



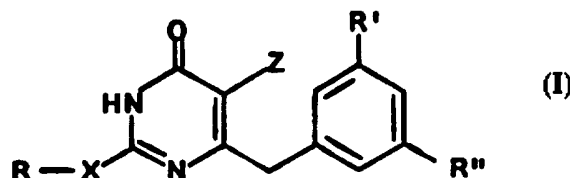
## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
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| (21) International Application Number: PCT/EP95/03912<br>(22) International Filing Date: 4 October 1995 (04.10.95)<br>(30) Priority Data:<br>MI94A002023 4 October 1994 (04.10.94) IT<br>(71) Applicants (for all designated States except US): ISTITUTO SUPERIORE DI SANITA' [IT/IT]; Viale Regina Elena, 299, I-00161 Roma (IT). UNIVERSITA' DEGLI STUDI DI CAGLIARI [IT/IT]; Via Università, I-09124 Cagliari (IT).<br>(72) Inventors; and<br>(75) Inventors/Applicants (for US only): ARTICO, Marino [IT/IT]; Via E. Negri, 64, I-00128 Roma (IT). MASSA, Silvio [IT/IT]; Via Vincenzo Tangorra, 1, I-00191 Roma (IT). MAI, Antonello [IT/IT]; Via G. Gallesi, 25, I-00010 Lunghezza (IT). LA COLLA, Paolo [IT/IT]; Strada Poggio dei Pini, 5a, I-09012 Capoterra (IT). MARONGIU, Maria, Elena [IT/IT]; Via Dante, 99, I-09128 Cagliari (IT). TRA-MONTANO, Enzo [IT/IT]; Via Foscato, 12, I-08100 Nuoro (IT).<br>(74) Agent: GERVASI, Gemma; Notarbartolo & Gervasi S.r.l., Viale Bianca Maria, 33, I-20122 Milano (IT). |    | (81) Designated States: AL, AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).<br><br>Published<br>With international search report.<br>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments. |

(54) Title: SUBSTITUTED 6-BENZYL-4-OXOPYRIMIDINES, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

## (57) Abstract

Substituted 6-benzyl-4-oxypyrimidines having formula (I) are described, wherein: X is selected from the group consisting of O and S; R is selected from the group consisting of C<sub>1-4</sub> alkyl and C<sub>5-6</sub> cycloalkyl; R', R'' and Z, equal or different among them mean H or C<sub>1-4</sub> alkyl considering that, when X = O, R and R' cannot be both equal to H; their pharmaceutically acceptable salts and their soluble derivatives; one of their preparation processes and their use for the preparation of pharmaceutical compositions useful for the treatment of viral infections.



pharmaceutical compositions useful for the treatment of

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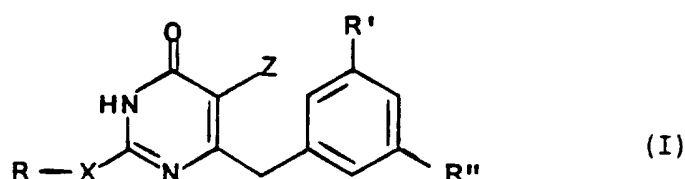
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SUBSTITUTED 6-BENZYL-4-OXOPYRIMIDINES, PROCESS FOR THEIR PREPARATION  
AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

FIELD OF THE INVENTION

The present invention refers to compounds having general formula (I):



5 wherein:

X is selected from the group consisting of O and S;

R is selected from the group consisting of C<sub>1-4</sub> alkyl and C<sub>5-6</sub> cycloalkyl;

R', R'' and Z, equal or different among them mean H or C<sub>1-4</sub> alkyl

10 considering that, when X=O, R and R' can not be both equal to H; their pharmaceutically acceptable salts and their soluble derivatives;

one of their preparation processes and their use for the preparation of pharmaceutical compositions useful for the treatment of viral infections, particularly of immunodeficiency virus (HIV) infections.

15 PRIOR ART

The pandemic diffusion of the acquired immunodeficiency syndrome (AIDS) makes urgent the development of chemotherapeutic agents able to halt the replication of the two retroviruses responsible for the infection:

HIV-1 and HIV-2.

Among the various phases characterizing the replication cycle of these viruses the transcription phase of the viral genome (a single RNA filament) in double strand DNA is the most studied one.

5 Such a phase, taking place early after the infection, is catalyzed by virus specific enzyme, the reverse transcriptase (RT). The products of pharmaceutical interest able to inhibit the RT may be essentially divided into two classes: nucleosides analogues and non-nucleoside compounds. The four drugs used until now in the AIDS therapy, i.e.  
10 AZT, ddI, dhT and ddC, belong to the first class. Other molecules having very different chemical structure, some of which are undergoing clinical trials, belong to the second one. The 3,4-dihydro-2-alkoxy-6-benzyl-4-oxopyrimidines (DABO) structurally similar to the compounds according to the present invention and having antiviral properties are  
15 described in Antiviral Chemistry and Chemotherapy (1993) 4(6), pp. 361-368. Unfortunately the clinical experience has pointed out two major limits of the therapy with said antivirals.

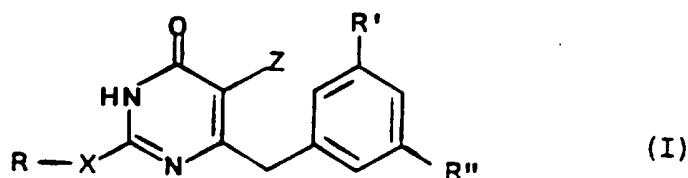
Following chronical treatment, on the one hand collateral toxicity phenomena appear (remarkable in the case of the nucleosides analogous).

20 On the other hand, drug-resistant mutants appear (very quickly in the case of non-nucleoside RT inhibitors). It is therefore evident the necessity to have available always new molecules active and useful in this field of application.

#### DETAILED DESCRIPTION OF THE INVENTION

25 The present invention allows to overcome the above mentioned drawbacks

by compounds having general formula (I)



wherein:

X is selected from the group consisting of O and S;

R is selected from the group consisting of C<sub>1-4</sub> alkyl and C<sub>5-6</sub> cycloalkyl;

5 R', R'' and Z, equal or different among them mean or C<sub>1-4</sub> alkyl considering that, when X=O, R and R' can not be both equal to H;

their pharmacologically acceptable salts and their soluble derivatives.

