C_{3-6}alkenyl may be substituted with one, two or three substituents selected from hydroxy, C_{1-4}alkyloxy, C_{1-4}alkyl thio, aryloxy, arylthio, amino, mono- or di(C_{1-4}alkyl)amino and aryl; or

- R_4 and R_5 taken together form a bivalent radical of formula -R_4-R_5-wherein -R_4-R_5- represents -CH=CH-CH=CH- or -$(CH_2)_t$- , wherein t represents 3 or 4;

-R_6 represents hydrogen, hydroxy,C_{1-4}alkyloxy,C_{1-6}alkyl, C_{3-6}alkenyl, aryl, C_{1-4}alkyl, amino, mono- or di(C_{1-4}alkyl)amino or alkylaryl;

- Y represents O or S;

- X represents a radical of formula:

$-(CH_2)_p-$

$-(CH_2)_q-Z-(CH_2)_r-$ or - CO-

wherein p represents 1, 2, 3, 4 or 5;

q represents 0, 1, 2, 3, 4 or 5;

r represents 0, 1, 2 or 3;

- Z represents NR_8, C(= O), CHOH, $CHNR_8R_9$; CF_2, O, S or CH=CH; wherein R_8 and R_9 each independently represent hydrogen or C_{1-4} alkyl;

or

N-oxides, stereochemically isomeric forms or a pharmaceutically acceptable addition salts thereof.

As used in the foregoing definitions and hereinafter halo defines fluoro, chloro, bromo and iodo; C_{1-4}-alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as methyl, ethyl, propyl, butyl and the like; C_{1-6}alkyl is meant to include C_{1-4}alkyl and the higher homologues thereof containing 5 to 6 carbon atoms such as, for example, pentyl, hexyl or the like; C_{3-6}alkenyl defines straight and branched chain hydrocarbon radicals containing one double bond and having from 3 to 6 carbon atoms, such as 2-propenyl, 3-butenyl, 2-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl and the like; and the carbon atom

of said C_{3-6}alkenyl being connected to a nitrogen atom preferably is saturated; C_{1-6}alkanediyl defines bivalent straight and branched chain saturated hydrocarbon radicals having from 1 to 6 carbon atoms, such as, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanediyl, 1,6-hexanediyl and the like. The term «C(=O)» refers to a carbonyl group. Aryl is phenyl or phenyl substituted with one, two or three substituents selected from C_{1-4}alkyl, C_{1-4}alkyloxy, halo and trifluoromethyl,

Preferred compounds according to the present invention are those in which X represents $-CH_2-$ or C (= O) and R_3 represents a phenyl group, substituted with two methyl groups, and the most preferred of them are those wherein R_3 represents a phenyl group substituted, in each meta position, with two methyl groups.

Preferably, in the compounds according to the present invention, R_1 and R_2 represent each a methyl group, R_4 represents an ethyl group, R_5 represents a methyl group and/or R_6 represents a hydrogen atom.

The most preferred compound of this invention is the 3-dimethylamino-4-(3,5-dimethylbenzyl)-5-ethyl-6-methylpyridin-2(1H)-one.

The compounds in which X is $-CH_2-$, R_3 represents a phenyl group optionally substituted, Y represents O and R_6 represents a hydrogen atom can be obtained by the general process represented on figure 1.

This first process comprises the following steps:

a) reacting a pyridine (2), substituted in position 2 with an alkoxy group and in position 3 with an amidoalkyl group, with a C_1-C_6 alkyllithium, resulting in a lithiated derivate (3) of the said pyridine.

b) transforming the lithiated derivate (3) into an organocopper reagent by reacting it with a complex formed by Cu I and dimethyl sulphide.

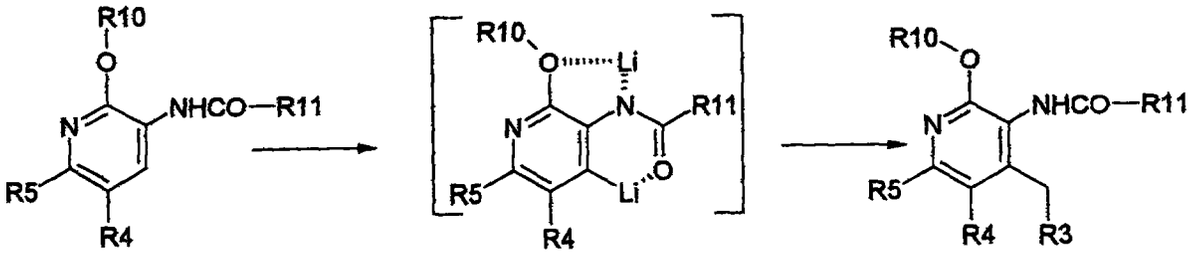
c) obtaining the pyridinone (4) by reacting the organocopper reagent with optionally substituted benzyl halide.

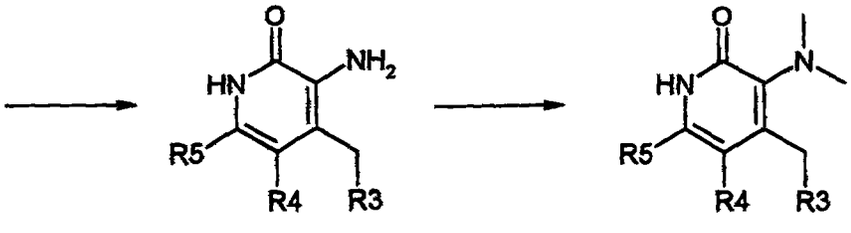
d) hydrolysing the protected pyridinone (4) and obtaining the deprotected pyridinone (5).

e) substituting the 3-amine group of the pyridinone (5) and obtaining the pyridinone (6).

This first process is summarized in the reaction Scheme I hereinafter:

SCHEME I





In this process R_{10} and R_{11} represent independently C_1-C_6 alkyl. In a preferred embodiment, R_{10} is a methyl group and R_{11} is a tert-butyl group.

The C_1-C_6 alkyllithium, reacted with the pyridine(2) can be a n-butyllithium.

The optionally substituted benzyl halide used in the step c) is preferably benzyl bromide.

The hydrolysis of the protected pyridinone(4), resulting in its deprotection, is advantageously obtained by adding hydrochloric acid to the pyridinone(4) and refluxing the mixture.

In a preferred embodiment, the amino group in position 3 of the pyridinone ring, deprotected during the step (d) is substituted by alkylation, by the Eschweiler-Clarke reaction.

Compounds wherein X represents $-(CH_2)_q-Z-(CH_2)_r-$, Y represents O, R_3 is an optionally substituted phenyl group and R_6 is an hydrogen atom can be obtained by a similar process.

Compounds wherein X represents C (= O), or $-CH_2-$, Y represents O, R_3 is an optionally substituted phenyl group and R_6 is an hydrogen atom can be obtained by a second process.

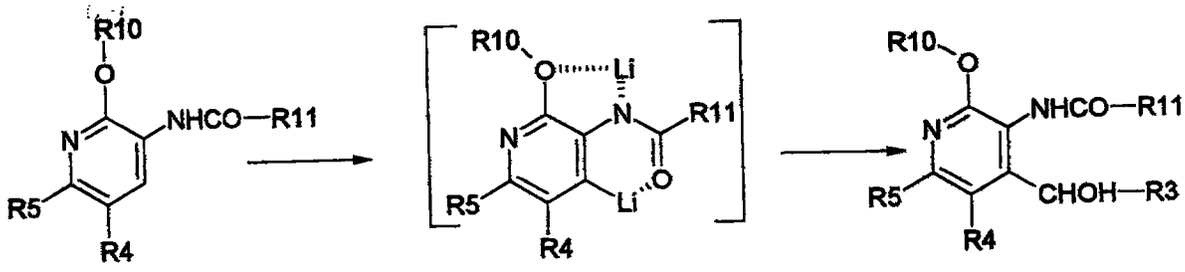
In this second process, the lithiated derivative (3) is reacted with an optionally substituted benzaldehyde, resulting in the intermediates of formula (7).

The intermediate (7) is oxidized to intermediate (8).

