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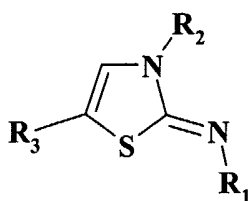
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(54) Title: THIAZOL-2-YL-IMINE COMPOUNDS AS PDE-7 INHIBITORS



(I)

(57) Abstract: A compound selected from those of formula (I), wherein: R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> are as defined in the description, and optionally, its optical isomers, N-oxide, and addition salts thereof with a pharmaceutically-acceptable acid or base, and medicinal products containing the same are useful as inhibitors of phosphodiesterase-7.



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## Thiazol-2-yl-imine compounds as PDE-7 inhibitors

The present invention relates to thiazol-2-yl-imine derivatives, a process for their preparation, and pharmaceutical compositions containing them. These new compounds are  
5 useful as phosphodiesterase 7 (PDE7) inhibitors. Further contained in this invention are pharmaceutical compositions containing these phosphodiesterase 7 inhibitors as active principle for the treatment of diseases for which treatment by PDE7 inhibitor is relevant. These medicinal products are useful in particular for treating T-cell-related diseases, autoimmune diseases, visceral pain, osteoarthritis, multiple sclerosis, osteoporosis, chronic  
10 obstructive pulmonary disease, allergic rhinitis, asthma, cancer, acquired immune deficiency syndrome, allergy, fertility diseases or inflammatory bowel disease.

Phosphodiesterases (PDE) play an important role in various biological processes by hydrolysing the key second messengers adenosine and guanosine 3',5'-cyclic monophosphates (cAMP and cGMP respectively) into their corresponding 5'-monophosphate nucleotides.  
15 Therefore, inhibition of PDE activity produces an increase of cAMP and cGMP intracellular levels that activate specific protein phosphorylation pathways involved in a variety of functional responses.

At least eleven isoenzymes of mammalian cyclic nucleotide phosphodiesterases, numbered PDE 1 through PDE 11, have been identified on the basis of primary structure,  
20 substrate specificity or sensitivity to cofactors or inhibitory drugs.

Among these phosphodiesterases, PDE7 is a cAMP-specific PDE. The biochemical and pharmacological characterization showed a high-affinity cAMP-specific PDE ( $K_m=0.2 \mu\text{M}$ ), that is not affected by cGMP potent selective PDE isoenzyme inhibitors.

PDE7 activity or protein has been detected in T-cell lines, B-cell lines, airway  
25 epithelial (AE) cell lines and several foetal tissues.

Increasing cAMP levels by selective PDE7 inhibition appears to be a potentially promising approach to specifically block T-cell mediated immune responses. Further studies have demonstrated that elevation of intracellular cAMP levels can modulate inflammatory and immunological processes. This selective approach could presumably be

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devoid of the side effects associated with known selective PDE inhibitors (e.g. PDE3 or PDE4 selective inhibitors) and which limit their use.

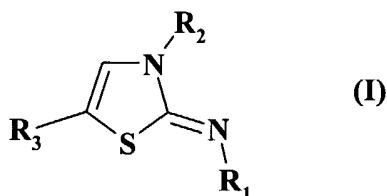
A functional role of PDE7 in T-cell activation has also been disclosed; therefore selective PDE7 inhibitors would be candidates for the treatment of T-cell-related diseases.

5 AE cells actively participate in inflammatory airway diseases by liberating mediators such as arachidonate metabolites and cytokines. Selective inhibition of PDE7 may be a useful anti-inflammatory approach for treating AE cells related diseases.

Thus, there is a need for selective PDE7 inhibitors, which are active at very low concentrations.

10 The applicant has identified novel thiazol-2-yl-imine compounds that are phosphodiesterase inhibitors, and more specifically compounds that are selective PDE7 inhibitors.

More specifically, the present invention relates to compounds of formula (I) :



15 wherein:

- R<sub>1</sub> represents a group selected from cycloalkyl, heterocycloalkyl, aryl and heteroaryl, those groups being optionally substituted by one or more groups, identical or different, selected independently of each other from halogen, trifluoromethyl, nitro, cyano, oxo, -NR<sub>4</sub>R<sub>5</sub>, -CO<sub>2</sub>R<sub>4</sub>, -CONR<sub>4</sub>R<sub>5</sub>, -OR<sub>4</sub>, -S(O)<sub>n</sub>R<sub>4</sub>, -S(O)<sub>n</sub>NR<sub>4</sub>R<sub>5</sub>, tetrazolyl, and (C<sub>1</sub>-C<sub>6</sub>)alkyl

20 which is optionally substituted by 1 to 3 groups, identical or different, selected independently of each other from -OR<sub>4</sub>, -NR<sub>4</sub>R<sub>5</sub>, and -CO<sub>2</sub>R<sub>4</sub>, wherein:

✓ n is an integer from 0 to 2 inclusive,

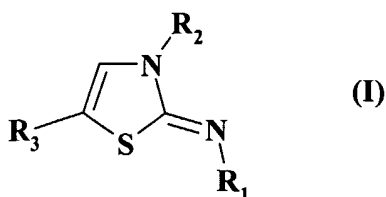
✓ R<sub>4</sub> and R<sub>5</sub>, identical or different, independently of each other, represent a hydrogen atom or a group of formula -X<sub>1</sub>-R<sub>a</sub> wherein:

25 - X<sub>1</sub> represents a single bond or a (C<sub>1</sub>-C<sub>6</sub>)alkylene group,

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- $R_a$  represents a group selected from  $(C_1-C_6)$ alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl,
  - $R_2$  represents a group selected from  $(C_1-C_6)$ alkyl,  $(C_2-C_6)$ alkenyl,  $(C_2-C_6)$ alkynyl, aryl and cycloalkyl,
- 5 •  $R_3$  represents a group selected from cycloalkyl, heterocycloalkyl, aryl and heteroaryl, these groups being optionally substituted by one or more groups, identical or different, selected independently of each other from halogen, nitro, cyano, trifluoromethyl, oxo,  $(C_1-C_6)$ alkyl,  $-OR_6$ ,  $-NR_6R_7$ ,  $-COR_6$ ,  $-CO_2R_6$ ,  $-CONHOH$ ,  $-CONR_6R_7$ ,  $-S(O)_mR_6$ ,  $-S(O)_m-NR_6R_7$ ,  $-NR_6COR_7$ ,  $-NR_6SO_2R_7$ ,  $-N(SO_2R_7)_2$ ,  $-NR_6-CO-NR_7R_8$ ,  $C(=N-CN)NR_6R_7$ ,  $NR_8-C(=N-CN)NR_6R_7$  and tetrazolyl optionally substituted with a  $(C_1-C_4)$ alkyl, wherein:
- 10 ✓  $m$  is an integer from 0 to 2 inclusive,
- ✓  $R_6$  and  $R_7$ , identical or different, independently of each other, represent a hydrogen atom or a group of formula  $-X_2-R_b$  wherein:
- $X_2$  represents a single bond or a  $(C_1-C_6)$ alkylene group,
  - 15 -  $R_b$  represents a group selected from  $(C_1-C_6)$ alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, these groups being optionally substituted by 1 to 3 groups, identical or different, selected independently of each other from hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_6)$ alkyl, amino, mono $(C_1-C_6)$ alkylamino, di $(C_1-C_6)$ alkylamino (each alkyl being identical or different, independently of each other), carboxy,
  - 20  $(C_1-C_6)$ alkoxycarbonyl, and benzyl,
  - $R_8$  represents a hydrogen atom or a  $(C_1-C_6)$ alkyl group,
- optionally the racemics forms thereof, isomers thereof, N-oxides thereof, and the pharmaceutically acceptable acid or base salts thereof.