As it can be noticed, the compounds of the present invention differ from the DABO described in the above reported literature owing to the

10 presence of one S atom in the place of the O atom or owing to the presence of substituents on the benzylic ring. In Tables 3 and 4 the activity of some compounds according to the invention is reported, while in the Table 5 the data obtained with the above mentioned DABO compounds are reported by comparison. In the light of the biological

15 activity data, the products having formula (I) wherein:

X = O, Z = H, R = cyclohexyl, R' = CH<sub>3</sub>, R'' = H

X = O, Z = H, R = cyclohexyl, R' = CH<sub>3</sub>, R'' = CH<sub>3</sub>

X = O, Z = CH<sub>3</sub>, R = sec-butyl, R' = CH<sub>3</sub>, R'' = CH<sub>3</sub>

X = S, Z = H, R = iso-propyl, R' = CH<sub>3</sub>, R'' = H

- X = S, Z = H, R = sec-butyl, R' = CH<sub>3</sub>, R'' = H  
X = S, Z = H, R = cyclopentyl, R' = CH<sub>3</sub>, R'' = H  
X = S, Z = CH<sub>3</sub>, R = methyl, R' = H, R'' = H  
X = S, Z = CH<sub>3</sub>, R = cyclopentyl, R' = H, R'' = H  
5 X = S, Z = CH<sub>3</sub>, R = cyclohexyl, R' = H, R'' = H  
X = S, Z = CH<sub>3</sub>, R = cyclopentyl, R' = CH<sub>3</sub>, R'' = H  
X = S, Z = CH<sub>3</sub>, R = cyclopentyl, R' = CH<sub>3</sub>, R'' = H

turned out to be particularly interesting.

PREPARATION OF THE COMPOUNDS HAVING FORMULA (I) WHEREIN X = S (see

10 scheme "A")

Thiourea (43 mmol) and the suitable methyl phenylacetylacetate (31.5 mmol) are added to a solution of sodium methoxide obtained dissolving metallic sodium (0.063 g-atoms) in anhydrous methanol (50 ml) and the resulting mixture is left to reflux under magnetic agitation for 5  
15 hours. After cooling the solvent is evaporated at reduced pressure, the residue is taken back with water (200 ml) and the mixture is acidified to pH 5 with 0.5 N acetic acid and extracted with ethyl acetate (3 x 100 ml).

The solid in case separated (raw 2-thiouracil) is vacuum filtered,  
20 stove dried and crystallized by a suitable solvent while the reunited organic extracts are washed with a saturated solution of NaCl (2 x 100 ml), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated at reduced pressure to give the 2-thio(5-alkyl)-6-benzyl(substituted)uracil (1).

Subsequently, according to the method A, methyl iodide (8 mmol; 1.13 g)  
25 is added to a solution containing the suitable 2-thiouracil derivative

(4 mmol) dissolved in anhydrous N,N-dimethylformamide (2 ml) and the mixture is left under agitation at room temperature until the starting material disappears by the thin-layer chromatography check (silica gel/n-hexane: ethyl acetate: methanol 12:3:1). Subsequently the solution is diluted with water (200 ml), the aqueous phase is extracted with ethyl acetate (3 x 50 ml) and the reunited organic extracts are washed with a solution saturated with sodium thiosulfate (100 ml), with a solution saturated with NaCl (100 ml), dried ( $\text{Na}_2\text{SO}_4$ ) and deprived of the solvent.

10 The 3,4-dihydro-2-methylthio-(5-alkyl)-6-benzyl(substituted)-4-oxopyrimidine derivatives (2) so obtained are then purified by a suitable solvent.

Alternatively, according to the methods B and C, anhydrous potassium carbonate (4.2 mmol) and the suitable alkyl halide (4.4 mmol) are added to a solution containing the suitable 2-thiouracil derivative (4 ml) dissolved in anhydrous N,N-dimethylformamide (2 ml) and the resulting mixture is left under agitation at room temperature (method B) or at 80 °C (method C) until the starting material disappears by the thin-layer chromatography check (silica gel/n-hexane: ethyl acetate: methanol 12:3:1).

Subsequently the solution is diluted with water (200 ml), it is acidified to pH 5 with 0.5 N acetic acid and the aqueous phase is extracted with ethyl acetate (3 x 50 ml). The reunited organic extracts are washed with a saturated solution of sodium thiosulfate (100ml), with a saturated solution of NaCl (100 ml), dried ( $\text{Na}_2\text{SO}_4$ ) and

concentrated at reduced pressure.

The 3,4-dihydro-2-alkylthio-(5-alkyl)-6-benzyl (substituted)-4-oxopyrimidine derivatives (3) and (4) so obtained are then purified by crystallization from a suitable solvent or by chromatography (silica  
5 gel/n-hexane: ethyl acetate: methanol 12:3:1). The physico-chemical data of some of the obtained products are reported in the Table 1.

PREPARATION OF THE COMPOUNDS HAVING GENERAL FORMULA (I) WHEREIN X = O

(see scheme B)

SOC<sub>l</sub><sub>2</sub> (21.3 ml) is slowly added under nitrogen atmosphere to the  
10 suitable phenylacetic acid (43.2 mmol) and the resulting solution has been warmed for 2 hours. After cooling the solvent has been dried at reduced pressure.

A solution of the raw 3'-methyl or 3',5'-dimethyl phenylacetyl chloride (160 mmol) so obtained in 50 ml of anhydrous CH<sub>2</sub>Cl<sub>2</sub> has been added in 2  
15 hours, at 0 °C and under nitrogen atmosphere, to a suspension of 23.75 g (165 mmol) of 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum acid) in 65 ml of anhydrous CH<sub>2</sub>Cl<sub>2</sub> containing 32.5 ml (400 mmol) of anhydrous pyridine, under strong agitation. The agitation has been continued for 1 hour at 0 °C and for a further hour at room temperature, then the  
20 mixture has been poured on ice and treated with 2N HCl. The organic layer has been picked up and the aqueous solution washed two times with CH<sub>2</sub>Cl<sub>2</sub>. The organic phase and the extracts have been reunited, washed with brine and dried.

The evaporation of the solvent under reduced pressure gave the acylated  
25 product 5 as a brown solid which has been put to reflux in 200 ml of

CH<sub>3</sub>OH for 20 hours.

After vacuum evaporation of the solvent and chromatographic purification the compounds 6 are respectively obtained.

Metallic sodium (3.68 g) is added to a solution of the above mentioned  
5 compounds 6 in methanol (250 ml) and the solution is stirred to complete dissolution of the metal. CH<sub>3</sub>I is dropped in the solution and the resulting mixture is reflux warmed for 4 hours.