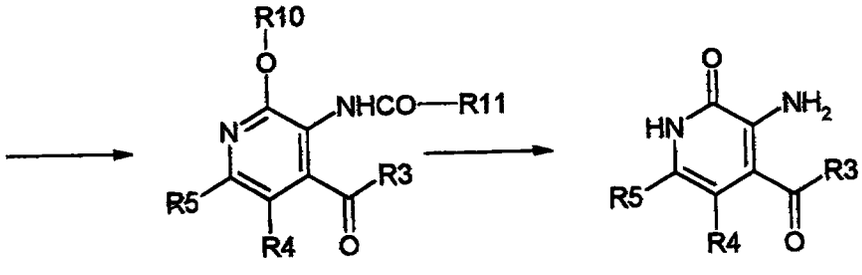
The intermediate (8) is thereafter deprotected by hydrolysis, as in the first process, resulting in the pyridinone (9) of general formula I.

This second process is summarized in the reaction scheme II hereinafter.

Reaction scheme II



(2) (3) (7)

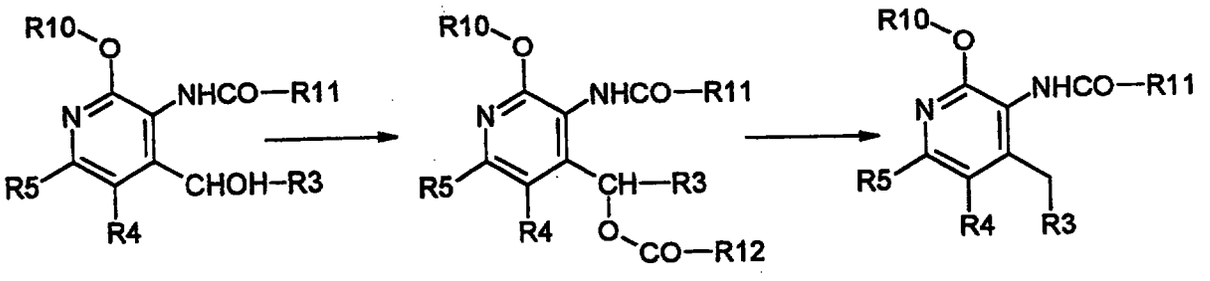


(8) (9)

Preferably the oxidation of the intermediate (7) is performed in the presence of manganese dioxide.

The intermediate (7) can also be transformed into corresponding ester (10) wherein R_{12} represents a C_1-C_4 alkyl group whose hydrogenolysis provides pyridinone(4) in better yields. Preferably, the ester (10) wherein R_{12} is CH_3 is prepared by treatment of intermediate (7) with acetic anhydride. Subsequently hydrogenolysis is performed under hydrogen atmosphere and in the presence of a catalyst, especially 30% paladized charcoal. This process is summarized in the reaction scheme III

Reaction scheme III



(7) (10) (4)

Other compounds of general formula I, and wherein X is $(CH_2)_p$ or $(CH_2)_q$-Z-$(CH_2)_r$ or C(=O), and R_3 is other than phenyl and R_6 is other than hydrogen can be obtained by these processes, appropriately adapted by the man skilled in the art.

The compounds according to the present invention, in which X is S can be obtained by the process described in the article of **DOLLE et al.** (1995, previously cited) or in the corresponding patent application WO 97/05 113, the contents of which are included in the present application.

The compounds can also be obtained by other processes known by the man skilled in the art.

The present invention relates moreover to the intermediates of the processes hereabove disclosed. In particular it relates to the lithiated derivative of formula (3).

The compounds of the present invention are useful in the inhibition of HIV reverse transcriptase, and in particular HIV-1 reverse transcriptase and the prevention or treatment of infection by the human immuno deficiency virus (HIV) and of HIV-related diseases , such as AIDS.

For these purposes, the compounds of the present invention may be administered orally, parenterally (including sub-cutaneous injections, intravenous, intramuscular, intrasternal injection or infusion tectoniques), by inhalation spray, or rectally, in dosage unit formulations containing pharmaceutically acceptable carriers, adjuvants and vehicles.

Thus, another object of the present invention is a method, and a pharmaceutical composition for treating HIV related diseases, HIV infection, and in particular AIDS.

The invention relates also to these compounds for use as medecine and to their use for the manufacture of a medecine for the treatment of HIV related diseases, HIV infection, and in particular AIDS.

These pharmaceutical compositions may be in the form of orally-administrable suspensions or tablets, nasal sprays, sterile injectable preparations, or suppositories.

The present invention is illustrated without being limited by the following examples.

EXAMPLES:

EXAMPLE 1

Preparation of 3-dimethylamino-4-(3,5-dimethylbenzyl)-5-ethyl-6-methylpyridin-2(1H)-one.

1) 5-Ethyl-2-methoxy-6-methyl-3-pivaloylaminopyridine.

This compound has been prepared as indicated by **DOLLE et al.** (1997, Tetrahedron, vol.53, n°37, 12.505-12.524). The content of this article is hereby incorporated by reference.

3,68g of 3-Amino-5-ethyl-2-methoxy-6-methylpyridine (22,14 mmol), obtained as indicated by **HOFFMAN et al.** (1993, J. Med. Chem., 36, 953-966), was dissolved in a mixture of dichloromethane (260 ml) and triethylamine (3.39 ml). The mixture was cooled at 0°C and 3.00 ml of trimethylacetyl chloride was added dropwise. The solution was stirred at 0°C for 15 min. and then washed with 100 ml water. The aqueous layer was extracted with 3 x 200 ml dichloromethane. The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography using dichloromethane as eluant to provide the 5-ethyl-2-methoxy-6-methyl-3-pivaloylaminopyridine (5.31g; 96%). Elemental analysis calculated for $C_{14}H_{22}N_2O_2$; C, 67.17. H, 8.86; N, 11:19; O, 12.78; found : C, 67.11; H, 8.56; N, 10.91; 0, 12.67.

2)4-(3,5-Dimethylbenzyl)-5-ethyl-2-methoxy-6-methyl-3-pivaloylaminopyridine .

i) By lithiation of 5-ethyl-2-methoxy-6-methyl-3-pivaloylaminopyridine:

5-ethyl-2-methoxy-6-methyl-3-pivaloylaminopyridine and 3,5-dimethylbenzyl bromide were dried in the presence of phosphorus pentoxide under vacuum at room temperature during 24 hours. Copper iodide ($Cu^{I}I$) was dried in the presence of phosphorus pentoxide under vacuum at 50°C for 24 hours. 5-ethyl-2-methoxy-6-methyl-3-pivaloylaminopyridine (1.06g) and freshly distilled tetramethylethylenediamine (TMEDA) (2.24 mL) were dissolved in dry tetrahydrofuran (THF) (26 mL) and the mixture was cooled at -78°C under a nitrogen atmosphere. n-Butyllithium (1.6 M in hexane, 9.26 mL) was added dropwise. The mixture was stirred for 1 hour at O°C.

$Cu^{I}I$:dimethyl sulfide complex, prepared by adding dimethylsulfide (14 mL) to a suspension of copper iodide (2.82g) in dry THF (52 ml) at -78°C under N_2 atmosphere, was then added dropwise to the mixture at -78°C. The mixture was stirred at O°C for 30 min and cooled again at -78°C to allow the addition of 3,5-dimethylbenzyl bromide (3.81g) dissolved in THF (4 mL). The resulting mixture was stirred at O°C for 3 hours and at room temperature for 12 hours. 16 mL of water and 20 mL of 28% aqueous ammonium hydroxide were added. The aqueous layer was extracted with 3 x 80 mL of ether. The combined organic layers were washed with 40 mL of brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography using cyclohexane-ethyl acetate (1:0 to 8:2) as eluant giving 4-(3,5-dimethylbenzyl)-5-ethyl-2-methoxy-6-methyl-3-pivaloylaminopyridine (577 mg, 37%) mp 138-139°C.

ii) By hydrogenolysis of ± (5-ethyl-2-methoxy-6-methyl-3-pivaloylaminopyridin-4-yl)-(3,5-dimethylphenyl)-methyl acetate.

(+, -) (5-Ethyl-2-methoxy-6-methyl-3-pivaloylaminopyridin-4-yl)-(3,5-dimethylphenyl)-methylacetate.