25 Preferably, the present invention relates to compounds of formula (I)



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wherein R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> are as defined above, with the exclusion of the following compounds:

- (3-Cyclohexyl-5-phenyl-3H-thiazol-2-ylidene)-phenyl-amine,  
2-phenylimino-3-phenyl-5-(2,5-dihydroxy-3,4,6-trichlorophenyl)thiazoline,  
5 2-phenylimino-3-phenyl-5-(3,5,6-trichloro-1,4-benzoquinon-2-yl)thiazoline, and,  
(3-allyl-5-phenyl-3H-thiazol-2-ylidene)-*o*-tolyl-amine.

The substituent R<sub>1</sub> that is preferred according to the invention is the group selected from cycloalkyl and aryl each of those groups being optionally substituted by 1 to 3 groups selected from halogen, trifluoromethyl, -CO<sub>2</sub>R<sub>4</sub>, -OR<sub>4</sub>, and tetrazolyl, in which R<sub>4</sub>  
10 represents a hydrogen atom or a (C<sub>1</sub>-C<sub>6</sub>)alkyl group.

More particularly, the substituent R<sub>1</sub> that is preferred according to the invention is the cyclohexyl group optionally substituted by one hydroxy group, or the phenyl group optionally substituted by one tetrazolyl group or one -CO<sub>2</sub>R<sub>4</sub> group in which R<sub>4</sub> represents a hydrogen atom or a (C<sub>1</sub>-C<sub>6</sub>)alkyl group.

15 The substituent R<sub>2</sub> that is preferred according to the invention is a (C<sub>1</sub>-C<sub>6</sub>)alkyl group.

More particularly, the substituent R<sub>2</sub> that is preferred according to the invention is the methyl group.

The substituent R<sub>3</sub> that is preferred according to the invention is a group selected  
20 from aryl and heteroaryl which are optionally substituted by one to three groups, identical or different, independently of each other, as defined in the general definition of compounds of formula (I).

More particularly, the substituent R<sub>3</sub> that is preferred according to the invention is a group selected from phenyl, pyridyl, thienyl, isoxazolyl, pyrazolyle, pyrazinyl, quinolyl,  
25 quinoxaliny, 1*H*-quinoxaliny-2-one, quinazoliny, 3*H*-quinazoliny-4-one, 1*H*-quinazoliny-2,4-dione, indolyle, benzisoxazolyl, phtalaziny, and benzo[1,3]dioxolyle,

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which are optionally substituted by one to three groups, identical or different, independently of each other, as defined in the general definition of compounds of formula (I).

As a preferred embodiment, the substituent  $R_3$  that is particularly interesting for the invention is the phenyl group substituted by one to three groups, identical or different, selected independently of each other from halogen,  $-OR_6$ ,  $-CO_2R_6$ ,  $-CONR_6R_7$ ,  $-S(O)_mR_6$ ,  $-S(O)_m-NR_6R_7$ ,  $-NR_6COR_7$ , and tetrazolyl, wherein:

- ✓  $m$  is an integer from 0 to 2 inclusive,
- ✓  $R_6$  and  $R_7$ , identical or different, independently of each other, represent a hydrogen atom or a group of formula  $-X_2-R_b$  wherein:
  - $X_2$  represents a single bond or a  $(C_1-C_6)$ alkylene group,
  - $R_b$  represents a group selected from  $(C_1-C_6)$ alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, these groups being optionally substituted by 1 to 3 groups, identical or different, selected independently of each other from hydroxy,  $(C_1-C_6)$ alkoxy,  $(C_1-C_6)$ alkyl, amino, mono $(C_1-C_6)$ alkylamino, di $(C_1-C_6)$ alkylamino (each alkyl being identical or different, independently of each other), carboxy,  $(C_1-C_6)$ alkoxycarbonyl, and benzyl.

In another preferred embodiment, the substituent  $R_3$  that is particularly interesting for the invention is the group selected from quinoxalinylyl, 1*H*-quinoxalinylyl-2-one, quinazolinylyl, 3*H*-quinazolinylyl-4-one, and 1*H*-quinazolinylyl-2,4-dione, which are optionally substituted by one to three groups, identical or different, selected independently of each other from halogen,  $(C_1-C_6)$ alkyl,  $-OR_6$ , and  $-NR_6R_7$ , wherein:

$R_6$  and  $R_7$ , identical or different, independently of each other, represent a hydrogen atom or a group of formula  $-X_2-R_b$  wherein:

- $X_2$  represents a single bond
- $R_b$  represents a group  $(C_1-C_6)$ alkyl, which is optionally substituted by one group selected from hydroxy,  $(C_1-C_6)$ alkoxy, amino, mono $(C_1-C_6)$ alkylamino, and di $(C_1-C_6)$ alkylamino (each alkyl amino being identical or different, independently of each other).

According to a first embodiment, the invention relates to compounds of formula (I) wherein:

- R<sub>1</sub> represents a cyclohexyl group optionally substituted by one hydroxy group, or a phenyl group optionally substituted by one tetrazolyl group or one -CO<sub>2</sub>R<sub>4</sub> group in which  
5 R<sub>4</sub> represents a hydrogen atom or a (C<sub>1</sub>-C<sub>6</sub>)alkyl group,
- R<sub>2</sub> represents a methyl group,
- R<sub>3</sub> represents a phenyl group substituted by one to three groups, identical or different, selected independently of each other from halogen, -OR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>7</sub>, -S(O)<sub>m</sub>R<sub>6</sub>, -S(O)<sub>m</sub>-NR<sub>6</sub>R<sub>7</sub>, -NR<sub>6</sub>COR<sub>7</sub>, and tetrazolyl, wherein:  
10 ✓ m is an integer from 0 to 2 inclusive,  
✓ R<sub>6</sub> and R<sub>7</sub>, identical or different, independently of each other, represent a hydrogen atom or a group of formula -X<sub>2</sub>-R<sub>b</sub> wherein:
  - X<sub>2</sub> represents a single bond or a (C<sub>1</sub>-C<sub>6</sub>)alkylene group,
  - R<sub>b</sub> represents a group selected from (C<sub>1</sub>-C<sub>6</sub>)alkyl, cycloalkyl, heterocycloalkyl,  
15 aryl and heteroaryl, these groups being optionally substituted by 1 to 3 groups, identical or different, selected independently of each other from hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)alkyl, amino, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino, di(C<sub>1</sub>-C<sub>6</sub>)alkylamino (each alkyl amino being identical or different, independently of each other), carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxycarbonyl, and benzyl.

20 According to a second embodiment, the invention relates to compounds of formula (I) wherein:

- R<sub>1</sub> represents a cyclohexyl group optionally substituted by one hydroxy group, or a phenyl group optionally substituted by one tetrazolyl group or one -CO<sub>2</sub>R<sub>4</sub> group in which R<sub>4</sub> represents a hydrogen atom or a (C<sub>1</sub>-C<sub>6</sub>)alkyl group,
- 25 • R<sub>2</sub> represents a methyl group,

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- R<sub>3</sub> represents a group selected from quinoxalinylyl, 1*H*-quinoxalinylyl-2-one, quinazolinylyl, 3*H*-quinazolinylyl-4-one, 1*H*-quinazolinylyl-2,4-dione, which are optionally substituted by one to three groups, identical or different, selected independently of each other from halogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, -OR<sub>6</sub>, and -NR<sub>6</sub>R<sub>7</sub>, wherein R<sub>6</sub> and R<sub>7</sub>, identical or different, independently of each other, represent a hydrogen atom or a group of formula -X<sub>2</sub>-R<sub>b</sub> wherein:
  - X<sub>2</sub> represents a single bond,
  - R<sub>b</sub> represents a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, which is optionally substituted by one group selected from hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, amino, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino, and di(C<sub>1</sub>-C<sub>6</sub>)alkylamino (each alkyl amino being identical or different, independently of each other).