After cooling the solvent has been removed and the residue has been treated with H<sub>2</sub>O (200 ml) and extracted with CHCl<sub>3</sub> (3 x 100 ml). The  
10 organic layer has been washed with brine (2 x 100 ml), dried and evaporated to give a residue which, purified by chromatography, has given the compounds 7 as a yellow oil.

A solution of the compounds 6 or 7 (10 mmol) in CH<sub>3</sub>OH (50 ml) has been added to a suspension of O-methylisourea hydrogensulfate (15 mol) and  
15 Ca(OH)<sub>2</sub> (16 mmol) under strong agitation. The resulting mixture has been stirred at room temperature for 72 hours and then concentrated, acidified to pH 5 with 0.5 N acetic acid and extracted with ethyl acetate (3 x 50 ml). The organic extracts have been washed with brine (100 ml), dried and dry evaporated. The residue, purified by  
20 crystallization from a suitable solvent gave the pure compounds 8.

Metallic potassium (100 mmol) in small pieces has been slowly added under agitation to the suitable alcohol (200 ml) freshly distilled on sodium. The dissolution of the metal has been completed by warming the mixture at 70-80 °C and then the derivatives 8 (10 mmol) are added and  
25 the obtained mixture is reflux warmed under nitrogen atmosphere. The

reaction has been stopped when the chromatographic check confirmed the disappearance of the starting 4-pyrimidone.

The mixture has been diluted with water (100 ml) after cooling, acidified to pH 5 with 0.5 N acetic acid and extracted with ethyl acetate (3 x 50 ml).

The reunited extracts have been washed with brine (100 ml), dried and evaporated to give the raw products 9 which have been purified by column chromatography and crystallized again by a suitable solvent.

In some cases the methoxy group in the position 2 of the compounds 8 wherein  $R = R_2 = H$ ,  $R_1 = CH_3$  or  $R = R_1 = R_2 = CH_3$  has been removed with formation of the respective compounds 10 wherein  $R = R_1 = H$ ,  $R_2 = CH_3$  and  $R = R_1 = R_2 = CH_3$  as collateral products.

The physico-chemical data of some of the obtained products are reported in the Table 2.

The products obtained acting as above described with the relative data of cytotoxicity and anti-HIV 1 activity are reported in the Tables 3 and 4.

#### BIOLOGICAL ACTIVITY

In order to illustrate the activity of the compounds in the HIV-1 infections the results in vitro are reported relating to:

- cytotoxicity for different cell lines and bone marrow cells from HIV seronegative subjects;
- inhibitory activity with regard to HIV-1;
- capability to inhibit the reverse transcriptase of HIV-1 in tests with recombinant enzyme (rRT) of HIV-1.

The cells used in this study were MT-4 and C8166, both T4 lymphocytes lines permissive for the HIV replication. The cells were suspended in RPMI 1640 added with fetal calf serum (FCS) at 10%, penicillin 100 U/ml and streptomycin 100 µg/ml.

- 5 The cell cultures were incubated at 37 °C in 5% CO<sub>2</sub> atmosphere and were periodically checked to verify the absence of mycoplasmas contamination.

For the evaluation of the compounds cytotoxicity a colorimetric method has been employed based on the use of a tetrazolium salt, the 3-(4,5  
10 dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium-bromide (MTT), which is transformed by the mitochondrial enzyme succinic dehydrogenase into a blue coloured product, the formazane, the amount of which turns out to be directly proportional to the number of viable cells.

- In short 50 µl of RPMI containing  $1 \times 10^4$  cells (MT-4, C8166, U937,  
15 PBL) were added, in 96 wells multiplates, to 50 µl of RPMI containing or not scalar dilutions of the compounds under examination. After 4 days of incubation at 37 °C 20 µl of MTT (2.5 µg/ml) have been added to each well. After 4 hours of incubation at 37 °C the produced formazane was solubilized by adding 150 µl/well of an isopropanol solution  
20 containing 0.34% of HCl and 5% of Nonidet P40 (NP-40), a non-ionic detergent.

The amount of formazane was then determined at the spectrophotometer by evaluation of the optical density at 570 nm. The values shown in the columns CC<sub>50</sub> represent the compound concentrations required to reduce  
25 by 50% the MTT metabolization and, therefore, the cell viability; the

mitochondrial metabolic process is, in fact, in a linear relation with the cell viability. As it is shown in the Tables, the major part of the compounds has low or null cytotoxicity in non infected cells, even at the maximum concentrations tested. The inhibition of the virus-induced  
5 cytopathogenicity constituted the estimation criterion of the anti-HIV-1 activity of the compounds.

The virus used in the antiviral tests (HIV-1, strain III<sub>B</sub>) has been obtained from the chronically infected H9/III<sub>B</sub> cells supernatant. The virus stock solutions were tited in C8166 and maintained at -80 °C till  
10 the moment of use. MT-4 cells, seeded at a density equal to  $1 \times 10^6$ /ml, were infected with HIV-1 at a multiplicity of infection (m.o.i.) equal to 0.01. After 1 hour of incubation at 20 °C and subsequent removal of the inoculum, the cells were washed three times and then suspended again at a density equal to  $1 \times 10^5$ /ml, in absence or in presence of  
15 the test compounds.

After 4 days of incubation at 37 °C the cell survival was determined with the above mentioned MTT method, in order to compute the values of EC<sub>50</sub> representing the compound concentration necessary to reduce by 50% the virus-induced cytopathogenicity.

20 The results reported in the Tables show that the test compounds are active in inhibiting the HIV-1 multiplication in MT-4 cells. They, owing to the lack of citotoxicity, have a selectivity index (meant as ratio between cytotoxicity and anti-HIV activity) particularly favourable.

25 In order to complete the antiviral activity analysis of the compounds

we proceeded to estimate the effects of the interaction of the various molecules with the target enzyme, the reverse transcriptase (RT). The gene of this enzyme has been formerly cloned in an expression vector, the protein has been expressed in E.coli and subsequently has been

5 purified to obtain a preparation with a high purity degree. The tests with the recombinant RT (rRT) have been carried out at 37 °C for 30 minutes in 50 µl containing 50 mM tris-HCl (pH 7.8), 1 mM dithiotreitol, 80 mM KCl, 6 mM MgCl<sub>2</sub>, 0.1 mg/ml bovine serum albumin, 10 µM [<sup>3</sup>H]-dTTP (1Ci/mmol) or [<sup>3</sup>H]-dGTP (1 Ci/mmol), 0.05 OD<sub>260</sub>

10 units/ml of Poly(rC)-oligo(dG)<sub>12-18</sub> and 0.002 units of enzyme. A unit is defined as the amount of enzyme necessary to incorporate 1 nmol of [<sup>3</sup>H]-dTTP in the "template-primer" Poly(rA)-oligo(dT)<sub>10</sub> in one minute at 37 °C. After incubation, 40 µl of the reaction have been transferred on Whatman GF/A glass fiber filters and processed for the determination

15 of the acid insoluble radioactivity after treatment with trichloroacetic acid. The values reported in the Tables (IC<sub>50</sub>) represent the compound concentration required to reduce the enzyme activity by 50%.

