USE OF PURINE DERIVATIVES FOR THE MANUFACTURE OF A MEDICAMENT

The invention relates to the use of purine derivatives in the manufacture of a medicament intended for the treatment of pathologies in which an imbalance between cell division and apoptosis is involved and more particularly in which excessive apoptosis is the cause of the pathology.

It also relates to some of these purine derivatives.

The pathologies in which an imbalance between cell division and apoptosis is involved are in particular chronic lymphoid leukemia and kidney diseases, such as polycystic kidney disease.

Chronic lymphoid leukemia, CLL, is a heterogeneous group of diseases characterized by the accumulation of CD5+ monoclonal B cells in the blood, bone marrow and hematopoietic organs.

It is a disease in which the monoclonal B cells undergo no or little natural apoptosis (cell death) and comprise a small contingent of B cells involved in the cell cycle. In this sense, this disease is a disease rather different from the diseases in which an excessive proliferation, which is not stopped, of the monoclonal cells is observed, in which the monoclonal cells are highly involved in the cell cycle and in which the resistance to apoptosis (cell death) constitutes a phenomenon of secondary pathogenicity.

CLL is commonly classified into separate categories, including B-cell chronic lymphoid leukemia and T-cell chronic lymphoid leukemia. The term "CLL" is commonly understood to mean B-cell chronic lymphoid leukemia (B-CLL).

B-cell chronic lymphoid leukemia, known as B-CLL, is a disease of the B lymphocyte responsible for the accumulation of B lymphocytes of lymphocytic morphology, expressing membrane antigens characteristic of the disease, such as the CD5 and CD23 molecules, in the blood, causing hyperlymphocytosis, in the bone marrow, causing bone marrow failure, and in the lymph nodes, causing polyadenopathy.

B-CLL has been characterized as a single biological entity with a variable progressive nature.

The Binet prognosis classification makes it possible to arrange the profile of progression of the disease into three stages A, B and C.

Among the subjects in stage A of the disease, 41% will progress towards stages B and C. Among the biological parameters, the lymphocyte doubling time of less than 6 months, a rise in the level of soluble CD23 or a rise in the activity of serum thymidine kinase are considered as indicating poor prognosis. The fully identified genetic parameters of poor prognosis include the unmutated forms of the disease (immunoglobulin heavy chain gene in the germinal position on 14q32), deletion abnormalities of the 11q and 17p chromosomes or additional chromosomal abnormalities of 12q+ type. The patients who are carriers of B-CLL and who express these biological characters have a short progression time: thus, 50% of the unmutated patients have progressed in 24 months; 50% of the patients exhibiting a 17p-, an 11q- or a 12q+ have progressed at 15 months. If patients of stage A express these biological criteria for seriousness, the patients of stage B and C should benefit from an active therapeutic attitude.

Although current treatments bring about remissions of the disease, all the patients relapse and there currently exists a consensus in stating that CLL

remains an incurable disease.

The real question which is posed today is that of defining, in stage A of the disease, the patients who exhibit a biological potential to progress to a serious state.

The best first-line treatment for B-CLL remains to be defined.

Purine analogs, in particular fludarabine, remain by far the most studied in B-CLL. Fludarabine alone induces a better overall level of response than the use of multidrug therapies comprising alkylating agents and a corticotherapy. Fludarabine induces more complete hematologic remission (7 to 40%) than multidrug therapies of CHOP or CAP (chloraminophene) type.

Despite the better response observed with fludarabine, the benefit observed with regard to overall survival remains marginal. Current therapeutic endeavors are directed at the combinations of fludarabine with conventional chemotherapy, for example fludarabine plus cyclophosphamide, in particular in the resistant forms of the disease. Life expectancy is only 12 months in patients resistant to fludarabine. Nevertheless, the toxicity of the treatment, in particular hematologic toxicity, is increased with these combinations.

Infection is observed in 50% of the patients treated with a combination of fludarabine and cyclophosphamide. Documented sepsis or pneumopathy is observed during the treatment in 25% of the patients treated, undocumented fever and/or hospitalization in 25% of the others.

A therapeutic revolution was achieved by the advent of therapeutic antibodies. In B-CLL, two therapeutic antibodies have emerged: rituximab and alemtuzumab. In B-CLL, the activity of rituximab is handicapped by the

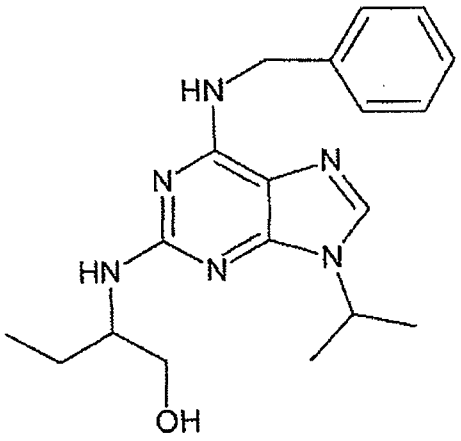
low expression of the target, the CD20 antigen, on the B lymphocyte of CLL. Rituximab is deployed in B-CLL in synergy with purine analogs and/or cyclophosphamide (overall response of 59% observed with the fludarabine/ cyclophosphamide/rituximab combination in patients resistant to fludarabine, including only 5% of complete response).

The activity of alemtuzumab, directed against an antigen expressed on the leukocyctes and the leukemic B lymphocytes of CLL, with a very heterogeneous membrane density of the antigen, is handicapped by its high immunosuppressive activity and the high incidence of reactivations of cytomegalic infections and opportunist infections during or after treatment: the antibody exhibits a high T immunosuppressive activity. The hematologic response to alemtuzumab is 33%; the antibody is capable of destroying clonal B lymphcytes in the blood and the bone marrow but have little effect in the lymph nodes. These points limit the use of the antibody in this indication. Radioimmunotherapy with anti-CD20 coupled to yytrium-90 (Zevalin) induces a low percentage of remission in B-CLL and is responsible for significant myelosuppression.

Patent US 6 812 232 describes purine analogs similar to those of the invention for their activity in inhibiting cell proliferation. In point of fact, in CLL, excessive cell proliferation has stopped.

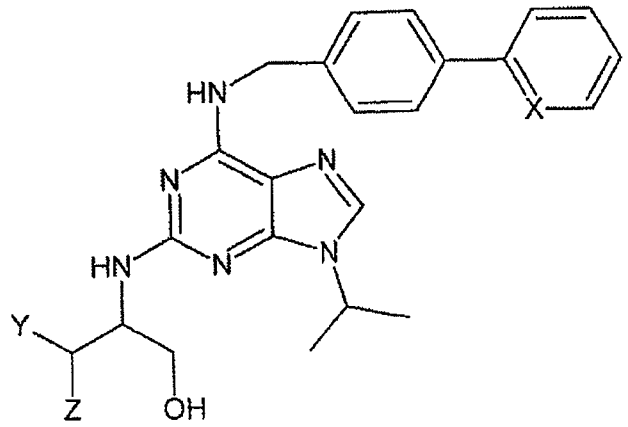
Patent application WO2005/002584 provides, for its part, for the use of roscovitine, preferably in its (R) absolute configuration, in the treatment of chronic lymphoid leukemia and more particularly of B-cell chronic lymphoid leukemia.

Roscovitine is a purine having the following formula:



In point of fact, it has now been discovered that roscovitine derivatives have a much higher activity than roscovitine in the treatment of pathologies in which an imbalance between cell division and apoptosis is involved and that they also have, in some cases, a better solubility than roscovitine.

Thus, the invention provides for the use of at least one compound of following formula I:



Formula I

in which:

- X is C or N,
- Y is CH_3 or OH, and
- Z is H or CH_3,

or one of its pharmaceutically acceptable salts, hydrates, esters or isomers,

in the manufacture of a medicament intended to treat

pathologies in which an imbalance between cell division and apoptosis is involved.