The preferred compounds of the invention are:

- N-{4-[(2*Z*)-2-(cyclohexylimino)-3-methyl-2,3-dihydro-1,3-thiazol-5-yl]phenyl}acetamide,
- N-{4-[(2*Z*)-2-[(3-hydroxycyclohexyl)imino]-3-methyl-2,3-dihydro-1,3-thiazol-5-yl]phenyl}acetamide,
- 7-[(2*Z*)-2-(cyclohexylimino)-3-methyl-2,3-dihydro-1,3-thiazol-5-yl]quinazolin-4-amine,
- and 7-{(2*Z*)-2-[(3-hydroxycyclohexyl)imino]-3-methyl-2,3-dihydro-1,3-thiazol-5-yl}quinazolin-4-amine.

The optical isomers, the N-oxides, as well as the addition salts with a pharmaceutically acceptable acid or base, of the preferred compounds form an integral part of the invention.

The compounds provided by this invention are those defined in formula (I). In formula (I), it is understood that :

- a (C<sub>1</sub>-C<sub>6</sub>)alkyl group denotes a linear or branched group containing from 1 to 6 carbon atoms ; example of such groups, without implying any limitation are methyl, ethyl, propyl, isopropyl, tert-butyl, neopentyl, hexyl, ...
- a (C<sub>1</sub>-C<sub>6</sub>)alkylene group denotes a (C<sub>1</sub>-C<sub>6</sub>)alkyl group as defined hereinbefore which is comprised between two groups ; example of such groups, without implying any limitation are methylene (-(CH<sub>2</sub>-), ethylene (-(CH<sub>2</sub>)<sub>2</sub>-), ...



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- a (C<sub>2</sub>-C<sub>6</sub>)alkenyl group denotes a linear or branched group containing from 2 to 6 carbon atoms, and one or more carbon-carbon double bonds ; examples of such groups without implying any limitation are vinyl, allyl, 3-buten-1-yl, 2-methyl-buten-1-yl, hexenyl, ...
- 5 - a (C<sub>2</sub>-C<sub>6</sub>)alkynyl group denotes a linear or branched group containing from 2 to 6 carbon atoms, and one or more carbon-carbon triple bonds ; examples of such groups without implying any limitation are ethynyl, propynyl, 3-butyne-1-yl, 2-methyl-butyne-1-yl, hexynyl, ...
- a (C<sub>1</sub>-C<sub>6</sub>)alkoxy group means the alkyl group as mentioned above bound through an oxygen atom ; examples of such groups without implying any limitation are methoxy, ethoxy, *n*-propyloxy, *tert*-butyloxy, ...
- 10 - a mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino denotes an amino group substituted by one (C<sub>1</sub>-C<sub>6</sub>)alkyl group as defined hereinbefore ; example of such groups, without implying any limitation are methylamino, isobutylamino, ethylamino, ...
- 15 - a di(C<sub>1</sub>-C<sub>6</sub>)alkylamino denotes an amino group substituted by two (C<sub>1</sub>-C<sub>6</sub>)alkyl groups as defined hereinbefore, each alkyl group being identical or different independently of each other ; example of such groups, without implying any limitation are dimethylamino, diethylamino, methylethylamino, ...
- an aryl group denotes an aromatic monocyclic or bicyclic system containing from 5 to 10 carbon atoms, and in the case of a bicyclic system, one of the ring of which is aromatic in character, and the other ring of which may be aromatic or partially hydrogenated and it being understood that in the case of a bicyclic system when the second ring is partially hydrogenated then it may be optionally substituted by one or two oxo groups; examples of such groups without implying any limitation are, phenyl, naphthyl, indenyl, benzocyclobutenyl, benzocyclohexyl, benzocyclohex-3-enyl, benzocyclopentyl, benzocyclohexyl-1-one, ...
- 25 - a heteroaryl group denotes an aryl group as described above in which 1 to 4 carbon atoms are replaced by 1 to 4 hetero atoms, identical or different, selected independently of each other from oxygen, sulfur and nitrogen ; examples of such groups without implying any limitation are furyl, thienyl, pyrrolyl, pyrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzofuryl, benzothienyl, indolyl, quinolyl, isoquinolyl, benzodioxolyl, benzodioxinyl, benzisoxazolyl, phtalazinyl, benzo[1,2,5]thiadiazolyl, benzo[1,2,5]oxadiazolyl,
- 30

benzopyrrolinyl, quinoxalinyl, 1*H*-quinoxalinyl, quinazolinyl, 3*H*-quinazolinyl-4-one, 1*H*-quinazolinyl-2,4-dione,...

- a cycloalkyl group denotes a monocyclic or polycyclic system containing from 3 to 10 carbon atoms, this system being saturated or partially unsaturated but without aromatic character and it being understood that in the case of a polycyclic system each cycle could be fused together or formed a link; examples of such groups without implying any limitation are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl, cycloheptyl, adamantyl, decalinyl, norbornyl, cyclo[2,2,1]heptyl, cyclo[2,2,2]octyl ...

- a heterocycloalkyl group denotes a cycloalkyl group as defined hereinbefore in which 1 to 4 carbon atoms are replaced by 1 to 4 hetero atoms, identical or different, selected independently of each other from oxygen, sulfur, and nitrogen,

- an acyl group denotes a (C<sub>1</sub>-C<sub>6</sub>)alkyl group or a aryl group as defined above bound through a carbonyl group ; examples of such groups without implying any limitation are acetyl, ethylcarbonyl, benzoyl, ...

- a (C<sub>1</sub>-C<sub>6</sub>)alkoxycarbonyl denotes a (C<sub>1</sub>-C<sub>6</sub>)alkoxy group as defined hereinbefore bound through a carbonyl group ; examples of such groups without implying any limitation are methoxycarbonyl, ethoxycarbonyl, tert-butyloxycarbonyl,...

- optical isomers refer to racemates, enantiomers and diastereoisomers.

The invention also relates to the pharmaceutically acceptable salts of the compounds of formula (I). A review of the pharmaceutically acceptable salts will be found in *J. Pharm. Sci.*, 1977, 66, 1-19.

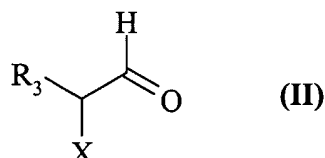
Pharmaceutically acceptable acids mean non-toxic mineral or organic acids. Among those there may be mentioned, without implying any limitation, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphonic acid, nitric acid, citric acid, acetic acid, trifluoroacetic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, tartaric acid, maleic acid, ascorbic acid, oxalic acid, methanesulfonic acid, camphoric acid, benzoic acid, toluenesulfonic acid, etc...

Pharmaceutically acceptable bases mean non-toxic mineral or organic bases. Among those, there may be mentioned, without implying any limitation, sodium hydroxide, potassium hydroxide, calcium hydroxide, triethylamine, tert-butylamine,

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dibenzylethylenediamine, piperidine, pyrrolidine, benzylamine, quaternary ammonium hydroxides, etc...