The analysis of the values of IC<sub>50</sub> reveals a good correlation with the values of EC<sub>50</sub> confirming that the specific target of the compounds

20 object of the invention is the reverse transcriptase.

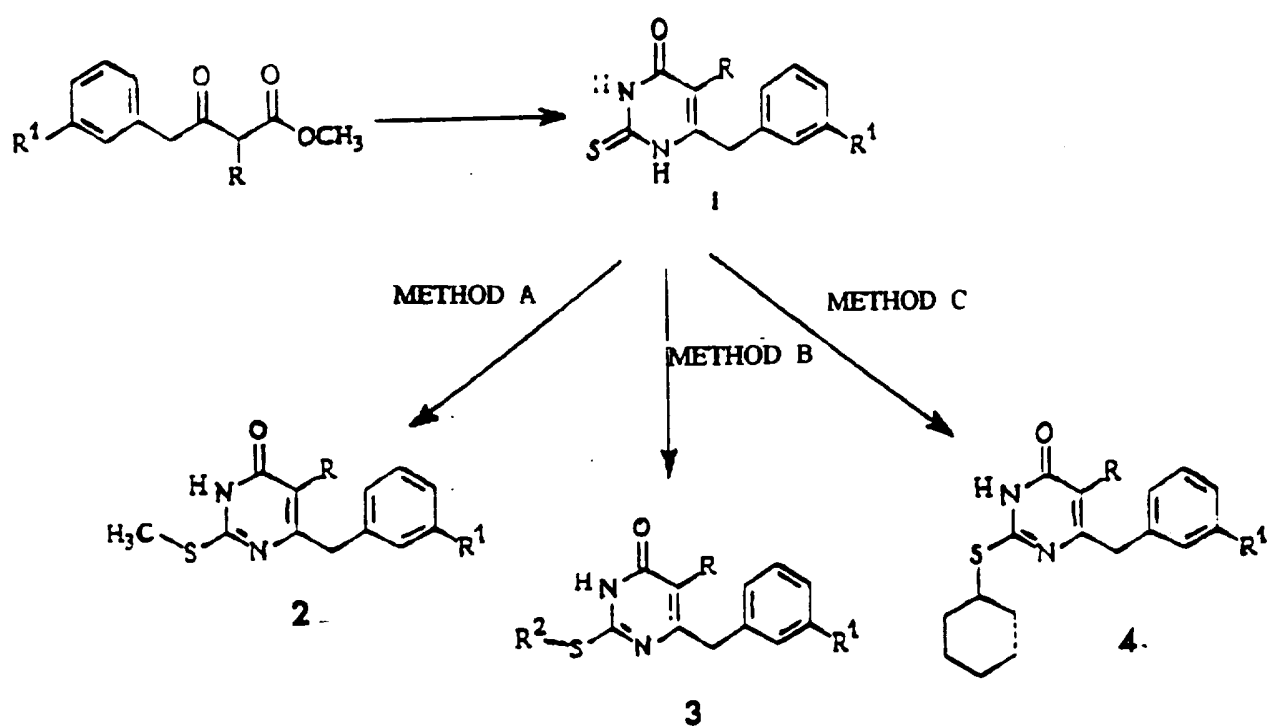
SCHEME "A"

TABLE 1

Physico-chemical characteristics of the compounds 2,3,4  
according to the scheme "A"

| Comp. R | R <sup>1</sup> | R <sup>2</sup> | m.p. (°C)   | solv. of<br>cryst. | yield           |    |
|---------|----------------|----------------|-------------|--------------------|-----------------|----|
| 2       | H              | H              | methyl      | 183-184            | benzene         | 98 |
| 2       | H              | Me             | methyl      | 159.5-160.0        | benzene         | 94 |
| 2       | Me             | H              | methyl      | 199-200            | benzene         | 98 |
| 2       | Me             | Me             | methyl      | 195-196            | benz./cyclohex. | 97 |
| 3       | H              | H              | iso-propyl  | 123.5-124.5        | cyclohexane     | 97 |
| 3       | H              | H              | iso-butyl   | 131.5-132.5        | cyclohexane     | 90 |
| 3       | H              | H              | sec-butyl   | 100-102            | cyclohexane     | 82 |
| 3       | H              | H              | cyclopentyl | 147-148            | cyclohexane     | 84 |
| 3       | H              | Me             | iso-propyl  | 122-123            | cyclohexane     | 86 |
| 3       | H              | Me             | iso-butyl   | 111-112            | n-hexane        | 78 |
| 3       | H              | Me             | sec-butyl   | 76-78              | n-hexane        | 69 |
| 3       | H              | Me             | cyclopentyl | 157-158            | benz./cyclohex. | 76 |
| 3       | Me             | H              | iso-propyl  | 150-151            | cyclohexane     | 95 |
| 3       | Me             | H              | iso-butyl   | 114.5-115.0        | n-hexane        | 92 |
| 3       | Me             | H              | sec-butyl   | 127.5-128.0        | n-hexane        | 90 |
| 3       | Me             | H              | cyclopentyl | 166-167            | cyclohexane     | 85 |
| 3       | Me             | Me             | iso-propyl  | 135-136            | cyclohexane     | 94 |
| 3       | Me             | Me             | iso-butyl   | 110.5-111.0        | n-hexane        | 90 |
| 3       | Me             | Me             | sec-butyl   | 121-122            | n-hexane        | 82 |
| 3       | Me             | Me             | cyclopentyl | 169-170            | cyclohexane     | 89 |
| 4       | H              | H              | cyclohexyl  | 172-173            | benz.-cyclohex. | 72 |
| 4       | H              | Me             | cyclohexyl  | 177-178            | benz.-cyclohex. | 68 |
| 4       | Me             | H              | cyclohexyl  | 180-182            | benz.-cyclohex. | 70 |
| 4       | Me             | Me             | cyclohexyl  | 179-180            | benz.-cyclohex. | 62 |