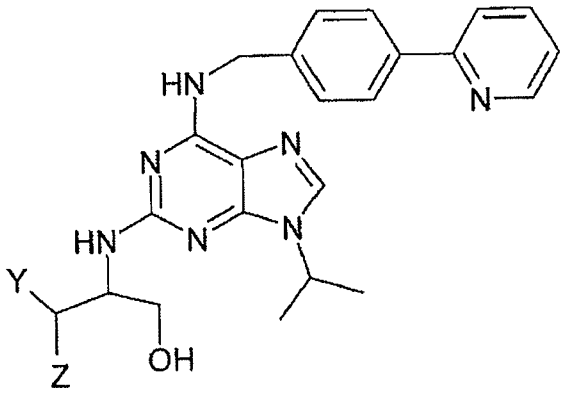
In a first alternative form of the invention, the pathology is chronic lymphoid leukemia.

More particularly, the pathology is B-cell chronic lymphoid leukemia.

In a second alternative form of the invention, the pathology is a kidney disease and more particularly polycystic kidney disease.

A preferred salt for use in the manufacture of a medicament for treating pathologies in which an imbalance between cell division and apoptosis is involved is the oxalate salt of the compounds of formula I.

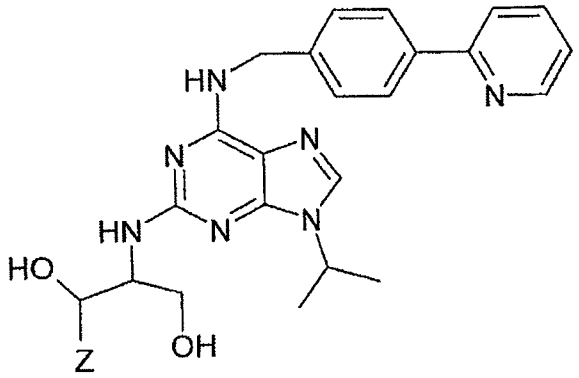
Preferably, the at least one compound used has the following formula I-1, which corresponds to the formula I in which X is N:



Formula I-I

This is because the compounds are from 4 to 5 times more active in cell models of chronic lymphoid leukemia and polycystic kidney disease and from 5 to 10 times more soluble in an aqueous medium than their correspondants in which X is C, as will be seen below.

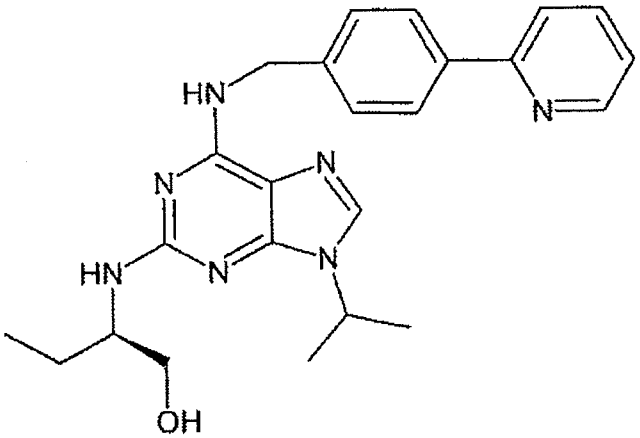
However, more preferably, the at least one compound used has the following formula I-II, which corresponds to the formula I in which X is N and Y is OH:



Formula I-II

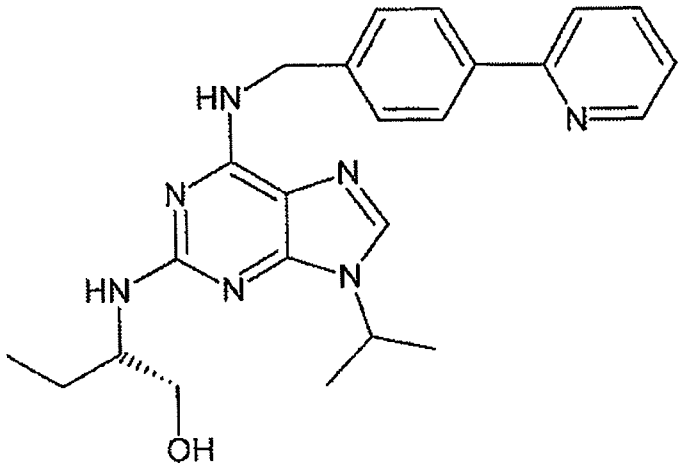
The compounds with the structure I-II exhibit an activity comparable to that of the I-I derivatives but their solubility in an aqueous medium is further increased.

More particularly and in a first preferred embodiment, the at least one compound used in the manufacture of a medicament for treating these pathologies is the compound of formula I in which X is N, Y is CH_3 and Z is H. This compound has an (R) absolute configuration and has the following formula Ia:



Formula Ia

In a second very particularly preferred embodiment of the invention, the at least one compound has the (S) absolute configuration. This compound has the following formula Ib:

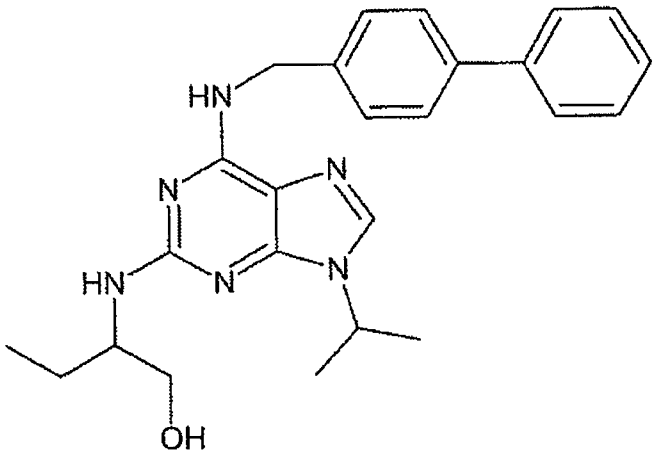


Formula Ib

This is particularly surprising since, in the prior art, it is generally the compounds with the (R) absolute configuration which make it possible to obtain the best results.

In a third very particularly preferred embodiment of the invention, the at least one compound of formula Ia or Ib is in the form of its oxalate salt.

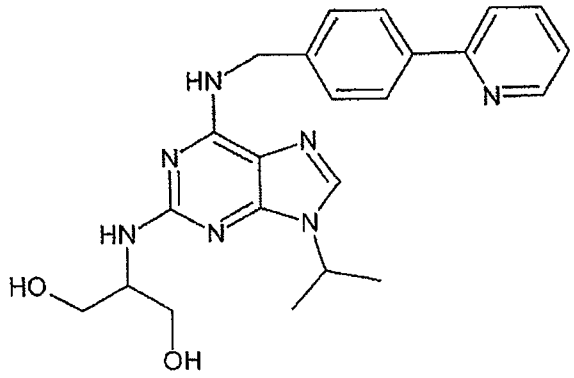
However, in a fourth preferred embodiment of the invention, the at least one compound used in the manufacture of a medicament for treating pathologies in which an imbalance between cell division and apoptosis is involved is the compound of formula I in which X is C, Y is CH_3 and Z is H. This compound has the following formula Ic:



Formula Ic

This compound can be used both in its (S) or (R) absolute configuration and in the form of a mixture of these.