The invention also relates to a process for the preparation of compounds of formula (I), which uses as starting material a  $\alpha$ -haloaldehyde compound of formula (II):



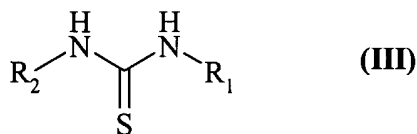
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wherein  $\text{R}_3$  is as defined in the compound of formula (I), and X represents a halogen atom like bromine or chlorine,

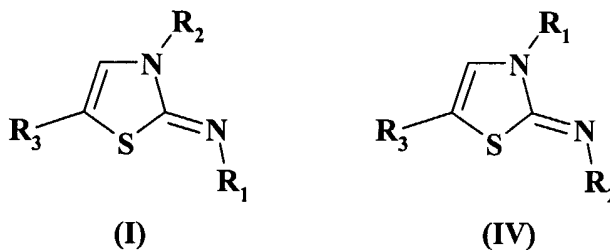
compound of formula (II) reacting :

- either in the presence of a polar solvent like for example, but without any limitations methanol or acetone, under heating condition with a thiourea of formula (III):

10



in which  $\text{R}_1$  and  $\text{R}_2$  are as defined in the compound of formula (I), to give a mixture of compounds of formula (I) and (IV):

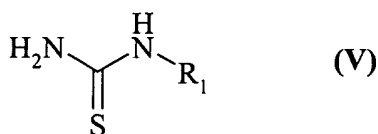


15

wherein  $\text{R}_1$ ,  $\text{R}_2$  and  $\text{R}_3$  are as defined hereinbefore,

compound of formula (I) being easily separated of the compound of formula (IV),

- or in the presence of an inert solvent under heating condition, with a thiourea of formula (V):

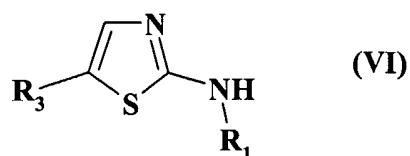


20

in which  $\text{R}_1$  is as defined in the compound of formula (I),

- 11 -

to give the compound of formula (VI):



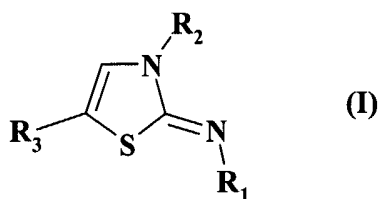
wherein  $R_1$  and  $R_3$  are as defined hereinbefore,

5 compound of formula (VI) being condensed with a compound of formula (VII):



wherein  $R_2$  is as defined in the compound of formula (I) and  $L_1$  represents a leaving group like, for example but without any limitation, bromine, chlorine, iodine, triflate, or mesylate group,

10 to give the compounds of general formula (I) in which  $R_1$ ,  $R_2$  and  $R_3$  are as defined hereinbefore :

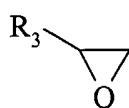


Compounds of formula (I) constitute compounds of the invention, which are purified, where appropriate, according to a conventional purification technique, which are separated,  
 15 where appropriate, into their different isomers according to a conventional separation technique, and which are converted, where appropriate, into addition salts thereof with a pharmaceutically-acceptable acid or base, or into N-oxide thereof.

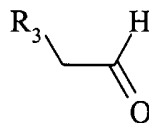
The compounds of formulae (II), (III), (V) and (VII) are commercially available or are obtained easily by using classical reactions of organic synthesis well known by the man  
 20 skilled in the art.

For illustrating this point, compound of formula (II) could be easily obtained by using as starting material an epoxy compound of formula (II/a) or an aldehyde derivative of formula (II/b):

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(II/a)



(II/b)

in which R<sub>3</sub> represents a cycloalkyl, an aryl, a heterocycloalkyl or an heteroaryl as described in the general definition of compound of formula (I),

5 compounds of formula (II/a) being then treated with a halide compound like trimethylsilyl bromine in basic medium to yield in the first step the  $\alpha$ -halogeno- $\beta$ -hydroxy derivative, which is treated by an oxidative agent to give the starting material (II), or compounds of formula (II/b) which is reacted with an halogenated agent like dibromide, dichloride or perbromide of pyridinium bromide, to give easily the starting material (II).

10 The compounds of the invention that are present in the form of a mixture of diastereoisomers are isolated in a pure form by using conventional separation techniques such as chromatography.

As mentioned above, compounds of formula (I) of the present invention are phosphodiesterase inhibitors, and more particularly inhibitors of the enzyme PDE7.

15 The present invention also relates to pharmaceutical compositions comprising as active ingredient at least one compound of formula (I), an isomer thereof, a N-oxide thereof, or an addition salt thereof with a pharmaceutically acceptable acid or base, alone or in combination with one or more pharmaceutically acceptable, inert, non-toxic excipients or carriers.

20 The invention also relates to a pharmaceutical composition comprising as active principle an effective amount of a compound of formula (I) alone or in combination with one or more pharmaceutically acceptable excipients or carriers. This pharmaceutical composition is useful for the treatment of a disease for which treatment by PDE7 inhibitor is relevant.

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More particularly, the pharmaceutical composition described above is useful for treating a pathology in which the disease to be treated is selected from T-cell-related diseases, autoimmune diseases, inflammatory diseases, respiratory diseases, CNS diseases, allergic diseases, endocrine or exocrine pancreas diseases, and gastrointestinal diseases.

5 In a preferred embodiment the pharmaceutical composition is useful to treat a disease which is selected from visceral pain, inflammatory bowel disease, osteoarthritis, multiple sclerosis, osteoporosis, chronic obstructive pulmonary disease (COPD), allergic rhinitis, asthma, cancer, acquired immune deficiency syndrome (AIDS) and graft rejection.

10 Among the pharmaceutical compositions according to the invention, there may be mentioned more especially those that are suitable for oral, parenteral (intravenous, intramuscular or subcutaneous), per- or trans-cutaneous, intravaginal, rectal, nasal, perlingual, buccal, ocular or respiratory administration.

15 Pharmaceutical compositions according to the invention for parenteral injections especially include aqueous and non-aqueous sterile solutions, dispersions, suspension and emulsions, and also sterile powders for reconstituting injectable solutions or dispersions.

Pharmaceutical compositions according to the invention for oral administration in solid form especially include tablets or dragées, sublingual tablets, sachets, gelatin capsules and granules, for oral, nasal, buccal or ocular administration in liquid form, especially include emulsions, solutions, suspensions, drop, syrups and aerosols.

20 Pharmaceutical compositions for rectal or vaginal administration are preferably suppositories, and those for per- or trans-cutaneous administration especially include powders, aerosols, creams, ointment, gels and patches.

The pharmaceutical compositions mentioned hereinbefore illustrate the invention but do not limit it in any way.

Among the pharmaceutically acceptable, inert, non-toxic excipients or carriers there may be mentioned, by way of non-limiting example, diluents, solvents, preservatives, wetting agents, emulsifiers, dispersing agents, binders, swelling agents, disintegrating agents, retardants, lubricants, absorbents, suspending agents, colorants, aromatizing agents  
5 etc...

The useful dosage varies according to the age and weight of the patient, the administration route, the pharmaceutical composition used, the nature and severity of the disorder and the administration of any associated treatments. The dosage ranges from 1 mg to 1 g per day in one or more administrations. The compositions are prepared by methods  
10 that are common to those skilled in the art and generally comprise 0.5% to 80% by weight of active principle (compound of formula (I)) and 20% to 99.5% by weight of pharmaceutically acceptable excipients or carriers.

The compounds of the invention are PDE inhibitors, and particularly PDE7 inhibitors.