## SCHEME "B"

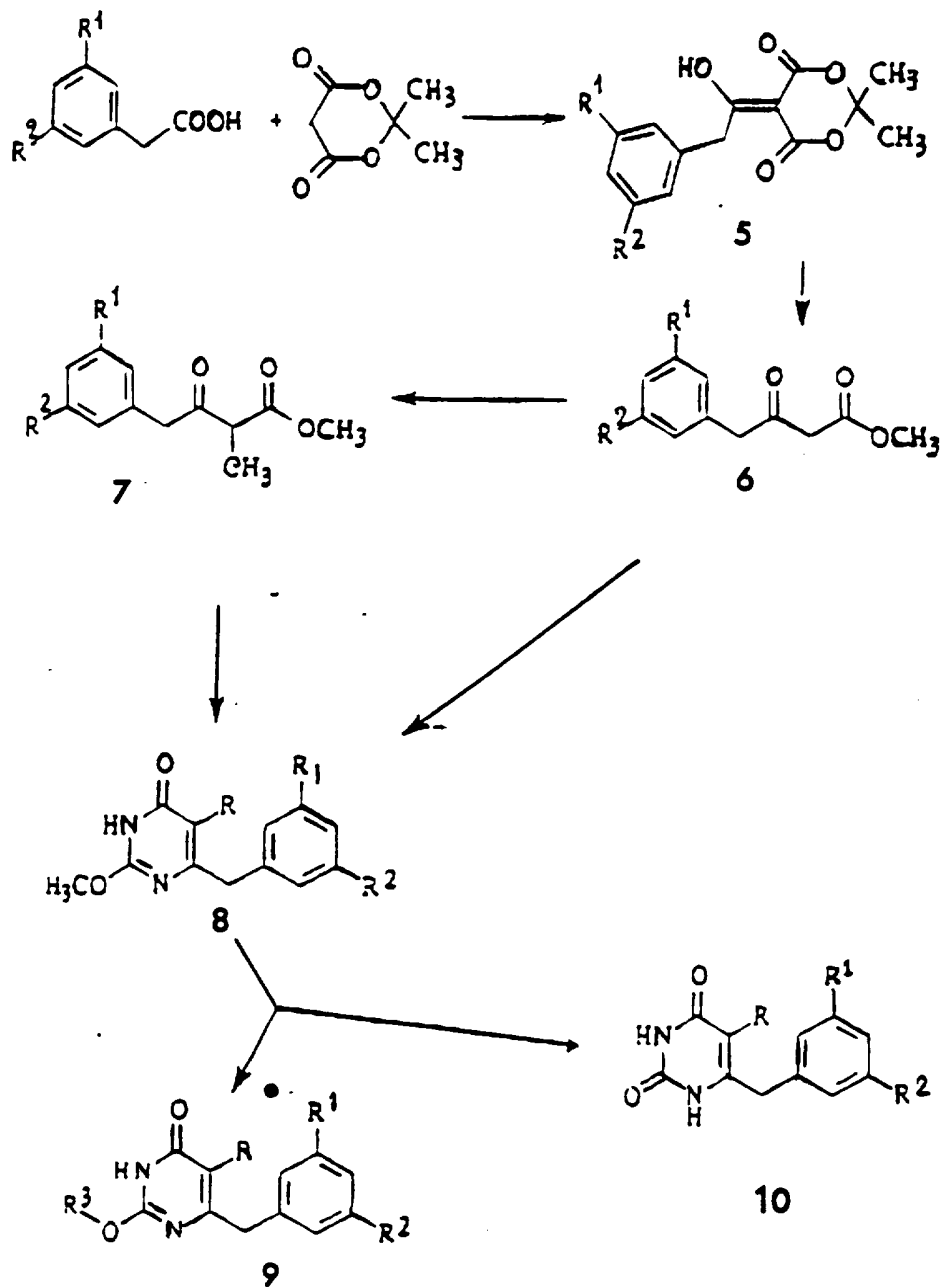


TABLE 2

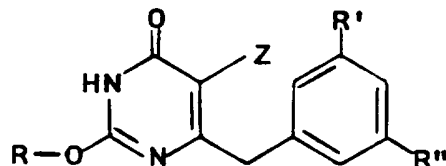
Physico-chemical characteristics of the compounds 9  
according to the scheme "B"

| R               | R <sup>1</sup>  | R <sup>2</sup>  | R <sup>3</sup> | m.p.<br>(°C) | yield | chromat.<br>syst.a | Cryst.<br>solv.b |
|-----------------|-----------------|-----------------|----------------|--------------|-------|--------------------|------------------|
| H               | CH <sub>3</sub> | H               | iso-propyl     | 124-126      | 22    | B                  | E/G              |
| H               | CH <sub>3</sub> | H               | sec-butyl      | 144-145      | 35    | B                  | E                |
| H               | CH <sub>3</sub> | H               | iso-butyl      | 92-93        | 16    | B                  | E                |
| H               | CH <sub>3</sub> | H               | cyclo-pentyl   | 129-131      | 24    | B                  | H/G              |
| H               | CH <sub>3</sub> | H               | cyclo-hexyl    | 150-151      | 20    | B                  | F                |
| CH <sub>3</sub> | CH <sub>3</sub> | H               | iso-propyl     | 200-204      | 18    | B                  | E                |
| CH <sub>3</sub> | CH <sub>3</sub> | H               | sec-butyl      | 123-124      | 24    | B                  | H                |
| CH <sub>3</sub> | CH <sub>3</sub> | H               | iso-butyl      | 110-112      | 12    | B                  | D                |
| CH <sub>3</sub> | CH <sub>3</sub> | H               | cyclo-pentyl   | 198-199      | 20    | B                  | H                |
| CH <sub>3</sub> | CH <sub>3</sub> | H               | cyclo-hexyl    | 210-211      | 26    | B                  | G                |
| H               | CH <sub>3</sub> | CH <sub>3</sub> | iso-propyl     | 162-164      | 26    | B                  | E                |
| H               | CH <sub>3</sub> | CH <sub>3</sub> | sec-butyl      | 166-167      | 32    | B                  | E                |
| H               | CH <sub>3</sub> | CH <sub>3</sub> | iso-butyl      | 115-116      | 20    | B                  | G                |
| H               | CH <sub>3</sub> | CH <sub>3</sub> | cyclo-pentyl   | 173-176      | 28    | B                  | C                |
| H               | CH <sub>3</sub> | CH <sub>3</sub> | cyclo-hexyl    | 187-189      | 28    | B                  | H/E              |
| CH <sub>3</sub> | CH <sub>3</sub> | CH <sub>3</sub> | sec-butyl      | 158-159      | 22    | B                  | E                |
| CH <sub>3</sub> | CH <sub>3</sub> | CH <sub>3</sub> | iso-butyl      | 163-165      | 32    | B                  | E                |
| CH <sub>3</sub> | CH <sub>3</sub> | CH <sub>3</sub> | cyclo-pentyl   | 189-190      | 18    | B                  | E                |
| CH <sub>3</sub> | CH <sub>3</sub> | CH <sub>3</sub> | cyclo-hexyl    | 227-228      | 20    | B                  | E                |

<sup>a</sup>A = silica gel/chloroform; B = silica gel/ethyl acetate:chloroform (1:2)

<sup>b</sup>C = ethanol; D = ethyl acetate; E = cyclohexane; F = n-hexane; G = petroleum ether; H = benzene.