However, in a fifth preferred embodiment of the invention, the at least one compound used is the compound of formula I in which X is N, Y is OH and Z is H. This compound has the following formula Id:

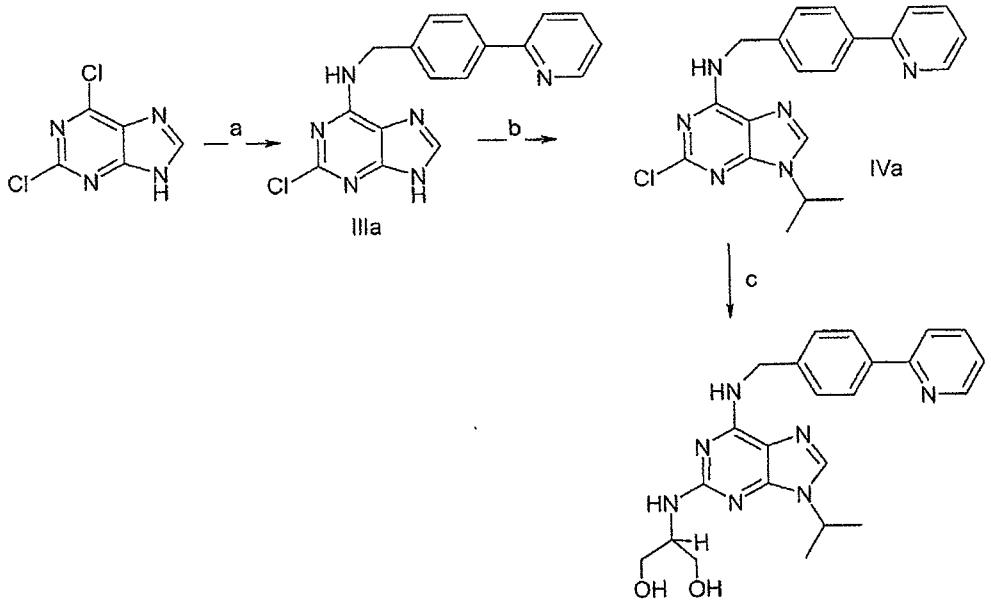


Formula Id

The compound Id can be obtained as described in the following example 1.

Example 1 : Preparation of the compound Id

This compound is obtained in 3 stages starting from dichloropurine according to the following scheme:



Reactants and conditions:
a: 4-(2-Pyridyl)benzylamine, n-BuOH, 110°C; b: 2-bromopropane, K_2CO_3, DMSO; c: serinol, heating 160°C, 8h).

Stage 1: **2-Chloro-6-[4-(2-pyridyl)phenylmethylamino]-purine (IIIa)**

4-(2-Pyridyl)benzylamine (2.0 g, 1.05 mmol) and 3 ml of NEt_3 are added to a solution of 2,6-dichloropurine (2.3 g, 10 mmol) in 20 ml of *n*-BuOH. After heating at 110°C for 3 h, the mixture is cooled to 20°C and the solid is filtered off, washed with 5 ml of cold butanol and then dried under vacuum. Yd = 85%. M.p. >250°C. ^1H NMR (d_6-DMSO) δ 4.80 (s, 2H, CH_2); 7.20 (m, 1H, $H_{pyridyl}$); 7.45 (d, 2H, H_{phenyl}); 7.72 (m, 2H, $H_{pyridyl}$); 7.95 (m, 3H, H_{phenyl} and H-8), 8.54 (d, 1H, J = 4.8 Hz, $H_{pyridyl}$).

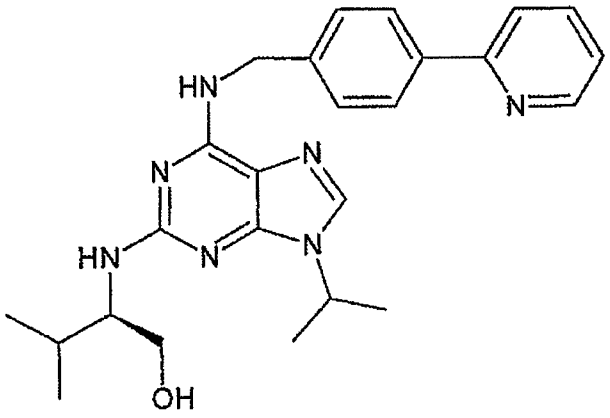
Stage 2:
2-Chloro-9-isopropyl-6-[4-(2-pyridyl)phenylmethyl-amino]purine (IVa)

K_2CO_3 (3.5 g, 24 mmol) and 1.9 ml (20 mmol) of 2-bromopropane are added to a solution of 2-chloro-6-[4-(2-pyridyl)phenylmethylamino]purine (8 mmol) in 10 ml of DMSO at 18-20°C. After stirring at 18-20°C for 5 h, 2-bromopropane (0.5 ml) is again added and stirring is

continued at 20°C for 5 h. After adding 50 ml of cold (5°C) water, the mixture is extracted with EtOAc (3 × 10 ml) and the organic phases are washed with brine (3 × 10 ml) and dried over Na_2SO_4. The derivative IVa crystallizes by evaporation of the solvent. It is triturated from 2 ml of 2-propanol and filtered off.
Yd 86%. ^1H NMR ($CDCl_3$): δ 1.58 (d, 6H); 4.79 (hept, 1H); 4.85 (broad s, 2H); 6.59 (broad s, 1H); 7.20-7.23 (m, 1H); 7.49 (d, 2H); 7.73-7.71 (m, 2H); 7.79 (s, 1H); 7.98 (d, 2H); 8.71 (d, 1H).

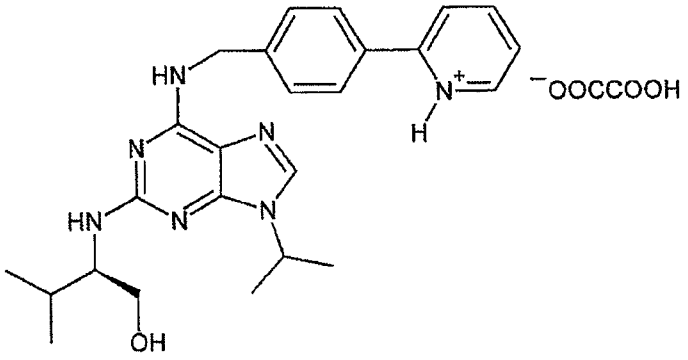
Stage 3: **2-(1,3-Dihydroxyprop-2-ylamino)-6-[4-(2-pyridyl)phenylmethylamino]-9-isopropylpurine Id**
A mixture of the compound IVa (10 mmol) and of serinol (2-aminopropane-1,3-diol) (2 ml) is heated under N_2 at 160°C for 8 h. After cooling to 20°C, 20 ml of water are added and the mixture is extracted with EtOAc (4 × 10 ml). The organic solution is washed with 2 × 20 ml of water, dried and evaporated. The derivative Id crystallizes by triturating from Et_2O.
M.p. 114-117°C. Yd 74%. ^1H NMR ($CdCl_3$) δ 1.52 (d, 6H); 3.78 (m, 4H); 3.96 (m, 1H); 4.55 (hept, 1H); 4.76 (s, 2H); 5.40 (s, 1H); 6.20 (s, 1H); 7.12 (m, 1H); 7.38 (d, 2H); 7.48 (s, 1H); 7.62 (m, 2H); 7.90 (d, 2H); 8.60 (d, 1H).

In a sixth preferred embodiment of the invention, the at least one compound used is the compound of formula I in which X is N, Y is CH_3 and Z is CH_3. This compound has the following formula Ie:



Formula Ie

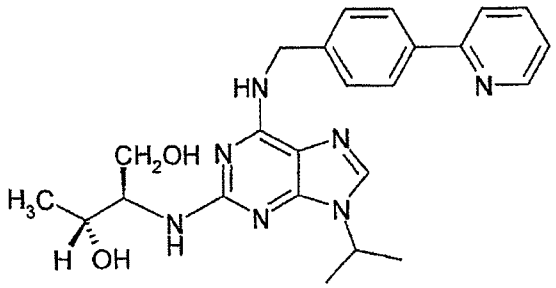
In a seventh preferred embodiment of the invention, the at least one compound used is the oxalate salt of the compound of formula Ie. This compound has the following formula If:



Formula If

It should be noted that one of the nitrogens of the purine may be involved in the formation of the salt, which corresponds to the combination of one molecule of the purine with the diacid.