Preferably, the compounds of the invention are selective PDE7 inhibitors.  
15 "Selective PDE7 inhibitors" refers to compounds which have an  $IC_{50}$  for PDE7 at least 5 times lower than the  $IC_{50}$  for a PDE distinct from PDE7, and preferably at least 10 times, 15 times, 20 times, 30 times, 40 times, 50 times or 100 times lower than the  $IC_{50}$  value for a PDE distinct from PDE7.

A PDE distinct from PDE7 refers preferably to a PDE chosen from PDE1, PDE3,  
20 PDE4 or PDE5.

The examples that follow illustrate the invention but do not limit it in any way. The compounds described in these examples could be obtained by the following synthetic ways.

The starting materials used are products that are known or that are prepared  
25 according to known operating procedures.

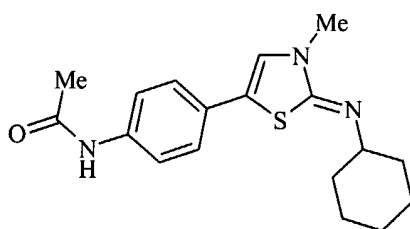
The structures of the compounds described in the Examples are determined according to the usual spectrophotometric techniques (infrared, nuclear magnetic

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resonance, mass spectrometry, ...). The reactions are monitored by tin layer chromatography (T.L.C.).

## **EXAMPLES**

5 **Example 1: N-{4-[(2Z)-2-(cyclohexylimino)-3-methyl-2,3-dihydro-1,3-thiazol-5-yl]phenyl}acetamide**



***Step 1: N-cyclohexyl-5-(4-nitrophenyl)-1,3-thiazol-2-amine***

A solution of bromo(4-nitrophenyl)acetaldehyde and potassium thiocyanate (1.2  
10 equivalents) in methanol is stirred at room temperature for 1 hour. The cyclohexylamine (1,05 equivalents) is added drop-wise and the mixture is heated under reflux until completion of the reaction (5-12 hours). After cooling to 0°C the precipitate is filtered off and washed with water. The crude material is purified by usual silica gel chromatography to give the desired compound.

15 ***Step 2: N-[(2Z)-3-methyl-5-(4-nitrophenyl)-1,3-thiazol-2(3H)-ylidene]cyclohexanamine***

To a solution of the compound, obtained in the preceding Step 1, in anhydrous dioxane, methyltrifluoromethane sulfonate (1.1 equivalents) is added. The resultant mixture is stirred for 24 hours until disappearance of starting material. 2 equivalents of triethylamine  
20 are added, then the mixture is concentrated by distillation under reduced pressure. The residue is purified via column chromatography on silica gel to give the desired nitro compound.

***Step 3: N-[(2Z)-5-(4-aminophenyl)-3-methyl-1,3-thiazol-2(3H)-ylidene]-N-cyclohexylamine***



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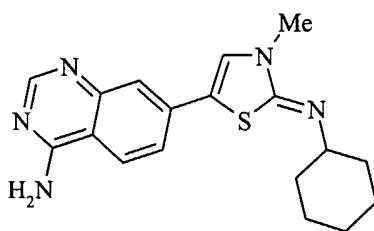
Tin chloride dihydrate is added to a solution of the compound, obtained in the preceding Step 2, in ethanol at 70°C and the mixture is refluxed for 3 hours until reaction completion. The mixture is then filtered through a pad of celite and the filtrate is evaporated under vacuum to dryness. The crude material is basified with a saturated solution of sodium bicarbonate then extracted with ethyl acetate. The organic layer is washed with water and brine, dried over MgSO<sub>4</sub>, filtered and concentrated under vacuum. The residue is chromatographed over silica gel to give the desired compound.

**Step 4: *N*-{4-[(2*Z*)-2-(cyclohexylimino)-3-methyl-2,3-dihydro-1,3-thiazol-5-yl]phenyl}acetamide**

10

To a solution of the compound, obtained in the preceding Step 3, and triethylamine (1.05 equivalent) in tetrahydrofuran at 0°C, 1 equivalent of acetyl chloride is added and after 15 minutes of stirring the mixture is allowed to room temperature for 5 hours until disappearance of starting material. The mixture is concentrated under vacuum and the residue is purified by chromatography on silica gel the expected compound.

**Example 2: 7-[(2*Z*)-2-(cyclohexylimino)-3-methyl-2,3-dihydro-1,3-thiazol-5-yl]quinazolin-4-amine**



**Step 1: 7-[2-(cyclohexylamino)-1,3-thiazol-5-yl]quinazolin-4(3*H*)-one**

20 A solution of bromo-(4-oxo-3,4-dihydro-quinazolin-7-yl)acetaldehyde and *N*-cyclohexylthiourea in dimethylformamide is heated at 70°C until completion of the reaction (5-12 hours). The mixture is quenched with 10% dimethylamine in ethanol and the solvent is removed under reduced pressure. The crude is purified by chromatography on silica gel to isolate the desired compound.

**Step 2: 7-[(2Z)-2-(cyclohexylimino)-3-methyl-2,3-dihydro-1,3-thiazol-5-yl]quinazolin-4(3H)-one**

To a solution of the compound, obtained in the preceding Step 1, in anhydrous dioxane, methyltrifluoromethane sulfonate (1.1 equivalents) is added. The resulting mixture is stirred for 24 hours. 2 equivalents of triethylamine are added, then the mixture is concentrated by distillation under reduced pressure. The residue is purified by chromatography over silica gel to give the desired product.

**Step 3: N-[(2Z)-5-(4-chloroquinazolin-7-yl)-3-methyl-1,3-thiazol-2(3H)-ylidene]-N-cyclohexylamine**

A mixture of the compound obtained in the preceding Step 2, thionyl chloride and a catalytic amount of dimethylformamide in toluene is refluxed for 3 hours before distillation of solvents under reduced pressure. The residue is diluted in dichloromethane then neutralized with triethylamine until pH=7. The organic phase is washed with water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude material is quickly purified by chromatography on silica gel to give the desired product.

**Step 4: 7-[(2Z)-2-(cyclohexylimino)-3-methyl-2,3-dihydro-1,3-thiazol-5-yl]quinazolin-4-amine**

A solution of the compound obtained in the preceding Step 3 in a 2N solution of NH<sub>3</sub> in isopropanol is stirred for 6 hours at 60°C until disappearance of starting material. The mixture is then concentrated. To this residue a solution of NaOH (0.1N) is added and the aqueous solution is extracted with dichloromethane. The organic layer is washed with water, brine and dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to give the crude material which is purified by chromatography on silica gel to give the desired compound.

**Example 3: Biological results / In vitro inhibition of the phosphodiesterase 7 and of other phosphodiesterases**

The capacity of the compounds of the invention to inhibit cyclic nucleotide phosphodiesterases is evaluated by measuring their  $IC_{50}$  (concentration necessary to inhibit the enzymatic activity by 50 %).

PDE3A3, PDE4D3, PDE7A1 are cloned and expressed in insect cells Sf21 using the  
5 baculovirus expression system and we uses directly the cell culture supernatant as enzyme source. The source of PDE1 and of PDE5 are human cell lines (respectively TPH1 human monocytes and MCF7 human caucasian breast adenocarcinoma).

They are obtained partially purified on an anion exchange column (Mono Q) according to a method adapted from Lavan B.E., Lakey T., Houslay M.D. Biochemical  
10 Pharmacology, 1989, 38 (22), 4123-4136.

Measurement of the enzymatic activity for the various types of PDE is then made according to a method adapted from W.J. Thompson et al. 1979, Advances in Cyclic Nucleotide Research, Vol. 10 : 69-92, ed. G. Brooker et al. Raven Press, NY.

