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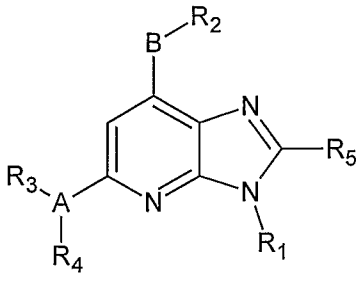
(54) Title: PERHARIDINES AS CDK INHIBITORS



(I)

(57) Abstract: The invention relates to trisubstituted or tetrasubstituted imidazo[4,5b] pyridines, to their uses as well as to a process for manufacturing them. The compounds of the invention have the following formula (I), wherein A, B and R1-R5 are defined in the description. The invention founds application, in particular, in the pharmaceutical field.

PERHARIDINES AS CDK INHIBITORS

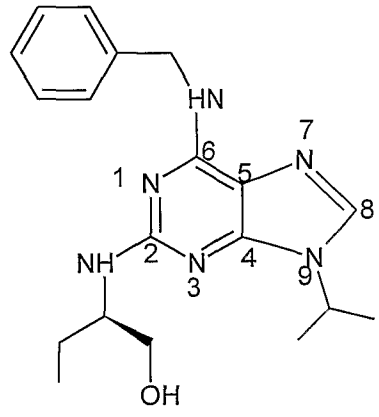
The invention relates to trisubstituted or tetrasubstituted imidazo[4,5-b] pyridines, to their uses as well as to a process for manufacturing them.

Cyclin-dependent kinases (CDKs) play an important role of regulator in the regulation of cell division, apoptosis, transcription, neuronal functions, and exocytosis.

The frequent deregulation of CDKs in human tumors and the involvement of CDK5 in Alzheimer's, Parkinson's and Nieman-Pick diseases, ischemia and stroke, as well as in various kidney diseases such as mesangial proliferative glomerulonephritis, crescentic glomerulonephritis, collapsing glomerulopathy, proliferative lupus nephritis, polycystic kidney diseases, diabetic nephropathy and acute kidney injury, cisplatin-induced nephrotoxicity, in inflammation such as in pleural inflammation, arthritis, glaucoma, in type 2 diabetes, in viral infections (HSV, HCMV, HPV, HIV), in unicellular parasite diseases such as those due to *Plasmodium*, *Leishmania*, etc....have stimulated an active search for chemical CDK inhibitors.

Among the numerous inhibitors that have been identified, Roscovitine, one of the early compounds, appears to be relatively potent and selective.

Roscovitine is a purine having the following formula:



Because of its cell growth inhibiting and neuroprotective activities, this purine is currently considered as a potential drug to treat, respectively, cancers, renal diseases, various neurodegenerative diseases and inflammations.

Besides, the selectivity of pharmacological inhibitors of protein kinases is an important issue and Roscovitine is a relatively selective CDKs inhibitor compared to other inhibitors, including the already commercialised inhibitor Gleevec®.

However, Roscovitine interacts with pyridoxal kinase.

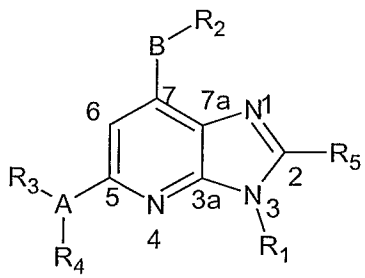
A study of the interaction of Roscovitine and its derivatives with pyridoxal kinase is reported in Tang et al, J. Biol. Chem, 280, 35, September 2, 2005, 31220-31229.

Pyridoxal kinase catalyzes the phosphorylation of pyridoxal, pyridoxamine and pyridoxine in the presence of ATP and Zn^{2+}. This constitutes an essential step in the synthesis of pyridoxal 5'-phosphate, the active form of vitamin B_6, a cofactor for over 140 enzymes. Interaction with the pyridoxal kinase system is thus likely to lead to unwanted side effects.

Thus, such an interaction is, on the one hand, detrimental to the synthesis of the active form of vitamine B_6, and/or, on the other hand, detrimental to the availability of Roscovitine and its derivatives, in patients treated with this type of CDKs inhibitors.

Therefore, the aim of the invention is to provide derivatives of Roscovitine having CDKs inhibitor properties but less or no interaction with pyridoxal kinase.

For this aim, the invention proposes compounds of the following formula I:



Formula I

wherein:

A is CH or N or O,

R_3 is:

- H, or
- a C_1-C_5 alkyl group, or
- =O, or
- a (C_1-C_3) alkyl-C=O group in which the alkyl group is optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or amino groups, and/or alkyloxy groups, and/or ketone groups,

R_4 is:

- H, or
- a C_1-C_6 alkyl group optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or amino groups, and/or alkyloxy groups, and/or ketone groups,
- a C_3-C_6 cycloalkyl group optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or amino groups, and/or alkyloxy groups, and/or ketone groups, or
- a (C_1-C_5)alkyl(C_3-C_6)cycloalkyl group optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or amino groups, and/or alkyloxy groups, and/or ketone groups, or
- =O, or
- O=CCF_3, or
- a C_1-C_6 alkyl group substituted by an ester group such as a O-acyl group, or an amino acyl group derived from natural, or non natural amino acids, or an acetyl group or a nicotinyl group,

or A, R_3 and R_4 together form a C_5-C_7 cycloalkyl group, optionally containing one or more heteroatoms, preferably a piperazine group,

B is O or S or NH or a halogen atom,

R_1 is:

- a C_1-C_6 alkyl group optionally substituted by one or more hydroxy groups, or
- a C_3-C_6 cycloalkyl group optionally substituted by one or more hydroxy groups, or
- an aryl group optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyloxy groups, and/or optionally containing one or more heteroatoms, or
- a C_1-C_5 alkylaryl group, the aryl group being optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyl groups, and/or C_1-C_3 alkyloxy groups, and/or optionally containing one or more heteroatoms,

R_2 is:

- an aryl group optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyloxy groups, and/or carboxylic acid groups, and/or carboxylic ester groups, and/or amine groups, and/or CF_3 groups, and/or optionally containing one or more heteroatoms, thus creating a 2-pyridyl group, or a 3-pyridyl group, or a 4-pyridyl group, or a 2-thienyl or a 3-thienyl group, or
- a methylbiaryl group, wherein each aryl cycle is optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyloxy groups, and/or CF_3 groups, and/or carboxylic acid groups, and/or carboxylic ester groups, and/or amine groups, and/or optionally containing one or more heteroatoms, or
- a methylaryl group, the aryl cycle being optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyloxy groups, and/or CF_3 groups, and/or optionally containing one or more heteroatoms, thus creating a 2-pyridyl group, or a 3-pyridyl group, or a 4-pyridyl group, or a 2-thienyl group or a 3-thienyl group,
- a biaryl group, each aryl cycle optionally containing one or more heteroatoms thus creating a 2-pyridyl group, or a 3-pyridyl group, or a 4-pyridyl group, or a 2-thienyl group or a 3-thienyl group, or each aryl cycle is optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyloxy groups, and/or CF_3 groups, and/or carboxylic acid groups, and/or carboxylic ester groups, and/or amine groups,

or B and R_2 together form a non aromatic cycle,

R_5 is:

- a halogen atom, or
- a hydrogen atom, or
- a C_1-C_5 alkyl group optionally substituted by one or more hydroxy groups and/or amine groups and/or halogen atoms and/or carboxylic acid groups, or

- a (C_1-C_4)alkyl(C_3-C_6)cycloalkyl group in which the cycloalkyl group is optionally substituted by one or more hydroxy groups and/or amine groups and/or halogen atoms and/or carboxylic acid groups,

and the salts, hydrates, and stereoisomers thereof.

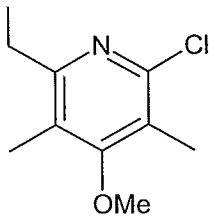
As used herein, the term "biaryl" designates two aryl cycles linked by a single bond and the term "carboxylic acid group" designates a –COOH group.

In a first preferred embodiment of the invention, in Formula I, A is N.

In a second preferred embodiment of the invention, in Formula I, A is CH.

In a third preferred embodiment of the invention, in Formula I, A is O.

In each of the preferred embodiment of the invention, in Formula I, preferably R1 group is an ethyl, or a methyl, or an isopropyl, or a methylcyclopropyl, or a cyclopentyl, a phenyl group, or a benzyl group or a methylpyridyl group, or



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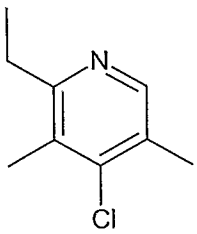


In each of the preferred embodiments of the invention, in Formula I, preferred B-R_2 group is one of those identified in the following table 1:

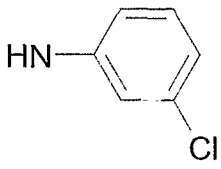
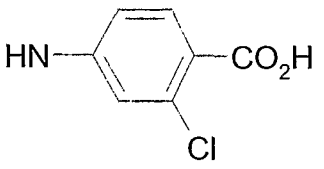
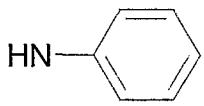
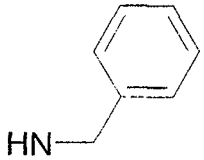
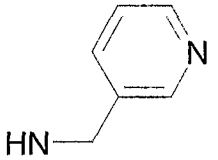
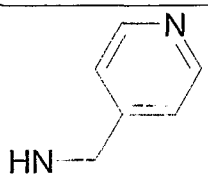
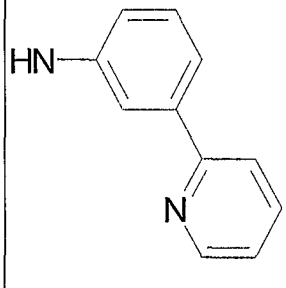
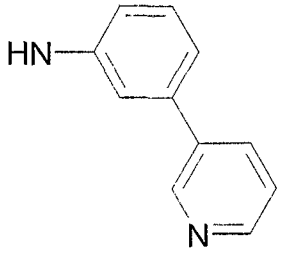
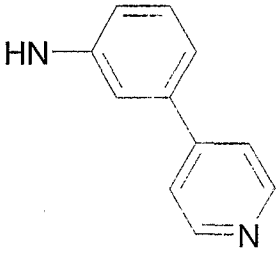
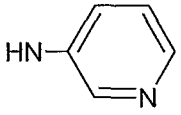
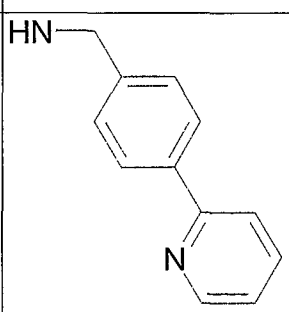
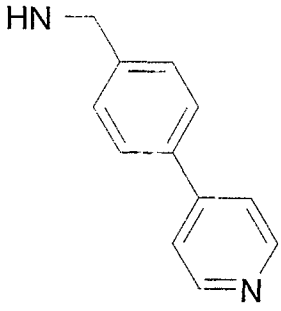
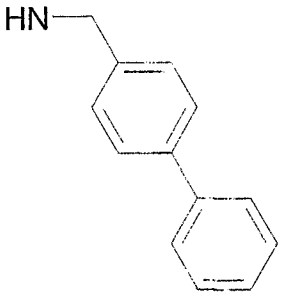
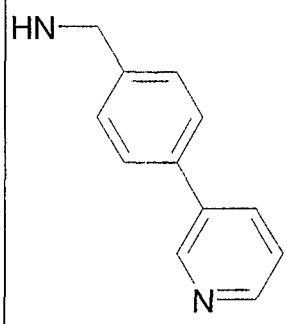
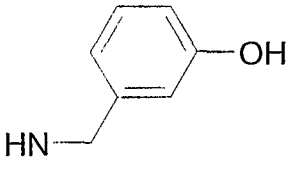
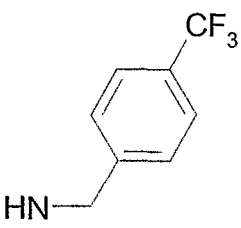
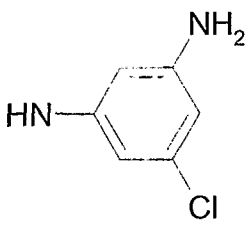
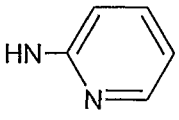
			
			
			
			
			

Table 1

Still in each of the preferred embodiments of the invention, in Formula I, preferably the R_4-A-R_3 subsituent is one of the groups identified in the following table 2:

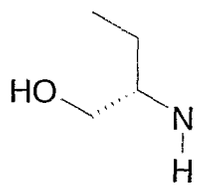
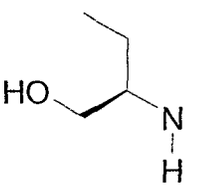
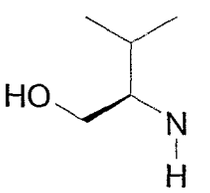
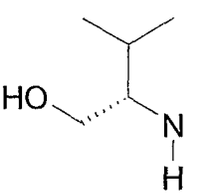
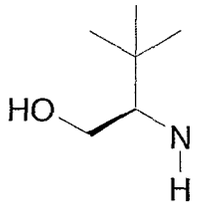
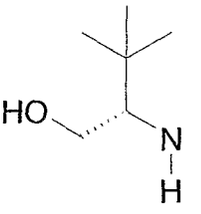
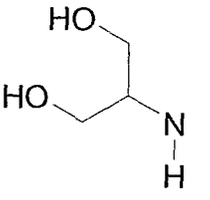
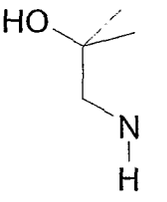
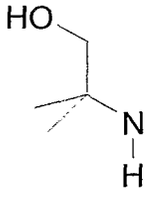
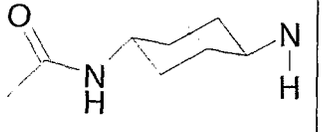
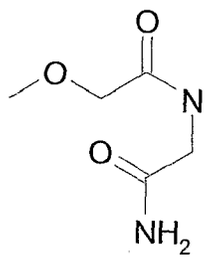
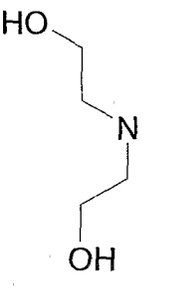
	or 	or 	or 
or 	or 	or 	or 
or 	or 	or 	or 

Table 2

Furthermore, in each of the preferred embodiments of the invention, preferably R_4-A-R_3 is an ester functionality.

Indeed, although these esters exhibit moderate or low in vitro activity, they behave in vivo as prodrugs of the bioactive compounds of Formula I of the invention.

In such prodrugs, which are esters of the compound of formula I of the invention, preferred R_4-A-R_3 groups are those identified in the following table 3.

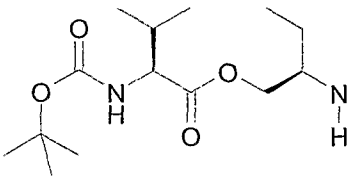
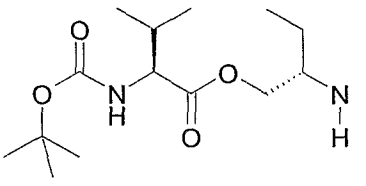
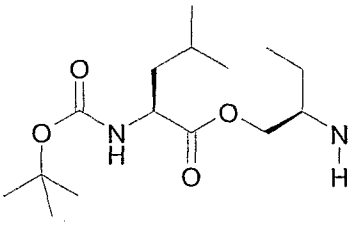
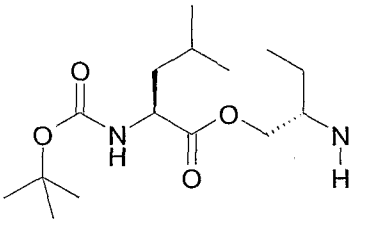
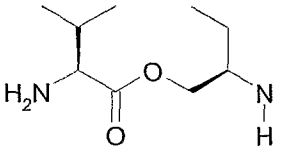
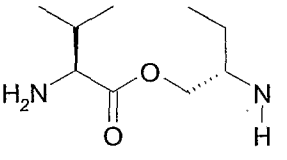
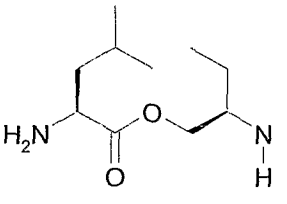
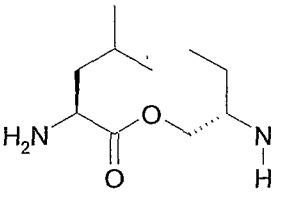
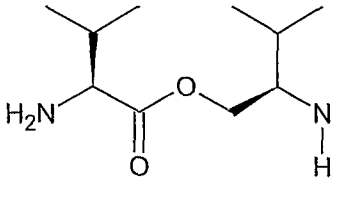
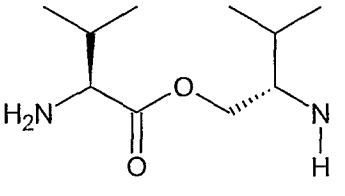
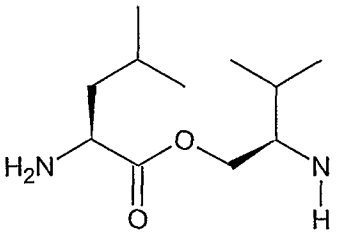
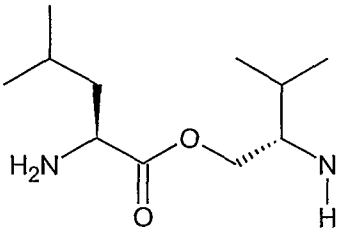
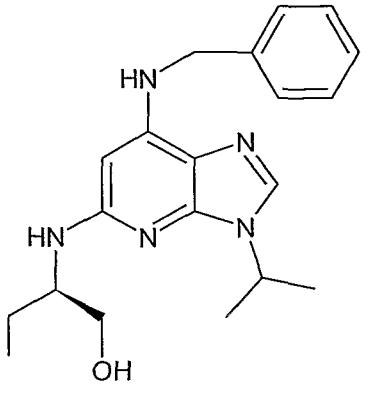
	
	
	
	
	
	

Table 3

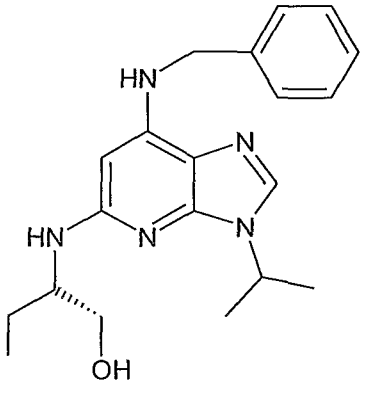
A preferred compound of the invention is the compound having the following formula Ia:



Formula Ia.

This compound has an absolute configuration (*R*) and is hereinafter also referred to as "perharidine A".

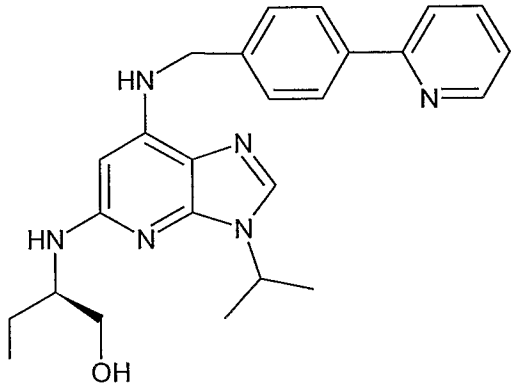
But, the (*S*) isomer of perharidine A, having the following formula Ib, is also preferred:



Formula Ib.

This compound is hereinafter also referred to as "perharidine B".

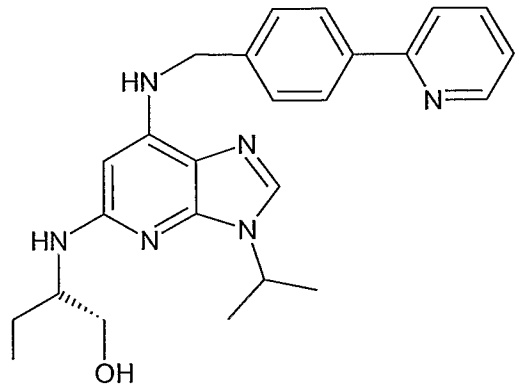
Another preferred compound of the invention has the following formula Ic:



Formula Ic.

This compound is hereinafter also referred to as "perharidine C".

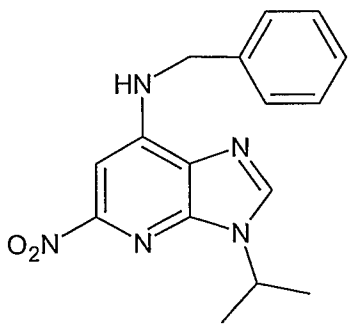
Still another preferred compound of the invention has the following formula Id:



Formula Id.

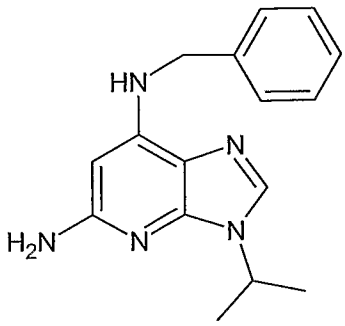
This compound is hereinafter also referred to as "perharidine D".