8.34g of (+, -)-(3,5-dimethylphenyl)-(5-ethyl-2-methoxy-6-methyl-3-pivaloylaminopyridin-4-yl)-methanol, prepared as described below, was dissolved in pyridine (200 mL) and added to acetic anhydride (10.24 mL), and the solution was stirred for 1.5 h at room temperature and for 60 h at 60°C. An additional 10.24 mL of acetic anhydride (108.51 mmol) was added and heating was continued at 60°C for 24 h. The pyridine was evaporated under reduced pressure and the residue was taken up in 500 mL of ethyl acetate. The organic layer was washed with 170 mL of an aqueous saturated sodium bicarbonate solution, 170 mL of water and 170 mL of brine, dried over magnesium sulfate and the solvent was evaporated. The residue was purified by column chromatography using dichloromethane-ethanol (1:0 to 95:5) to give the titled compound (8.78g, 95%) mp 70-71°C.

A mixture of this compound (850 mg) and Pd-C (30%, 850mg) in acetic acid-water-dioxane (42.5 mL, 2:1:2, v/v/v) was stirred at room temperature for 24 hours under 10 atm of hydrogen. The catalyst was removed by filtration and washed with ethanol. The solvent of the combined filtrates was evaporated under reduced pressure giving 4-(3,5-dimethylbenzyl)-5-ethyl-2-methoxy-6-methyl-3-pivaloylaminopyridine (726 mg, 99%) which was identical to the compound as prepared in example 1.2.i).

3) **3-Amino-4-(3,5-dimethylbenzyl)-5-ethyl-6-methylpyridin-2(1H)-one.**

3M aqueous hydrochloric acid (150 mL) was added to a suspension of 4-(3,5-dimethylbenzyl)-5-ethyl-2-methoxy-6-methyl-3-pivaloylaminopyridine (2.36 g) in water (300 mL). The mixture was refluxed

for 3.5 h and then stirred at room temperature for 12 h. The solution was basified by adding concentrated ammonium hydroxyde and was extracted with 3 x 800 mL ethyl acetate. The combined organic layers were washed with 110 mL brine, dried over magnesium sulfate and concentrated under reduced pressure giving 3-amino-4-(3,5-dimethylbenzyl)-5-ethyl-6-methylpyridin-2(1H)-one . (1.79g, 100%). mp 204-205°C.

4) 3-Dimethylamino-4-(3,5-dimethylbenzyl)-5-ethyl-6-methylpyridin-2-(1H)-one .

To a stirred solution of 3-amino-4-(3,5-dimethylbenzyl)-5-ethyl-6-methylpyridin-2(1H)-one (200 mg) and 37% of aqueous formaldehyde (0.60 mL) in 5 mL of acetonitrile was added 139 mg of sodium cyanoborohydride. Glacial acetic acid (0.07 mL) was added dropwise and the reaction mixture was stirred at room temperature for 2 hours. An additional 0.07 mL of glacial acetic acid was added, and stirring was continued for 30 minutes. The solvent was evaporated and 15 mL ether were added to the resulting residue. The organic layer was washed with 3 x 30 mL 1N aqueous potassium hydroxide and 3 mL brine, dried over magnesium sulfate and concentrated under reduced pressure to give 3-dimethylamino-4-(3,5-dimethylbenzyl)-5-ethyl-6-methylpyridin-2(1H)-one (200 mg, 91%) mp 229-230°C.

EXAMPLE 2: 1) Biological activity of the compound according to example 1.

1. Material and Methods

The antiviral activity, the expression and purification of the recombinant HIV-RT enzyme, the reverse transcriptase activities and the inhibition of RT were evaluated as described in WO 97/05 113.

The retrovirucidal effect and the reverse transcription were measured as described hereinafter.

1.1. Retrovirucidal effect.

HIV-1 viral suspensions were obtained by coculture of MT4 cells and H9 cells chronically infected by HIV-I_{Lai} isolate. 200µl of a cell supernatant containing viral particles (HIV-I_{Lai}: 100 $TCID_{50}$) were incubated at room temperature with various concentrations of different inhibitors. After 3 hours, virions were washed through 0.02µm anopore membrane in 1.5 mL Vectaspin tube (Whatman) for 10 minutes at 5 000 g . Each of the three subsequent washes was performed in the same conditions after the viral concentrate was refilled with 500 µL of RPMI medium. Then, the viral concentrate was readjusted to the initial volume with RPMI plus 10% foetal calf serum (FCS). The residual infectivity was assayed on P4 cells as described by **CHARNEAU et al.**. (1994, J. Mol. Biol., 241, 651-662). Briefly, P4 cells were plated using 100 µL of DMEM medium plus 10% FCS in 96 plate multi-wells at 20 x 10^5 cells per mL. After overnight incubation at 37°C, the supernatant was discarded and the viral preparation (200 µL) was added. One day later the wells were washed three times in PBS. Each well was refilled with 200 µL of a reaction buffer containing 50 mM Tris-HCl pH 8.5, 100 mM 2-mercaptoethanol, 0.05% Triton X-100 and 5 mM 4-methylumbelliferyl β-D-galactopyranoside (MUG). After 3 hours at 37°C, the level of the reaction was measured in a fluorescence microplate reader.

1.2) Reverse transcription.

The plasmid pAV4 containing the 50-997 HIV-1 nucleotide fragment (MAL strain) in pSP64, under the control of the bacteriophage T7 promoter was a kind gift from **Dr. J.L. DARLIX** (INSERM-Lyon, France). E. coli HB 101 recA⁻ was used for plasmid amplification. After digestion of this clone with PstI and in vitro transcription using T7 RNA polymerase, a HIV-1 genomic RNA fragment starting at position +50 of the MAL sequence was obtained. In vitro transcription using T7 RNA polymerase as performed as follows. Three µg of linearized plasmid DNA were transcribed in 100 µL of 40 mM Tris -HCl pH 8.O, 8 mM $MgCl_2$, 10 mM spermidine, 25 mM NaCl, 10 mM dithiothreitol, 0.5 mM of each ribonucleoside triphosphate, with 100 units of T7 RNA polymerase and in the presence of 20 units of human placenta ribonuclease inhibitor , for 2 hours at 37°C. After treatment with 12 units of Rnase-free Dnase I (for 10 minutes at 37°C), the RNA transcripts were extracted with 1 volume of phenol/chloroform/isoamyl alcohol (24:24:l) and with chloroform and precipitated in 2.5 volumes of ethanol and 0.3 M ammonium acetate (pH 5.5).

Reverse transcription was performed in a total volume of 50 µL containing 50 mM Tris-HCl pH 8.0, 6 mM $MgCl_2$, 2 mM dithiothreitol, 12 mM NaCl, 150 nM HIV-1 RNA, and either 200 nM of a synthetic oligodeoxynucleotide primer (18-mer ODN) complementary to the PBS of HIV-1 RNA, or 200 nM $tRNA^{Lys3}$. When the 18-mer ODN was used as primer, incubation was carried out at 37°C with the template and 300 nM RT. After 30 minutes, 10 µ Ci [α-^{32}P]dGTP (3000 Ci/mmol) and 0.1 mM of each dNTP were added and the incubation proceeded for 30 minutes at 37°C. With $tRNA^{Lys3}$ as primer, the same conditions were used except that tRNA and RNA were prehybridized by heating for 2 minutes at 90°C and then slowly cooled. Samples were extracted with phenol-chloroform and

collected by ethanol precipitation. Reaction products were analyzed on 8% polyacrylamide-TBE (90 mM Tris pH 8.3, 90 mM borate, 2 mM EDTA)-7 M urea gels.

RESULTS

The antiviral activity of the compounds according to example 1 has been tested on various strains.

On HIV-LAI wild type this compound shows the following activities: IC50 = 0,2nM; CC50 > 10^5 nM (S.I. > 33.333).

On an HIV-1 novirapine resistant strain the activities of the compound of example 1 are as follows:

$IC_{50} > 10^4$nM

$CC_{50} > 10^4$nM

The compound of example 1 has been also tested on various HIV strains and primary cell cultures. The table 1 illustrates the activity of this compound on these strains.

The retrovirucidal effect of the compound according to example 1 has been tested. Table 2 illustrates this effect at various doses of this compound.

The IC_{50} of the compound of example 1 for the inhibition of the reverse transcriptase is 20 nM.