The substrate used is cGMP for PDE1 and PDE5 and cAMP for PDE 3, PDE 4 and  
15 PDE 7. The substrate concentration is 0.2 $\mu$ M for PDE 1, PDE 3 and PDE 5, 0,25 $\mu$ M for PDE 4 and 50nM for PDE 7.

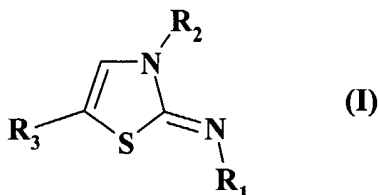
The enzymatic reaction is stopped after 1 hour for PDE 1, PDE 3 and PDE 5 and 10 minutes for PDE 4 and PDE 7.

In order to determine their  $IC_{50}$ , compounds of the invention are assayed at 8 to 11  
20 concentrations ranging from 0.02nM to 100 $\mu$ M for PDE 4 and PDE 7 and at least at 6 concentrations ranging from 0,1 $\mu$ M to 30 $\mu$ M for PDE 1, 3 and 5.

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**CLAIMS**

1. A compound selected from those of formula (I):



wherein:

- 5 •  $R_1$  represents a group selected from cycloalkyl, heterocycloalkyl, aryl and heteroaryl, those groups being optionally substituted by one or more groups, identical or different, selected independently of each other from halogen, trifluoromethyl, nitro, cyano, oxo,  $-NR_4R_5$ ,  $-CO_2R_4$ ,  $-CONR_4R_5$ ,  $-OR_4$ ,  $-S(O)_nR_4$ ,  $-S(O)_nNR_4R_5$ , tetrazolyl, and  $(C_1-C_6)$ alkyl which is optionally substituted by 1 to 3 groups, identical or different, selected
- 10 independently of each other from  $-OR_4$ ,  $-NR_4R_5$ , and  $-CO_2R_4$ , wherein:
- ✓  $n$  is an integer from 0 to 2 inclusive,
  - ✓  $R_4$  and  $R_5$ , identical or different, independently of each other, represent a hydrogen atom or a group of formula  $-X_1-R_a$  wherein:
    - $X_1$  represent a single bond or a  $(C_1-C_6)$ alkylene group,
    - 15 -  $R_a$  represents a group selected from  $(C_1-C_6)$ alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl,
  - $R_2$  represents a group selected from  $(C_1-C_6)$ alkyl,  $(C_2-C_6)$ alkenyl,  $(C_2-C_6)$ alkynyl, aryl and cycloalkyl,
  - $R_3$  represents a group selected from cycloalkyl, heterocycloalkyl, aryl and heteroaryl,
- 20 these groups being optionally substituted by one or more groups, identical or different, selected independently of each other from halogen, nitro, cyano, trifluoromethyl, oxo,  $(C_1-C_6)$ alkyl,  $-OR_6$ ,  $-NR_6R_7$ ,  $-COR_6$ ,  $-CO_2R_6$ ,  $-CONHOH$ ,  $-CONR_6R_7$ ,  $-S(O)_mR_6$ ,  $-S(O)_m-NR_6R_7$ ,  $-NR_6COR_7$ ,  $-NR_6SO_2R_7$ ,  $-N(SO_2R_7)_2$ ,  $-NR_6-CO-NR_7R_8$ ,  $C(=N-CN)NR_6R_7$ ,  $NR_8-C(=N-CN)NR_6R_7$  and tetrazolyl optionally substituted with a  $(C_1-C_4)$ alkyl wherein:
- 25 ✓  $m$  is an integer from 0 to 2 inclusive,

- 20 -

- ✓ R<sub>6</sub> and R<sub>7</sub>, identical or different, independently of each other, represent a hydrogen atom or a group of formula -X<sub>2</sub>-R<sub>b</sub> wherein:
- X<sub>2</sub> represents a single bond or a (C<sub>1</sub>-C<sub>6</sub>)alkylene group,
  - R<sub>b</sub> represents a group selected from (C<sub>1</sub>-C<sub>6</sub>)alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, these groups being optionally substituted by 1 to 3 groups, identical or different, selected independently of each other from hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)alkyl, amino, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino, di(C<sub>1</sub>-C<sub>6</sub>)alkylamino (each alkyl amino being identical or different, independently of each other), carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxycarbonyl, and benzyl,
- 10 ✓ R<sub>8</sub> represents a hydrogen atom or a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, optionally the racemics forms thereof, isomers thereof, N-oxides thereof, and the pharmaceutically acceptable acid or base salts thereof, with the exclusion of the following compounds:
- (3-Cyclohexyl-5-phenyl-3H-thiazol-2-ylidene)-phenyl-amine,
- 15 2-phenylimino-3-phenyl-5-(2,5-dihydroxy-3,4,6-trichlorophenyl)thiazoline, 2-phenylimino-3-phenyl-5-(3,5,6-trichloro-1,4-benzoquinon-2-yl)thiazoline, and, (3-allyl-5-phenyl-3H-thiazol-2-ylidene)-*o*-tolyl-amine;
- it being understood that:
- an aryl group denotes an aromatic monocyclic or bicyclic system containing from 5 20 to 10 carbon atoms, and in the case of a bicyclic system, one of the ring of which is aromatic in character, and the other ring of which may be aromatic or partially hydrogenated and it being understood that in the case of a bicyclic system when the second ring is partially hydrogenated then it may be optionally substituted by one or two oxo groups,
  - 25 - a heteroaryl group denotes an aryl group as described above in which 1 to 4 carbon atoms are replaced by 1 to 4 hetero atoms, identical or different, selected independently of each other from oxygen, sulfur and nitrogen,
  - a cycloalkyl group denotes a monocyclic or polycyclic system containing from 3 to 10 carbon atoms, this system being saturated or partially unsaturated but without aromatic 30 character and it being understood that in the case of a polycyclic system each cycle could be fused together or formed a link,

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- a heterocycloalkyl group denotes a cycloalkyl group as defined hereinbefore in which 1 to 4 carbon atoms are replaced by 1 to 4 hetero atoms, identical or different, selected independently of each other from oxygen, sulfur, and nitrogen.

2. A compound of formula (I) according to claim 1 characterized in that :

- 5
- R<sub>1</sub> represents a group selected from cycloalkyl and aryl, each of these groups being optionally substituted by 1 to 3 groups selected from halogen, trifluoromethyl, -CO<sub>2</sub>R<sub>4</sub>, -OR<sub>4</sub>, and tetrazolyl, in which R<sub>4</sub> represents a hydrogen atom or a (C<sub>1</sub>-C<sub>6</sub>)alkyl group,
  - R<sub>2</sub> and R<sub>3</sub> being as described in the compound of formula (I),
- optionally the racemics forms thereof, isomers thereof, N-oxides thereof, and the
- 10 pharmaceutically acceptable acid or base salts thereof.

3. A compound of formula (I) according to anyone of claims 1 or 2, characterized in that:

- R<sub>1</sub> represents :
    - a cyclohexyl group optionally substituted by one hydroxy group,
    - or a phenyl group optionally substituted by one tetrazolyl group or one -CO<sub>2</sub>R<sub>4</sub>
- 15 group in which R<sub>4</sub> represents a hydrogen atom or a (C<sub>1</sub>-C<sub>6</sub>)alkyl group,
- R<sub>2</sub> and R<sub>3</sub> being as described in the compound of formula (I),
- optionally the racemics forms thereof, isomers thereof, N-oxides thereof, and the pharmaceutically acceptable acid or base salts thereof.