But the compound of the invention having the following formula Ie is also preferred:



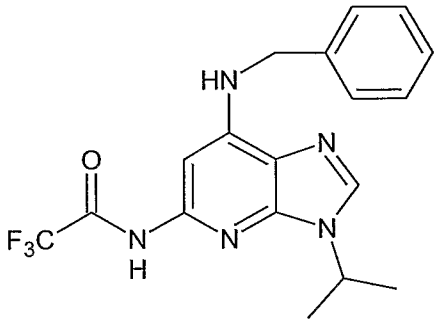
Formula Ie.

The compound of the invention having the following formula If is also a preferred compound:



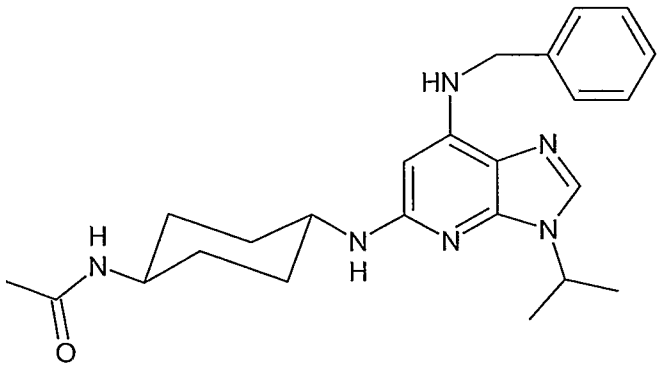
Formula If.

The compound of the invention having the following formula Ig is also preferred:



Formula Ig.

Furthermore, the compound of the invention having the following formula Ih is also preferred.



Formula Ih.

The stereoisomers, hydrates, and salts of each and all of the compounds of the invention cited above are also in the scope of the invention.

As it will be noted, in the compounds of Formulas Ia to Ig, A is N.

But other preferred compounds of the invention are those corresponding to these compounds of Formula Ia to Ig, in which A is CH or A is O.

The compounds of the invention may be manufactured by any appropriate process well-known from the man skilled in the art.

However when A is N, on the one hand, these compounds may not be prepared by the classical process of synthesis of 2, 6, 9-trisubstituted purines.

This classical process involves a step in which the 2-chlorine-substituted purine is heated in presence of an amino-alcohol for obtaining, for example, Roscovitine, at a temperature comprised between 145°C and 170°C.

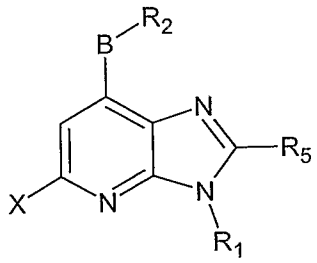
But when applying this process to the corresponding 3, 5, 7-trisubstituted imidazo [4,5-b] pyridine, no reaction occurred.

When rising the temperature, only degradation products were obtained.

On the other hand, applying the classical process for preparing deazapurine was also found not appropriate.

Indeed, this classical process described by Francis, JE and Moskal, MA in Can J Chem 1992, 70 pages 1288-1295, first involves the formation on an amidine by reaction of a secondary amide with a aminocyanoimidazole using phosphoryl chloride as reagent. In a second step, the amidine is cyclised into the imidazopyridine using NaH as base. This process could not be applied to prepare the compounds object of the present invention as it only affords derivatives bearing an unsubstituted amino group in position 7. Further when substituents contain hydroxyl groups they should be protected during the formation of the heterocycle. In another synthesis described by Koch, M in WO 2006/027366, the nature of the substituent than can be introduced in position 5 is limited as formed from a nitroso group and by the same process, only the unsubstituted 7-amino group is described.

To palliate the drawbacks of the processes of the prior art, the invention proposes an original and versatile process in which the compounds of the following formula II are used:



Formula II

wherein:

B is O or S or NH or a halogen atom,

R_1 is:

- a C_1-C_6 alkyl group optionally substituted by one or more hydroxy groups, or
- a C_3-C_6 cycloalkyl group optionally substituted by one or more hydroxy groups, or
- an aryl group optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyloxy groups, and/or optionally containing one or more heteroatoms, or
- a C_1-C_5 alkylaryl group, the aryl group being optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyl groups, and/or C_1-C_3 alkyloxy groups, and/or optionally containing one or more heteroatoms,

R_2 is:

- an aryl group optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyloxy groups, and/or carboxylic acid groups, and/or carboxylic ester groups, and/or amine groups, and/or CF_3 groups, and/or optionally containing one or more heteroatoms, thus creating a 2-pyridyl group, or a 3-pyridyl group, or a 4-pyridyl group, or a 2-thienyl or a 3-thienyl group, or
- a methylbiaryl group, wherein each aryl cycle is optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyloxy groups, and/or CF_3 groups, and/or carboxylic acid groups, and/or carboxylic ester groups, and/or amine groups, and/or optionally containing one or more heteroatoms, or
- a methylaryl group, the aryl cycle being optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyloxy groups, and/or

CF_3 groups, and/or optionally containing one or more heteroatoms, thus creating a 2-pyridyl group, or a 3-pyridyl group, or a 4-pyridyl group, or a 2-thienyl group or a 3-thienyl group,

- a biaryl group, each aryl cycle optionally containing one or more heteroatoms thus creating a 2-pyridyl group, or a 3-pyridyl group, or a 4-pyridyl group, or a 2-thienyl group or a 3-thienyl group, or each aryl cycle is optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyloxy groups, and/or CF_3 groups, and/or carboxylic acid groups, and/or carboxylic ester groups, and/or amine groups,

or B and R_2 together form a non aromatic cycle,

R_5 is:

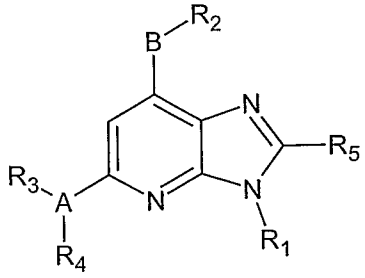
- a halogen atom, or
- a hydrogen atom, or
- a C_1-C_5 alkyl group optionally substituted by one or more hydroxy groups and/or amine groups and/or halogen atoms and/or carboxylic acid groups, or
- a (C_1-C_4)alkyl(C_3-C_6)cycloalkyl group in which the cycloalkyl group is optionally substituted by one or more hydroxy groups and/or amine groups and/or halogen atoms and/or carboxylic acid groups,

X is Cl or Br or I or NH_2.

These compounds of formula II are also in the scope of the invention.

Preferred compounds of Formula II are those in which X is I.

Thus, the invention also proposes a process for manufacturing compounds of the following formula I:



Formula I

wherein:

A is N,

R_3 is:

- H, or
- a C_1-C_5 alkyl group, or
- =O, or
- a (C_1-C_3) alkyl-C=O group in which the alkyl is optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or amino groups, and/or alkyloxy groups, and/or ketone groups,

R_4 is:

- H, or
- a C_1-C_6 alkyl group optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or amino groups, and/or alkyloxy groups, and/or ketone groups,
- a C_3-C_6 cycloalkyl group optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or amino groups, and/or alkyloxy groups, and/or ketone groups, or
- a (C_1-C_5)alkyl(C_3-C_6)cycloalkyl group optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or amino groups, and/or alkyloxy groups, and/or ketone groups, or
- =O, or
- O=CCF_3, or
- a C_1-C_6 alkyl group substituted by an ester group such as a O-acyl group, or an amino acyl group derived from natural, or non natural amino acids, or an acetyl group or a nicotinyl group,

or A, R_3 and R_4 together form a C_5-C_7 cycloalkyl group, optionally containing one or more heteroatoms, preferably a piperazine group,

B is O or S or NH or a halogen atom,

R_1 is:

- a C_1-C_6 alkyl group optionally substituted by one or more hydroxy groups, or

- a C_3-C_6 cycloalkyl group optionally substituted by one or more hydroxy groups, or
- an aryl group optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyloxy groups, and/or optionally containing one or more heteroatoms, or
- a C_1-C_5 alkylaryl group, the aryl group being optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyl groups, and/or C_1-C_3 alkyloxy groups, and/or optionally containing one or more heteroatoms,

R_2 is:

- an aryl group optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyloxy groups, and/or carboxylic acid groups, and/or carboxylic ester groups, and/or amine groups, and/or CF_3 groups, and/or optionally containing one or more heteroatoms, thus creating a 2-pyridyl group, or a 3-pyridyl group, or a 4-pyridyl group, or a 2-thienyl or a 3-thienyl group, or
- a methylbiaryl group, wherein each aryl cycle is optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyloxy groups, and/or CF_3 groups, and/or carboxylic acid groups, and/or carboxylic ester groups, and/or amine groups, and/or optionally containing one or more heteroatoms, or
- a methylaryl group, the aryl ring being optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyloxy groups, and/or CF_3 groups, and/or optionally containing one or more heteroatoms, thus creating a 2-pyridyl group, or a 3-pyridyl group, or a 4-pyridyl group, or a 2-thienyl group or a 3-thienyl group,
- a biaryl group, each aryl cycle optionally containing one or more heteroatoms thus creating a 2-pyridyl group, or a 3-pyridyl group, or a 4-pyridyl group, or a 2-thienyl group or a 3-thienyl group, or each aryl cycle is optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyloxy groups, and/or CF_3 groups, and/or carboxylic acid groups, and/or carboxylic ester groups, and/or amine groups,

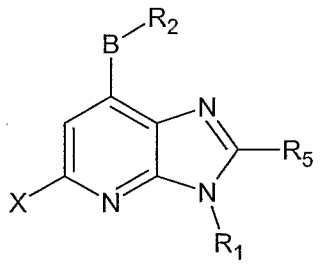
or B and R_2 together form a non aromatic cycle,

R_5 is:

- a halogen atom, or
- a hydrogen atom, or
- a C_1-C_5 alkyl group optionally substituted by one or more hydroxy groups and/or amine groups and/or halogen atoms and/or carboxylic acid groups, or
- a (C_1-C_4)alkyl(C_3-C_6)cycloalkyl group in which the cycloalkyl group is optionally substituted by one or more hydroxy groups and/or amine groups and/or halogen atoms and/or carboxylic acid groups,

and the salts, hydrates, and stereoisomers thereof,

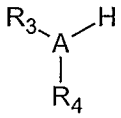
comprising a step of reaction of a compound of the following formula II:



Formula II

wherein B, R_2, R_1 and R_5 are as defined above for the compounds of formula I and X is Br, Cl, I or NH_2.

In a first embodiment of the process of the invention, this step of reaction is a step of coupling the compounds of Formula II in which X is Cl, Br or I with a compound of the following Formula III:



Formula III

wherein A, R_3 and R_4 are as defined for Formula I, in presence of a catalyst selected from $Pd(OAc)_2$, tris(dibenzylidenacetone)dipalladium also called,

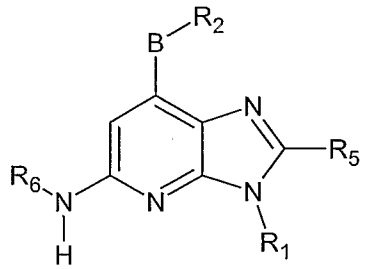
Pd_2dba_3 or CuI, and optionally in presence of a ligand such as 2,2'-bis(diphenylphosphino)-1,1-binaphtyl also called Binap or ethyleneglycol or a diketone.

In a second embodiment of the process of the invention, this step of reaction is a step of coupling a compound of Formula II in which X is NH_2 with a compound of the following Formula IV:

$Y\text{-}R_6$

Formula IV

in which Y is I, Br or Cl and R_6 is R_3 or R_4, for obtaining a compound of the following formula V:



Formula V

and when R_3 and R_4 are different from H, followed by a step of coupling the compound of Formula V with a compound of the following Formula VI:

$Y\text{-}R_7$

Formula VI

in which Y is I, Br or Cl and R_7 is R_3 when R_6 is R_4 or R_7 is R_4 when R_6 is R_3,

said coupling steps being carried out in basic conditions.

In all the embodiments of the process of the invention, preferably, X and Y are I or Br, more preferably I, in each occurence.

The invention also proposes a compound according to the invention or obtained by the process of the invention for use as medicament.

Another object of the invention is a pharmaceutical composition comprising at least one compound of the invention, or obtained by the process of the invention, and at least one pharmaceutically acceptable excipient.

A further object of the invention is the use of at least one compound of the invention, or obtained by the process of the invention, in the manufacture of a

medicament for the treatment of a disease due to an abnormal proliferation of cells, either tumoral or non-tumoral by nature.

In one embodiment of said use according to the invention, said disease is a tumor, such as a solid tumor, metastatic or not, or leukemia.

In another embodiment, said disease is a neurodegenerative disease involving abnormal activity of CDK5 and/or CDK1.

More particularly, said neurodegenerative disease is Parkinson's disease.

But, said neurodegenerative disease may also be Alzheimer's disease and related Taupathies.

In still another embodiment, said disease is a viral disease, such as HIV, Herpes, cytomegalovirus, etc...

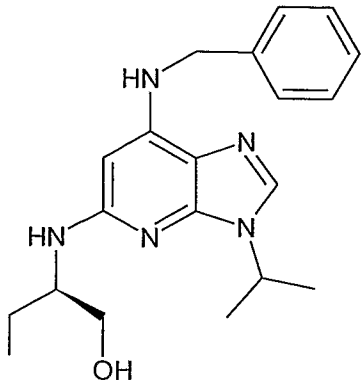
Also, the invention encompasses the use of at least one compound of the invention, or obtained by the process of the invention, in the manufacture of a medicament for the treatment of pain.

Furthermore, at least one compound of the invention, or obtained by the process of the invention, is advantageously used in the manufacture of a medicament or in a method of treatment of renal diseases such as mesangial proliferative glomerulonephritis, crescentic glomerulonephritis, collapsing glomerulopathy, proliferative lupus nephritis, polycystic kidney diseases, diabetic nephropathy, acute kidney injury and cisplatin-induced nephrotoxicity.

But, at least one compound of the invention or at least one compound obtained by the process of the invention is also of interest in the manufacture of a medicament and/or a method of treatment of inflammations such as pleural inflammation, arthritis, cystic fibrosis or glaucomas

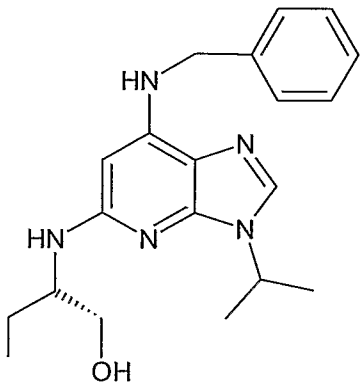
Finally compounds of the invention are also of interest to enhance insulin production by the pancreas in the case of type 2 diabetes.

In all the embodiments and variations of the use of at least one compound of the invention, preferably, said at least one compound has the following formula Ia:



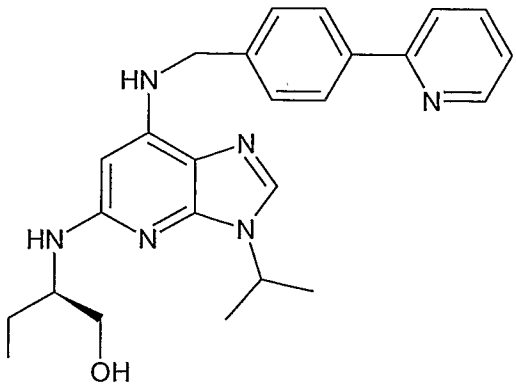
Formula Ia

More preferably, said at least one compound is the compound of the following formula Ib:



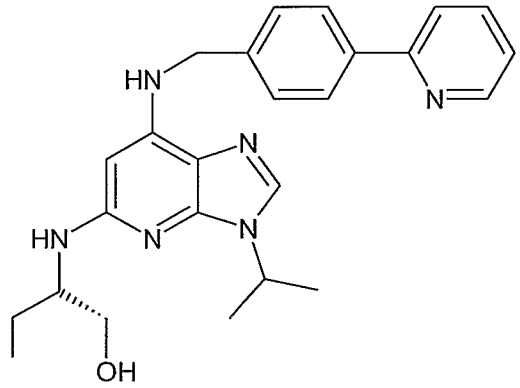
Formula Ib

But in another preferred variation said at least one compound is the compound of the following formula Ic:



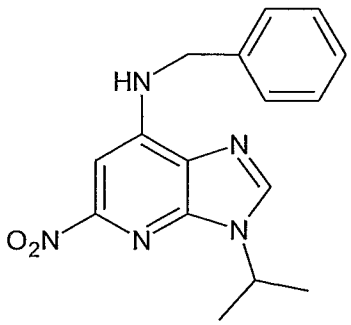
Formula Ic

However in another preferred variation of the use of at least one compound of the invention, said at least one compound is the compound of the following formula Id:



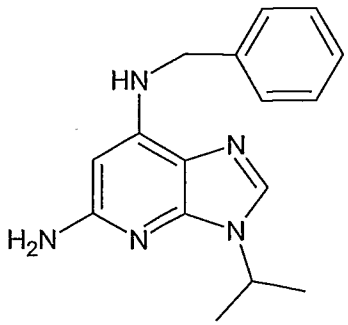
Formula Id

In another variation of the use of at least one compound of the invention, said at least one compound is the compound of the following formula Ie:



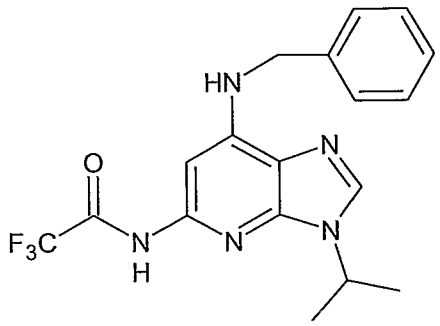
Formula Ie

But, said at least one compound may also be the compound of the following formula If:



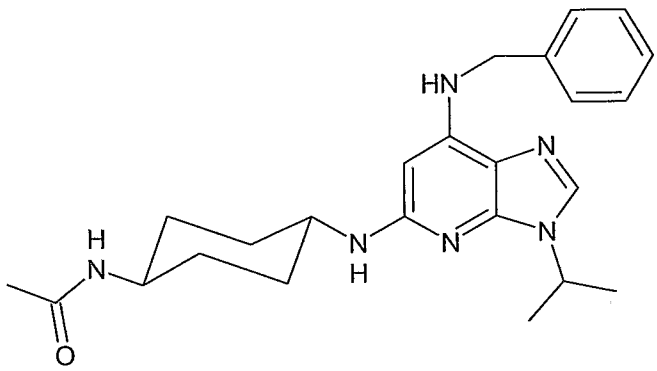
Formula If

But, said at least one compound may also be the compound of the following formula Ig:



Formula Ig.

Furthermore, said at least one compound may also be the compound of the following formula Ih:



Formula Ih.

The salts, hydrates and stereoisomers of the compounds of formula Ia to Ih may also be used as the at least one compound.