TABLE 1-Anti HIV-1 activity of the compound of example 1 on various HIV strains and primary cell cultures

IC_{50}(nM)/CC_{50}(nM)

Compound	HIV-1 IIIIB /MT4	HIV-1 AZTres. /MT4	HIV-1 IIIB /PBMC	HIV-2 D 194 /PBMC	HIV-1 Bal/ Mono/macro-phages
Example 1	2.4/>1000	0.2/>1000	0.58/>1000	>1000/> 1000	0.004/>1000

TABLE 2: Inhibition of infectivity of the compound of example 1

Dosage of compound of example 1	% inhibition of infectivity
10 nM	26%
100 nM	46%
1 µm	83%
10 µm	99%

EXAMPLE 3: Other 3-(amino- or aminoalkyl) pyridinone derivatives and their retrovirucidal activity against two different HIV-1 strains.

3.1 Compounds:

Further compounds according to the general formula (I) (compounds n°1-25, 27-108, 110-125, 127-145 and 147-203) as well as four intermediate compounds used for synthesis (compounds n°26, 109, 126 and 146) have been synthesized and are listed in table 3 below.

The meaning of each of the groups Y, Q and R3 - R6 is defined for every exemplified pyridinone derivative.

3.2 RETROVIRUCIDAL EFFECT

The retrovirucidal effect of each pyridinone derivative listed in table 3 has been assayed according to the teachings of example 2, excepted that the anti-viral effect has been tested on the two following HIV-1 strains:

a) HIV-1 strain IIIB (see example 2);

b) HIV-1 strain 103 N which is a mutant strain bearing a point mutation in the reverse transcriptase gene leading to an enzyme wherein the initial Lys-103 residue is replaced for a Asn residue.

HIV-1 103N strain exhibits resistance to the reverse transcriptase inhibitor TIBO R82913 (**BALZARINI J. et al**. 1993, Virology, 192: 246-253). The HIV-1 103 N strain has also been described by **SAHLBERG et al.**,(1998, Antiviral Res., 37 (3) : ASS) and **BALZARINI et al.** (1996, Antimicrobial Agents and Chemotherapy, 40 (6): 1454-1466).

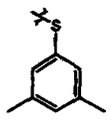
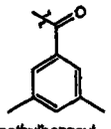
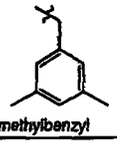
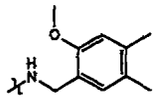
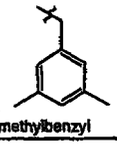
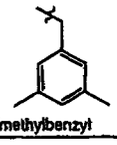
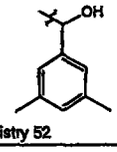
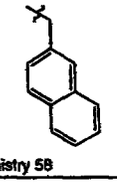
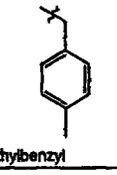
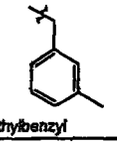
The results are expressed as pIC_{50} (pIC_{50} = - log IC_{50}), of every of compound as regards to each of the HIV-1 strains IIIB and 103N. Thus, the pIC_{50} value of compound n°1 as regards to HIV-1 IIIB being 7,6999, the IC_{50} can be directly deduced as being equal to $10^{-7,6999}$M.

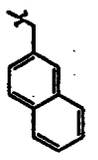
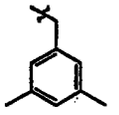
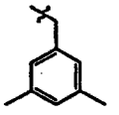
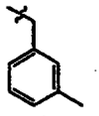
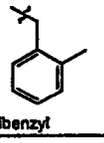
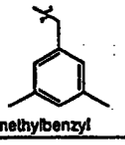
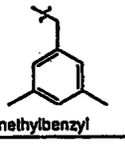
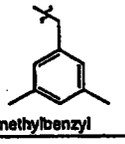
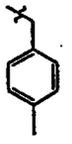
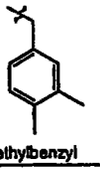
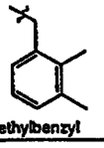
Such high retrovirucidal activities had never been observed previously when using prior art reverse transcriptase inhibitors.

Consequently, the novel pyridinone derivatives according to the present invention are of a high therapeutical value against HIV related diseases, particularly against HIV-1 related diseases.

This Sheet Has Been Replaced

TABLE 3

	Y	Q	R3	R4	R5	R6	HIV1 pIC50 strain IIIB	HIV1 pIC50 strain 103N
1	O	NH2	 Chemistry 4	Et	Me	H	7.699	6.671
2	O	NH2	 3,5-Dimethylbenzoyl	Et	Me	H	6.612	6.64
3	O	NMe2	 3,5-Dimethylbenzyl	Et	Me	H	8.004	7.438
4	O	 Chemistry 33	 3,5-Dimethylbenzyl	Et	Me	H	5.094	<4
5	O	NH2	 3,5-Dimethylbenzyl	Et	Me	H	6.261	5.636
6	O	NH2	 Chemistry 52	Et	Me	H	5.795	5.026
7	O	NH2	 Chemistry 58	Et	Me	H	<4	<4
8	O	NH2	 4-Methylbenzyl	Et	Me	H	4.373	4.39
9	O	NH2	 3-Methylbenzyl	Et	Me	H	5.373	5.103

10	o	NMe2	 Chemistry 82	Et	Me	H	6.241	4.389
11	o	NMe2	 3,5-Dimethylbenzyl	Et	Me	Me	7.215	6.094
12	o	NEt2	 3,5-Dimethylbenzyl	Et	Me	H	8.022	6.363
13	o	NMe2	 3-Methylbenzyl	Et	Me	H	8.624	7.622
14	o	NMe2	 2-Methylbenzyl	Et	Me	H	7.676	5.849
15	o	NH2	 3,5-Dimethylbenzyl	H	H	H	<4.17	4.138
16	o	NMe2	 3,5-Dimethylbenzyl	H	H	H	5.061	4.401
17	o	N(n-Pr)2	 3,5-Dimethylbenzyl	Et	Me	H	6.285	4.379
18	o	NMe2	 4-Methylbenzyl	Et	Me	H	6.454	4.895
19	o	NMe2	 3,4-Dimethylbenzyl	Et	Me	H	7.447	5.947
20	o	NMe2	 2,3-Dimethylbenzyl	Et	Me	H	6.926	5.585

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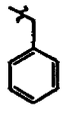
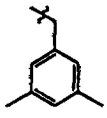
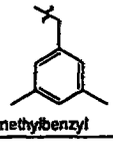
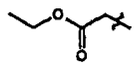
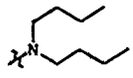
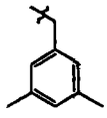
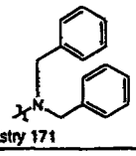
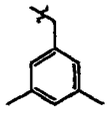
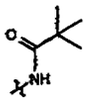
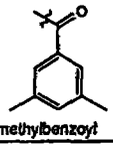
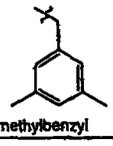
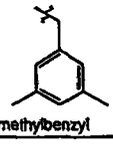
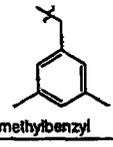
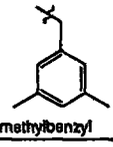
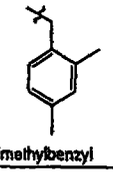
21	O	NMe2	 Benzyl	Et	Me	H	6.409	6.65
22	O	NMe2	 3,5-Dimethylbenzyl	Et	Me	Benzyl	4.603	<4
23	O	NMe2	 3,5-Dimethylbenzyl	Et	Me	 Chemistry 163	5.254	<4
24	O	 Chemistry 165	 3,5-Dimethylbenzyl	Et	Me	H	4.262	<4
25	O	 Chemistry 171	 3,5-Dimethylbenzyl	Et	Me	H	<4	4.259
26	O	 Chemistry 177	 3,5-Dimethylbenzoyl	Et	Me	H		
27	O	NH2	 3,5-Dimethylbenzyl	Me	Et	H	5.949	5.098
28	O	NMe2	 3,5-Dimethylbenzyl	Me	Et	H	8.032	6.943
29	O	NHCH2Ph	 3,5-Dimethylbenzyl	Et	Me	H	6.555	5.496
30	O	 Piperidin-1-yl	 3,5-Dimethylbenzyl	Et	Me	H	6.214	4.224
31	O	NH2	 2,4-Dimethylbenzyl	Et	Me	H	<4	<4