In an eighth preferred embodiment of the invention, the at least one compound used is the compound of the following formula Ig:



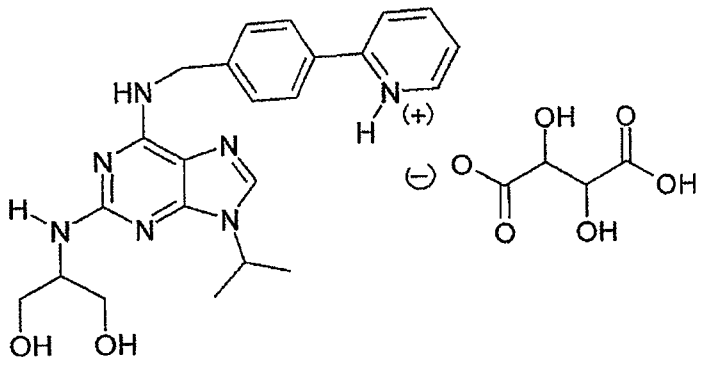
Formula Ig

This compound is **(1R,2R)-2-(1,3-dihydroxybut-2-ylamino)-6-[4-(2-pyridyl)phenylmethylamino]-9-isopropylpurine Ig**

It is obtained in the same way as the product Id but replacing, in the final stage, aminopropanediol with L-threoninol or (1R,2R)-2-aminobutane-1,3-diol.

It has the following characteristics, measured by NMR: NMR: 1.2 (d, 3H); 1.4 (d, 6H); 3.70 (m, 4H); 4.10 (m, 1H), 4.52 (hept, 1H); 4.72 (broad s, 2H); 5.50 (s, 1H); 6.2 (broad s, 1H); 7.15 (m, 1H); 7.4 (d, 2H); 7.42 (s, 1H); 7.55 (m, 2H); 7.85 (d, 2H); 8.60 (d, 1H).

In a ninth preferred embodiment of the invention, the at least one compound used is the compound of following formula Ih:



Formula Ih

It should be noted that one of the nitrogens of the purine may be involved in the formation of the salt, which corresponds to the combination of one molecule of the purine with the diacid. The three isomers of tartaric acid can be used.

This compound is 2-(1,3-dihydroxyprop-2-ylamino)-6-[4-(2-pyridyl)phenylmethylamino]-9-isopropylpyrine tartrate (Ih).

It is obtained in the following way:

2.1 mmol of tartaric acid, dissolved in isopropanol (1 ml), are added to a solution, brought to 70-80°C, of 2 mmol of Id in solution in isopropanol (1 ml). After cooling, the tartrate of Id is isolated by filtration.

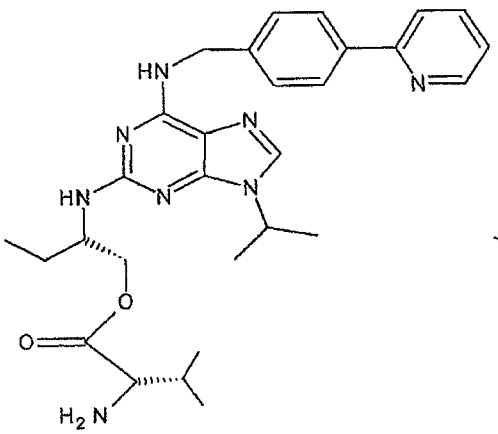
The salts, such as fumarates or hydrochlorides, the hydrates and the esters of the compounds of formulae Ia, Id and Ig and also the isomers of the compounds of formulae Ic and Ig can also advantageously be used.

In particular, the esters of the compounds of formula I also come within the invention.

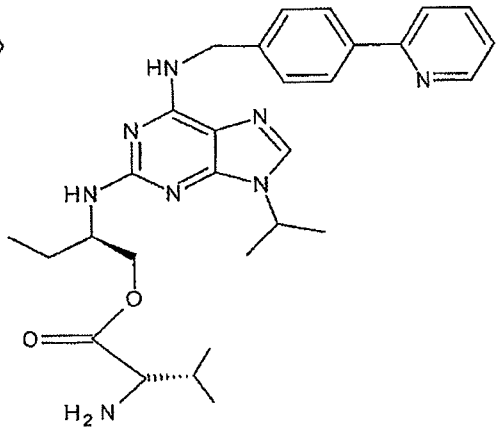
The preferred esters of the compounds of formula I are acyl esters, such as acetyl esters, nicotinyl esters and esters of amino acids of the L series or D series.

Other preferred esters are formed from amino acids, such as valine or leucine.

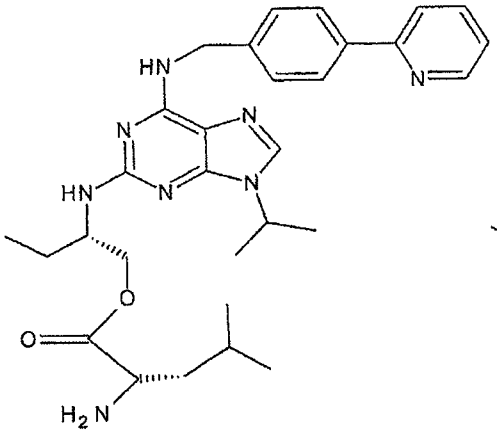
The particularly preferred esters have the following formulae II-1 to II-4:



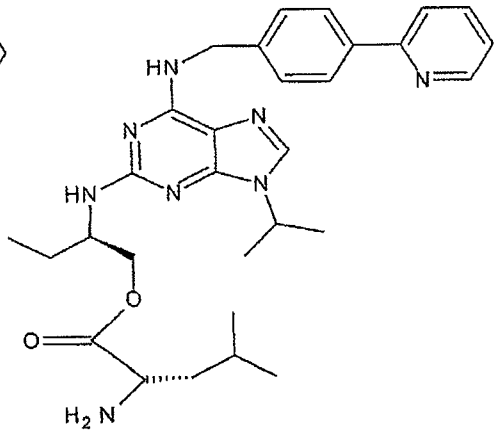
Formula II-1



Formula II-2



Formula II-3



Formula II-4

This is because these esters are precursors (prodrugs) of the products of formula I.

Their use in the manufacture of a medicament intended to treat pathologies in which an imbalance between cell division and apoptosis is involved is also a subject matter of the invention.

A better understanding of the invention will be achieved and other characteristics and advantages of the invention will become more clearly apparent on reading the explanatory description which follows, which is made with reference to the figures, in which:

- the appended figure 1 shows the induction of cell death by the compound of formula Ia and the oxalate salt of the compound of formula Ia in chronic lymphoid leukemia cells, in comparison with the induction of cell death induced by roscovitine,
- figure 2 shows the induction of cell death by the compounds of formulae Ie and If in chronic lymphoid leukemia cells.

The effects of roscovitine and of the compound of formula Ia and of its oxalate salt were tested at various concentrations in kinase assays.

These tests were carried out as follows:

Buffers

buffer A: 10 mM $MgCl_2$, 1 mM EGTA, 1 mM DTT, 25 mM tris-HCl pH 7.5, 50 µg heparin/ml.

buffer C: 60 mM glycerophosphate, 15 mM p-nitrophenyl phosphate, 25 mM MOPS (pH 7.2), 5 mM EGTA, 15 mM $MgCl_2$, 1 mM DTT, 1 mM sodium vanadate, 1 mM phenyl phosphate.

Preparation and assaying of the kinases

The kinase activities were assayed in buffer A or C at 30°C and a final ATP concentration of 15 µM. Controls are carried out with appropriate dilutions of dimethyl sulfoxide.

CDK1/cyclin B (starfish M-phase ovocytes, native) and *CDK5/p25* (human, recombinant) were prepared and assayed as described in Leclerc S. et al., J. Biol. Chem., 2001, 276, 251-60. Assaying is carried out with 1 mg histone H1/ml, in the presence of 15 µm [γ-^{33}P]ATP (3000 Ci/mmol; 10 mCi/ml) in a final volume of 30 µl. After incubating at 30°C for 30 min, 25 µl aliquots of supernatant were deposited on 2.5 × 3 cm pieces of Whatman P8 phosphocellulose papers and then, 20 sec. later, the filters were washed 5 times in a solution of 10 ml of phosphoric acid/liter. The filters are subsequently counted in the presence of 1 ml of ACS (Amersham).

CDK2/cyclin A and CDK2/cyclin E (human, recombinant, expressed in insect cells) are assayed like CDK1.