The invention will be better understood and further features and advantages thereof will become apparent when reading the description which follows, which is made in a reference to examples which are only illustrative and which do not limit the scope of the invention and in reference to the figures in which:

- Figure 1 shows the results of the silver staining assay carried out with 500 µM or 100 µM, respectively, of (*R*)-Roscovitine, or of the compound of Formula Ic, or of the compound of Formula Id, for determining the interaction of the compounds of the invention and Roscovitine with pyridoxal kinase,

- Figure 2 shows an immunoblot corresponding to Figure 1 for showing the effect of (*R*)- Roscovitine, of the compound of Formula Ic, and of the compound of Formula Id, at a concentration of 500 µM and 100 µM, on kinase PDXK and CDK5,

- Figure 3 shows the effects of (*R*)-Roscovitine, of the compound of Formula Ia, and of the compound of Formula Ib, at different concentrations, on the cell viability of SH-SY5Y neuroblatoma cells,

- Figure 4 shows the effects of (*R*)-Roscovitine, of the compound of Formula Ia, and the of compound of Formula Ib, at different concentrations, on caspases activity (DEVDase) measured in arbitrary fluorescent units (a.f.u.) of SH-SY5Y neuroblastome cells,

- Figure 5 shows the effects of different concentrations of (*R*)-Roscovitine, of the compound of Formula Ia, and of the compound of Formula Ic, on the MTS reduction of SH-SY5Y neuroblastoma cells,

- Figure 6 shows the effects of different concentrations of (*R*)-Roscovitine, of the compound of Formula Ia, and of the compound of Formula Ic, on capases activity (DEVDase activity) expressed in arbitrary fluorescent units (a.f.u), of SH-SY5Y neuroblastoma cells,

- Figure 7 shows the effects of (*R*)-Roscovitine, of the compound of Formula Ia, of the compound of Formula Ib, and of the compound of Formula Ic, at different concentrations, on retinoblastoma protein phosphorylation of SH-SY5Y neuroblastoma cells. In this Figure, the upper scale applies to (*R*)-Roscovitine, the compounds of Formula Ia and of Formula Ib, and the lower scale applies to the compound of Formula Ic,

- Figure 8 shows the effects of (*R*)-Roscovitine, of the compound of Formula Ia, of the compound of Formula Ib, and of the compound of Formula Ic, at different concentrations, on retinoblastoma total protein of SH-SY5Y neuroblastoma cells. In this Figure, the upper scale applies to (*R*)-Roscovitine, the compounds of Formula Ia and of Formula Ib, and the lower scale applies to the compound of Formula Ic,

- Figure 9 shows the effects of (*R*)-Roscovitine, of the compound of Formula Ia, of the compound of Formula Ib, and of the compound of Formula Ic, at different concentrations, on RNA polymerase II Ser2 phosphorylation of SH-SY5Y neuroblastoma cells. In this Figure, the upper scale applies to (*R*)-Roscovitine, the

compounds of Formula Ia and of Formula Ib, and the lower scale applies to the compound of Formula Ic,

- Figure 10 shows the effects of (*R*)-Roscovitine, of the compound of Formula Ia, of the compound of Formula Ib, and of the compound of Formula Ic, at different concentrations, on RNA polymerase II total protein of SH-SY5Y neuroblastoma cells. In this Figure, the upper scale applies to (*R*)-Roscovitine, the compounds of Formula Ia and of Formula Ib, and the lower scale applies to the compound of Formula Ic,

- Figure 11 shows the effects of (*R*)-Roscovitine, of the compound of Formula Ia, of the compound of Formula Ib, and of the compound of Formula Ic, at different concentrations, on protein phosphatase1-alpha phosphorylation on Thr320 of SH-SY5Y neuroblastoma cells. In this Figure, the upper scale applies to (*R*)-Roscovitine, the compounds of Formula Ia and of Formula Ib, and the lower scale applies to the compound of Formula Ic,

- Figure 12 shows the effects of (*R*)-Roscovitine, of the compound of Formula Ia, of the compound of Formula Ib, and of the compound of Formula Ic, at different concentrations, on Mcl-1 survival factor of SH-SY5Y neuroblastoma cells. In this Figure, the upper scale applies to (*R*)-Roscovitine, the compounds of Formula Ia and of Formula Ib, and the lower scale applies to the compound of Formula Ic,

- Figure 13 shows the effects of (*R*)-Roscovitine, of the compound of Formula Ia, of the compound of Formula Ib, and of the compound of Formula Ic, at different concentrations, on p53 total protein levels of SH-SY5Y neuroblastoma cells. In this Figure, the upper scale applies to (*R*)-Roscovitine, the compounds of Formula Ia and of Formula Ib, and the lower scale applies to the compound of Formula Ic,

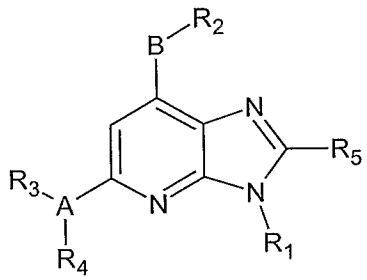
- Figure 14 shows the effects of (*R*)-Roscovitine, of the compound of Formula Ia, of the compound of Formula Ib, and of the compound of Formula Ic, at different concentrations, on p27 total protein levels of SH-SY5Y neuroblastoma cells. In this Figure, the upper scale applies to (*R*)-Roscovitine, the compounds of Formula Ia and of Formula Ib, and the lower scale applies to the compound of Formula Ic,

- Figure 15 shows the effects of (*R*)-Roscovitine, of the compound of Formula Ia, of the compound of Formula Ib, and of the compound of Formula Ic, at different concentrations, on PARP cleavage SH-SY5Y neuroblastoma cells. In this Figure, the upper scale applies to (*R*)-Roscovitine, the compounds of Formula Ia and of Formula Ib, and the lower scale applies to the compound of Formula Ic, and

- Figure 16 shows the effects of (*R*)-Roscovitine, of the compound of Formula Ia, of the compound of Formula Ib, and of the compound of Formula Ic, at different concentrations, on actin total protein of SH-SY5Y neuroblastoma cells, as loading control for Figures 5 to 14. In this Figure 16, the upper scale applies to (*R*)-Roscovitine, the compounds of Formula Ia and of Formula Ib, and the lower scale applies to the compound of Formula Ic.

The compounds of the invention have a structure which is close to the structure of Roscovitine but they are deazapurines.

More precisely, the compounds of the invention have the following formula I:



Formula I

wherein:

A is CH or N or O,

R_3 is:

- H, or
- a C_1-C_5 alkyl group, or
- =O, or
- a (C_1-C_3) alkyl-C=O group in which the alkyl is optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or amino groups, and/or alkyloxy groups, and/or ketone groups,

R_4 is:

- H, or
- a C_1-C_6 alkyl group optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or amino groups, and/or alkyloxy groups, and/or ketone groups,

- a C_3-C_6 cycloalkyl group optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or amino groups, and/or alkyloxy groups, and/or ketone groups, or
- a (C_1-C_5)alkyl(C_3-C_6)cycloalkyl group optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or amino groups, and/or alkyloxy groups, and/or ketone groups, or
- =O, or
- O=CCF_3, or
- a C_1-C_6 alkyl group substituted by an ester group such as a O-acyl group, or an amino acyl group derived from natural, or non natural amino acids, or an acetyl group or a nicotynyl group,

or A, R_3 and R_4 together form a C_5-C_7 cycloalkyl group, optionally containing one or more heteroatoms, preferably a piperazine group,

B is O or S or NH or a halogen atom,

R_1 is:

- a C_1-C_6 alkyl group optionally substituted by one or more hydroxy groups, or
- a C_3-C_6 cycloalkyl group optionally substituted by one or more hydroxy groups, or
- an aryl group optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyloxy groups, and/or optionally containing one or more heteroatoms, or
- a C_1-C_5 alkylaryl group, the aryl group being optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyl groups, and/or C_1-C_3 alkyloxy groups, and/or optionally containing one or more heteroatoms,

R_2 is:

- an aryl group optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyloxy groups, and/or carboxylic acid groups, and/or carboxylic ester groups, and/or amine groups, and/or CF_3 groups, and/or optionally containing one or more heteroatoms, thus creating a 2-pyridyl group,

or a 3-pyridyl group, or a 4-pyridyl group, or a 2-thienyl or a 3-thienyl group, or

- a methylbiaryl group, wherein each aryl cycle is optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyloxy groups, and/or CF_3 groups, and/or carboxylic acid groups, and/or carboxylic ester groups, and/or amine groups, and/or optionally containing one or more heteroatoms, or
- a methylaryl group, the aryl cycle being optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyloxy groups, and/or CF_3 groups, and/or optionally containing one or more heteroatoms, thus creating a 2-pyridyl group, or a 3-pyridyl group, or a 4-pyridyl group, or a 2-thienyl group or a 3-thienyl group,
- a biaryl group, each aryl cycle optionally containing one or more heteroatoms thus creating a 2-pyridyl group, or a 3-pyridyl group, or a 4-pyridyl group, or a 2-thienyl group or a 3-thienyl group, or each aryl cycle is optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyloxy groups, and/or CF_3 groups, and/or carboxylic acid groups, and/or carboxylic ester groups, and/or amine groups,

or B and R_2 together form a non aromatic cycle,

R_5 is:

- a halogen atom, or
- a hydrogen atom, or
- a C_1-C_5 alkyl group optionally substituted by one or more hydroxy groups and/or amine groups and/or halogen atoms and/or carboxylic acid groups, or
- a (C_1-C_4)alkyl(C_3-C_6)cycloalkyl group in which the cycloalkyl group is optionally substituted by one or more hydroxy groups and/or amine groups and/or halogen atoms and/or carboxylic acid groups,

and the salts, hydrates, and stereoisomers thereof.

Preferred substituents A, B, and R_1 to R_6 in formula I as well as preferred compounds of that formula I have been previously defined.

The essential difference between Roscovitine and the compounds of formula I is the fact that the nitrogen in position 7 in the core of Roscovitine is replaced by a carbon in the compounds of formula I.

Otherwise stated, the pyrimidine cycle in the core of Roscovitine is replaced by a pydirine cycle in the compounds of the invention.

This difference is the key feature of the compounds of the invention which gives to the compounds of the invention their unique properties: they have less interaction with pyridoxal kinase than the purine type compounds of the prior art as shown in Figure 1.

Indeed, the interaction of the compounds of the invention with pyridoxal kinase has been determined by the following method: (silver staining assay)

1000 µg of porcine brain lysate (100 µl of lysate at 10 µg/µl)completed with 100 µM of Roscovitine, or 100 µM of the compound of formula Id, or 100 µM of the compound of formula Ie have been loaded on agarose beads and washed with the bead buffer (50 mM Tris pH 7.4, 5 mM NaF, 250 mM NaCl, 5 mM EDTA, 5 mM EGTA, 0.1 % NP-40, 10 µg/ml of leupeptin, aprotinin and soybean trypsin inhibitor and 100 µM benzamidine)

The results of these tests are shown in Figure 1.

As can be seen in Figure 1, the compounds of the invention exhibit a competitor effect for CDK5, which demonstrates that they indeed have an interaction with that enzyme.

Roscovitine exhibited a competitor effect for secondary targets Erk2 and PDXK. In contrast, the compounds of the invention exhibited no or little competitor effect for pyridoxal kinase and Erk2, which demonstrates that these proteins are not or very weak targets for the compounds of the invention.

Otherwise stated, the compounds of the invention exhibit an increased specificity for CDKs as compared to Roscovitine.

In addition, compared to the purine derivatives, it was noticed that they were somewhat less inhibitory towards CDK9, a kinase that should not be inhibited due to its key role in the transcription.

Furthermore, the inventors have discovered that when, in formula I, B-R_2 is different from NH_2, or has a short length of chain, and preferably contains at least one aryl group, the effects of the compounds of formula I on cell survival are enhanced despite modest difference in their effects on CDKs. Furthermore subtle differences in their selectivity (reduced effect on CDK9) suggest that less non-specific effects can be expected from these molecules compared to their purine counterparts.

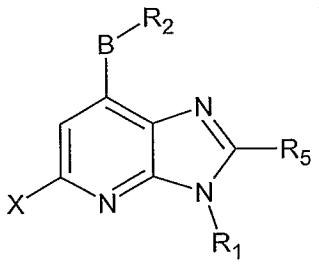
Thus, the compounds of the present invention are trisubstituted or tetrasubstituted imidazo[4,5-b] pyridines, i.e 1-deazapurines.

The compounds of the invention have been tested as to their effects on different CDKs and cell lines as compared to Roscovitine.

These tests and their results are reported hereinafter in the section entitled "Results".

Furthermore, for those compounds of the invention in which A is N, the inventors have discovered a particularly appropriate process for their manufacture.

This process is based on the use of an intermediate compound which has the following formula II:



Formula II

wherein:

B is O or S or NH

R_1 is:

- a C_1-C_6 alkyl group optionally substituted by one or more hydroxy groups, or
- a C_3-C_6 cycloalkyl group optionally substituted by one or more hydroxy groups, or
- an aryl group optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyloxy groups, and/or optionally containing one or more heteroatoms, or

- a C_1-C_5 alkylaryl group, the aryl group being optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyl groups, and/or C_1-C_3 alkyloxy groups, and/or optionally containing one or more heteroatoms,

R_2 is:

- an aryl group optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyloxy groups, and/or carboxylic acid groups, and/or carboxylic ester groups, and/or amine groups, and/or CF_3 groups, and/or optionally containing one or more heteroatoms, thus creating a 2-pyridyl group, or a 3-pyridyl group, or a 4-pyridyl group, or a 2-thienyl or a 3-thienyl group, or
- a methylbiaryl group, wherein each aryl cycle is optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyloxy groups, and/or CF_3 groups, and/or carboxylic acid groups, and/or carboxylic ester groups, and/or amine groups, and/or optionally containing one or more heteroatoms, or
- a methylaryl group, the aryl cycle being optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyloxy groups, and/or CF_3 groups, and/or optionally containing one or more heteroatoms, thus creating a 2-pyridyl group, or a 3-pyridyl group, or a 4-pyridyl group, or a 2-thienyl group or a 3-thienyl group,
- a biaryl group, each aryl cycle optionally containing one or more heteroatoms thus creating a 2-pyridyl group, or a 3-pyridyl group, or a 4-pyridyl group, or a 2-thienyl group or a 3-thienyl group, or each aryl cycle is optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyloxy groups, and/or CF_3 groups, and/or carboxylic acid groups, and/or carboxylic ester groups, and/or amine groups,

or B and R_2 together form a non aromatic cycle,

R_5 is:

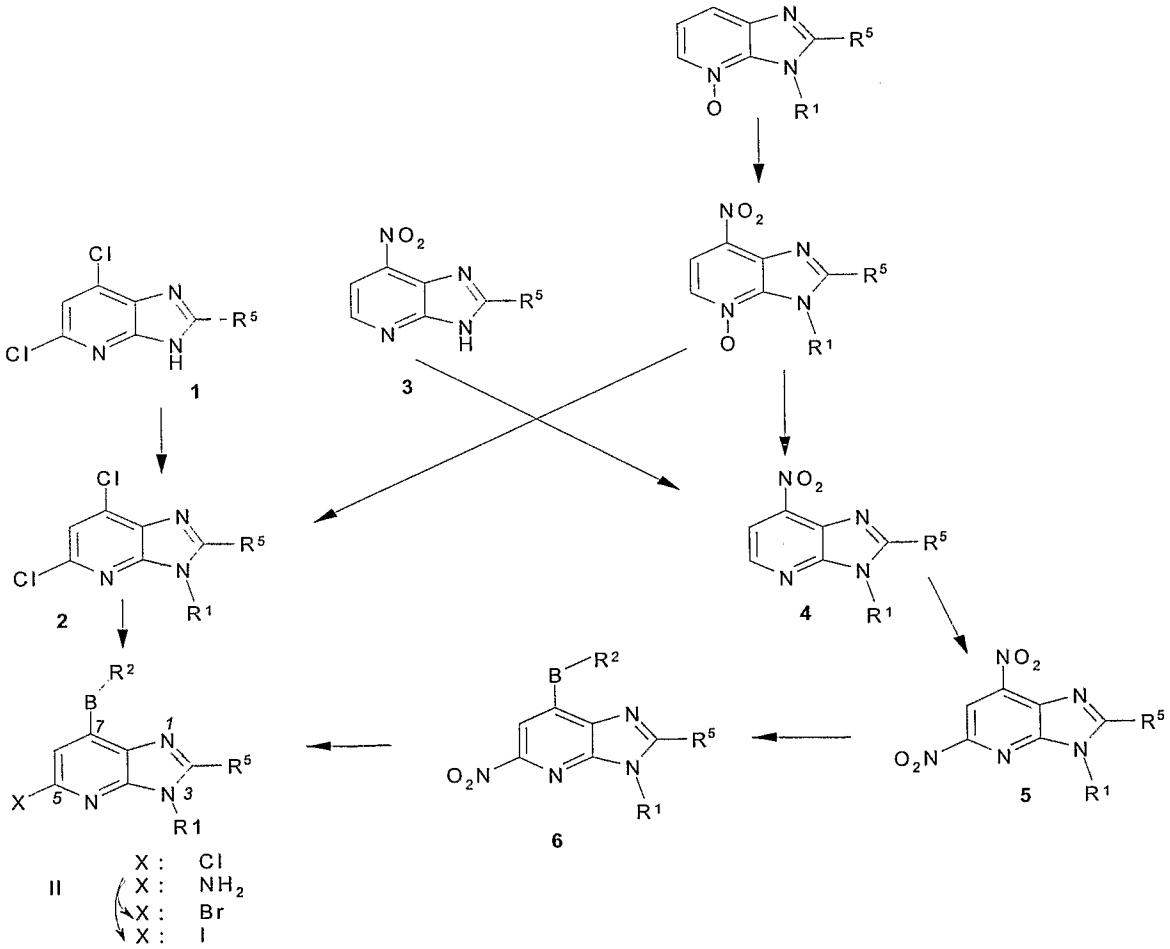
- a halogen atom, or
- a hydrogen atom, or

- a C_1-C_5 alkyl group optionally substituted by one or more hydroxy groups and/or amine groups and/or halogen atoms and/or carboxylic acid groups, or
- a (C_1-C_4)alkyl(C_3-C_6)cycloalkyl group in which the cycloalkyl group is optionally substituted by one or more hydroxy groups and/or amine groups and/or halogen atoms and/or carboxylic acid groups,

X is Cl or Br or I or NH_2,

These intermediate compounds are also in the scope of the invention.

Access to these compounds of Formula II is depicted in the following scheme 1.



Scheme1

Three routes were used to prepare precursors of formula II:

Route a = 5,7- dichloroimidazopyridine **1** obtained as described in G. Cristalli and al, "Nucleosides and nucleotides", 1985, 4, 625-639, was reacted with R_1X

(X= Br or I) in basic conditions to afford **2** which was further reacted with R_2BH in butanol, using a tertiaryalkylamine (e.g NEt_3 or NBu_3) as base, at 90-100 °C to give IIa X= Cl.

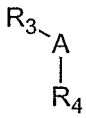
Route b= Alkylation of **3** prepared according to known procedure in similar condition as for **1** led to **4** which is reacted with terabutylammonium nitrate to afford the dinitro compound **5**. Reaction of **5** with R_2BH in hot butanol or in DMF at 20-30 °C gave **6** which was reduced into IIb X = NH_2 using Fe, HCl; IIb X = NH_2. IIb could be converted into either IIc X= Br or into IId when X = I. The conversion of IIb into IId was achieved upon heating in CH_2I_2 and an organic nitrite such as *tert*-butylnitrite or isopentylnitrite.

Route c= The third route is closely related to the second route. The alkylation step, that is to say the introduction of group R1 is performed earlier.

The process of manufacture of the compounds of Formula I makes use of the compounds of Formula II.

In a first embodiment, the process makes use of the compounds of Formula II in which X is Cl, Br or I, preferably I.

This process involves a step of coupling a compound of formula II with a nucleophile of the following formula III:



to afford a compound of formula I.

The coupling procedure uses a metal catalyst such as $Pd(OAc)_2$, Pd_2dba_3 or CuI in basic conditions.

The base can be a carbonate such as Cs_2CO_3, a metal alcoholate such as *tert*-butylOK or *tert*-butylONa.

The metal catalysts are in most cases used with added ligands such as (±)Binap, Xantphos, or ethylene glycol or diketones. Examples of diketones ligands are described by Shafir et al in J. Amer. Chem. Soc. 2006, 126, 8742-8743 and Shafir, J. Amer. Chem. Soc 2007, 129, 3490-3491.

But, in a second embodiment, the process of the invention makes use of of formula I in which X is NH_2.

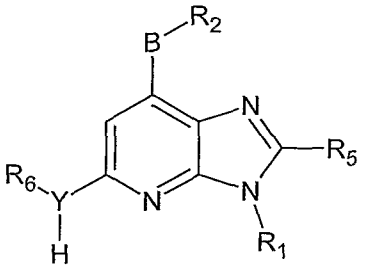
In this second embodiment, one or two coupling steps are to be performed depending on the nature of the wanted substituent R_3 and R_4.

Thus, the nucleophile compound of formula II in which X is NH_2 is coupled with an electrophile having the following formula IV:

$Y\text{-}R_6$,

Formula IV

in which Y is I, Br or Cl and R_6 is R_3 or R_4 for obtaining a compound of the following formula V:



Formula V

The most preferably, Y is I.

Then, when R_3 and R_4 are different from H, the compound of formula V is coupled with a compound of the following formula VI:

$Y\text{-}R_7$

Formula VI

in which Y is Br or Cl or I, the most preferably I, and R_7 is R_3 if in formula V R_6 is R_4, or R_7 is R_4 if the compound of formula V R_6 is R_3.

These coupling steps are carried out, as for the first embodiment of the process of the invention, in basic conditions.

The more preferably, X and Y are I or Br, and the most preferably I, in each occurrence.

The invention will be now described by means of preferred embodiments.

Example 1: Preparation of Perharidine B (compound of formula Ib).

5,7-Dichloro-3-*iso*-propylimidazo[4,5-b]pyridine 2.

A stirred solution of 5,7-Dichloroimidazo[4,5-b]pyridine (5 g, 26.5 mmol.) in DMSO (50 mL) was cooled in an ice bath, and treated with K_2CO_3 (14.6 g, 106.2 mmol.) and 2-bromopropane (12.47 mL, 132.8mmol.). The mixture was allowed to warm to 18 °C and stirred overnight. The DMSO was removed in *vacuo*. A mixture of the residue and water (100 mL) was extracted with AcOEt (3x300 mL). The extractions were combined, washed with brine (300 mL), dried over (Na_2SO_4) and concentrated. Chromatography of the residue on silica gel with toluene-AcOEt-CH_2Cl_2 3:1:1 gave 5,7-Dichloro-3-*iso*-propylimidazo[4,5-b]pyridine. (Yield: 57%).

^{1}H NMR (400 MHz, $CDCl_3$): d 1.67 (d, 6H) ; 5.01 (m, 1H,) ; 7.95 (s, 1H) ; 8.39 (s, 1H)

7-Benzylamino-5-chloro-3-*iso*-propylimidazo [4,5-b]pyridine IIa.

A mixture of **2** (1.87g, 8.1 mmol.), benzylamine (1.4 mL, 13 mmol.) and 1.5 mL of Et_3N in 10 mL of DMF was stirred at room temperature overnight under N_2 atmosphere. The DMF was removed in *vacuo*. Water (150 mL) was added and extracted with CH_2Cl_2 (3 x 100 mL). The organic phases were dried (Na_2SO_4) and concentrated. Chromatography of the residue on silica gel with toluene-AcOEt- 3:2 gave **3** (82%). **3a** could also be prepared upon heating for 1 hour, a mixture of **2**, benzylamine and triethylamine in n-butanol at 90°C. After concentration in vacuo, **3a** was isolated by column chromatography in 75 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): d 1.5 (d, 6H) ; 4.49 (d, 2H,) ; 4.88 (m, 1H) ; 5.75 (t, 1H) ; 6.31 (s, 1H) ; 7.3-7.25 (m, 5H) ; 7.7 (s, 1H).