4. A compound of formula (I) according to claim 1 characterized in that R<sub>2</sub> represents a

20 (C<sub>1</sub>-C<sub>6</sub>)alkyl group,

R<sub>1</sub> and R<sub>3</sub> being as described in the compound of formula (I), optionally the racemics forms thereof, isomers thereof, N-oxides thereof, and the pharmaceutically acceptable acid or base salts thereof.

5. A compound of formula (I) according to claim 1 characterized in that R<sub>2</sub> represents a

25 methyl group,

R<sub>1</sub> and R<sub>3</sub> being as described in the compound of formula (I), optionally the racemics forms thereof, isomers thereof, N-oxides thereof, and the pharmaceutically acceptable acid or base salts thereof.

6. A compound of formula (I) according to claim 1 characterized in that R<sub>3</sub> represents a group selected from aryl and heteroaryl which are optionally substituted by one to three groups, identical or different, selected independently of each other from halogen, nitro, cyano, trifluoromethyl, oxo, (C<sub>1</sub>-C<sub>6</sub>)alkyl, -OR<sub>6</sub>, -NR<sub>6</sub>R<sub>7</sub>, -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CONHOH,  
 5 -CONR<sub>6</sub>R<sub>7</sub>, -S(O)<sub>m</sub>R<sub>6</sub>, -S(O)<sub>m</sub>-NR<sub>6</sub>R<sub>7</sub>, -NR<sub>6</sub>COR<sub>7</sub>, -NR<sub>6</sub>SO<sub>2</sub>R<sub>7</sub>, -N(SO<sub>2</sub>R<sub>7</sub>)<sub>2</sub>, -NR<sub>6</sub>-CO-NR<sub>7</sub>R<sub>8</sub>, and tetrazolyl, wherein:

- ✓ m is an integer from 0 to 2 inclusive,
  - ✓ R<sub>6</sub> and R<sub>7</sub>, identical or different, independently of each other, represent a hydrogen atom or a group of formula -X<sub>2</sub>-R<sub>b</sub> wherein:
    - 10 - X<sub>2</sub> represents a single bond or a (C<sub>1</sub>-C<sub>6</sub>)alkylene group,
    - R<sub>b</sub> represents a group selected from (C<sub>1</sub>-C<sub>6</sub>)alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, these groups being optionally substituted by 1 to 3 groups, identical or different, selected independently of each other from hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)alkyl, amino, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino, di(C<sub>1</sub>-C<sub>6</sub>)alkylamino  
 15 (each alkyl amino being identical or different, independently of each other), carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxycarbonyl, and benzyl,
    - ✓ R<sub>8</sub> represents a hydrogen atom or a (C<sub>1</sub>-C<sub>6</sub>)alkyl group,
- R<sub>1</sub> and R<sub>2</sub> being as described in the compound of formula (I), optionally the racemics forms thereof, isomers thereof, N-oxides thereof, and the  
 20 pharmaceutically acceptable acid or base salts thereof.

7. A compound of formula (I) according to anyone of claims 1 or 6 characterized in that R<sub>3</sub> represents a group selected from phenyl, pyridyl, thienyl, isoxazolyl, pyrazolyle, pyrazinyl, quinolyl, quinoxaliny, 1*H*-quinoxaliny-2-one, quinazoliny, 3*H*-quinazoliny-4-one, 1*H*-quinazoliny-2,4-dione, indolyle, benzisoxazolyl, phtalazinyl,  
 25 and benzo[1,3]dioxolyle, which are optionally substituted by one to three groups, identical or different, selected independently of each other from halogen, nitro, cyano, trifluoromethyl, oxo, (C<sub>1</sub>-C<sub>6</sub>)alkyl, -OR<sub>6</sub>, -NR<sub>6</sub>R<sub>7</sub>, -COR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CONHOH, -CONR<sub>6</sub>R<sub>7</sub>, -S(O)<sub>m</sub>R<sub>6</sub>, -S(O)<sub>m</sub>-NR<sub>6</sub>R<sub>7</sub>, -NR<sub>6</sub>COR<sub>7</sub>, -NR<sub>6</sub>SO<sub>2</sub>R<sub>7</sub>, -N(SO<sub>2</sub>R<sub>7</sub>)<sub>2</sub>, -NR<sub>6</sub>-CO-NR<sub>7</sub>R<sub>8</sub>, and tetrazolyl, wherein:

- 30 ✓ m is an integer from 0 to 2 inclusive,

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- ✓ R<sub>6</sub> and R<sub>7</sub>, identical or different, independently of each other, represent a hydrogen atom or a group of formula -X<sub>2</sub>-R<sub>b</sub> wherein:
- X<sub>2</sub> represents a single bond or a (C<sub>1</sub>-C<sub>6</sub>)alkylene group,
  - R<sub>b</sub> represents a group selected from (C<sub>1</sub>-C<sub>6</sub>)alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, these groups being optionally substituted by 1 to 3 groups, identical or different, selected independently of each other from hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)alkyl, amino, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino, di(C<sub>1</sub>-C<sub>6</sub>)alkylamino (each alkyl amino being identical or different, independently of each other), carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxycarbonyl, and benzyl,
- 5
- 10 ✓ R<sub>8</sub> represents a hydrogen atom or a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, R<sub>1</sub> and R<sub>2</sub> being as described in the compound of formula (I), optionally the racemics forms thereof, isomers thereof, N-oxides thereof, and the pharmaceutically acceptable acid or base salts thereof.

8. A compound of formula (I) according to anyone of claims 1, 6 and 7, characterized in that R<sub>3</sub> represents a phenyl group substituted by one to three groups, identical or different, selected independently of each other from halogen, -OR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>7</sub>, -S(O)<sub>m</sub>R<sub>6</sub>, -S(O)<sub>m</sub>-NR<sub>6</sub>R<sub>7</sub>, -NR<sub>6</sub>COR<sub>7</sub>, and tetrazolyl, wherein:

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- ✓ m is an integer from 0 to 2 inclusive,
  - ✓ R<sub>6</sub> and R<sub>7</sub>, identical or different, independently of each other, represent a hydrogen atom or a group of formula -X<sub>2</sub>-R<sub>b</sub> wherein:
- X<sub>2</sub> represents a single bond or a (C<sub>1</sub>-C<sub>6</sub>)alkylene group,
  - R<sub>b</sub> represents a group selected from (C<sub>1</sub>-C<sub>6</sub>)alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, these groups being optionally substituted by 1 to 3 groups, identical or different, selected independently of each other from hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)alkyl, amino, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino, di(C<sub>1</sub>-C<sub>6</sub>)alkylamino (each alkyl amino being identical or different, independently of each other), carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxycarbonyl, and benzyl,
- 20
- 25
- optionally the racemics forms thereof, isomers thereof, N-oxides thereof, and the pharmaceutically acceptable acid or base salts thereof.



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9. A compound of formula (I) according to anyone of claims 1, 6 and 7, characterized in that  $R_3$  represents a group selected from quinoxaliny, 1*H*-quinoxaliny-2-one, quinazoliny, 3*H*-quinazoliny-4-one, and 1*H*-quinazoliny-2,4-dione, which are optionally substituted by one to three groups, identical or different, selected independently of each other from halogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, -OR<sub>6</sub>, and -NR<sub>6</sub>R<sub>7</sub>, wherein:

$R_6$  and  $R_7$ , identical or different, independently of each other, represent a hydrogen atom or a group of formula -X<sub>2</sub>-R<sub>b</sub> wherein:

- X<sub>2</sub> represents a single bond,
- R<sub>b</sub> represents a group (C<sub>1</sub>-C<sub>6</sub>)alkyl, which is optionally substituted by one group selected from hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, amino, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino, and di(C<sub>1</sub>-C<sub>6</sub>)alkylamino (each alkyl amino being identical or different, independently of each other),

optionally the racemics forms thereof, isomers thereof, N-oxides thereof, and the pharmaceutically acceptable acid or base salts thereof.