CDK9/cyclin T (human, recombinant, expressed in insect cells) is assayed like CDK1/cyclin B, with a pRB fragment (AA773-928) (3.5 µg/assay) as substrate.

GSK-3 α/β (pig brain, native, affinity-purified) is assayed like CDK1/cyclin B but in buffer A and with a specific GSK-3 substrate (GS-1: YRRAAVPPSPSLSRHSSPHQSpEDEEE) (Bach S. et al., J. Biol. Chem., 2005, 280, 31208-19).

CK1δ/e (pig brain, native, affinity-purified) is assayed like CDK1/cyclin B but in buffer A and with a

specific substrate, RRKHAAIGSpAYSITA (Reinhardt J. et al., Protein Expr. & Purif., 2007, 54, 101-9).

DYRK1A (human, recombinant, expressed in E. coli cells) is assayed like CDK1/cyclin B.

The mean inhibitory concentration IC_{50} values were calculated from the dose/response curves and are listed in μM in the following table I.

Kinase	(R)-Roscovitine	Compound of formula Ia (R) form	Compound of formula Ib (S) form
CDK1/cyclin B	0.33	0.09	0.15
CDK2/cyclin A	0.21	0.072	0.080
CDK2/cyclin E	0.17	0.041	0.060
CDK5/p25	0.28	0.11	0.12
CDK7/cyclin H	0.80	1.10	-
CDK9/cyclin T	0.23	0.18	0.11
CK1	4.00	0.40	0.61
DYRK1A	3.00	3.60	0.9
Erk2	11.00	3.60	2.1
GSK-3α/β	60.00	12.0	≥ 30.00

Table I

It is seen, from table I, that, for all the protein kinases, the compound of formula Ib of (S) configuration exhibits inhibitory activities for the various kinases which are similar to the activities of roscovitine and which are slightly lower than the activities of the compound of formula Ia, that is to say of its homolog of (R) absolute configuration.

However, when the compound of formula Ia and its oxalate salt and compounds of formulae Ie and If were tested on B chronic lymphoid leukemia cells taken from patients having this type of chronic lymphoid leukemia, it is found that, surprisingly, these compounds have an apoptosis-inducing activity on the CLL cells which is much greater, from 50 to 100 times greater, than the activity of roscovitine, as is seen in figures 1 and 2.

Furthermore, the effect of compounds Ia, Ib, Ic, Id, Ie

and If and of the oxalate salt of the compound Ia on the induction of cell death of the B2 lymphocytes originating from patients was compared with the effect of (R)-roscovitine on this same induction.

The B2 lymphocytes are lymphocytes involved in B2-cell chronic lymphoid leukemia.

Cell viability is determined by the reduction of 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS).

Cell death is determined by the measurement of the level of the activity of the lactate dehydrogenase (LDH) released during lysis of the cells. The two processes are described in detail in "Ribas J. and Boix J.. Cell differentiation, caspase inhibition, and macromolecular synthesis blockage, but not BCL-2 or BCL-XL proteins protect SH-SY5Y cells from apoptosis triggered by two CDK inhibitory drugs. Exp. Cell Res., 2004, 295, 9-24".

The results obtained are shown in the following table 2:

Compound of formula	**Induction of cell death**
(R)-Roscovitine	8.96
Ia	0.20
Ib	0.09
Ia oxalate	0.2
Ic	1.25
Id	0.25
Ie	0.51
If	0.38

Table 2

In table 2, the values shown are the mean inhibitory concentration IC_{50} values, expressed in μM.

The effect of the compounds Ib and Id of the invention on polycystic kidney disease was also tested on the MDCK line in comparison with (R) roscovitine. The compounds Ib and Id are 50 to 60 times more active than roscovitine.

The solubility of the compounds of the invention in which X is N, it has been said, are 5 to 10 times more soluble in water than those in which X is C.

Thus, the compound of formula Ic, in which X is C, has a solubility in water of 0.5 µg/ml, whereas the corresponding compound in which X is N, that is to say the compound of formula Ib, has a solubility in water of 3.3 µg/ml.

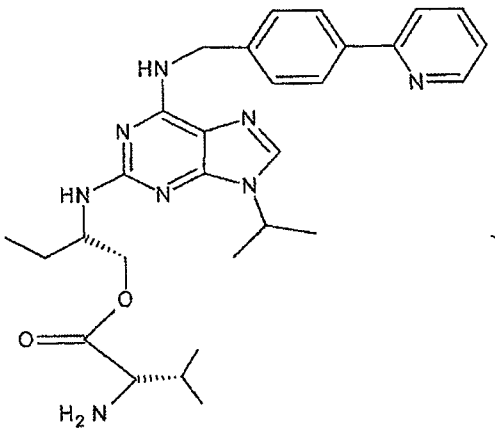
The compounds of formulae Ib to Ih *per se* are also subject-matters of the invention.

The esters of the compounds of formula I also come within the invention.

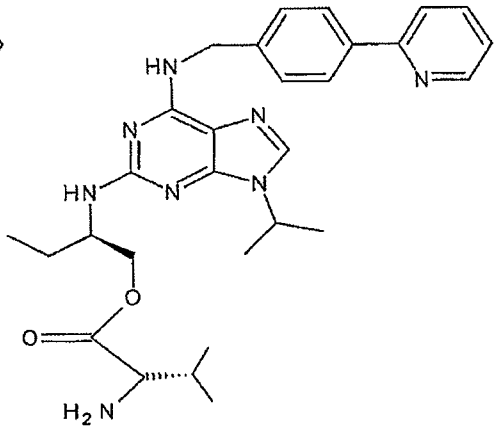
The preferred esters of the compounds of formula I are acyl esters, such as acetyl esters, nicotinyl esters and esters of amino acids of the L series or D series.

The preferred esters are formed from amino acids, such as valine or leucine.

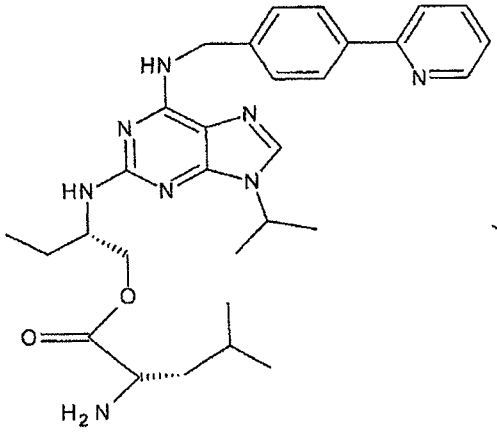
The particularly preferred esters have the following formulae II-1 to II-4:



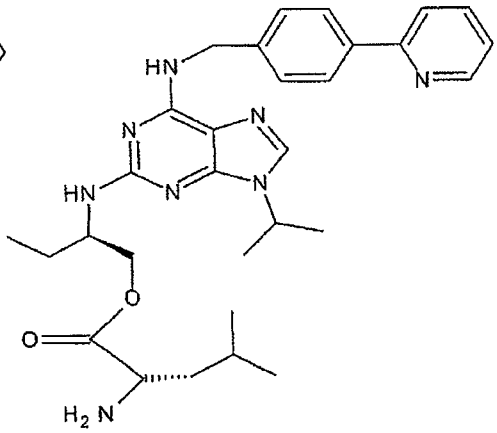
Formula II-1



Formula II-2



Formula II-3



Formula II-4

This is because these esters are precursors (prodrugs) of the products of formula I.

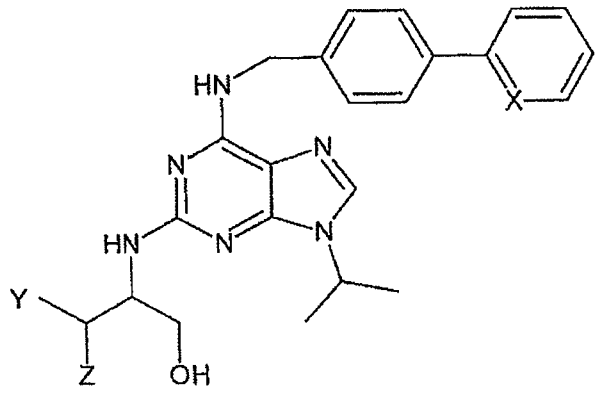
Thus, the compounds of the invention are particularly effective for use in the manufacture of a medicament for treating chronic lymphoid leukemia. They are also particularly appropriate for administration in a method for the treatment of patients affected by chronic lymphoid leukemia.