Perharidine B: (S)-7-Benzylamino-5-[(2-butyl-1ol)amino]-3-*iso*-propylimidazo[4,5-b]pyridine Ib.

To a suspension of (540 mg, 1.8 mmol) of 7-Benzylamino-5-chloro-3-*iso*-propylimidazo[4,5-b]pyridine, **3a**, in toluene (20 mL) with (S)-(+)-2-Amino-1-butanol, in the presence of palladium acetate (4 mol %), and BINAP (4 mol %) in refluxing toluene (20 mL) using potassium *tert*-butoxide (282 mg, 2.5mmol). The reaction mixture was heated under N_2 for 5 hours. After cooling water (10 mL) was added and extracted with CH_2Cl_2 (3 x 10 mL). The organic layer were dried (Na_2SO_4) and concentrated. Chromatography of the residue on silica gel with AcOEt-1% MeOH afforded **Ib** (42%).

^{1}H NMR (400 MHz, $CDCl_3$): d 0.95 (t, 3H) ; 1.49(m, 8H) ; 3.55(m, 1H) ; 3.77(m, 2H) ; 4.48(d, 2H) ; 4.62(hept, 1H) ; 4.85(brt, 1H) ; 5.35(s, 1H) ; 6.10(brs, 1H) ; 7.30(m, 5H) ; 7.65 (s, 1H).

Example 2: Preparation of Perharidine A (compound of formula Ia).

By the first embodiment of the process of the invention, the synthesis of Perharidine A was performed from 3a as described for Perharidine B except that (R)-(-)-2-Amino-1-butanol was used in the last step. Yield: 38 %.

Example 3: Preparation of Perharidine D (compound of formula Id).

The same procedure detailed in example 1 was followed.

This product was prepared as described for **3a** upon heating in 50 mL n-butanol a mixture of 4-(2-pyridyl)-benzylamine trifluoroacetate (0.15 mol), triethylamine 5 mL and 5,7-Dichloro-3-*iso*-propylimidazo[4,5-b]pyridine **2** (0.1 mol).

5-Chloro-3-*Iso*-Propyl-7-[4-(2-pyridyl)-benzylamino]-imidazo[4,5-b]pyridine IIb.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52(d, 6H, 2 CH_3); 4.56(d, 2H, CH_2); 4.94(hept, 1H, CH, iPr); 5.89(t, 1H, NH); 6.35(s, 1H, 6-H) ; 7.35 m , 1H, pyridyl); 7.45(d, 2H, phenyl) ; 7.75(m, 2H, pyridyl) ; 7.83(s, 1H, H-2); 7.95(d, 2H, phenyl) ; 8.70(d, 1H, pyridyl).

Perharidine D: (S)-7-[4-(2-Pyridyl)-benzylamino]-5-[(2-butyl-1ol)amino]-3-*iso*-propylimidazo[4,5-b]pyridine Id.

Yield: 35 %.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03(t, 3H, CH_3); 1.50(d, 6H, 2 CH_3); 3.51(m, 1H, C<u>H</u>-OH); 3.75(m, 2H, C<u>H</u>-OH + C<u>H</u>-NH); 4.20(br s, 1H, OH); 4.50(d, 2H, CH_2-Ar); 5.44(s, 1H, H-6) 5.85(t, 1H, NH); 7;25(m, 1H, pyridyl); 7.45(d, 2H, phenyl); 7.65(s, 1H, H-2); 7.75(m, 2H, pyridyl); 7.98(d, 2H, phenyl); 8.70,(d, 1H, pyridyl).

Example 4: Preparation of Perharidine C (compound of formula Ic).

The synthesis of **Perharidine C** was performed from **IIb** as described for **Perharidine D** except that (R)-(-)-2-Amino-1-butanol was used in the last step. Yield: 47 %.

Example 5: Preparation of Perharidines from 7-nitroimidazo[4,5-b]pyridine.

3-*Iso*-propyl-7-nitroimidazo[4,5-b]pyridine 4.

The alkylation of 7-nitro-imidazo[4,5-b]pyridine **3** was performed in the same conditions than for the synthesis of 2. Yield: 76 %.

^{1}H-NMR (400 MHz, $CDCl_3$): d 1.61 (d, 6H, 2 CH_3); 4.99(hept, 1H, CH, iPr); 7.90(d, 1H, H-6); 8.36(s, 1H, H-2); 8.52(d, 1H, H-5).

3-*Iso*-Propyl-5,7-dinitro-imidazo [4,5-b]pyridine 5.

To a solution of 22.63 g of tetrabutylammonium nitrate in 100 mL CH_2Cl_2 at 0°C, was added 10.33 mL of trifluoroacetic anhydride. After stirring 20 min at 0°C, this solution was added to 3-Isopropyl-7-nitroimidazo[4,5-b]pyridine **3** (10.21, 0.049 mol) in 130 mL CH_2Cl_2 kept at 0°C after stirring 2 hours at 0 °C, the solution is poured into a cold (5 °C) saturated solution of $NaHCO_3$. The organic layer was washed once with H_2O, dried and concentrated in vacuo. Yield 97%.

^{1}H NMR (400 MHz, $CDCl_3$): d 1.76(d, 6H, $2CH_3$); 5.10(hept, 1H, CH, iPr); 8.63(s, 1H, H-2); 8.96(s, 1H, H-6).

7-Benzylamino-3-*Iso*-Propyl-5-nitroimidazo[4,5-b]pyridine 6a

To a solution of 5,7-dinitro-3-*iso*-propylimidazo[4,5-b]pyridine, **5**, in DMF was added NEt_3 and benzylamine. After 6 h stirring at 20 °C, 15 mL Et_2O was added and the solid which precipited was filtered and washed with Et_2O.

^{1}H NMR (400 MHz, $CDCl_3$): d 1.65(d, 6H, $2CH_3$); 4.65(d, 2H, CH_2); 4.92(hept, 1H, CH, iPr); 6.95(t, 1H, NH); 7.24(s, 1H, H-6); 7.42(m, 5H, phenyl); 7.98(s, 1H, H-2).

The biarylderivative was prepared by the same process.

3-*Iso*-Propyl-5-nitro-7-[4-(2-pyridyl)-benzylamino]-imidazo[4,5-b]pyridine 6b

^{1}H NMR (400 MHz, $CDCl_3$): d 1.55(d, 6H, 2 CH_3); 4.63(d, 2H, CH_2); 5.01(hept, 1H, CH, iPr); 6.88(br s, 1H, NH); 7.22(m, 1H, pyridyl); 7.49(d, 2H, phenyl); 7.68(dd, 1H, pyridyl); 8.01(d, 2H, phenyl); 8.04(s, 1H, H-2); 8.66(d, 1H, pyridyl).

5-Amino-3-*Iso*-Propyl-7 -benzylamino-imidazo[4,5-b]pyridine IIb

To a suspension of 5.5 g of Fe in 30 mL EtOH was added slowly 2 mL 12 N HCl. The mixture was stirred at 75 °C for 1 hour. After cooling at 65 °C, 12 mL 25 % NH_4Cl solution was added. The mixture was stirred 5 min and **6a** (0.02 mol, in 5 mL EtOH) was added. The mixture is heated at 75 °C for 2 hour. After cooling to rt, 5 g celite was added the mixture was filtrated on celite and the remaining solids were washed several times with ethanol. The combined filtrates were concentrated and extracted with a CH_2Cl_2 and 10 % Na_2CO_3. Concentration of the organic layer led to crystallisation of the amine **IIb.**Yield: 98 %.

^{1}H NMR (400 MHz, $CDCl_3$): d 1.45(d, 6H, $2CH_3$); 4.12(brs, 2H, NH_2); 4.68(hept, 1H, CH, iPr); 5.48(s, 1H, H-6); 5.53(t, 1H, H-2); 7.15-7.35(m, 5H, phenyl); 7.55(s, 1H, H-6).

The biaryl derivative **IIc** was prepared by the same process.

5-Amino-3-*Iso*-Propyl-7-[4-(2-pyridyl)-benzylamino]-imidazo[4,5-b]pyridine IIc

Yield: 95 %.

^{1}H NMR (400 MHz, $CDCl_3$): d 1.55 (d, 6H, 2 CH_3); 4.55(d, 2H, CH_2); 4.92(hept, 1H, CH, iPr); 5.80(t, 1H, NH); 6.74(s, 1H, H-6); 7.22(m, 1H, pyridyl); 7.47(d, 2H, phenyl); 7.62(m, 2H, pyridyl); 7.98(d, 2H, phenyl); 8.70(m, 1H, pyridyl).

5-Benzylamino-3-*Iso*-Propyl-7-iodo-imidazo[4,5-b]pyridine IId

To a stirred suspension of 0.1 mol of 5-Amino-3-*Iso*-Propyl-7-benzylamino-imidazo[4,5-b]pyridine **IIb** in 100 mL CH_2I_2 at 60 °C was added slowly 0.2 mol isopentylnitrite. After 1 hour stirring at 60 °C, diiodomethane was distilled in vacuo (0.1 mm). The residue was taken up with a mixture of CH_2Cl_2 and saturated $NaHCO_3$. The organic layer was separated and washed with H_2O, dried and concentrated to afford **IId.**

Yield: 95 %.

^{1}H NMR (400 MHz, $CDCl_3$): d 1.51(d, 6H, 2 CH_3); 4.40(d, 2H, CH_2); 4.82(hept, 1H, CH, iPr); 5.56 (t, 1H, NH); 6.64 (s, 1H, H-6); 7.28(m, 5H, phenyl); 7.75(s, 1H, H-2).

The biaryl derivative **IIe** was prepared by the same process.

3-*Iso*-Propyl-7-iodo-5-[4-(2-pyridyl)-benzylamino]-imidazo[4,5-b]pyridine IIe

Yield: 95 %.

^{1}H NMR (400 MHz, $CDCl_3$): d 1.55(d, 6H, 2 CH_3); 4.55(d, 2H, CH_2); 4.92(hept, 1H, CH, iPr); 5.80(t, 1H, NH); 6.74(s, 1H, H-6); 7.22(m, 1H, pyridyl); 7.47(d, 2H, phenyl); 7.62(m, 2H, pyridyl); 7.98(d, 2H, phenyl); 8.70(m, 1H, pyridyl).

3-*Iso*-Propyl-5-(4-N-acetylcyclohexylamino)-7-[4-(2-pyridyl)-benzylamino]-imidazo[4,5-b]pyridine Ih

To a mixture of K_3PO_4 (900 mg, 0.022 mol), CuI (50 mg, 0.25 mmol), was added 4 mL 1-butanol, 0.5 mL ethyleneglycol, (0.010 mol) 5-Benzylamino-3-*Iso*-Propyl-7-iodo-imidazo[4,5-b]pyridine **IId** and trans-4-N-acetylaminocyclohexylamine (0.010 mol). The flask was flushed with nitrogen, closed and heated for 18 h at 90 °C. After cooling to rt, The residue was taken up with a mixture of CH_2Cl_2 and H_2O. The organic layer was dried and concentrated. Column chromatography gave 3-*Iso*-Propyl-5-N-acetylcyclohexylamino-7-[4-(2-pyridyl)-benzylamino]-imidazo[4,5-b]pyridine.

Yield 94%.

^{1}H NMR (400 MHz, $CDCl_3$): d 1.35(m, 4H, cyclohexyl); 1.56(d, 6H, $2CH_3$); 1.98(s, 3H, CH_3CO); 2.20(m, 4H,cyclohexyl); 3.45(m,1H, cyclohexyl); 3.75(m,1H, cyclohexyl); 4.5(d, 2H, CH_2); 4.69(hept,1H, iPr); 5.32(d, 1H, NH); 5.35(s, 1H, H-6); 5.65(br s, NH); 7.35(m, 5H, phenyl); 7.58(s, 1H, H-2).

Similarly, **perharidines A, B, C** and **D** were obtained from the iododerivatives **IId** or **IIe** in 79 to 95 % yield.

The compounds obtained in examples 1-5 have been tested to determine their effects on different kinases and cell lines.

The following materials and methods have been used.

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 ß-glycerophosphate, 15 mM p-nitrophenylphosphate, 25 mM MOPS (pH 7.2), 5 mM EGTA, 15 mM $MgCl_2$, 1 mM DTT, 1 mM sodium vanadate, 1 mM phenylphosphate.

Kinase preparations and assays

Kinase activities were assayed in Buffer A or C, at 30 °C, at a final ATP concentration of 15 μM. Blank values were subtracted and activities expressed in % of the maximal activity, i.e. in the absence of inhibitors. Controls were performed with appropriate dilutions of dimethylsulfoxide.

CDK1/cyclin B (M phase starfish oocytes, native) and *CDK5/p25* (human, recombinant) were prepared as previously described (Leclerc S. et al., J Biol Chem 2001;276:251-60.). Kinase activity was assayed in buffer C, with 1 mg histone H1/ml, in the presence of 15 μM [γ-^{33}P] ATP (3,000 Ci/mmol; 10 mCi/ml) in a final volume of 30 μl. After 30 min. incubation at 30°C, 25 μl aliquots of supernatant were spotted onto 2.5 x 3 cm pieces of Whatman P81 phosphocellulose paper, and, 20 sec. later, the filters were washed five times (for at least 5 min. each time) in a solution of 10 ml phosphoric acid/liter of water. The wet filters were counted in the presence of 1 ml ACS (Amersham) scintillation fluid.

CDK2/cyclin A (human, recombinant, expressed in insect cells) was assayed as described for CDK1/cyclin B.

CDK9/cyclin T (human, recombinant, expressed in insect cells) was assayed as described for CDK1/cyclin B, but using a pRB fragment (amino acids.773-928) (3.5 μg/assay) as a substrate.

GSK-3α/β (porcine brain, native, affinity purified) was assayed, as described for CDK1 but in Buffer A and using a GSK-3 specific substrate (GS-1: YRRAAVPPSPSLSRHSSPHQSpEDEEE) (Sp stands for phosphorylated serine) (Bach S. et al. J Biol Chem 2005;280:31208-19).

CK1d/e (porcine brain, native, affinity purified) was assayed as described for CDK1 but using the CK1-specific peptide substrate RRKHAAIGSpAYSITA (Reinhardt J. et al. Protein Expr & Purif 2007;54:101-9).

Cell biology

Antibodies & Chemicals

AcDEVDafc and Q-VD-OPh were purchased from MPbiomedicals (Vannes, France). Cell Titer 96® containing the MTS reagent and CytoTox 96® kits were purchased from Promega (Madison, WI, USA). The protease inhibitor cocktail was from Roche (Penzberg, Germany). Unless otherwise stated, the non-listed reagents were from Sigma.

Monoclonal antibody against actin was obtained from Calbiochem (Madison, WI, USA). Monoclonal antibodies against retinoblastoma protein (Rb) were purchased from BD Biosciences (San Diego, CA, USA). Polyclonal antibody against phospho- Ser249/Thr252 -Rb was provided by Biosource (Camarillo, CA, USA). Polyclonal antibody against phospho-Thr320-protein phosphatase 1a (PP1a) and monoclonal antibody against caspase-9 were from Cell Signalling (Danvers, MA, USA). Polyclonal antibodies against RNA polymerase II and phospho-Ser2-RNA polymerase II were supplied by Covance Research Products (Berkeley, CA, USA). Polyclonal antibody against Mcl-1 was obtained from Santa Cruz Biotechnology (Santa Cruz, CA, USA).

Cell lines and culture conditions

SH-SY5Y human neuroblastoma cells were grown in DMEM medium (Invitrogen, Cergy Pontoise, France). The HEK 293 human embryonic kidney cell line was grown in MEM medium from Invitrogen. Human foreskin primary fibroblasts (kindly provided by Dr. Gilles Ponzio) were grown in DMEM supplemented with 2 mM L-glutamine and 20 mM HEPES. All the media were supplemented with antibiotics (penicillin-streptomycin) from Lonza and 10% volume of FCS from Invitrogen. Cells were cultured at 37°C with 5% CO_2. Drug treatments were performed on exponentially growing cultures at the indicated time and concentrations. Control experiments were carried out using appropriate dilutions of DMSO.

Cell death and cell viability assessments

Cell viability was determined by measuring the reduction of 3- (4,5-dimethylthiazol-2-yl)-5- (3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*–tetrazolium (MTS). Cell death was determined by measuring the level of lactate dehydrogenase activity (LDH) released upon cell lysis. Both procedures have been previously described in detail (Ribas J. et al. Oncogene 2006; 25:6304-18).

Caspase assay

Caspase activity was measured by determining the fluorescence released from the AcDEVDafc synthetic substrate after its direct addition to the culture medium, detergent lysis, and incubation at 37°. This method is devised for a 96 multiwell plate format. It allows kinetic determinations of caspase activation and the characterization of multiple drugs simultaneously (Ribas J. et al. Oncogene 2006, 25:6304-18).

Electrophoresis and Western blotting

Cells were resuspended and lysed for 30 minutes at 4°C in Homogenization Buffer [60 mM ß-glycerophosphate, 15 mM *p*-nitrophenyl phosphate, 25 mM MOPS (pH 7.2), 15 mM EGTA, 15 mM $MgCl_2$, 1 mM dithiothreitol, 1 mM sodium vanadate, 1 mM NaF, 1 mM phenylphosphate, 0.1 % Nonidet P-40 and protease inhibitor cocktail] and sonicated. After centrifugation (14000 rpm for 15 minutes at 4°C), the protein concentration was determined in the supernatants by the Bradford protein assay (Bio-Rad).

Whole cell extracts were prepared in buffer containing 100 mM Tris/HCl (pH. 6.8), 1 mM EDTA, 2 % SDS and protease inhibitor cocktail. Following heat denaturation for 5 minutes, proteins were separated on 10 % or 7 % NuPAGE pre-cast Bis-Tris or Tris-Acetate polyacrylamide mini gels (Invitrogen) with MOPS SDS (all but cytochrome C, RNA polymerase II and phospho-Ser2 - RNA polymerase II Western blots), MES SDS (cytochrome C), or Tris-Acetate SDS (RNA polymerase II and phospho-Ser2 - RNA polymerase II) running buffer depending on protein size. Proteins were transferred to 0.45 µm nitrocellulose filters (Schleicher and Schuell). These were blocked with 5 % low fat milk in Tris-Buffered Saline - Tween-20, incubated for 1 h with antibodies (anti-actin: 1:2000) or overnight at 4°C (cytochome C: 1:500), Rb (1:500), phospho-Rb (1:500), phospho-Thr320-PP1a (1:1000), RNA polymerase II (1:500), phosphor-Ser2-RNA polymerase II (1:500), Mcl-1 (1:500), caspase-9 (1:1000) and analyzed by Enhanced Chemiluminescence (ECL, Amersham).

Results of the biological tests.

Effects of the compounds of the invention

Effects on purified kinases

Perharidine A and B (*S* and *R* isomers) and their precursors were tested on various isolated, purified disease relevant protein kinases. (*R*)-Roscovitine was tested in parallel and used as a reference compound. Results are provided as IC50 values expressed in µM in the following Tables 4 and 5.

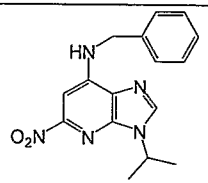
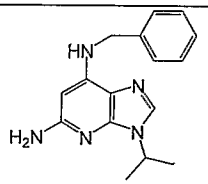
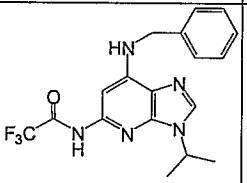
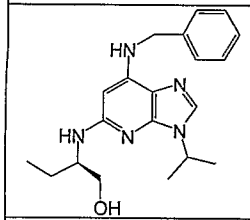
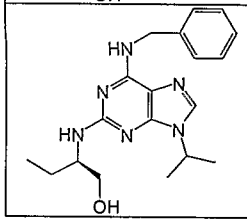
Tested compounds	Name	CDK1	CDK5	CDK7	GSK3	CK1	SH-SY5Y	HEK293
	Formula Ie	1.0	0.8	-	>10.0	1.0	74.0	46.0
	Formula If	4.0	3.8	-	>10.0	8.0	> 100.00	> 100.00
	Formula Ig	0.53	0.63	-	>10.0	3.0	> 100.00	> 100.00
	(*R*)-perharidine A Formula Ia	0.35	0.20	0.9	>30.0	4.0	16.2	35.6
	(*R*)-Roscovitine	0.35	0.20	0.8	>10.0	2.3	19.0 18.2	60.6 39.2

Table 4. Effects of perharidine and its precursors on kinases and cell survival in two cell lines.

The results presented in table 4 show the different intermediates that were synthesized to allow the synthesis of perharidines. Example Ib is the closest homolog to Roscovitine and their biological effects are compared. This shows that compound Ib displays very similar effects on isolated kinases as Roscovitine but improved efficacy on cell proliferation.

The compounds were tested at various concentrations in the kinase assays, as described in the Methods section. IC_{50} values were calculated from the dose-response curves shown and are reported in μM in the following table 5.