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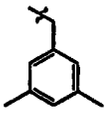
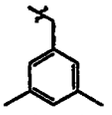
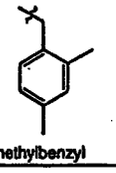
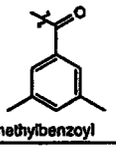
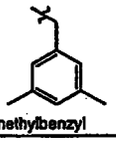
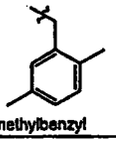
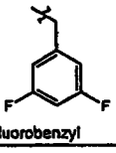
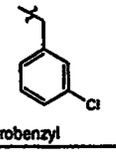
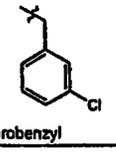
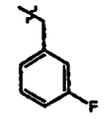
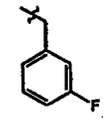
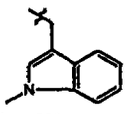
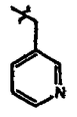
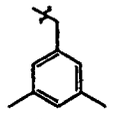
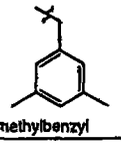
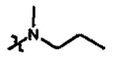
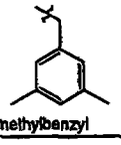
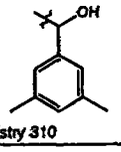
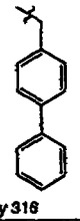
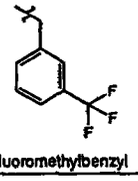
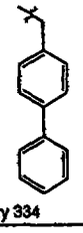
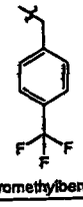
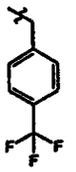
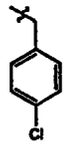
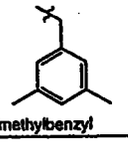
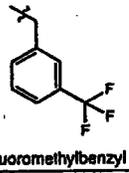
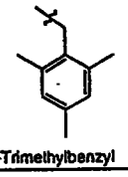
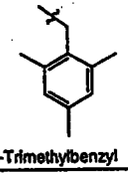
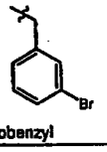
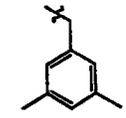
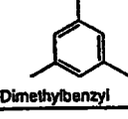
32	O	NH2	 3,5-Dimethylbenzyl	Me	Me	H	6.104	<5
33	O	NMe2	 3,5-Dimethylbenzyl	Me	Me	H	8.42	6.286
34	O	NMe2	 2,4-Dimethylbenzyl	Et	Me	H	5.019	<4
35	O	NMe2	 3,5-Dimethylbenzoyl	Et	Me	H	8.585	7.987
36	O	 N-Morpholino	 3,5-Dimethylbenzyl	Et	Me	H	6.763	<4
37	O	NMe2	 2,5-Dimethylbenzyl	Et	Me	H	6.796	5.729
38	O	NMe2	 3,5-Difluorobenzyl	Et	Me	H	8.155	7.402
39	O	NH2	 3-Chlorobenzyl	Et	Me	H	5	4.751
40	O	NMe2	 3-Chlorobenzyl	Et	Me	H	8.585	7.412
41	O	NH2	 3-Fluorobenzyl	Et	Me	H	5.131	4.473
42	O	NMe2	 3-Fluorobenzyl	Et	Me	H	8.569	7.18

43	o	NMe2	 Chemistry 280	Et	Me	H	7.377	6.422
44	o	NMe2	 Chemistry 286	Et	Me	H	7.889	6.355
45	o	NMe2	 3,5-Dimethylbenzyl	Et	Me	Et	5.519	4.095
46	o	NHMe	 3,5-Dimethylbenzyl	Et	Me	H	8.119	7.034
47	o	 Chemistry 303	 3,5-Dimethylbenzyl	Et	Me	H	7.767	6.968
48	o	NMe2	 Chemistry 310	Et	Me	H	8	6.711
49	o	NH2	 Chemistry 316	Et	Me	H	<4	<5
50	o	NH2	 3-Trifluoromethylbenzyl	Et	Me	H	<5	<5
51	o	NMe2	 Chemistry 334	Et	Me	H	5.384	<5
52	o	NH2	 4-Trifluoromethylbenzyl	Et	Me	H	<4	<5

53	o	NMe2		Et	Me	H	5.828	<5
54	o	NH2		Et	Me	H	<4	<5
55	o	NMe2		Et	Me	H	6.651	
56	o	Chemistry 363		Et	Me	H	8.194	7.11
57	o	NMe2		Et	Me	H	8.086	6.414
58	o	NH2		Et	Me	H	<4	<5
59	o	NMe2		Et	Me	H	5.029	<5
60	o	NMe2		Et	Me	H	8.444	7.001
61	o	Chemistry 393		Et	Me	H	7.693	5.922
62	o	Chemistry 399		Et	Me	H	6.604	5.305

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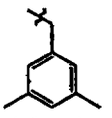
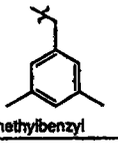
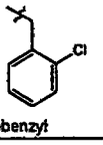
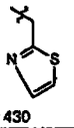
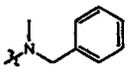
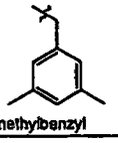
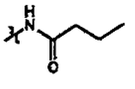
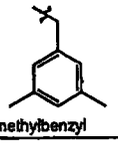
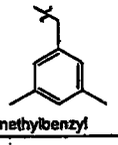
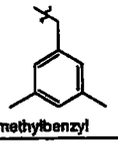
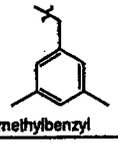
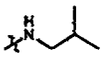
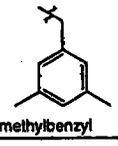
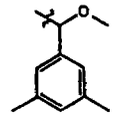
63	o	NMe2	 3,5-Dimethylbenzyl	Me	n-Pr	H	7.029	6.334
64	o	NHC(=O)-iPr	 3,5-Dimethylbenzyl	Et	Me	H		
65	o	NMe2	 2-Chlorobenzyl	Et	Me	H	8.284	6.405
66	o	NMe2	 Chemistry 430	Et	Me	H	7.588	5.72
67	o	 Chemistry 435	 3,5-Dimethylbenzyl	Et	Me	H	6.804	4.955
68	o	 Chemistry 441	 3,5-Dimethylbenzyl	Et	Me	H		
69	o	NH(n-Bu)	 3,5-Dimethylbenzyl	Et	Me	H	6.891	5.655
70	o	NMe2	 3,5-Dimethylbenzyl	 Chemistry 45	Me	H	7.752	7.159
71	o	NMe2	 3,5-Dimethylbenzyl	n-Pr	Me	H	7.777	7.049
72	o	 Chemistry 465	 3,5-Dimethylbenzyl	Et	Me	H	7.079	<4
73	o	NH2	 Chemistry 472	Et	Me	H	8.027	6.92

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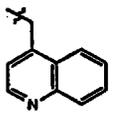
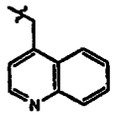
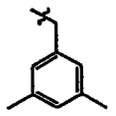
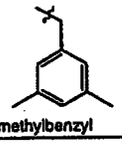
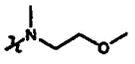
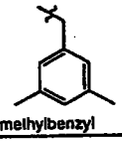
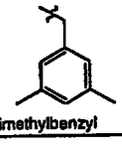
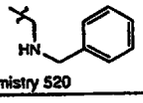
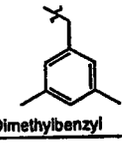
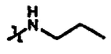
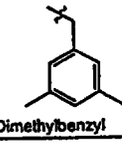
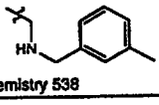
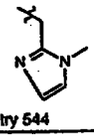
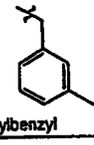
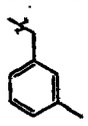
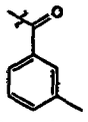
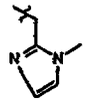
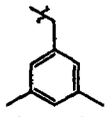
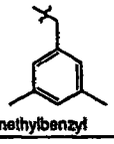
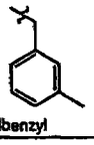
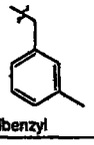
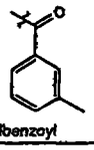
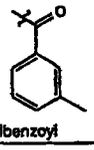
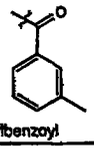
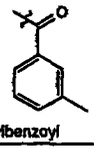
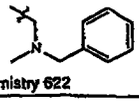
74	o	NH2		Et	Me	H	<4	<4
75	o	NMe2		Et	Me	H	5.252	4.132
76	o	NH2		H	i-Am	H	<5.494	<4
77	o	NMe2		H	i-Am	H	5.827	<4
78	o	 Chemistry 507		Et	Me	H	8.678	7.128
79	o	 Chemistry 513		Et	Me	H	6.987	5.47
80	o	NH2	 Chemistry 520	Et	Me	H	<4	<4
81	o	NHEt		Et	Me	H	7.866	6.444
82	o	 Chemistry 531		Et	Me	H	7.735	5.813
83	o	NH2	 Chemistry 538	Et	Me	H	<4.033	<4
84	o	NH2	 Chemistry 544	Et	Me	H	<4	<4
85	o	NH2	 3-Methylbenzyl	Me	Me	H	4.954	<4