They are also particularly effective for use in the manufacture of a medicament for treating kidney diseases and in particular polycystic kidney diseases. In the same way, they are particularly appropriate for administration in a method for the treatment of patients affected by a kidney disease and in particular by polycystic kidney disease.

A person skilled in the art will easily understand that the compounds of the invention can be used as a mixture with one another, of two or more, and also in combination with other compounds having a therapeutic activity in the treatment of chronic lymphoid leukemia or kidney diseases, such as polycystic kidney disease, and/or in combination with any pharmaceutically acceptable excipient in the manufacture of a medicament and that these combinations and mixtures also come within the invention.

WHAT IS CLAIMED IS:

1. The use of at least one compound of following formula I:



Formula I

in which:

- X is C or N,
- Y is CH_3 or OH, and
- Z is H or CH_3,

or one of its pharmaceutically acceptable salts, hydrates, esters or isomers,
in the manufacture of a medicament intended to treat pathologies in which an imbalance between cell division and apoptosis is involved.

2. The use as claimed in claim 1, characterized in that the pathology is a kidney disease, such as polycystic kidney disease.

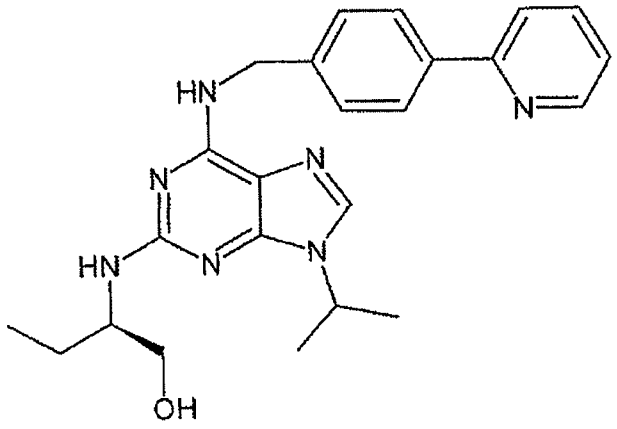
3. The use as claimed in claim 1, characterized in that the pathology is chronic lymphoid leukemia, more particularly B-cell chronic lymphoid leukemia.

4. The use as claimed in any one of the preceding claims, characterized in that the pharmaceutically acceptable salt is an oxalate or tartrate or hydrochloride or fumarate salt.

5. The use as claimed in any one of the preceding claims, characterized in that the at least one compound of the formula I in which X is N.

6. The use as claimed in any one of the preceding claims, characterized in that the at least one compound is the compound of formula I in which X is N and Y is OH.

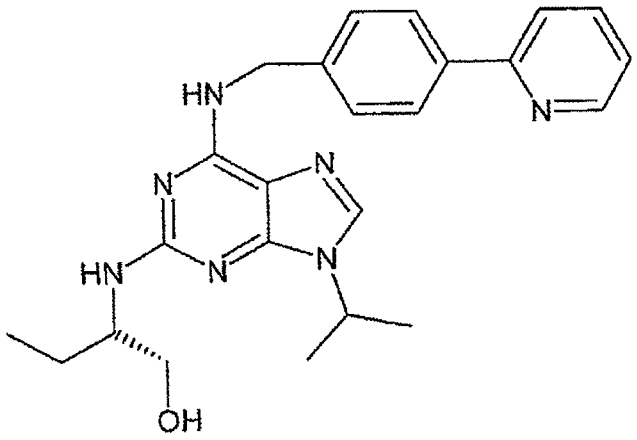
7. The use as claimed in any one of claims 1 to 5, characterized in that the at least one compound is the compound of formula I in which X is N, Y is CH_3 and Z is H, of following formula Ia:



Formula Ia

or one of its pharmaceutically acceptable salts, hydrates or esters.

8. The use as claimed in any one of claims 1 to 5, characterized in that the at least one compound is the compound of formula I in which X is N, Y is CH_3 and Z is H, of (S) absolute configuration of following formula Ib:

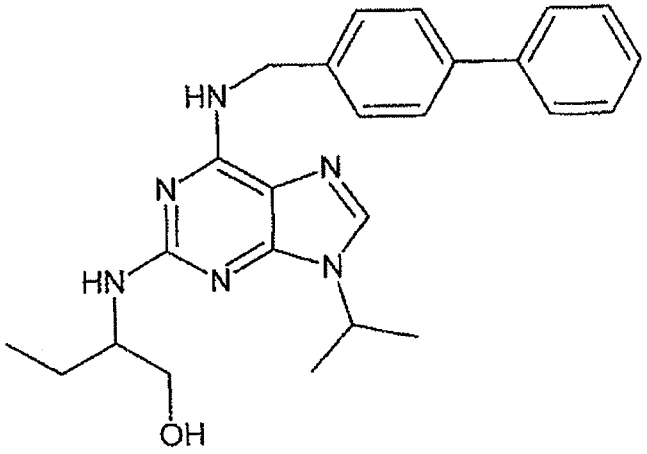


Formula Ib

or one of its pharmaceutically acceptable salts, hydrates or esters.

9. The use as claimed in claim 8, characterized in that the at least one compound is the oxalate salt of the compound of formula Ib.

10. The use as claimed in any one of claims 1 to 6, characterized in that the at least one compound is the compound of formula I in which X is N, Y is OH and Z is H, of following formula Ic:

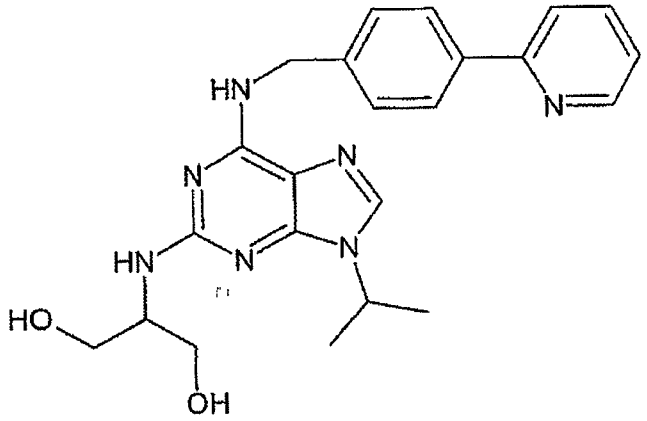


Formula Ic

or one of its pharmaceutically acceptable salts, hydrates or isomers.

11. The use as claimed in any one of claims 1 to 4,

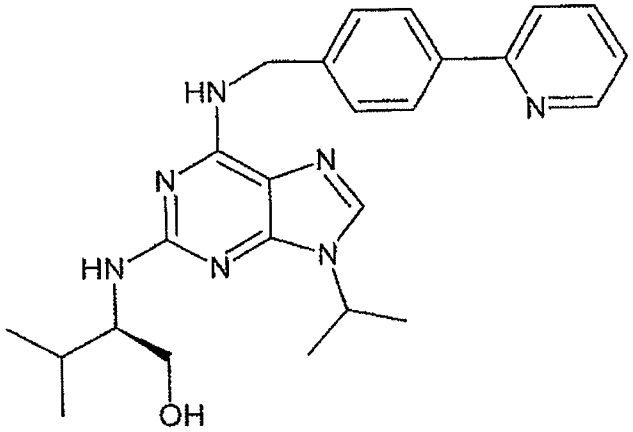
characterized in that the at least one compound is the compound of formula I in which X is C, Y is CH_3 and Z is H, of following formula Id:



Formula Id

or one of its pharmaceutically acceptable salts, hydrates or esters.