Kinase	(*R*)-roscovitine	(*R*)-perharidine A (compound Ia)	(*S*)-perharidine B (compound Ib)	(*R*) perharidine C (compound Ic)	(*S*) perharidine D (compound Id)
CDK1/cyclin B	0.33	0.43	0.73	0.46	0.27
CDK2/cyclin A	0.21	0.30	0.42	0.36	0.15
CDK2/cyclin E	0.17	0.18	0.31	0.25	0.10
CDK5/p25	0.28	0.40	0.50	0.60	0.20
CDK7/cyclin H	0.80	0.90	-	-	-
CDK9/cyclin T	0.23	0.48	1.30	0.53	0.12
CK1	4.00	11.0	4.80	1.10	1.90
DYRK1A	3.00	2.80	22.00	11.00	2.80
Erk2	11.00	7.00	9.00	22.00	9.00
GSK-3α/β	60.00	> 100.00	> 30.00	11.00	24.5

Table 5. Effects of Roscovitine and its perharidine analogs on the activity of 10 protein kinases targets.

Table 5 shows that, like (*R*)-perharidine (compound of formula Ia), its (*S*)-isomer (compound of formula Ib), as well as the compounds of formula Ic and Id show efficacies on CDKs which are similar to those of (*R*)-Roscovitine. However, CDK9 and DYRK1A appear to be somewhat less sensitive to these deazapurines than to (*R*)-Roscovitine.

Effects of perharidines on cell survival

Perharidine A and B (*R* and *S* isomers) and their precursors, as well as the compounds of formula Ic and Id, were tested on various cell lines (assay of survival

level with the MTS assay). (*R*)-Roscovitine was tested in parallel and used as a reference compound. Results are provided as IC_{50} values expressed in µM in Figures 3 and 5 and Tables 4 as well as in the following Table 6:

Cells	**(*R*)-Roscovitine**	**(*R*)-PerharidineA**	**(*S*)-Perharidine B**	**Compound of formula Ic**	**Compound of formula Id**
SH-SY5Y	17.0	14.3	28.0	1.46	0.66
HEK293	21.0	27.4	45.0	-	-
LS 174T	26.0	21.5	37.5	-	-
LS 174T (Oncodesign)	9.25	-	-	0.29	0.099
HCT116	20.8	-	-	-	-
HCT116 (Oncodesign)	6.97	-	-	0.60	0.30
HCT116 (Spheroids)	7 + 4	10 + 1.5	-	0.35 + 0.05	
Chronic Lymphocytic Leukemia	8.96	7.05	15.27	0.31	0.13

Table 6. Effects of Roscovitine and perharidine on cell survival in 5 cell lines.

The effects of these compounds were also evaluated on:

- cell survival. The results are shown in Figures 3 and 5,
- caspase activation. The results are shown in Figures 4 and 6,
- retinoblastoma protein phosphorylation on CDK2/CDK4 sites.

The results are shown in Figures 6 and 7.

It can be concluded from Figure 6 that compound Ic inhibits CDK2/4 in cells at lower concentrations than (*R*)-Roscovitine, while the compound of Formula Ia and the compound of Formula Ib have an effect similar to the one of (*R*)-Roscovitine and it can be concluded from Figure 8 that with (*R*)-Roscovitine and the compounds of Formula Ia, Ib and Ic, the total Rb is essentially constant.

- RNA polymerase II Ser2 phosphorylation), a CDK9/cyclin T phosphorylation site.

The results are shown in Figures 9 and 10.

It can be concluded from Figure 9 that the compound of compound Ic inhibits CDK9 in cells at lower concentration than (*R*)-Roscovitine, while the compounds of Formula Ia and the compound of Formula Ib have an efficiency similar to the one of (*R*)-Roscovitine and it can be concluded from Figure 10 that the total RNA pol II remains essentially constant as well with (*R*)-Roscovitine as with the compounds of Formula Ia, of Formula Ib, and of Formula Ic,

- protein phosphatases 1-a phosphorylation on Thr320, a CDK1/cyclin phosphorylation site.

The results are shown in Figure 11.

It can be concluded from Figure 11 that the compound of Formula Ic inhibits CDK1/cyclin B in cells at lower concentration than (*R*)-Roscovitine while the compounds of Formula Ia and of Formula Ib have an efficacy similar to the one of (*R*)-Roscovitine,

- down-regulation of survival factor Mcl-1.

The results are shown in Figure 12.

It can be concluded from Figure 12 that the compound of Formula Ic down-regulates the survival factor Mcl-1 in cells at lower concentration than (*R*)-Roscovitine, while compounds of Formula Ia and of Formula Ib have a potency similar to the one of (*R*)-Roscovitine,

- p53 total protein expression.

The results are shown in Figure 13.

It can be concluded from Figure 13 that compounds of Formula Ic triggers p53 total protein expression in cells at lower concentration than (*R*)-Roscovitine, while the compounds of Formula Ia and of Formula Ib have an efficacy similar to the one of (*R*)-Roscovitine ,

- p27 total protein down-regulation.

The results are shown in Figure 14.

It can be concluded from Figure 14 that the compounds of Formula Ic down-regulates p27 total protein in cells at lower concentration than (*R*)-Roscovitine, while the compounds of Formula Ia and of Formula Ib have an efficacy similar to the one of (*R*)-Roscovitine,

- PARP cleavage.

The results are shown in Figure 15.

It can be concluded from Figure 15 that the compounds of Formula Ic triggers PARP cleavage in cells at lower concentration than (*R*)-Roscovitine, while the compounds of Formula Ia and of Formula Ib have a potency similar to the one of (*R*)-Roscovitine.

- Actin total protein levels were used as a loading control with all compounds. The results are shown in Figure 16, demonstrating equal loading in the gels.

To summarize, these results show that:

[1] the compounds of Formula Ia and of Formula Ib exhibit anti-proliferative activities similar to those displayed by (*R*)-Roscovitine. The (*S*) isomer (compound of formula Ib) is somewhat less efficient, as reported for the (*S*)-isomer of Roscovitine.

[2] in contrast, and quite surprisingly, compound of formula Ic and Id display greatly enhanced anti-proliferative activities as compared to (*R*)-Roscovitine (20-100 fold), despite the fact that they have rather similar effects on kinases. Unexpectedly too, in contrast to (*R*)-Roscovitine, the (*S*) isomer is more active than the (*R*) isomer (Table 6).

[3] these effects and order of potency are confirmed when molecular actors involved in markers of CDK inhibition (CDK2/CDK4: retinoblastoma protein phosphorylation; CDK1: protein phosphatase 1a Thr320 phosphorylation; CDK9: RNA polymerase II Ser2 phosphorylation, p27 down-regulation) and apoptotic cell death are analyzed (p53 expression, down-regulation of survival factor Mcl-1, caspase activation, PARP cleavage) (Figure 4-9).

These compounds are thus greatly advantageous over Roscovitine in their effects on induction of cell death and cell proliferation arrest, despite apparently similar effects on their CDK targets. These results appear to correlate with reduced interactions with secondary targets such as pyridoxal kinase (Fig. 1).

Thus, the compounds of the invention or the compounds obtained by the process of the invention, due to their unique biological properties, as shown in the above examples, are of high interest for use in the manufacture of a medicament.

Indeed, not only they have biological effects at least identical and even superior to Roscovitine but they have less or no interaction with pyridoxal kinase.

Otherwise stated, they may be used as active ingredient in a pharmaceutical composition. Their use is of high interest for the manufacture of

medicament for the treatment of diseases in which an abnormal proliferation of cells, either tumoral or not, is involved. Such diseases are in particular a tumor, or leukemia or a non-tumoral but abnormal proliferation observed in various kidney diseases. But, due to their effects on CDK5 and their anti-apoptotic properties on differentiated cells, particularly neuronal cells, they may also be used in the treatment of a neurodegenerative disease such as Alzheimer's disease or Parkinson's disease, or in the treatment of stroke, ischemia and pain. Furthermore, they may also be used for the manufacture of a medicament for treating a viral disease due to their effect on CDK2 and CDK9.

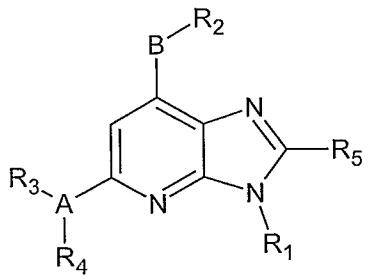
Furthermore, they may be used in the manufacture of a medicament and in a method of treatment of renal diseases, in particular of such as mesangial proliferative glomerulonephritis, crescentic glomerulonephritis, collapsing glomerulopathy, proliferative lupus nephritis, polycystic kidney diseases, diabetic nephropathy and acute kidney injury as well as for treating inflammation, pleural inflammation, arthritis or glaucoma, due to their effects on CDK5, and apoptosis. They may also be used in the treatment of diabetes type II, given their effects on CDK5, and consequently their ability to increase insulin secretion in pancreatic cells.

The compounds of the invention or obtained by the process of the invention may be used for manufacturing a medicament or for treating a particular disease, either alone, or as a mixture of two or more compounds of the invention, or even in association with other compounds of the prior art known as having an effect on the particular disease to be treated.

The compounds of formula Ia-Ih are particularly appropriate in the treatment of the above cited diseases.

CLAIMS

1. Compounds having the following formula I :



Formula I

wherein:

A is CH or N or O,

R_3 is:

- H, or
- a C_1-C_5 alkyl group, or
- =O, or
- a (C_1-C_3) alkyl-C=O group in which the alkyl is optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or amino groups, and/or alkyloxy groups, and/or ketone groups,

R_4 is:

- H, or
- a C_1-C_6 alkyl group optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or amino groups, and/or alkyloxy groups, and/or ketone groups,
- a C_3-C_6 cycloalkyl group optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or amino groups, and/or alkyloxy groups, and/or ketone groups, or
- a (C_1-C_5)alkyl(C_3-C_6)cycloalkyl group optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or amino groups, and/or alkyloxy groups, and/or ketone groups, or
- =O, or
- O=CCF_3, or

- a C_1-C_6 alkyl group substituted by an ester group such as a O-acyl group, or an amino acyl group derived from natural, or non natural amino acids, or an acetyl group or a nicotynyl group,

or A, R_3 and R_4 together form a C_5-C_7 cycloalkyl group, optionally containing one or more heteroatoms, preferably a piperazine group,
B is O or S or NH,

R_1 is:

- a C_1-C_6 alkyl group optionally substituted by one or more hydroxy groups, or
- a C_3-C_6 cycloalkyl group optionally substituted by one or more hydroxy groups, or
- an aryl group optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyloxy groups, and/or optionally containing one or more heteroatoms, or
- a C_1-C_5 alkylaryl group, the aryl group being optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyl groups, and/or C_1-C_3 alkyloxy groups, and/or optionally containing one or more heteroatoms,

R_2 is:

- an aryl group optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyloxy groups, and/or carboxylic acid groups, and/or carboxylic ester groups, and/or amine groups, and/or CF_3 groups, and/or optionally containing one or more heteroatoms, thus creating a 2-pyridyl group, or a 3-pyridyl group, or a 4-pyridyl group, or a 2-thienyl or a 3-thienyl group, or
- a methylbiaryl group, wherein each aryl cycle is optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyloxy groups, and/or CF_3 groups, and/or carboxylic acid groups, and/or carboxylic ester groups, and/or amine groups, and/or optionally containing one or more heteroatoms, or
- a methylaryl group, the aryl cycle being optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyloxy groups, and/or

CF_3 groups, and/or optionally containing one or more heteroatoms, thus creating a 2-pyridyl group, or a 3-pyridyl group, or a 4-pyridyl group, or a 2-thienyl group or a 3-thienyl group,

- a biaryl group, each aryl cycle optionally containing one or more heteroatoms thus creating a 2-pyridyl group, or a 3-pyridyl group, or a 4-pyridyl group, or a 2-thienyl group or a 3-thienyl group, or each aryl cycle is optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyloxy groups, and/or CF_3 groups, and/or carboxylic acid groups, and/or carboxylic ester groups, and/or amine groups,

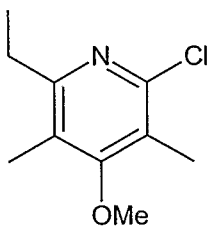
or B and R_2 together form a non aromatic cycle,

R_5 is:

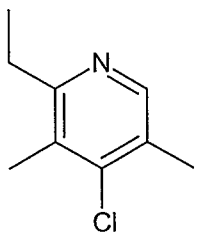
- a halogen atom, or
- a hydrogen atom, or
- a C_1-C_5 alkyl group optionally substituted by one or more hydroxy groups and/or amine groups and/or halogen atoms and/or carboxylic acid groups, or
- a (C_1-C_4)alkyl(C_3-C_6)cycloalkyl group in which the cycloalkyl group is optionally substituted by one or more hydroxy groups and/or amine groups and/or halogen atoms and/or carboxylic acid groups,

and the salts, hydrates, and stereoisomers thereof.

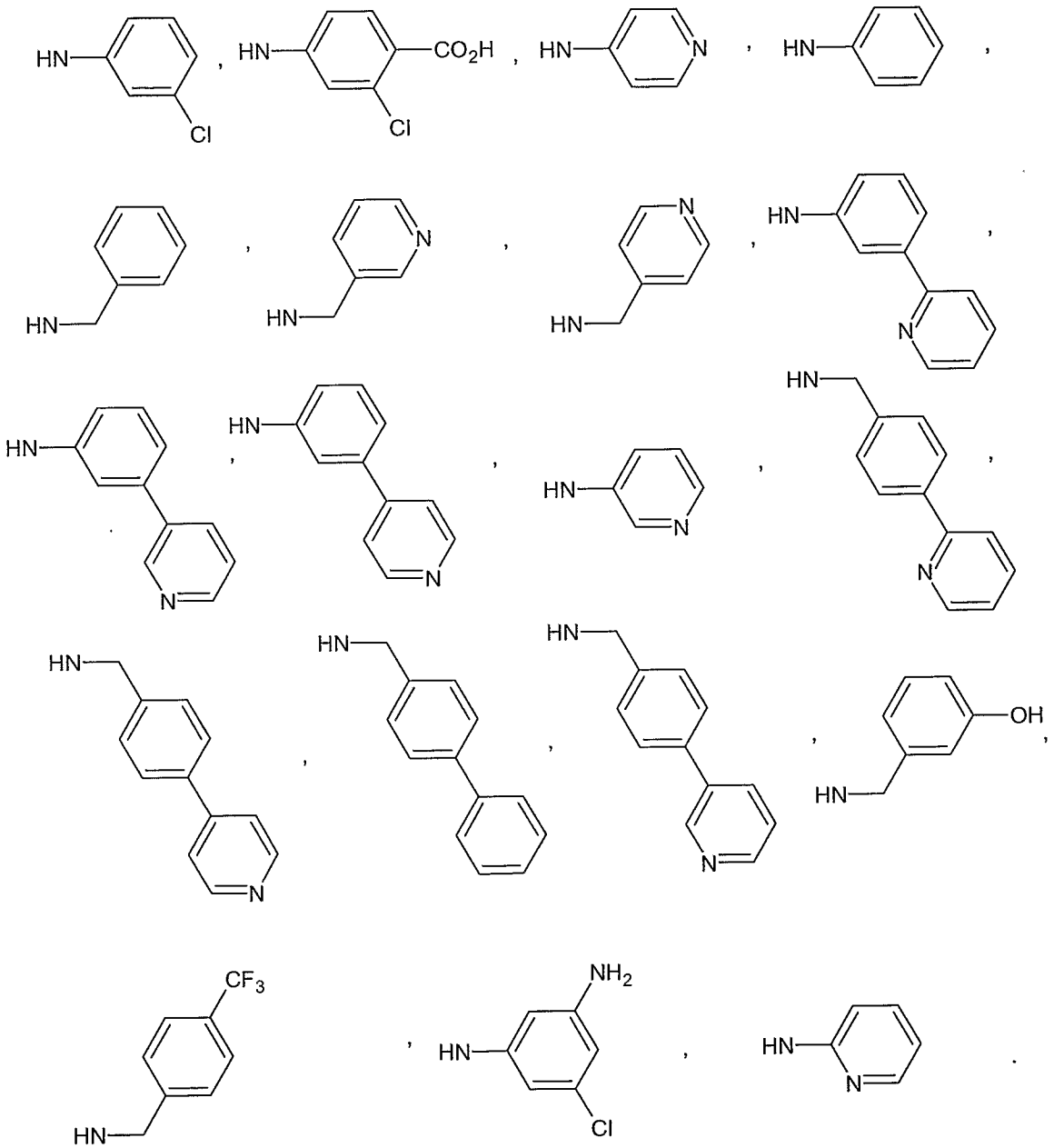
2. Compounds according claim 1 wherein, in Formula I, A is N.
3. Compound according to claim 2 wherein, in Formula I, C is CH.
4. Compound according to claim 2 wherein, in Formula I, A is O.
5. Compounds according to anyone of the preceding claim wherein, in Formula I, R_1 is an ethyl group or a methyl group or a cyclopentyl group or a phenylgroup, or a benzyl group, or a methylpyridyl group, or



or

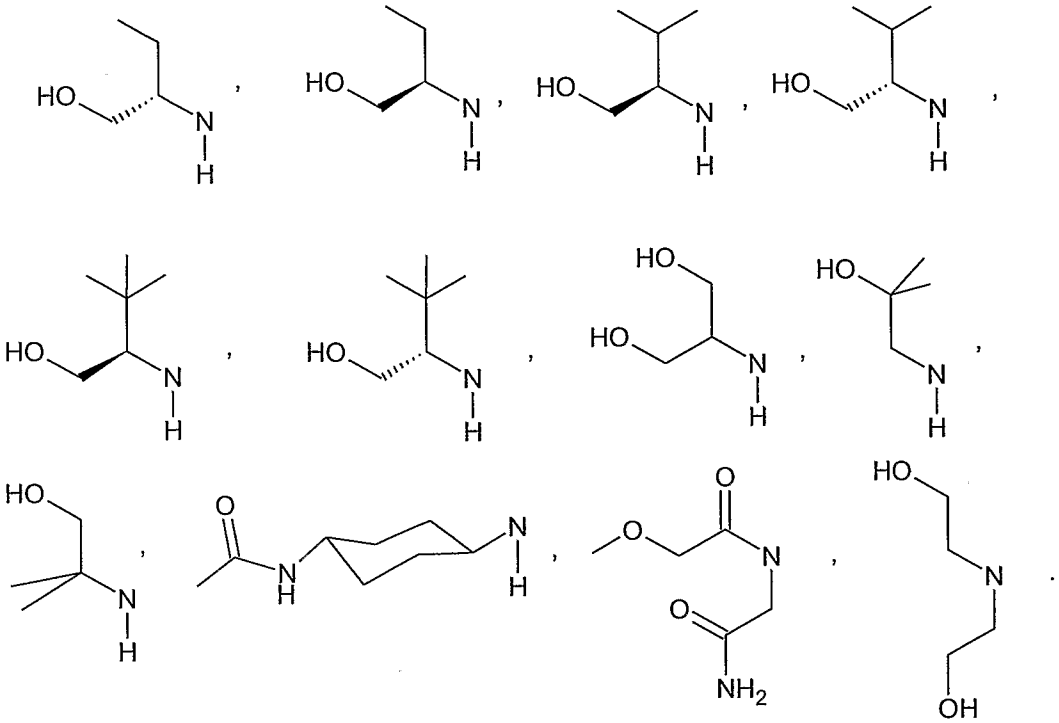


6. Compounds according to anyone of the preceding claims wherein, in Formula I, B-R_2 is chosen among the following groups:



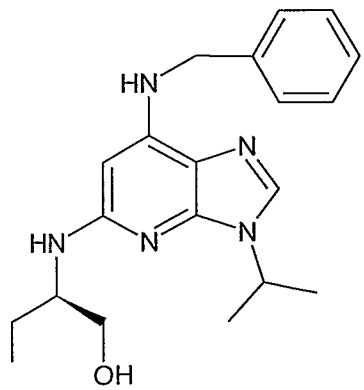
5

7. Compounds according to anyone of the preceding claims wherein, in Formula I, R_4-A-R_3 is chosen among the following groups:



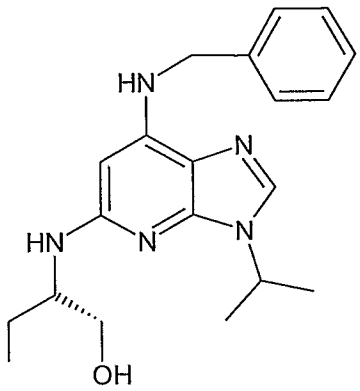
8. Compounds according to anyone of the preceding claims wherein, in Formula I, R_5 is H.