86	o	NMe2	 3-Methylbenzyl	Me	Me	H	7.863	5.936
87	o	NH2	 3-Methylbenzoyl	Et	Me	H	6.46	5.653
88	o	NMe2	 Chemistry 568	Et	Me	H	<4	
89	o	NH2	 3,5-Dimethylbenzyl	H	n-Bu	H	6.237	
90	o	NMe2	 3,5-Dimethylbenzyl	H	n-Bu	H	6.359	
91	o	NH2	 3-Methylbenzyl	(CH2)4	(CH2)4	H	5.73	
92	o	NMe2	 3-Methylbenzyl	(CH2)4	(CH2)4	H	7.807	
93	o	NMe2	 3-Methylbenzoyl	Et	Me	H	8.721	
94	o	NH2	 3-Methylbenzoyl	Me	Me	H	5.153	
95	o	NEt2	 3-Methylbenzoyl	Et	Me	H	8.268	
96	o	NMe2	 3-Methylbenzoyl	Me	Me	H	7.824	6.37
97	o	NH2	 Chemistry 622	Et	Me	H	<4	<4

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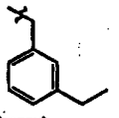
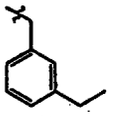
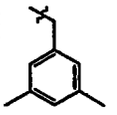
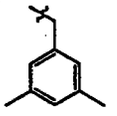
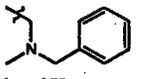
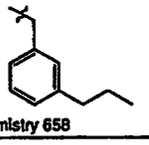
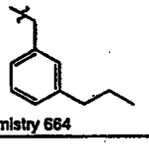
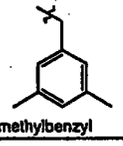
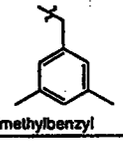
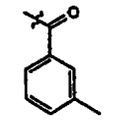
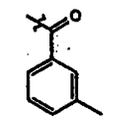
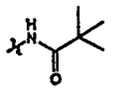
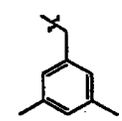
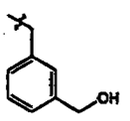
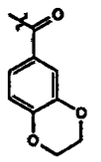
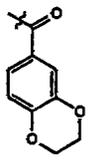
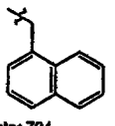
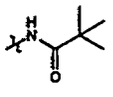
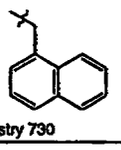
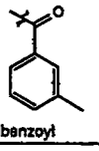
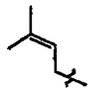
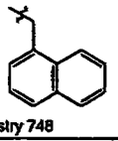
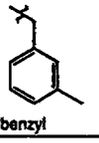
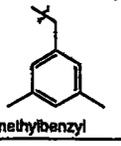
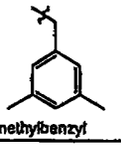
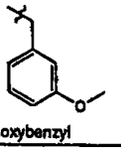
98	o	NH2	 3-Ethylbenzyl	Et	Me	H	5.358	4.978
99	o	NMe2	 3-Ethylbenzyl	Et	Me	H	8.569	6.718
100	o	NH2	 3,5-Dimethylbenzyl	H	Me	H	4.871	<4
101	o	NMe2	 3,5-Dimethylbenzyl	H	Me	H	6.341	4.25
102	o	NMe2	 Chemistry 652	Et	Me	H	4.369	<4
103	o	NH2	 Chemistry 658	Et	Me	H	5.747	
104	o	NMe2	 Chemistry 664	Et	Me	H	8	7.058
105	o	NH2	 3,5-Dimethylbenzyl	Cl	H	H	4.943	
106	o	NMe2	 3,5-Dimethylbenzyl	Cl	H	H	7.063	
107	o	NMe2	 3-Methylbenzoyl	(CH2)4	(CH2)4	H	7.231	
108	o	NMe2	 3-Methylbenzoyl	Me	Et	H	7.005	
109	o	 Chemistry 699	 3,5-Dimethylbenzyl	H	OMe	H		

110	o	NMe2	 Chemistry 706	Et	Me	H	7.783	
111	o	NH2	 Chemistry 712	Et	Me	H	<4	
112	o	NMe2	 Chemistry 718	Et	Me	H	6.394	
113	o	NH2	 Chemistry 724	Et	Me	H	5.273	
114	o	 Chemistry 729	 Chemistry 730	Et	Me	H		
115	o	NMe2	 3-Methylbenzoyl	Et	Me	 Chemistry 745	<4.307	
116	o	NMe2	 Chemistry 748	Et	Me	H	6.627	
117	o	CH2NMe2	 3-Methylbenzyl	(CH2)4	(CH2)4	H	<4.139	
118	o	NH2	 3,5-Dimethylbenzyl	Me	i-Pr	H	4.042	
119	o	NMe2	 3,5-Dimethylbenzyl	Me	i-Pr	H	5.114	
120	o	NH2	 3-Methoxybenzyl	Et	Me	H	5.033	