12. The use as claimed in any one of claims 1 to 5, characterized in that the at least one compound is the compound of formula I in which X is N, Y is CH_3 and Z is CH_3, of following formula Ie:

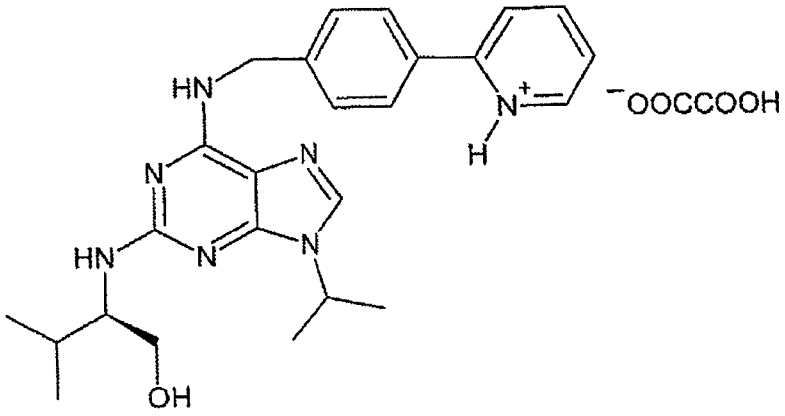


Formula Ie

or one of its pharmaceutically acceptable salts, hydrates or esters.

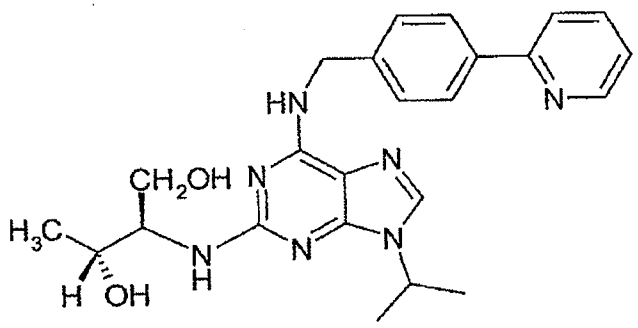
13. The use as claimed in any one of claims 1 to 4 and 12, characterized in that the at least one

compound is the oxalate salt of the compound of formula I in which X is N, Y is CH_3 and Z is CH_3, of following formula If:



Formula If

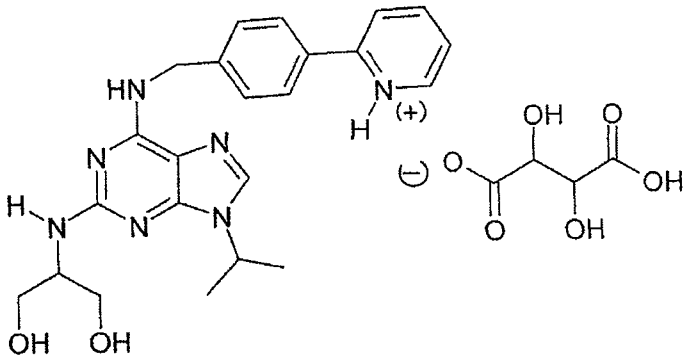
14. The use as claimed in any one of claims 1 to 5, characterized in that the at least one compound has the following formula Ig:



Formula Ig

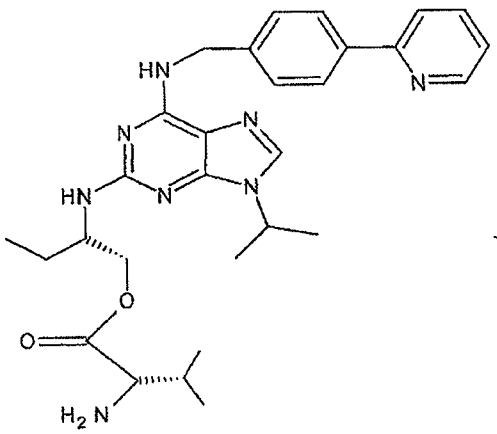
or one of the pharmaceutically acceptable salts, hydrates or isomers.

15. The use as claimed in any one of claims 1 to 6, characterized in that the at least one compound has the following formula Ih:

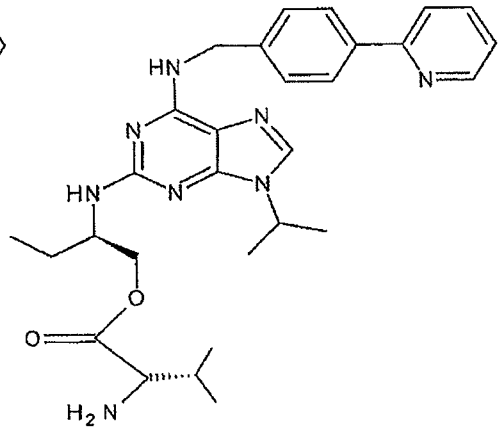


Formula Ih

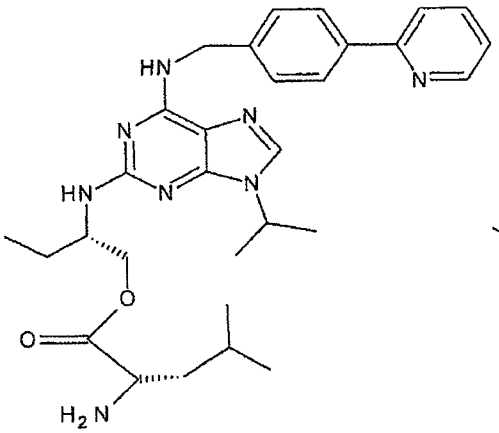
16. The use as claimed in any one of claims 1 to 3, characterized in that the at least one compound is an ester chosen from the compounds of following formulae II-1 to II-4:



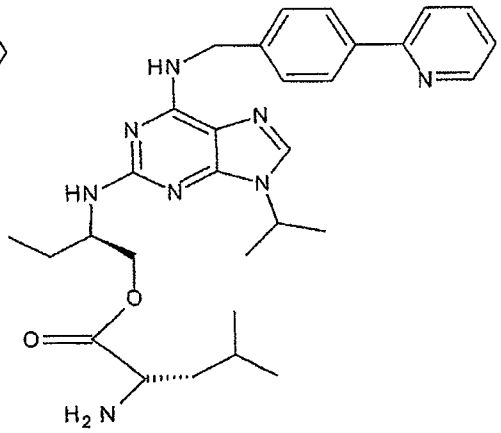
Formula II-1



Formula II-2

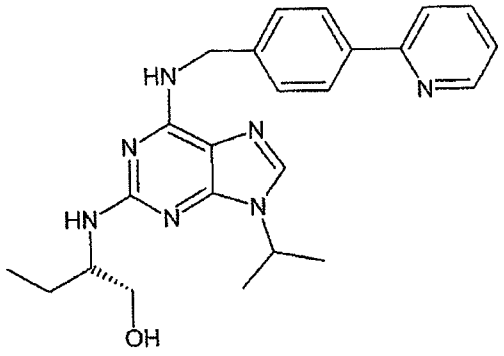


Formula II-3



Formula II-4

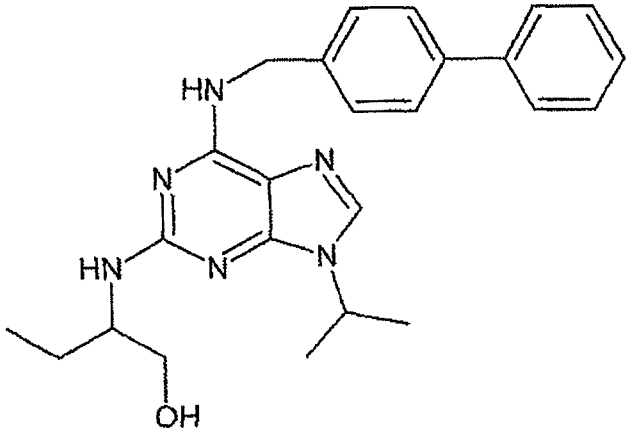
17. The compound of following formula Ib:



Formula Ib

or one of its salts, hydrates or esters.