9. Compound according to anyone of claims 1, 2 and 5-8 having the following formula Ia:



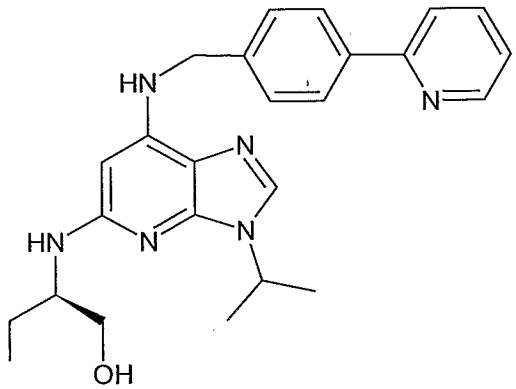
Formula Ia

10. Compound according to anyone of claims 1, 2 and 5-8 having the following formula Ib:



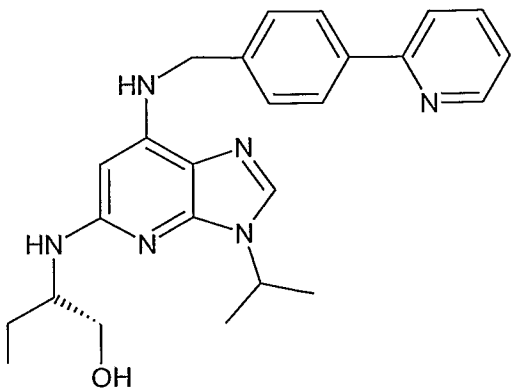
Formula Ib

11. Compound according to anyone of claims 1, 2 and 5-8 having the following formula Ic:



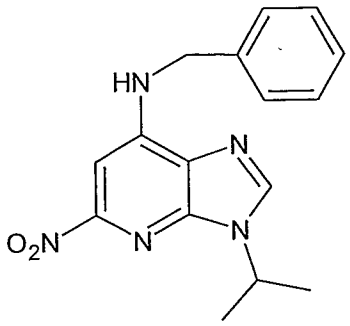
Formula Ic

12. Compound according to anyone of claims 1, 2 and 5-8 having the following formula Id:



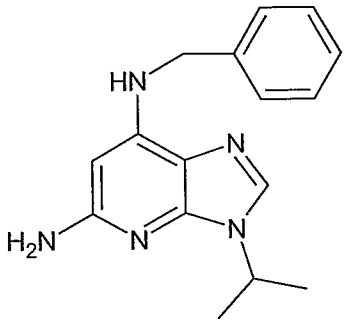
Formula Id

13. Compound according to anyone of claims 1, 2 and 5-8 having the following formula Ie:



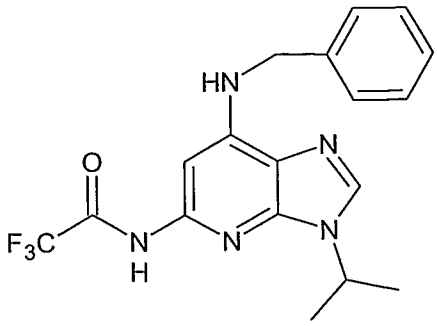
Formula Ie

14. Compound according to anyone of claims 1, 2 and 5-8 having the following formula If:



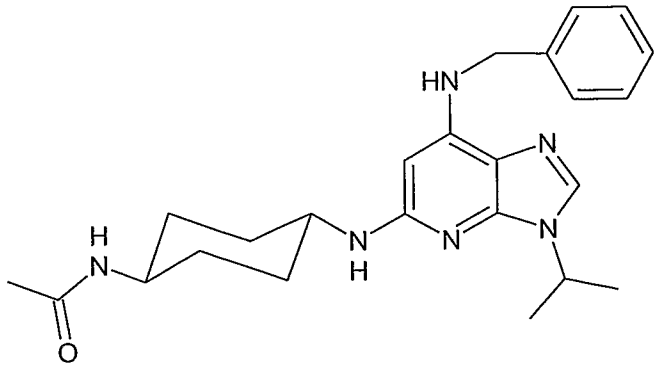
Formula If

15. Compound according to anyone of claims 1, 2 and 5-8 having the following formula Ig:



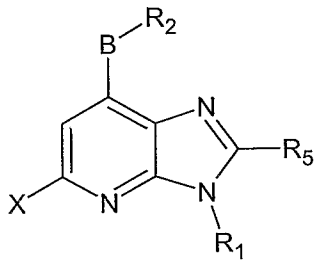
Formula Ig

16. Compound according to any one of claims 1, 2 and 5-8 having the following formula Ih:



Formula Ih

17. Compounds of the following formula II:



Formula II

wherein:

B is O or S or NH

R_1 is:

- a C_1-C_6 alkyl group optionally substituted by one or more hydroxy groups, or
- a C_3-C_6 cycloalkyl group optionally substituted by one or more hydroxy groups, or
- an aryl group optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyloxy groups, and/or optionally containing one or more heteroatoms, or
- a C_1-C_5 alkylaryl group, the aryl group being optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyl groups, and/or C_1-C_3 alkyloxy groups, and/or optionally containing one or more heteroatoms,

R_2 is:

- an aryl group optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyloxy groups, and/or carboxylic acid groups, and/or carboxylic ester groups, and/or amine groups, and/or CF_3 groups, and/or optionally containing one or more heteroatoms, thus creating a 2-pyridyl group, or a 3-pyridyl group, or a 4-pyridyl group, or a 2-thienyl or a 3-thienyl group, or
- a methylbiaryl group, wherein each aryl cycle is optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyloxy groups, and/or CF_3 groups, and/or carboxylic acid groups, and/or carboxylic ester groups, and/or amine groups, and/or optionally containing one or more heteroatoms, or
- a methylaryl group, the aryl cycle being optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyloxy groups, and/or CF_3 groups, and/or optionally containing one or more heteroatoms, thus creating a 2-pyridyl group, or a 3-pyridyl group, or a 4-pyridyl group, or a 2-thienyl group or a 3-thienyl group,
- a biaryl group, each aryl cycle optionally containing one or more heteroatoms thus creating a 2-pyridyl group, or a 3-pyridyl group, or a 4-pyridyl group, or a 2-thienyl group or a 3-thienyl group, or each aryl cycle is optionally substituted by one or more halogen atoms, and/or hydroxy groups, and/or C_1-C_3 alkyloxy groups, and/or CF_3 groups, and/or carboxylic acid groups, and/or carboxylic ester groups, and/or amine groups,

or B and R_2 together form a non aromatic cycle,

R_5 is:

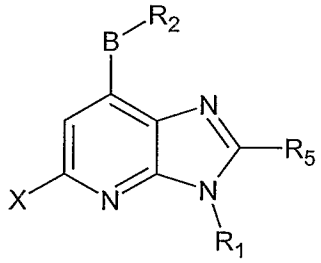
- a halogen atom, or
- a hydrogen atom, or
- a C_1-C_5 alkyl group optionally substituted by one or more hydroxy groups and/or amine groups and/or halogen atoms and/or carboxylic acid groups, or

- a (C_1-C_4)alkyl(C_3-C_6)cycloalkyl group in which the cycloalkyl group is optionally substituted by one or more hydroxy groups and/or amine groups and/or halogen atoms and/or carboxylic acid groups,

X is Cl or Br or I or NH_2,

18. Compounds according to claim 17 wherein, in formula II, X is I.

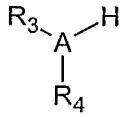
19. A process for manufacturing the compounds according to claim 2 comprising a step of reaction of a compound of the formula II:



Formula II

wherein B, R_2, R_1 and R_5 are as defined for the compounds according to claim 14.

20. The process of claim 19 wherein said step of reaction is a step of coupling the compounds of Formula II in which X is Cl, Br or I with a compound of the following Formula III:



Formula III

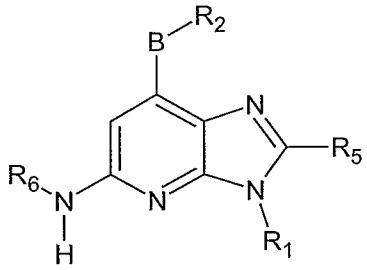
wherein A, R_3 and R_4 are as defined for Formula II, in presence of a catalyst selected from $Pd(OAc)_2$, Pd_2dba_3 or CuI, optionally in presence of a ligand Binap under basic conditions.

21. The process of claim 19 wherein said step of reaction is a step of coupling a compound of Formula II in which X is NH_2 with a compound of the following Formula IV:

$Y\text{-}R_6$

Formula IV

in which Y is I, Br or Cl and R_6 is R_3 or R_4, for obtaining a compound of the following formula V:



Formula V

optionally followed, when R_3 and R_4 are different form H, by a step of coupling the compound of Formula V with a compound of the following Formula VI:

$Y\text{-}R_7$

Formula VI

in which Y is I, Br or Cl and R_7 is R_3 when R_6 is R_4 or R_7 is R_4 when R_6 is R_3, said coupling steps being carried out in presence of a catalyst selected from $Pd(OAc)_2$, Pd_2 dba_3 or CuI, optionally in the presence of a ligand Binap, under basic conditions.

22. The process of anyone of claims 19-21 wherein in each occurrence X and Y are I.

23. A compound according to anyone of claims 1-16 or obtained by the process of anyone of claims 19-22 for use as medicament.

24. A pharmaceutical composition comprising at least one compound according to anyone of claims 1-16 or obtained by the process according to anyone of claims 19-22 and at least one pharmaceutically acceptable excipient.

25. Use of at least one compound according to anyone of claims 1-16 or obtained by the process of anyone of claims 19-22 in the manufacture of a medicament for the treatment of a disease due to an abnormal proliferation of cells.

26. The use according to claim 25 wherein said disease if chronic lymphoid leukemia or chronic myeloid leukemia.

27. The use according to claim 25 wherein said disease is a tumor.

28. The use according to claim 25 wherein said disease is a neurodegenerative disease.

29. The use according to claim 28 wherein said neurodegenerative disease is Parkinson's disease.

30. The use according to claim 28 wherein said neurodegenerative disease is Alzheimer's disease.

31. The use according to claim 28 wherein said neurodegenerative disease is stroke.

32. The use according to claim 25 wherein said disease is a viral disease.

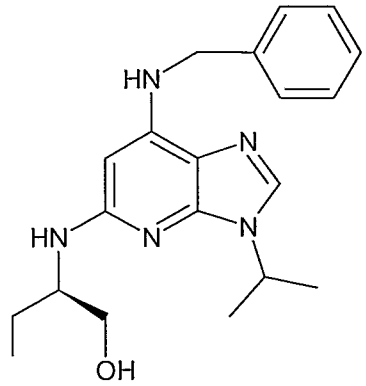
33. Use of at least one compound according to anyone of claims 1-16 or obtained by the process according to anyone of claims 19-22 in the manufacture of a medicament for the treatment of pain.

34. The use according to claim 25 wherein said disease is a kidney disease such as mesangial proliferative glomerulonephritis, crescentic glomerulonephritis, collapsing glomerulopathy, proliferative lupus nephritis, polycystic kidney diseases, diabetic nephropathy and acute kidney injury, cisplatin-induced nephrotoxicity.

35. The use according to claim 25 wherein said disease is an inflammation such as in pleural inflammation, arthritis, glaucoma.

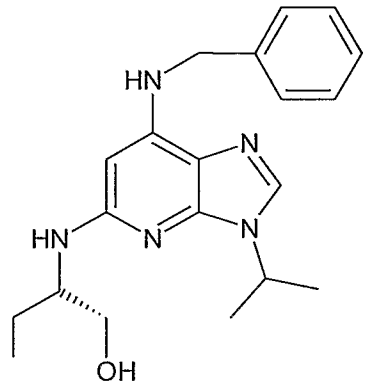
36. The use according to claim 25 wherein said disease is type 2 diabetes.

37. The use according to anyone of claims 25-36 wherein said at least one compound is the compound of the following formula Ia:



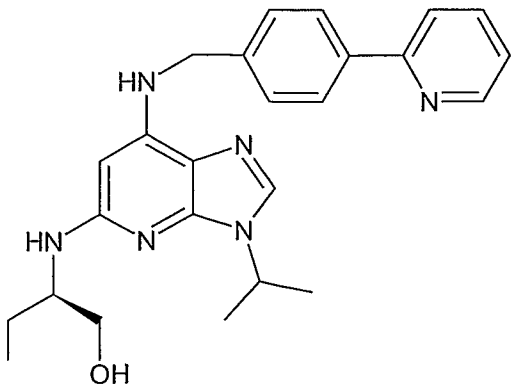
Formula Ia

38. The use according to anyone of claims 25-36 wherein said at least one compound is the compound of the following formula Ib:



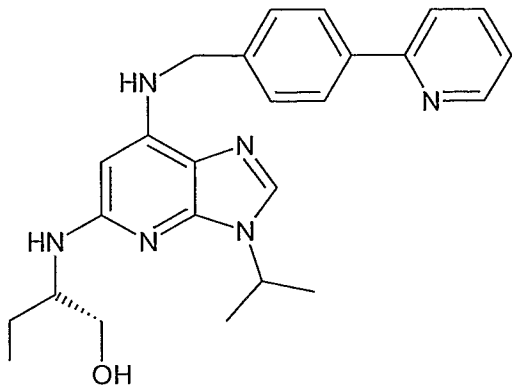
Formula Ib

39. The use according to anyone of claims 25-36 wherein said at least one compound is the compound of the following formula Ic:



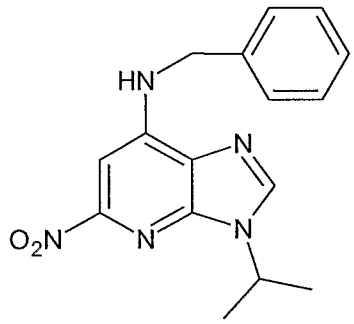
Formula Ic

40. The use according to anyone of claims 25-36 wherein said at least one compound is the compound of the following formula Id:



Formula Id

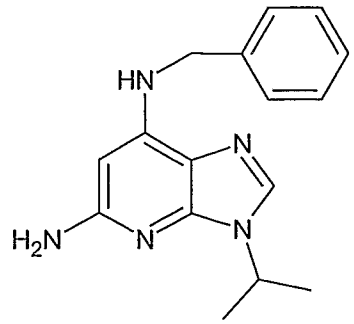
41. The use according to anyone of claims 25-36 wherein said at least one compound is the compound of the following formula Ie:



Formula Ie

and the salts, hydrates and stereoisomers thereof.

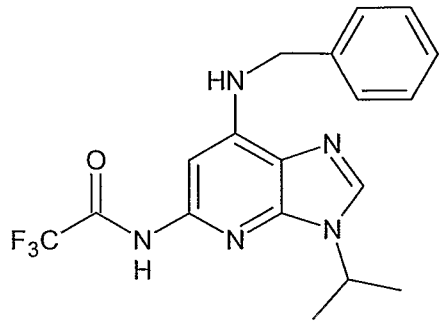
42. The use according to anyone of claims 25-36 wherein said at least one compound is the compound of the following formula If:



Formula If

and the salts, hydrates and stereoisomers thereof.

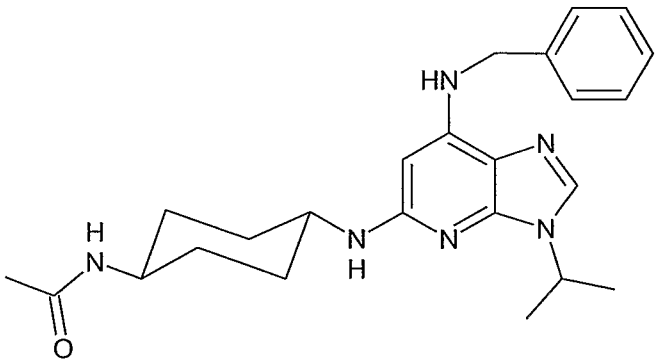
43. The use according to anyone of claims 25-36 wherein said at least one compound is the compound of the following formula Ig:



Formula Ig

and the salts, hydrates and stereoisomers thereof.

44. The use according to any one of claims 25-36 wherein said at least one compound is the compound of the following formula Ih:



Formula Ih

and the salts, hydrates and stereoisomers thereof.

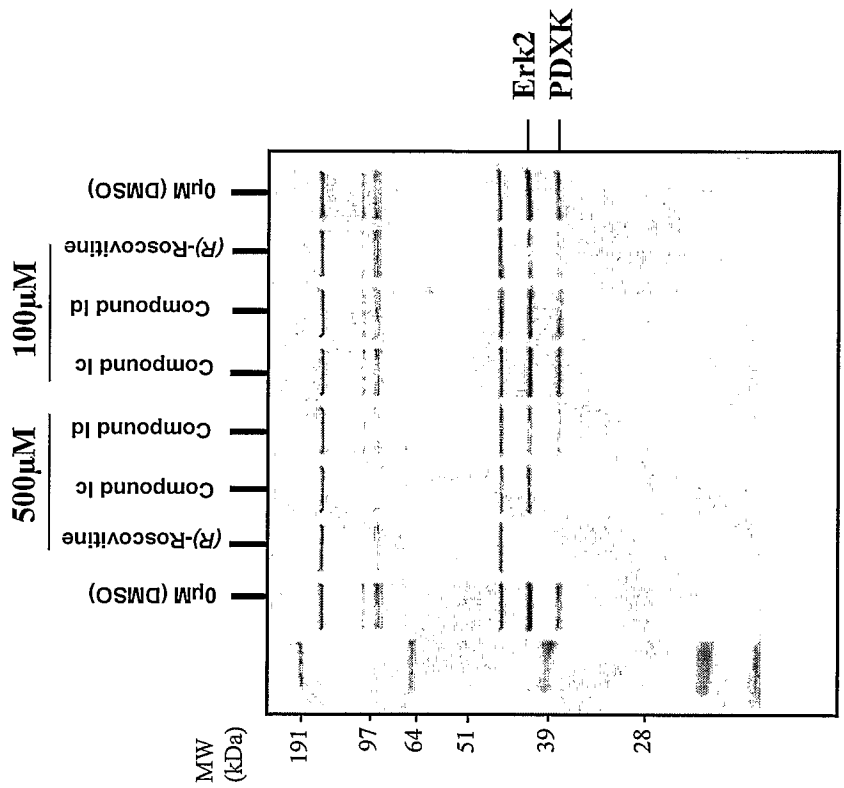

Erk2
PDXK
0µM (DMSO)
(R)-Roscovitine
Compound Ic
Compound Id
100µM
500µM
Compound Id
Compound Ic
(R)-Roscovitine
0µM (DMSO)
MW (kDa)
191
97
64
51
39
28

Figure 1

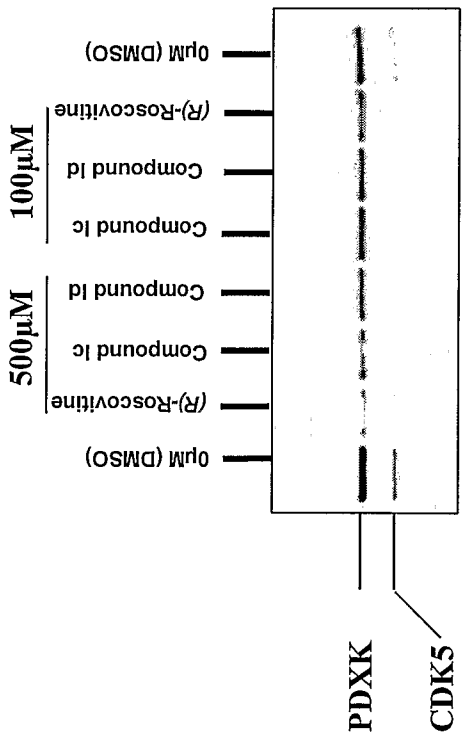

0µM (DMSO)
(R)-Roscovitine
Compound Id
Compound Ic
100µM
Compound Id
Compound Ic
(R)-Roscovitine
500µM
0µM (DMSO)
PDXK
CDK5

Figure 2

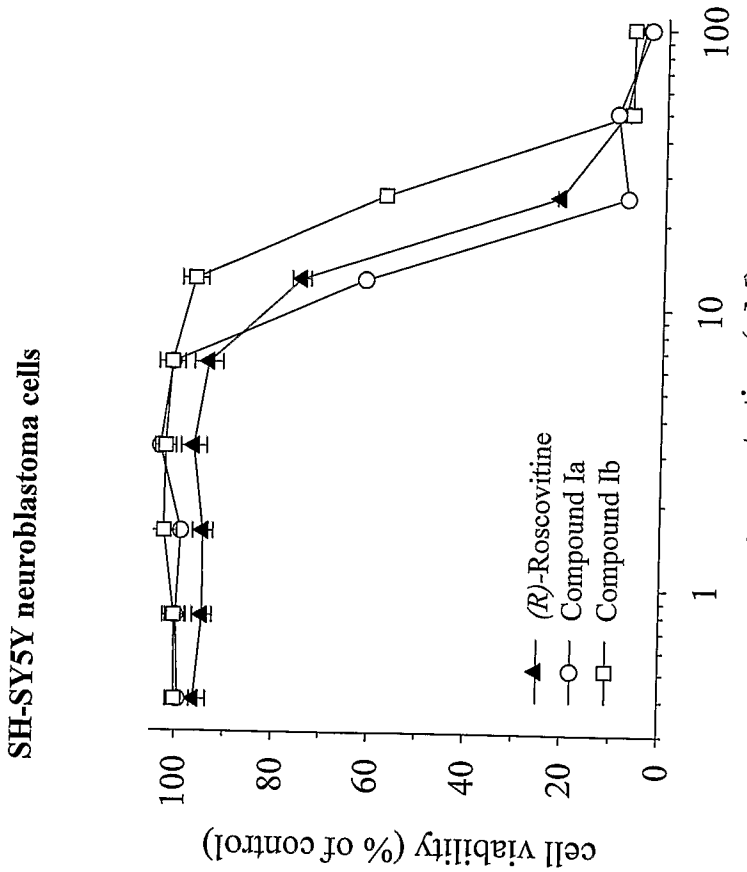

SH-SY5Y neuroblastoma cells
cell viability (% of control)
100
80
60
40
20
0
1
10
100
concentration (μM)
(R)-Roscovitine
Compound Ia
Compound Ib