15 10. A compound of formula (I) according to anyone of claims 1 to 8, characterized in that :

- R<sub>1</sub> represents a cyclohexyl group optionally substituted by one hydroxy group, or a phenyl group optionally substituted by one tetrazolyl group or one -CO<sub>2</sub>R<sub>4</sub> group in which R<sub>4</sub> represents a hydrogen atom or a (C<sub>1</sub>-C<sub>6</sub>)alkyl group,

- R<sub>2</sub> represents a methyl group,

- 20 • R<sub>3</sub> represents a phenyl group substituted by one to three groups, identical or different, selected independently of each other from halogen, -OR<sub>6</sub>, -CO<sub>2</sub>R<sub>6</sub>, -CONR<sub>6</sub>R<sub>7</sub>, -S(O)<sub>m</sub>R<sub>6</sub>, -S(O)<sub>m</sub>-NR<sub>6</sub>R<sub>7</sub>, -NR<sub>6</sub>COR<sub>7</sub>, and tetrazolyl, wherein:

✓ m is an integer from 0 to 2 inclusive,

- 25 ✓ R<sub>6</sub> and R<sub>7</sub>, identical or different, independently of each other, represent a hydrogen atom or a group of formula -X<sub>2</sub>-R<sub>b</sub> wherein:

- X<sub>2</sub> represents a single bond or a (C<sub>1</sub>-C<sub>6</sub>)alkylene group,
- R<sub>b</sub> represents a group selected from (C<sub>1</sub>-C<sub>6</sub>)alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, these groups being optionally substituted by 1 to 3 groups,

- 25 -

identical or different, selected independently of each other from hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)alkyl, amino, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino, di(C<sub>1</sub>-C<sub>6</sub>)alkylamino (each alkyl amino being identical or different, independently of each other), carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxycarbonyl, and benzyl,

5 optionally the racemics forms thereof, isomers thereof, N-oxides thereof, and the pharmaceutically acceptable acid or base salts thereof.

**11.** A compound of formula (I) according to anyone of claims 1 to 9, characterized in that :

- R<sub>1</sub> represents a cyclohexyl group optionally substituted by one hydroxy group, or a phenyl group optionally substituted by one tetrazolyl group or one -CO<sub>2</sub>R<sub>4</sub> group in which

10 R<sub>4</sub> represents a hydrogen atom or a (C<sub>1</sub>-C<sub>6</sub>)alkyl group,

- R<sub>2</sub> represents a methyl group,

- R<sub>3</sub> represents a group selected from quinoxaliny, 1*H*-quinoxaliny-2-one, quinazoliny, 3*H*-quinazoliny-4-one, 1*H*-quinazoliny-2,4-dione, which are optionally substituted by one to three groups, identical or different, selected independently of each other from halogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, -OR<sub>6</sub>, and -NR<sub>6</sub>R<sub>7</sub>, wherein R<sub>6</sub> and R<sub>7</sub>, identical or different, independently

15 of each other, represent a hydrogen atom or a group of formula -X<sub>2</sub>-R<sub>b</sub> wherein:

- X<sub>2</sub> represents a single bond,

- R<sub>b</sub> represents a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, which is optionally substituted by one group selected from hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, amino, mono(C<sub>1</sub>-C<sub>6</sub>)alkylamino, and di(C<sub>1</sub>-C<sub>6</sub>)alkylamino (each alkyl amino being identical or different, independently of

20 each other),

optionally the racemics forms thereof, isomers thereof, N-oxides thereof, and the pharmaceutically acceptable acid or base salts thereof.

25 **12.** A compound according to claim 1, which is selected from:

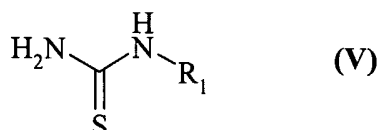
- N-{4-[(2*Z*)-2-(cyclohexylimino)-3-methyl-2,3-dihydro-1,3-thiazol-5-yl]phenyl}acetamide,

- N-{4-[(2*Z*)-2-[(3-hydroxycyclohexyl)imino]-3-methyl-2,3-dihydro-1,3-thiazol-5-yl]phenyl}acetamide,



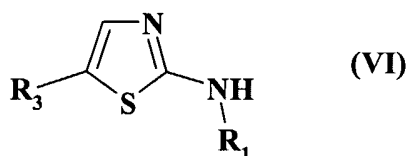
- 27 -

▪ or in the presence of an inert solvent under heating condition, with a thiourea compound of formula (V):



in which R<sub>1</sub> is as defined in the compound of formula (I),

5 to give the compound of formula (VI):



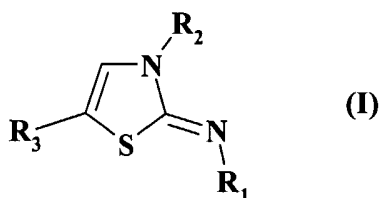
wherein R<sub>1</sub> and R<sub>3</sub> are as defined hereinbefore,

compound of formula (VI) being condensed with a compound of formula (VII):



wherein R<sub>2</sub> is as defined in the compound of formula (I) and L<sub>1</sub> represents a leaving group,

to give the compounds of general formula (I) in which R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> are as defined hereinbefore :



15

compounds of formula (I) constitute compounds of the invention, which are purified, where appropriate, according to a conventional purification technique, which are separated, where appropriate, into their different isomers according to a conventional separation technique, and which are converted, where appropriate, into addition salts thereof with a pharmaceutically-acceptable acid or base, or into N-oxide thereof.

**14.** A pharmaceutical composition comprising as active ingredient an effective amount of a compound as claim in anyone of claims 1 to 12, alone or in combination with one or more pharmaceutically acceptable excipients or carriers.

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**15.** A pharmaceutical composition according to claim 14 comprising as active principle an effective amount of a compound as claimed in anyone of claim 1 to 12 useful for the treatment of a disease for which treatment by PDE7 inhibitor is relevant.

**16.** A pharmaceutical composition according to claim 15 in which the disease to be treated  
5 is selected from T-cell-related diseases, autoimmune diseases, inflammatory diseases, respiratory diseases, CNS diseases, allergic diseases, endocrine or exocrine pancreas diseases, fertility diseases, and gastrointestinal diseases.

**17.** A pharmaceutical composition according to claim 15 in which the disease to be treated  
10 is selected from visceral pain, inflammatory bowel disease, osteoarthritis, multiple sclerosis, osteoporosis, chronic obstructive pulmonary disease (COPD), allergic rhinitis, asthma, cancer, acquired immune deficiency syndrome (AIDS) and graft rejection.

## INTERNATIONAL SEARCH REPORT

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| Internal application No<br>PCT/EP 03/02276 |
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## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/426 C07D277/42 C07D417/04 A61K31/427 A61P37/00

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)

IPC 7 C07D

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

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

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

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 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

° Special categories of cited documents :

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document but published on or after the international filing date

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\*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.

\*&amp;\* document member of the same patent family

Date of the actual completion of the international search

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Date of mailing of the international search report

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 PCT/EP 03/02276

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT |   |                       |
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PCT/EP 03/02276

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