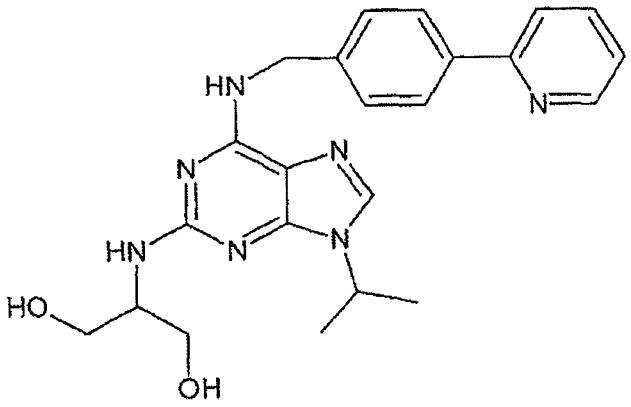
18. The compound of following formula Ic:



Formula Ic

or one of its salts, hydrates, esters or isomers.

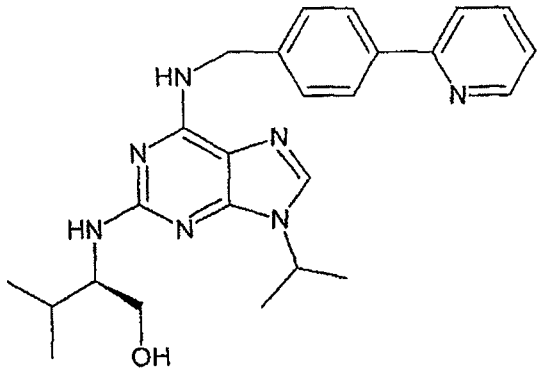
19. The compound of following formula Id:



Formula Id

or one of its salts, hydrates, esters or isomers.

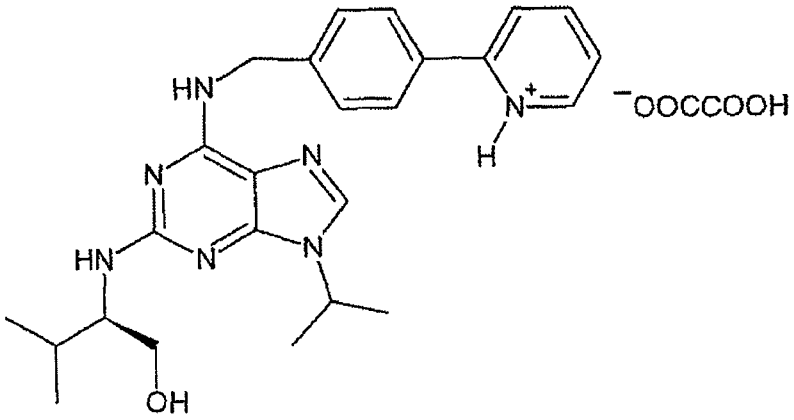
20. The compound of following formula Ie:



Formula Ie

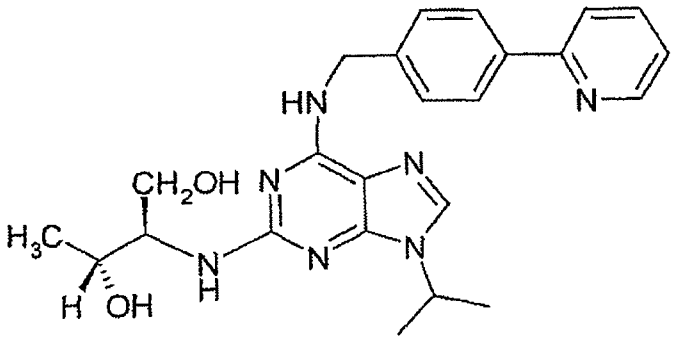
or the salts, hydrates or esters of the latter.

21. The compound of following formula If:



Formula If

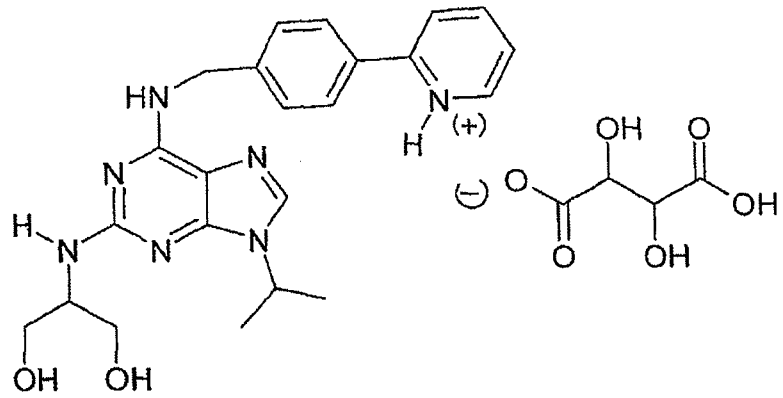
22. The compound of following formula Ig:



Formula Ig

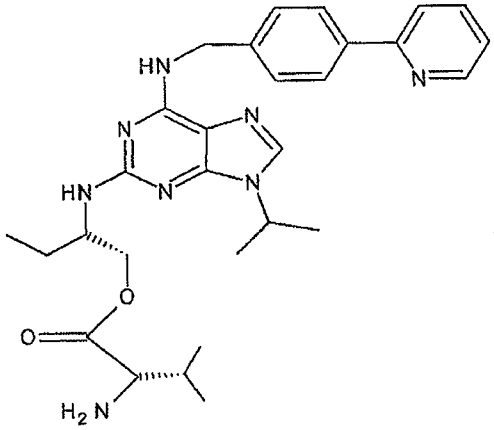
or one of its salts, hydrates, esters or isomers.

23. The compound of following formula Ih:

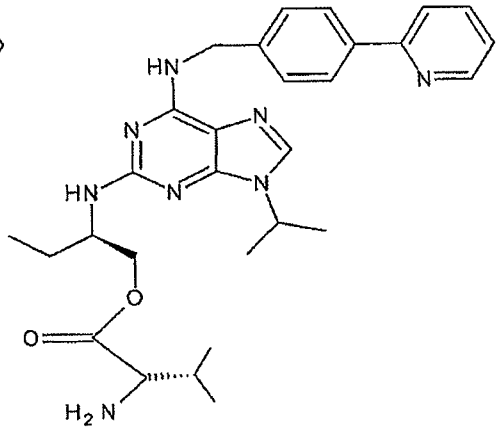


Formula Ih

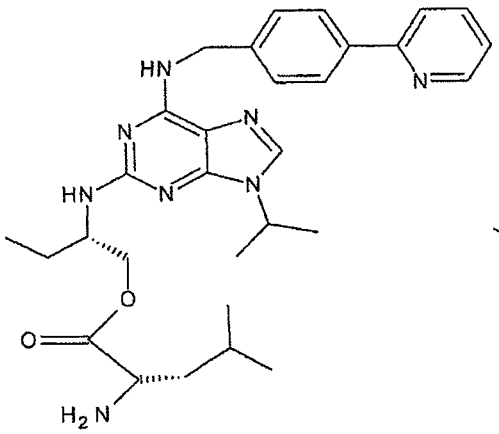
24. A compound, characterized in that it has the following formulae II-1 to II-4:



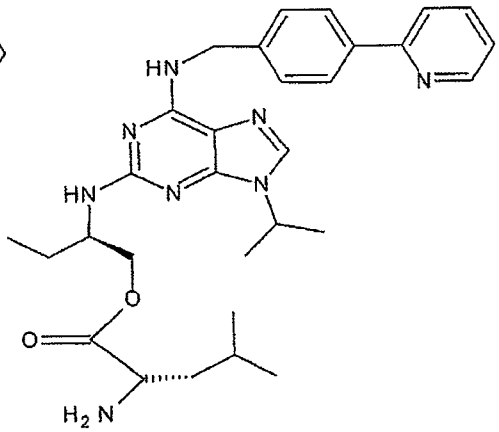
Formula II-1



Formula II-2



Formula II-3



Formula II-4