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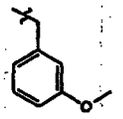
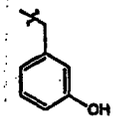
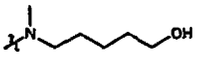
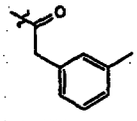
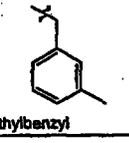
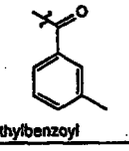
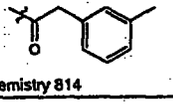
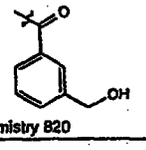
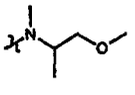
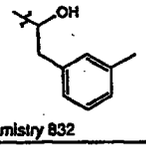
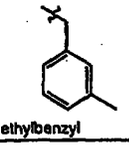
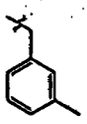
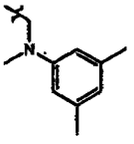
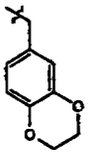
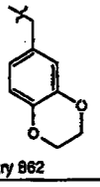
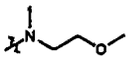
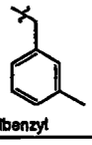
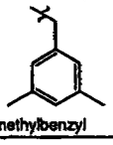
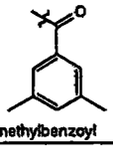
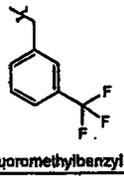
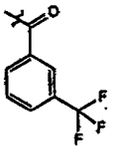
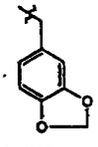
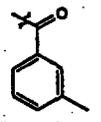
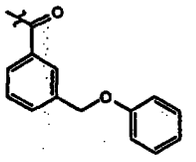
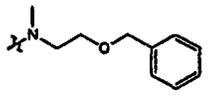
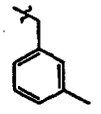
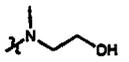
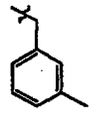
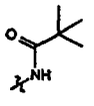
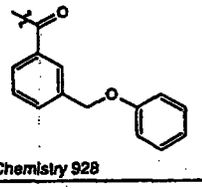
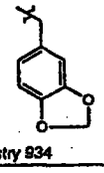
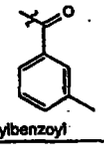
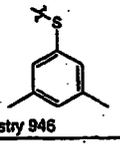
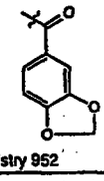
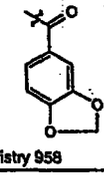
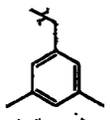
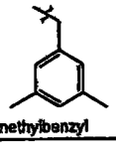
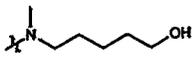
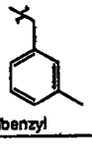
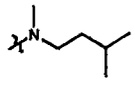
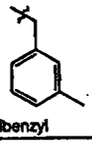
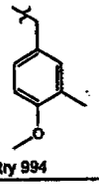
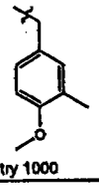
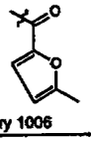
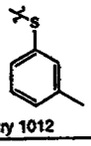
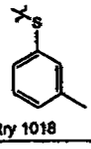
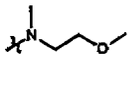
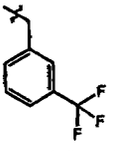
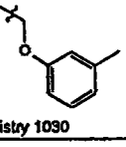
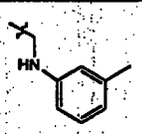
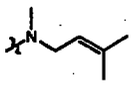
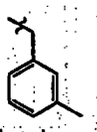
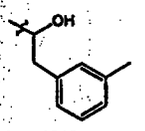
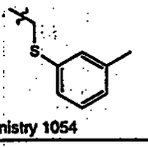
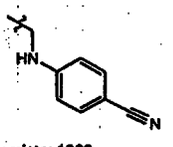
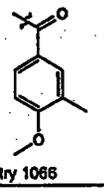
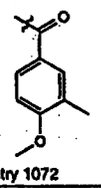
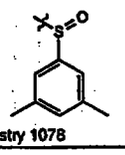
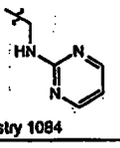
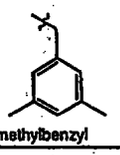
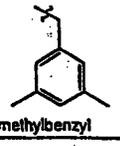
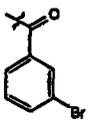
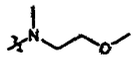
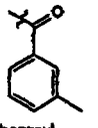
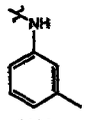
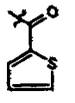
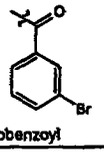
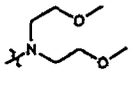
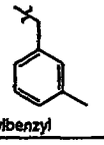
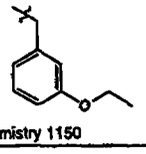
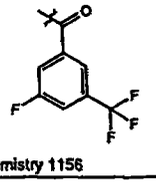
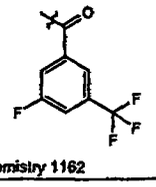
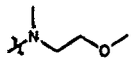
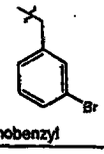
121	O	NMe2		Et	Me	H	8.469	6.948
122	O	NMe2		Et	Me	H	7.196	
123	O	Chemistry 789		Et	Me	H	8.444	6.918
124	O	NH2		Et	Me	H	4.389	
125	O	NHCHO		Et	Me	H		
126	O	NHCHO		Et	Me	H		
127	O	NMe2		Et	Me	H	4.174	
128	O	NMe2		Et	Me	H	7.848	
129	O	Chemistry 825		Et	Me	H	8.398	7.057
130	O	NH2		Et	Me	H	<4	
131	O	NH2		(CH2)3	(CH2)3	H	5.799	

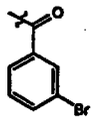
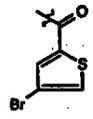
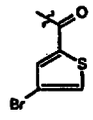
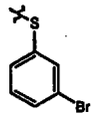
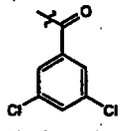
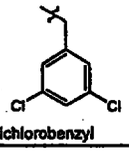
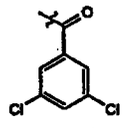
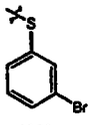
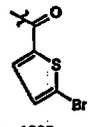
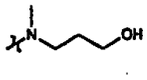
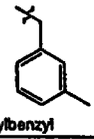
132	o	NMe2	 3-Methylbenzyl	(CH2)3	(CH2)3	H	7.863	
133	o	NMe2	 Chemistry 850	Et	Me	H	4.94	
134	o	NH2	 Chemistry 856	Et	Me	H	4.056	
135	o	NMe2	 Chemistry 862	Et	Me	H	6.688	
136	o		 3-Methylbenzyl	Et	Me	H	9	6.996
137	s	NMe2	 3,5-Dimethylbenzyl	Et	Me	H	7.658	
138	s	NMe2	 3,5-Dimethylbenzoyl	Et	Me	H	8.215	7.401
139	o	NHMe	 3-Trifluoromethylbenzyl	Et	Me	H	6.908	
140	o	NH2	 3-Trifluoromethylbenzoyl	Et	Me	H	5.766	
141	o	NH2	 Chemistry 898	Et	Me	H	4.642	

142	O	NH2		(CH2)3	(CH2)3	H	4.889	
143	O	NMe2		Et	Me	H	7.421	
144	O			Et	Me	H	6.446	
145	O			Et	Me	H	8.42	6.028
146	O			Et	Me	H		
147	O	NMe2		Et	Me	H	7.721	
148	O	NMe2		(CH2)3	(CH2)3	H	7.863	
149	O	NMe2		Et	Me	H	8.959	7.883
150	O	NH2		Et	Me	H	4.881	
151	O	NMe2		Et	Me	H	7.845	

152	o	NMe2	 3,5-Dimethylbenzyl	Et	Me	Ph	4.21	
153	o	NMe2	 3,5-Dimethylbenzyl	Et	Me	NH2	6.749	
154	o	 Chemistry 981	 3-Methylbenzyl	Et	Me	H	8.009	6.262
155	o	 Chemistry 987	 3-Methylbenzyl	Et	Me	H	7.514	
156	o	NH2	 Chemistry 994	Et	Me	H	4.934	
157	o	NMe2	 Chemistry 1000	Et	Me	H	6.413	
158	o	NMe2	 Chemistry 1006	Et	Me	H	8.041	6.625
159	o	NH2	 Chemistry 1012	Et	Me	H	7.011	
160	o	NMe2	 Chemistry 1018	Et	Me	H	8.678	7.177
161	o	 Chemistry 1023	 3-Trifluoromethylbenzyl	Et	Me	H	7.821	5.814
162	o	NMe2	 Chemistry 1030	Et	Me	H	6.418	5.026

163	o	NMe2		Et	Me	H	5.596	4.236
164	o	 Chemistry 1041	 3-Methylbenzyl	Et	Me	H	7.818	6.505
165	o	NMe2	 Chemistry 1048	Et	Me	H	4.354	<4
166	o	NMe2	 Chemistry 1054	Et	Me	H	5.693	4.518
167	o	NMe2	 Chemistry 1060	Et	Me	H	6.338	5.828
168	o	NH2	 Chemistry 1066	Et	Me	H	4.525	4.806
169	o	NMe2	 Chemistry 1072	Et	Me	H	7.101	5.771
170	o	NMe2	 Chemistry 1078	Et	Me	H	8.553	7.224
171	o	NMe2	 Chemistry 1084	Et	Me	H	5.895	4.74
172	o	NH2	 3,5-Dimethylbenzyl	(CH2)4	(CH2)4	H	6.419	4.903
173	o	NMe2	 3,5-Dimethylbenzyl	(CH2)4	(CH2)4	H	8.086	6.469

174	O	NMe2		Et	Me	H	8.921	7.68
175	O	 Chemistry 1107		Et	Me	H	8.921	7.717
176	O	NMe2	 Chemistry 1114	Et	Me	H	8.432	6.436
177	O	NH2	 Chemistry 1120	Et	Me	H	5.106	<4
178	O	NMe2	 Chemistry 1126	Et	Me	H	7.873	6.461
179	O	NHMe	 3-Bromobenzoyl	Et	Me	H	8.42	7.182
180	O	 Chemistry 1137	 3-Methylbenzyl	Et	Me	H	5.988	
181	O	NMe2	 Chemistry 1150	Et	Me	H	7.928	
182	O	NH2	 Chemistry 1156	Et	Me	H	5.933	
183	O	NMe2	 Chemistry 1162	Et	Me	H	8.481	
184	O	 Chemistry 1167	 3-Bromobenzyl	Et	Me	H	8.523	6.804