TABLE 3



| Substituents    |              |                 |                 | [μM]                          |                               |                               | S.I. |
|-----------------|--------------|-----------------|-----------------|-------------------------------|-------------------------------|-------------------------------|------|
| Z               | R            | R'              | R''             | <sup>a</sup> CC <sub>50</sub> | <sup>b</sup> EC <sub>50</sub> | <sup>c</sup> IC <sub>50</sub> |      |
| H               | H            | CH <sub>3</sub> | H               | >463                          | 92                            | >10                           | 5    |
| H               | methyl       | CH <sub>3</sub> | H               | >434                          | 108                           | >10                           | >4   |
| H               | iso-propyl   | CH <sub>3</sub> | H               | 263                           | 6.5                           | 1.0                           | 40   |
| H               | sec-butyl    | CH <sub>3</sub> | H               | 132                           | 1.8                           | -                             | 73   |
| H               | iso-butyl    | CH <sub>3</sub> | H               | >367                          | 3.3                           | 2.0                           | >111 |
| H               | cyclo-pentyl | CH <sub>3</sub> | H               | 352                           | 2.8                           | 3.1                           | 125  |
| H               | cyclo-hexyl  | CH <sub>3</sub> | H               | >335                          | 0.8                           | 1.8                           | >41  |
| H               | H            | CH <sub>3</sub> | CH <sub>3</sub> | -                             | -                             | -                             | -    |
| H               | methyl       | CH <sub>3</sub> | CH <sub>3</sub> | >410                          | 34.4                          | >10                           | >2   |
| H               | iso-propyl   | CH <sub>3</sub> | CH <sub>3</sub> | >367                          | 3.1                           | 3.2                           | >118 |
| H               | sec-butyl    | CH <sub>3</sub> | CH <sub>3</sub> | 104                           | 1.4                           | 1.0                           | 74   |
| H               | iso-butyl    | CH <sub>3</sub> | CH <sub>3</sub> | >349                          | 2.7                           | 3.4                           | >129 |
| H               | cyclo-pentyl | CH <sub>3</sub> | CH <sub>3</sub> | >335                          | 3.3                           | 3.0                           | >100 |
| H               | cyclo-hexyl  | CH <sub>3</sub> | CH <sub>3</sub> | >320                          | 1.1                           | 1.0                           | >291 |
| CH <sub>3</sub> | H            | CH <sub>3</sub> | H               | -                             | -                             | -                             | -    |
| CH <sub>3</sub> | methyl       | CH <sub>3</sub> | H               | 381                           | >381                          | -                             | -    |
| CH <sub>3</sub> | iso-propyl   | CH <sub>3</sub> | H               | >367                          | >367                          | -                             | -    |
| CH <sub>3</sub> | sec-butyl    | CH <sub>3</sub> | H               | 210                           | 4.6                           | -                             | 46   |
| CH <sub>3</sub> | iso-butyl    | CH <sub>3</sub> | H               | >350                          | 3.1                           | 2.1                           | >113 |
| CH <sub>3</sub> | cyclo-pentyl | CH <sub>3</sub> | H               | 335                           | 56.3                          | -                             | 6    |
| CH <sub>3</sub> | cyclo-hexyl  | CH <sub>3</sub> | H               | >330                          | 16.7                          | 1.7                           | >19  |
| CH <sub>3</sub> | H            | CH <sub>3</sub> | CH <sub>3</sub> | >410                          | 38                            | -                             | >11  |
| CH <sub>3</sub> | methyl       | CH <sub>3</sub> | CH <sub>3</sub> | >387                          | >387                          | -                             | -    |
| CH <sub>3</sub> | iso-propyl   | CH <sub>3</sub> | CH <sub>3</sub> | -                             | -                             | -                             | -    |
| CH <sub>3</sub> | sec-butyl    | CH <sub>3</sub> | CH <sub>3</sub> | >333                          | 0.8                           | -                             | >416 |
| CH <sub>3</sub> | iso-butyl    | CH <sub>3</sub> | CH <sub>3</sub> | 77                            | 40                            | -                             | 2    |
| CH <sub>3</sub> | cyclo-pentyl | CH <sub>3</sub> | CH <sub>3</sub> | >320                          | 29                            | -                             | >11  |
| H               | cyclo-hexyl  | CH <sub>3</sub> | CH <sub>3</sub> | >307                          | 14                            | -                             | >22  |

<sup>a</sup> Compound dose required to reduce the number of viable cells by 50%.

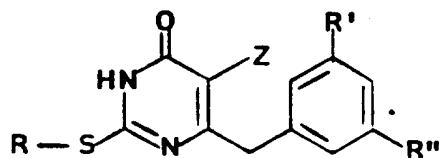
as determined by the MTT method;

<sup>b</sup> Compound dose required to protect 50% of MT-4 cells from the HIV-1 induced cytopathogenicity, as determined by the MTT method;

<sup>c</sup> Compound dose required to inhibit the rRT HIV-1 activity by 50%;

<sup>d</sup> Selectivity index, CC<sub>50</sub>/EC<sub>50</sub> ratio.