Figure 3

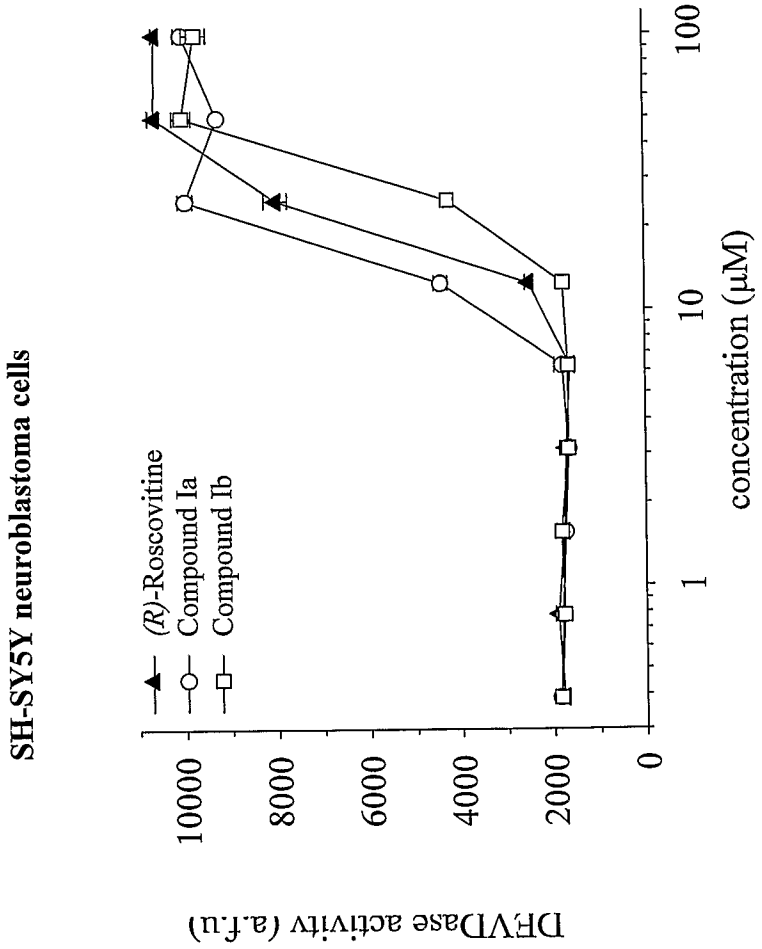

SH-SY5Y neuroblastoma cells
(R)-Roscovitine
Compound Ia
Compound Ib
DEVDase activity (a.f.u)
10000
8000
6000
4000
2000
0
1
10
100
concentration (μM)

Figure 4

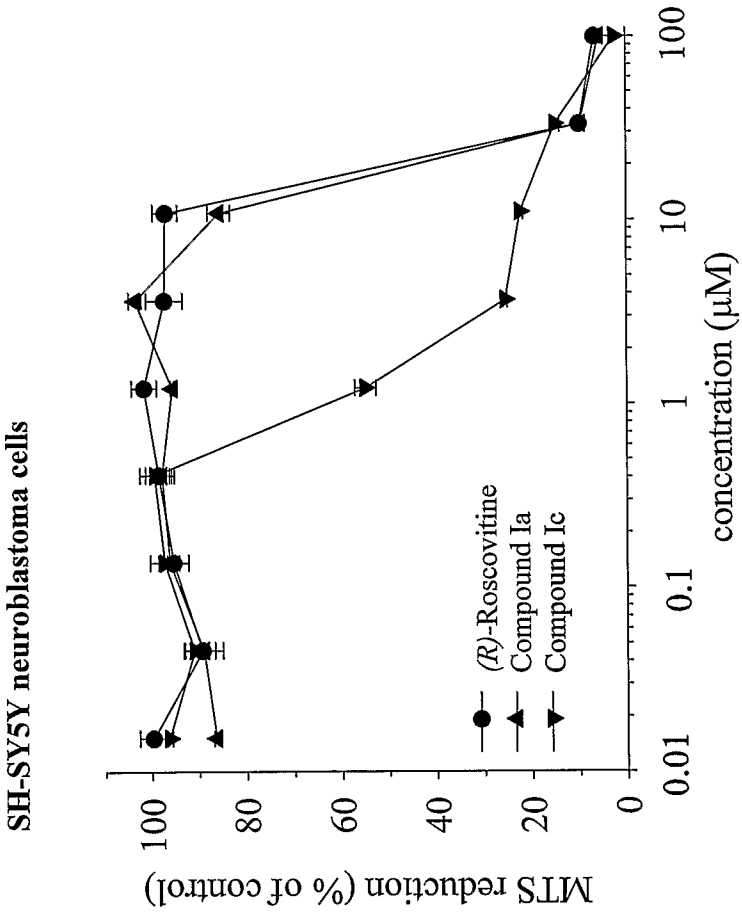

SH-SY5Y neuroblastoma cells
MTS reduction (% of control)
100
80
60
40
20
0
0.01
0.1
1
10
100
concentration (μM)
(R)-Roscovitine
Compound Ia
Compound Ic

Figure 5

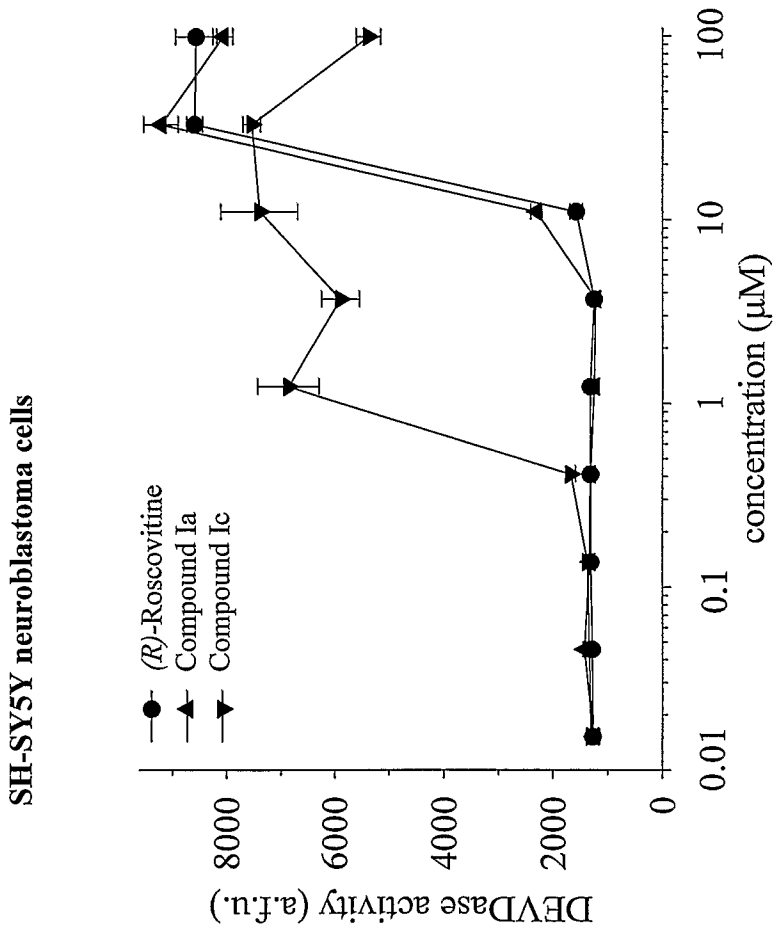

SH-SY5Y neuroblastoma cells
(R)-Roscovitine
Compound Ia
Compound Ic
DEVDase activity (a.f.u.)
8000
6000
4000
2000
0
0.01
0.1
1
10
100
concentration (μM)

Figure 6

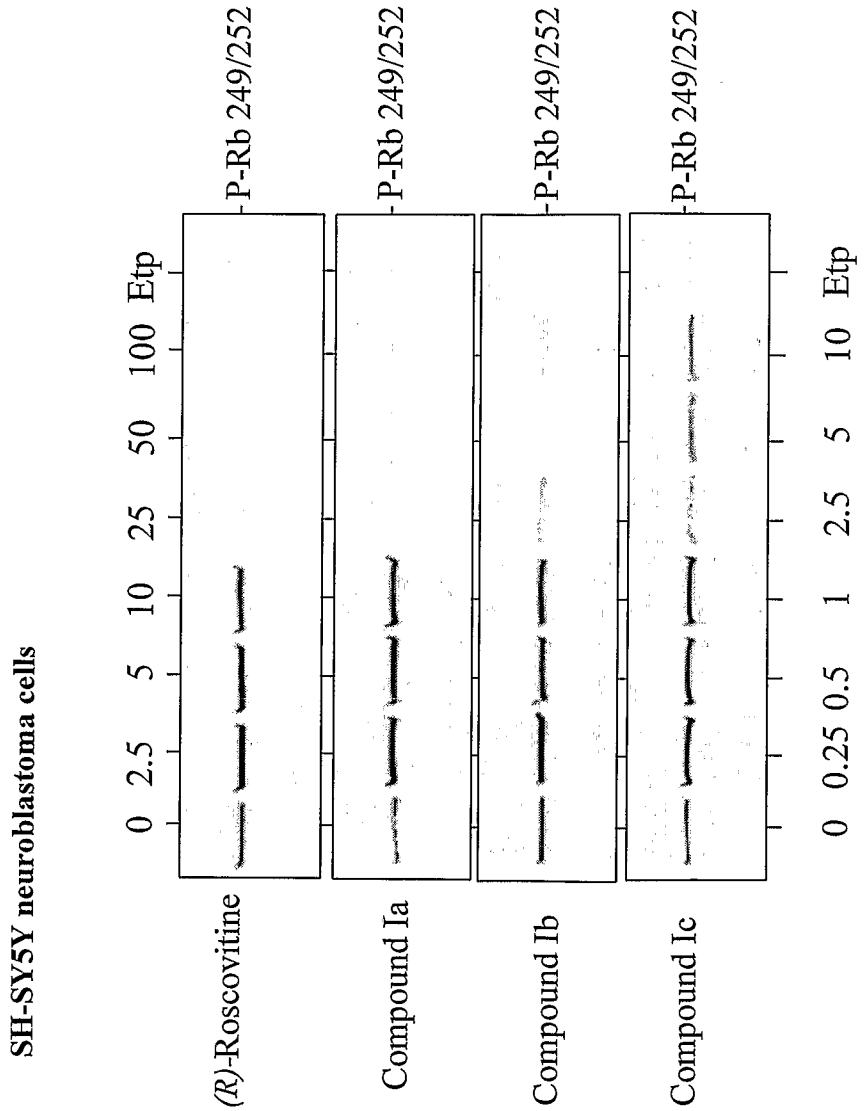

SH-SY5Y neuroblastoma cells
(R)-Roscovitine
Compound Ia
Compound Ib
Compound Ic
P-Rb 249/252
0 2.5 5 10 25 50 100 Etp
0 0.25 0.5 1 2.5 5 10 Etp
concentration (μM)

Figure 7

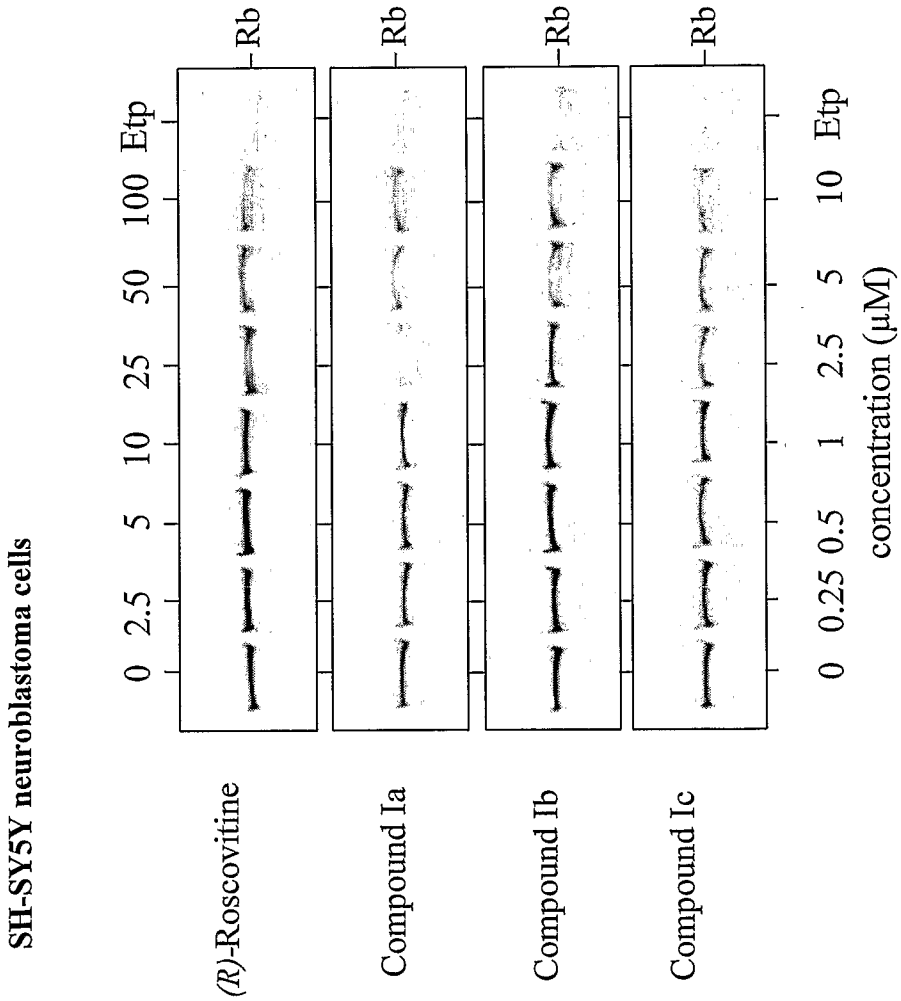

SH-SY5Y neuroblastoma cells
(R)-Roscovitine
Compound Ia
Compound Ib
Compound Ic
Rb
0 2.5 5 10 25 50 100 Etp
0 0.25 0.5 1 2.5 5 10 Etp
concentration (μM)

Figure 8

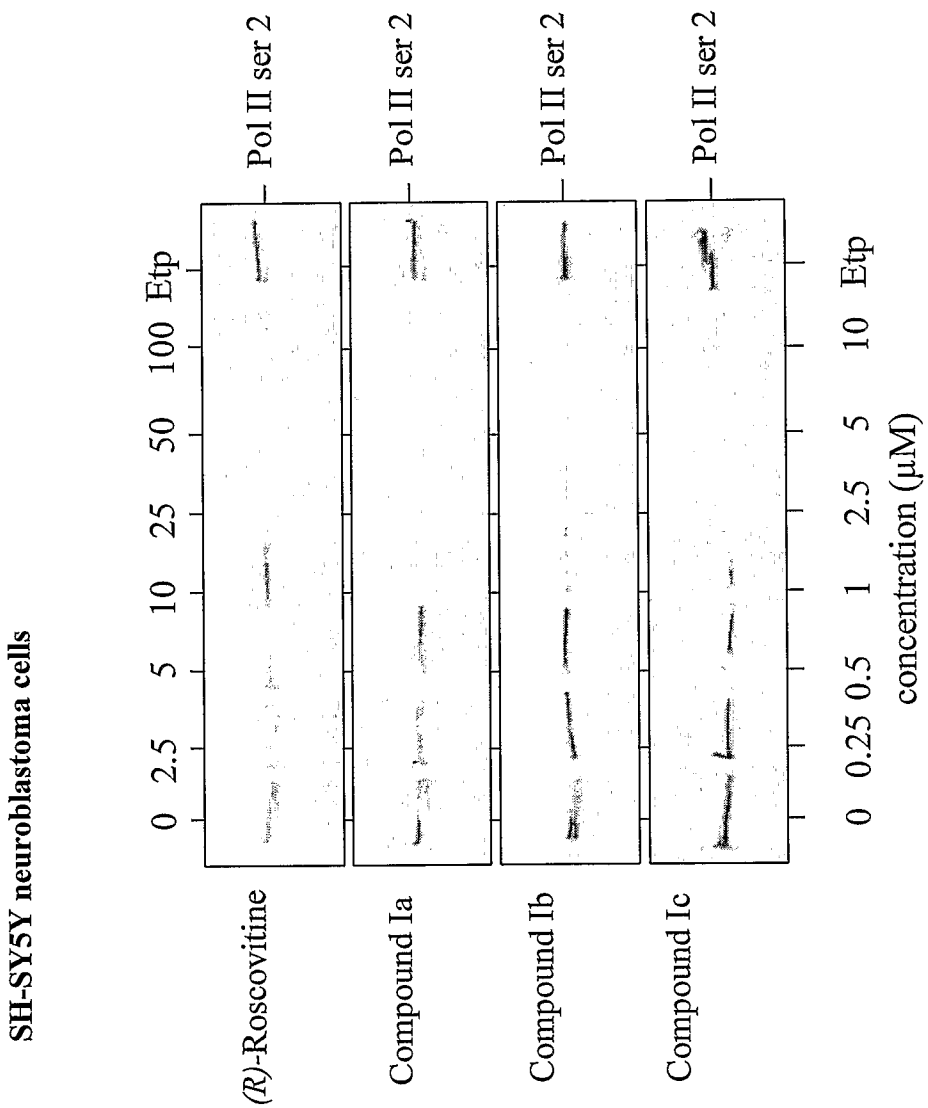

SH-SY5Y neuroblastoma cells
(R)-Roscovitine
Compound Ia
Compound Ib
Compound Ic
Pol II ser 2
Pol II ser 2
Pol II ser 2
Pol II ser 2
0 2.5 5 10 25 50 100 Etp
0 0.25 0.5 1 2.5 5 10 Etp
concentration (µM)

Figure 9

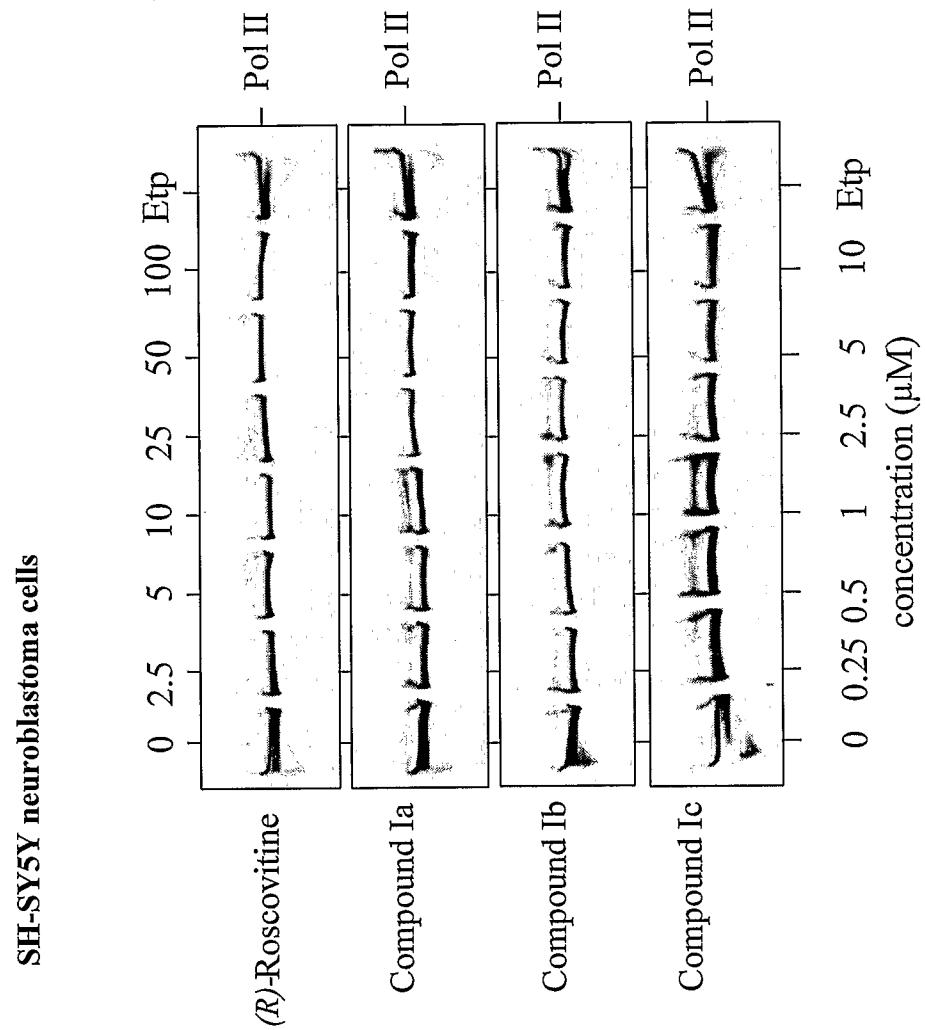

SH-SY5Y neuroblastoma cells
(R)-Roscovitine
Compound Ia
Compound Ib
Compound Ic
Pol II
Etp
0 2.5 5 10 25 50 100
0 0.25 0.5 1 2.5 5 10
concentration (μM)