185	o	 Chemistry 1173	 3-Bromobenzoyl	Et	Me	H	8.745	7.433
186	o	NH2	 Chemistry 1180	Et	Me	H	5.781	
187	o	NMe2	 Chemistry 1186	Et	Me	H	8.481	7.006
188	o	NH2	 Chemistry 1192	Et	Me	H	7.063	
189	o	NH2	 3,5-Dichlorobenzyl	Et	Me	H	6.401	
190	o	NH2	 3,5-Dichlorobenzoyl	Et	Me	H	7.757	
191	o	NMe2	 3,5-Dichlorobenzyl	Et	Me	H	8.097	7.553
192	o	NMe2	 3,5-Dichlorobenzoyl	Et	Me	H	8.699	8.319
193	o	NMe2	 Chemistry 1222	Et	Me	H	8.481	7.245
194	o	NH2	 Chemistry 1228	Et	Me	H	4.665	
195	o	 Chemistry 1233	 3-Methylbenzyl	Et	Me	H	8.569	6.52

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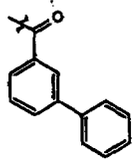
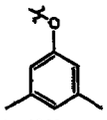
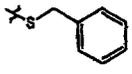
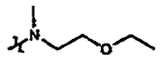
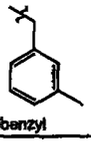
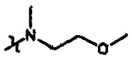
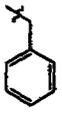
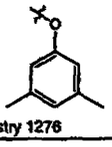
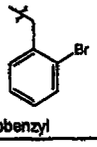
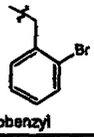
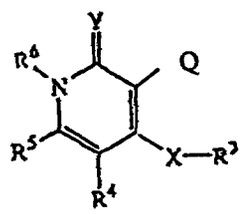
196	O	NMe2	 Chemistry 1240	Et	Me	H	6.411	
197	O	NH2	 Chemistry 1246	Et	Me	H	7.307	
198	O	NH2	 Chemistry 1252	Me	H	H	4.457	
199	O	 Chemistry 1257	 3-Methylbenzyl	Et	Me	H	7.924	
200	O	 Chemistry 1263	 Benzyl	Et	Me	H	8.42	5.95
201	O	NMe2	 Chemistry 1276	Et	Me	H	8.585	7.231
202	O	NH2	 2-Bromobenzyl	Et	Me	H	5.715	
203	O	NMe2	 2-Bromobenzyl	Et	Me	H	8.161	

CLAIMS:

1. A compound having the formula (1)



wherein:

- Q represents $-NR_1R_2$ or $-R_0NR_1R_2$ wherein:

*R_o represents C_{1-6} alkanediyl;

* R_1 and R_2 each independently represent C_{1-6}alkyl or C_{3-6}alkenyl; said C_{1-6}alkyl and C_{3-6}alkenyl may be substituted with one, two or three substituents selected from hydroxy, C_{1-4}alkyloxy, C_{1-4}alkylthio, aryloxy, arylthio, amino, mono- or di(C_{1-4}alkyl)amino and aryl; or

* R_1 and R_2 taken together may form a bivalent radical $-R_1-R_2-$ wherein $-R_1-R_2$ - represents $-(CH_2)_2-O-(CH_2)_2-$, $-(CH_2)_2-NR_7-(CH_2)_2$,

$-(CH_2)_2-CH(NHR_7)-(CH_2)_2-$ or $-(CH_2)_n$ wherein R_7 represents hydrogen or C_{1-4}alkyl and n represents 2, 3, 4, 5 or 6;

- R_3 represents aryl or a monocyclic or bicyclic heterocycle selected from pyridinyl, pyrimidinyl, thiazolinyl, furanyl, thienyl, imidazolyl, benzoxazolyl, benzothiazolyl, benzimidazolyl; said monocyclic or bicyclic heterocycle may optionally be substituted with one, two or three substituents each independently selected from hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, halo, trifluoromethyl, dimethylenoxy or phenyl,

$-R_4$ and R_5 each independently represent hydrogen, C_{1-6}alkyl,



C_{3-6}alkenyl, C_{1-4}alkoxy, C_{1-4}alkyloxyC_{1-4}alkyl, amino, mono- or di(C_{1-4}alkyl) amino, formyl, C_{1-4}alkylcarbonyl carboxyl, C_{1-4} alkyloxycarbonyl, or C_{1-4}alkyl aminocarbonyl; wherein C_{1-6}alkyl and C_{3-6}alkenyl may be substituted with one, two or three substituents selected from hydroxy, C_{1-4}alkyloxy, C_{1-4}alkyl thio, aryloxy, arylthio, amino, mono- or di(C_{1-4}alkyl)amino and aryl; or R_4 and R_5 taken together form a bivalent radical of formula -R_4-R_5-wherein -R_4-R_5- represents -CH=CH-CH=CH- or -$(CH_2)_t$, wherein t represents 3 or 4;

- R_6represents hydrogen, hydroxy,C_{1-4}alkyloxy, c_{1-6}alkyl, C_{3-6}alkenyl, aryl, C_{1-4}alkyl, amino, mono- or di(C_{1-4}alkyl)amino or alkylaryl;

- Y represents O or S;

- X represents a radical of formula:

$-(CH_2)_p$ (a) or

$-(CH_2)_q-Z-(CH_2)_r$ (b)

wherein p represents 1, 2, 3, 4 or 5;

q represents 0, 1, 2, 3, 4 or 5;

r represents 0, 1, 2 or 3;

- Z represents NR_8, C(= O), CHOH, $CHNR_8R_9$; CF_2, O, S or CH=CH; wherein R_8 and R_9 each independently represent hydrogen or C_{1-4} alkyl;

or

a N-oxide, a stereochemically isomeric form or a pharmaceutically acceptable addition salt thereof.

2. A compound according to claim 1 wherein R_1 and R_2 represent each a methyl group.

3. A compound according to claim 1 wherein X represents -CH_2- and R_3 represents a phenyl group substituted with two methyl groups.

4. A compound according to claim 1 which is the 3-dimethylamino-4-(3,5-dimethylbenzyl)-5-ethyl-6-methylpyridin-2(1H)-one.

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5. A process for the obtention of compounds according to claim 1 wherein X represents $-CH_2-$, Y represents O, R_3 is an optionally phenyl group substituted and R_6 is hydrogen comprising the following steps:

a) reacting a pyridine, substituted in position 2 with an alkoxy group and in position 3 with an amidoalkyl group, with a C_1-C_6 alkyllithium, resulting in a lithiated derivate of the said pyridine.

b) transforming said lithiated derivate into an organocopper reagent by reacting it with a complex formed by Cu I and dimethyl sulphide.

c) obtaining a protected pyridinone by reacting the organocopper reagent with optionally substituted benzyl halide.

d) hydrolysing said protected pyridinone and obtaining a deprotected pyridinone .

e) substituting the amine-3 group of said deprotected pyridinone and obtaining the desired pyridinone compound.

6. A process for the obtention of compounds according to claim 1 wherein X represents -C(= 0) , Y represents O, R_3 is an optionally substituted phenyl group , and R_6 is hydrogen wherein:

a) reacting a pyridine , substituted in position 2 with an alkoxy group and in position 3 with an amidoalkyl group, with a C_1-C_6 alkyllithium, resulting in a lithiated derivate of said pyridine.

b) reacting the lithiated derivative with an optionally substituted benzaldehyde, resulting in a substituted pyridinone ,

c) oxidizing said substituted pyridinone , resulting in a protected pyridinone ,

d) deprotecting said protected pyridinone by hydrolysis, resulting in the desired pyridinone compound .

7. Lithiated derivative having the following formula :



wherein R_4 and R_5 are as defined in claim 1, and R_{10} and R_{11} are independently C_1-C_6 alkyl.

8. Pharmaceutical compositions comprising a therapeutically effective amount of at least a compound according to claim 1 and pharmaceutical carriers.

9. Method of treatment of HIV-related diseases comprising the administration of an effective amount of a compound according to claim 1.

10. Method of treatment of HIV-infection comprising the administration of an effective amount of a compound according to claim 1.

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