TABLE 4



| Substituents    |              |                 |     | [μM]                          |                               |                               | d s.i. |
|-----------------|--------------|-----------------|-----|-------------------------------|-------------------------------|-------------------------------|--------|
| Z               | R            | R'              | R'' | <sup>a</sup> CC <sub>50</sub> | <sup>b</sup> EC <sub>50</sub> | <sup>c</sup> IC <sub>50</sub> |        |
| H               | methyl       | H               | H   | >431                          | 34.5                          | >10                           | 12     |
| H               | iso-propyl   | H               | H   | 332                           | 7.7                           | 3.0                           | 43     |
| H               | sec-butyl    | H               | H   | 150                           | 1.2                           | 1.7                           | 125    |
| H               | iso-butyl    | H               | H   | 186                           | 5.1                           | 3.4                           | 36     |
| H               | cyclo-pentyl | H               | H   | 147                           | 1.7                           | 2.8                           | 86     |
| H               | cyclo-hexyl  | H               | H   | >330                          | 0.8                           | 3.0                           | >412   |
| H               | H            | CH <sub>3</sub> | H   | 258                           | >258                          | >10                           | -      |
| H               | methyl       | CH <sub>3</sub> | H   | 317                           | 17                            | 6.7                           | 19     |
| H               | iso-propyl   | CH <sub>3</sub> | H   | >310                          | 1.3                           | 0.9                           | >238   |
| H               | sec-butyl    | CH <sub>3</sub> | H   | >347                          | 0.54                          | 1.2                           | >642   |
| H               | iso-butyl    | CH <sub>3</sub> | H   | >347                          | 12.5                          | 1.4                           | >28    |
| H               | cyclo-pentyl | CH <sub>3</sub> | H   | >333                          | 1.2                           | 2.6                           | >278   |
| H               | cyclo-hexyl  | CH <sub>3</sub> | H   | 87                            | 3                             | 3.6                           | 29     |
| CH <sub>3</sub> | H            | H               | H   | 431                           | 108                           | 10                            | -      |
| CH <sub>3</sub> | methyl       | H               | H   | >406                          | 1.2                           | 4.9                           | >338   |
| CH <sub>3</sub> | iso-propyl   | H               | H   | 140                           | 1.8                           | 1.5                           | 77     |
| CH <sub>3</sub> | sec-butyl    | H               | H   | 86                            | 0.6                           | 2.4                           | 140    |
| CH <sub>3</sub> | iso-butyl    | H               | H   | 62                            | 0.8                           | 2.2                           | 78     |
| CH <sub>3</sub> | cyclo-pentyl | H               | H   | 166                           | 0.6                           | 3.4                           | 270    |
| CH <sub>3</sub> | cyclo-hexyl  | H               | H   | >318                          | 0.6                           | 4.3                           | >530   |
| CH <sub>3</sub> | H            | CH <sub>3</sub> | H   | 284                           | >102                          | >10                           | -      |
| CH <sub>3</sub> | methyl       | CH <sub>3</sub> | H   | 385                           | 3.0                           | 2.5                           | 128    |
| CH <sub>3</sub> | iso-propyl   | CH <sub>3</sub> | H   | 100                           | 1.3                           | 2.5                           | 77     |
| CH <sub>3</sub> | sec-butyl    | CH <sub>3</sub> | H   | 100                           | 1.0                           | 2.7                           | 100    |
| CH <sub>3</sub> | iso-butyl    | CH <sub>3</sub> | H   | 100                           | 1.6                           | 4.6                           | 62     |
| CH <sub>3</sub> | cyclo-pentyl | CH <sub>3</sub> | H   | >318                          | 0.6                           | 4.4                           | >530   |
| CH <sub>3</sub> | cyclo-hexyl  | CH <sub>3</sub> | H   | >304                          | 0.6                           | 0.3                           | >506   |

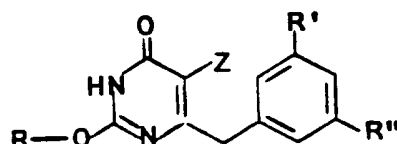
<sup>a</sup> Compound dose required to reduce the viability of the MT-4 cells by 50%, as determined by the MTT method;

<sup>b</sup> Compound dose required to protect 50% of the MT-4 cells from the HIV-1 induced cytopathogenicity, as determined by the MTT method;

<sup>c</sup> Compound dose required to inhibit by 50% the rRT HIV-1 activity;

<sup>d</sup> Selectivity index, CC<sub>50</sub>/EC<sub>50</sub> ratio.

TABLE 5



| Substituents    |              |    |     | [μM]                          |                               |                               | <sup>d</sup> S.I. |
|-----------------|--------------|----|-----|-------------------------------|-------------------------------|-------------------------------|-------------------|
| Z               | R            | R' | R'' | <sup>a</sup> CC <sub>50</sub> | <sup>b</sup> EC <sub>50</sub> | <sup>c</sup> IC <sub>50</sub> |                   |
| H               | H            | H  | H   | >1000                         | >200                          | >10                           | -                 |
| H               | methyl       | H  | H   | >1000                         | >200                          | >10                           | -                 |
| H               | iso-propyl   | H  | H   | 646                           | 26                            | 5.5                           | 25                |
| H               | sec-butyl    | H  | H   | 344                           | 5.5                           | 4.2                           | 62                |
| H               | iso-butyl    | H  | H   | -                             | -                             | -                             | -                 |
| H               | cyclo-pentyl | H  | H   | 466                           | 41                            | >10                           | 11                |
| H               | cyclo-hexyl  | H  | H   | 157                           | 9.0                           | >10                           | 17                |
| CH <sub>3</sub> | H            | H  | H   | >1000                         | >200                          | -                             | -                 |
| CH <sub>3</sub> | methyl       | H  | H   | 517                           | >200                          | -                             | -                 |
| CH <sub>3</sub> | iso-propyl   | H  | H   | 243                           | 16                            | -                             | 15                |
| CH <sub>3</sub> | sec-butyl    | H  | H   | 180                           | 2.9                           | -                             | 63                |
| CH <sub>3</sub> | cyclo-pentyl | H  | H   | >1000                         | 10                            | -                             | >100              |
| CH <sub>3</sub> | cyclo-hexyl  | H  | H   | 375                           | 4.7                           | -                             | 80                |

<sup>a</sup> Compound dose required to reduce the viability of the MT-4 cells by 50%, as determined by the MTT method;

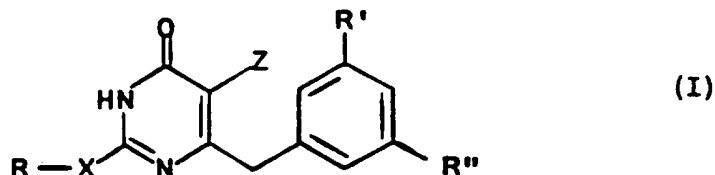
<sup>b</sup> Compound dose required to protect 50% of the MT-4 cells from the HIV-1 induced cytopathogenicity, as determined by the MTT method;

<sup>c</sup> Compound dose required to inhibit by 50% the rRT HIV-1 activity;

<sup>d</sup> Selectivity index, CC<sub>50</sub>/EC<sub>50</sub> ratio.