Figure 10

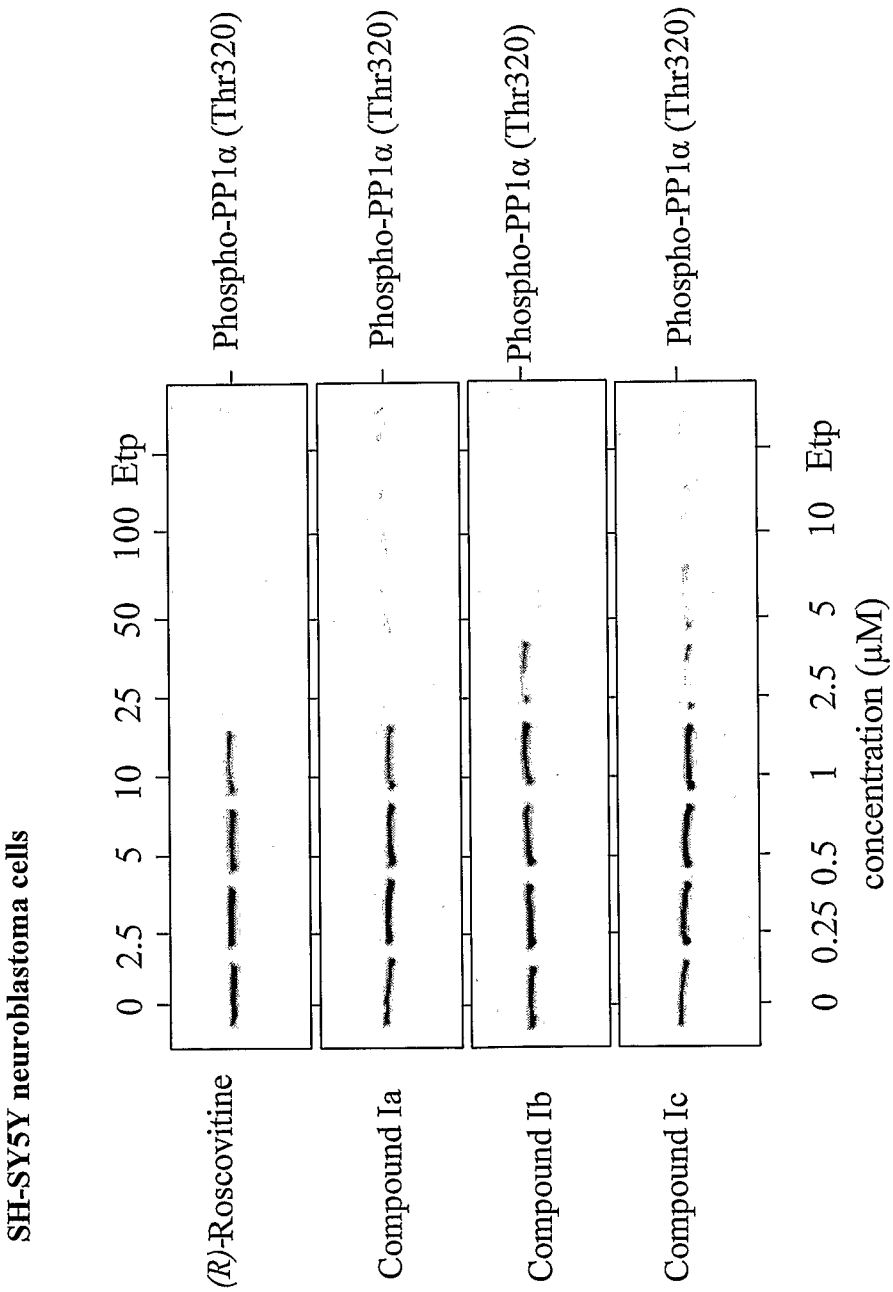

SH-SY5Y neuroblastoma cells
(R)-Roscovitine
Compound Ia
Compound Ib
Compound Ic
Phospho-PP1α (Thr320)
0 2.5 5 10 25 50 100 Etp
0 0.25 0.5 1 2.5 5 10 Etp
concentration (μM)

Figure 11

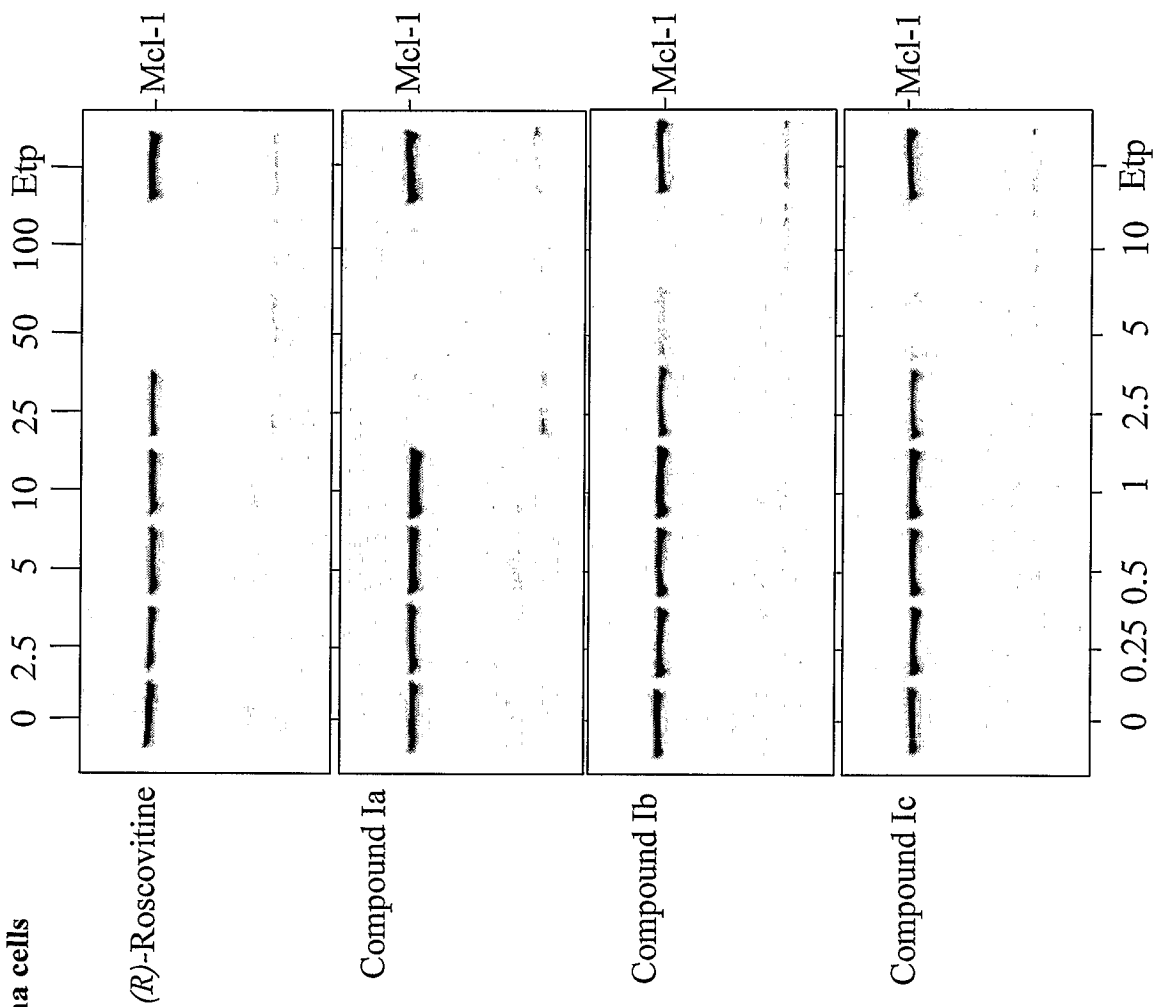

SH-SY5Y neuroblastoma cells
(R)-Roscovitine
Compound Ia
Compound Ib
Compound Ic
Mcl-1
0 2.5 5 10 25 50 100 Etp
0 0.25 0.5 1 2.5 5 10 Etp
concentration (μM)

Figure 12

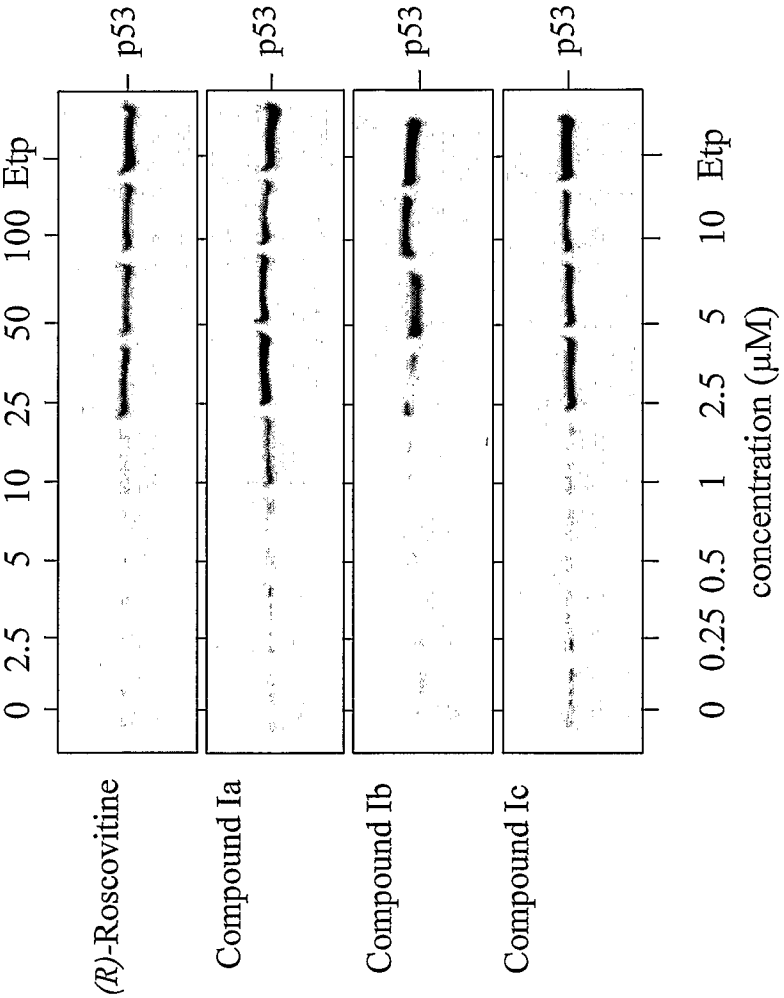

SH-SY5Y neuroblastoma cells
(R)-Roscovitine
Compound Ia
Compound Ib
Compound Ic
p53
0 2.5 5 10 25 50 100 Etp
0 0.25 0.5 1 2.5 5 10 Etp
concentration (μM)

Figure 13

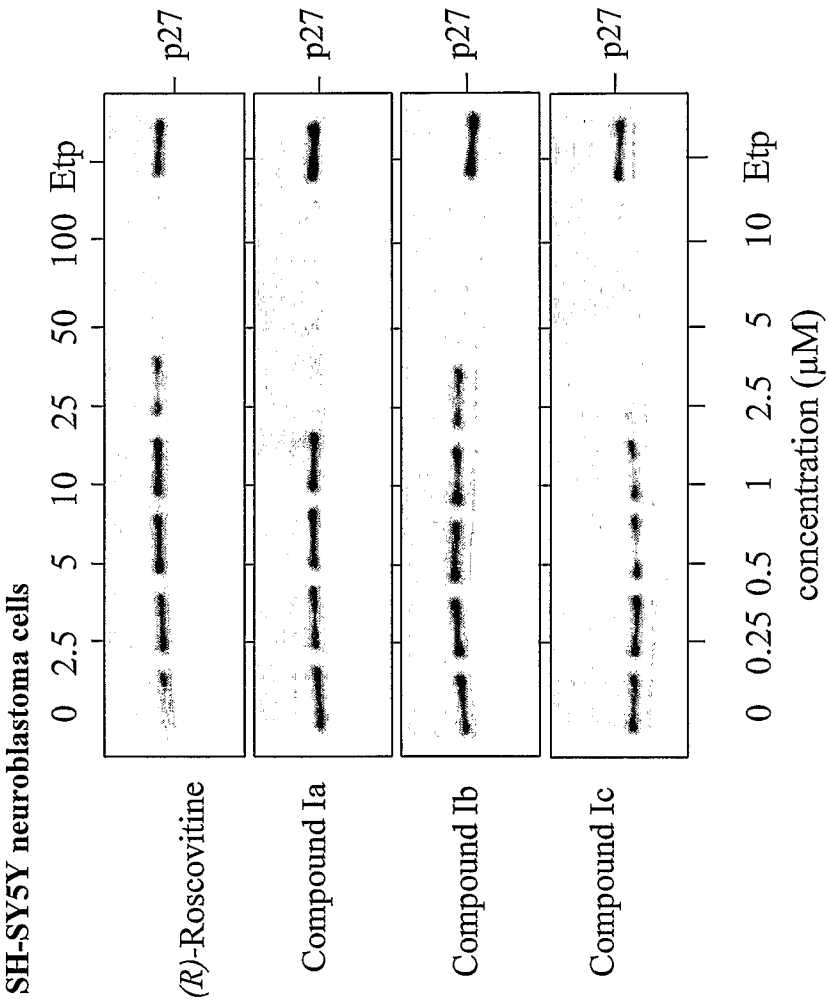

SH-SY5Y neuroblastoma cells
(R)-Roscovitine
Compound Ia
Compound Ib
Compound Ic
p27
0 2.5 5 10 25 50 100 Etp
0 0.25 0.5 1 2.5 5 10 Etp
concentration (μM)

Figure 14

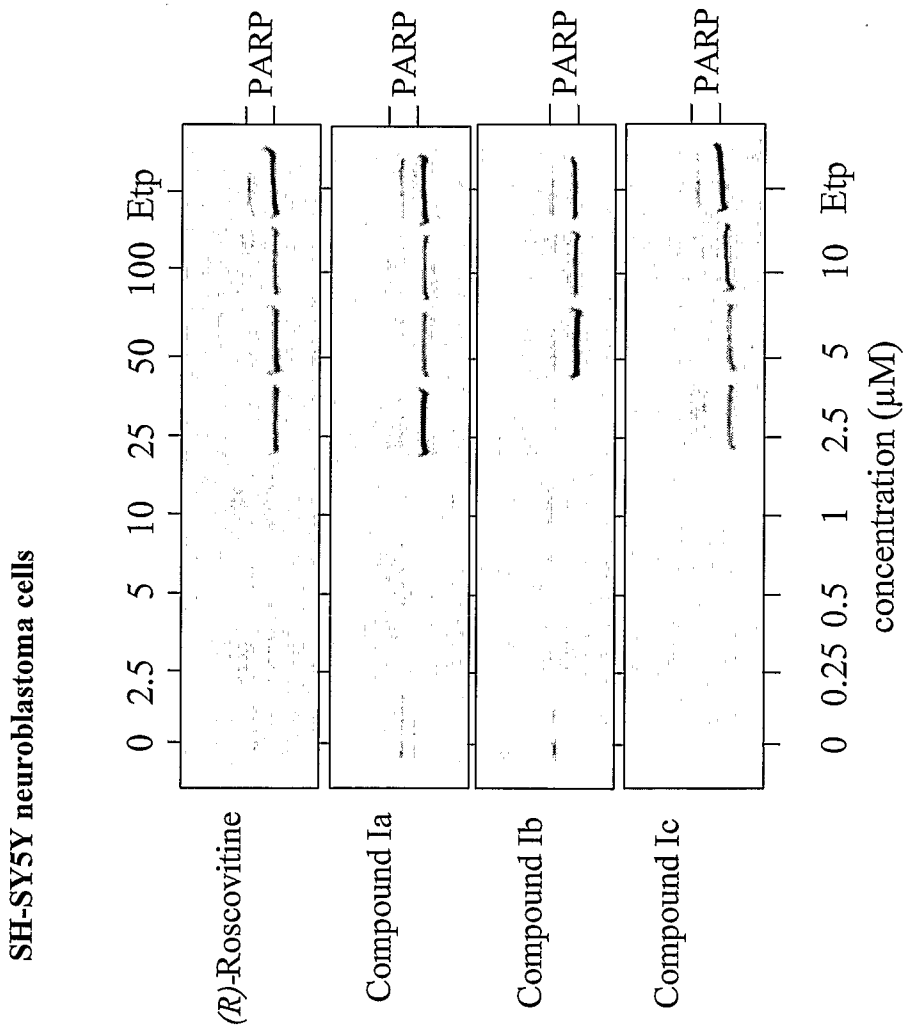

SH-SY5Y neuroblastoma cells
(R)-Roscovitine
Compound Ia
Compound Ib
Compound Ic
PARP
0 2.5 5 10 25 50 100 Etp
0 0.25 0.5 1 2.5 5 10 Etp
concentration (μM)

Figure 15

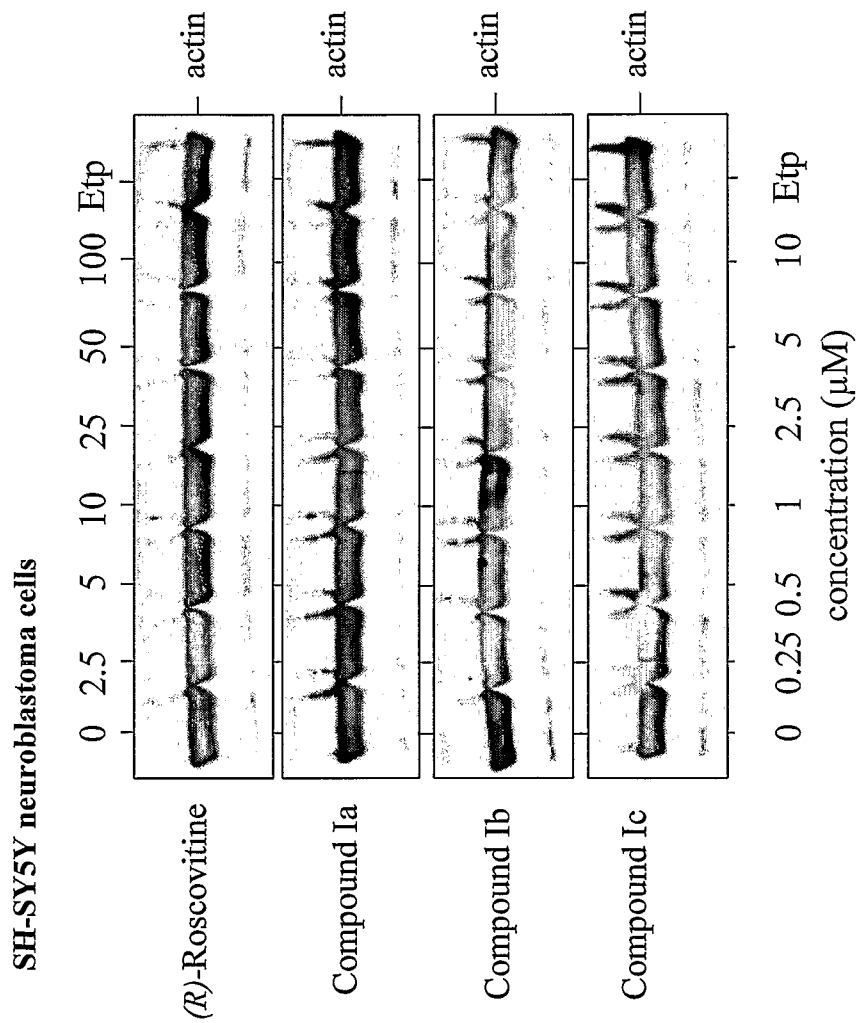

SH-SY5Y neuroblastoma cells
(R)-Roscovitine
Compound Ia
Compound Ib
Compound Ic
actin
0 2.5 5 10 25 50 100 Etp
0 0.25 0.5 1 2.5 5 10 Etp
concentration (μM)

Figure 16

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2007/003655

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/437 A61P35/00 A61P29/00 A61P25/00

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)
C07D A61K A61P

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)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 352 910 A (GRUENENTHAL GMBH [DE]) 15 October 2003 (2003-10-15) claims	1-44
X	WO 2006/027366 A (SOLVAY PHARM BV [NL]; KOCH MELLE [NL]; HARTOG JACOBUS A J [NL]; WANNER) 16 March 2006 (2006-03-16) claims	1-44

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[X] Further documents are listed in the continuation of Box C. [X] See patent family 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	Date of mailing of the international search report
2 October 2008	15/10/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Gregoire, Ariane

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2007/003655

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BACH S ET AL: "Roscovitine targets, protein kinases and pyridoxal kinase" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOCHEMICAL BIOLOGISTS, BIRMINGHAM,; US, vol. 280, no. 35, 23 June 2005 (2005-06-23), pages 31208-31219, XP002402137 ISSN: 0021-9258 cited in the application the whole document	1-44
A	WO 2006/021803 A (CYCLACEL LTD [GB]; BENIGNI ARIELA [IT]; ZOJA CARLA [IT]; REMUZZI GIUSE) 2 March 2006 (2006-03-02) the whole document	1-44

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2007/003655

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		AU 2003227593 A1	20-10-2003
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		US 2005096293 A1	05-05-2005
WO 2006027366 A	16-03-2006	CA 2579303 A1	16-03-2006
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		CA 2576159 A1	02-03-2006
		EP 1799230 A2	27-06-2007
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