CLAIMS

- 1 1. Compounds having general formula (I)



- 2 wherein:

- 3 X is selected from the group consisting of O and S;  
 4 R is selected from the group consisting of C<sub>1-4</sub> alkyl and C<sub>5-6</sub>  
 5 cycloalkyl;  
 6 R', R'' and Z, equal or different among them, mean H or C<sub>1-4</sub> alkyl  
 7 considering that, when X=O, R and R' can not be both equal to H;  
 8 their pharmaceutically acceptable salts and their soluble derivatives.

- 1 2. Compounds having general formula (I) as claimed in claim 1 wherein

2 X=S.

- 1 3. Compounds having general formula (I) as claimed in claim 1 wherein:

- 2 X = O, Z = H, R = cyclohexyl, R' = CH<sub>3</sub>, R'' = H  
 3 X = O, Z = H, R = cyclohexyl, R' = CH<sub>3</sub>, R'' = CH<sub>3</sub>  
 4 X = O, Z = CH<sub>3</sub>, R = sec-butyl, R' = CH<sub>3</sub>, R'' = CH<sub>3</sub>  
 5 X = S, Z = H, R = iso-propyl, R' = CH<sub>3</sub>, R'' = H  
 6 X = S, Z = H, R = sec-butyl, R' = CH<sub>3</sub>, R'' = H  
 7 X = S, Z = H, R = cyclopentyl, R' = CH<sub>3</sub>, R'' = H

- 8 X = S, Z = CH<sub>3</sub>, R = methyl, R' = H, R'' = H  
9 X = S, Z = CH<sub>3</sub>, R = cyclopentyl, R' = H, R'' = H  
10 X = S, Z = CH<sub>3</sub>, R = cyclohexyl, R' = H, R'' = H  
11 X = S, Z = CH<sub>3</sub>, R = cyclopentyl, R' = CH<sub>3</sub>, R'' = H  
12 X = S, Z = CH<sub>3</sub>, R = cyclopentyl, R' = CH<sub>3</sub>, R'' = H

1 4. Process for the preparation of the compounds having formula (I) as  
2 claimed in claim 1 wherein X = S, wherein: the suitable methyl  
3 phenylacetylacetate is reacted with thiourea in presence of sodium  
4 methoxide and the so obtained 2-thio(5-alkyl)-6-benzyl  
5 (substituted)uracils are reacted with methyl iodide, or with an alkyl  
6 halide in a basic medium.

1 5. Process for the preparation of the compounds having formula (I) as  
2 claimed in claim 1 wherein X = O, wherein: a 3'-methyl or 3',5'-  
3 dimethylphenylacetyl chloride is reacted with 2,2-dimethyl-1,3-dioxane-  
4 4,6-dione, the so obtained compound is reacted with CH<sub>3</sub>I, the so  
5 obtained compound (or its precursor) is reacted with O-methyl isourea  
6 hydrogensulfate and the obtained product is reacted with the suitable  
7 potassium alcoholate.

1 6. Use of the products as claimed in claim 1 for the preparation of  
2 pharmaceutical compositions having antiviral activity.

1 7. Use as claimed in claim 6 wherein the antiviral activity is an anti-  
2 HIV activity.

1 8. Use as claimed in claim 7 wherein the anti-HIV activity is an anti-  
2 HIV-1 activity.

- 1 9. A therapeutic method for treating viral infections consisting of the  
2 administering to a patient in need thereof a therapeutically effective  
3 amount of at least one compound having formula (I) according to claim  
4 1.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 95/03912

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D239/52 A61K31/505 C07D239/46

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

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                | Relevant to claim No. |
|------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X          | WO,A,91 18887 (SMITH-KLINE) 12 December 1991<br>see page 24; claims<br>---                                                                                                                                                                                                                                        | 1,2                   |
| A          | EP,A,0 123 402 (FUJISAWA) 31 October 1984<br>see claims<br>---                                                                                                                                                                                                                                                    | 1-8                   |
| P,X        | CHEMICAL ABSTRACTS, vol. 122, no. 1, 1995, Columbus, Ohio, US;<br>abstract no. 122513c,<br>S.MASSA,A.MAI 'SYNTHESIS AND ANTIVIRAL ACTIVITY OF 3,4-DIHYDRO-2-ALKOXY-6-BENZYL-4-OXOPYRIMIDINES'<br>page 23 ;<br>see abstract<br>P,X & ANTIVIRAL CHEM. CHEMOTHER.,<br>vol.6, no.1, 1995, ENGL.<br>pages 1 - 8<br>--- | 1-8                   |
|            | -/--                                                                                                                                                                                                                                                                                                              |                       |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

13 February 1996

Date of mailing of the international search report

16.02.96

Name and mailing address of the ISA

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Fax: (+31-70) 340-3016

Authorized officer

Francois, J

# INTERNATIONAL SEARCH REPORT

Int. onal Application No

PCT/EP 95/03912

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                             | Relevant to claim No. |
|------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| P,X        | <p>JOURNAL OF MEDICINAL CHEMISTRY,<br/>vol.38, no.17, 18 August 1995, WASHINGTON<br/>US<br/>pages 3258 - 3263<br/>A.MAI ET AL. 'SYNTHESIS AND ANTI-HIV-1<br/>ACTIVITY OF THIO ANALOGUES OF<br/>DIHYDROALKOXYBENZYLOXOPYRIMIDINES.'<br/>see page 3258 - page 3262<br/>-----</p> | 1-8                   |

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 95/ 03912

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

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

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claim 9 is directed to a method of treatment of the human body,  
the search has been carried out and based on the alleged effects of the  
attributed effects of the compounds (Rule 39.1.(iv)).
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such  
an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 95/03912

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|-------------------------------------------|---------------------|----------------------------|---------------------|
| WO-A-9118887                              | 12-12-91            | AU-B- 7971691              | 31-12-91            |
| EP-A-0123402                              | 31-10-84            | AU-B- 564793               | 27-08-87            |
|                                           |                     | AU-B- 2587484              | 27-09-84            |
|                                           |                     | CA-A- 1256107              | 20-06-89            |
|                                           |                     | DE-A- 3473875              | 13-10-88            |
|                                           |                     | JP-A- 59181265             | 15-10-84            |
|                                           |                     | JP-C- 1835761              | 11-04-94            |
|                                           |                     | JP-A- 62270563             | 24-11-87            |
|                                           |                     | SU-A- 1349698              | 30-10-87            |
|                                           |                     | SU-A- 1436872              | 07-11-88            |
|                                           |                     | US-A- 4824851              | 25-04-89            |
|                                           |                     | US-A- 4612376              | 16-09-86            |
|                                           |                     | US-A- 4746664              | 24-05-88            |