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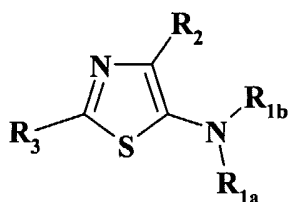
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(54) Title: (4,2-DISUBSTITUTED-THIAZOL-5-YL)AMINE COMPOUNDS AS PDE7 INHIBITORS



(I)

(57) Abstract: A compound selected from those of formula (I), wherein R_{1a}, R_{1b}, R₂, R₃ 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 specific inhibitors of phosphodiesterase-7 (PDE-7).

(4,2-disubstituted-thiazol-5-yl)amine compounds as PDE7 inhibitors

The present invention relates to (4,2-disubstituted-thiazol-5-yl)amine derivatives, a process for their preparation, and pharmaceutical compositions containing them. These
5 new compounds are 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 disease 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,
10 osteoporosis, chronic 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
15 (cAMP and cGMP respectively) into their corresponding 5'-monophosphate nucleotides. 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,
20 numbered PDE 1 through PDE 11, have been identified on the basis of primary structure, 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 ($K_m=0.2 \mu M$), that is not affected by cGMP potent selective PDE isoenzyme inhibitors.

25 PDE7 activity or protein has been detected in T-cell lines, B-cell lines, airway 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
30 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.

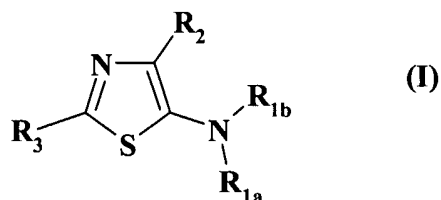
A functional role of PDE7 in T-cell activation has also been disclosed; therefore selective PDE7 inhibitors would be candidates for the treatment of T-cell-related diseases.

- 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 (4,2-disubstituted-thiazol-5-yl)amine 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_{1a} represents a group selected from hydrogen, (C₁-C₆)alkyl, and aryl(C₁-C₆)alkyl,
- R_{1b} 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,
- 20 -NR₄R₅, -CO₂R₄, -CONR₄R₅, -OR₄, -S(O)_nR₄, -S(O)_nNR₄R₅, tetrazolyl, and (C₁-C₆)alkyl which is optionally substituted by 1 to 3 groups, identical or different, selected independently of each other from -OR₄, -NR₄R₅, and -CO₂R₄, wherein:

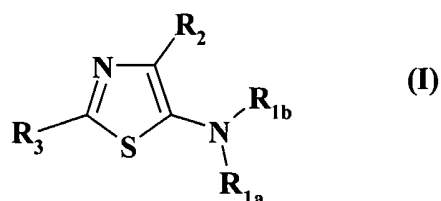
✓ n is an integer from 0 to 2 inclusive,

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- ✓ R₄ and R₅, identical or different, independently of each other, represent a hydrogen atom or a group of formula -X₁-R_a wherein:
- X₁ represents a single bond or a (C₁-C₆)alkylene group,
 - R_a represents a group selected from (C₁-C₆)alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl,
- 5
- R₂ represents a group selected from (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, aryl and cycloalkyl,
 - R₃ 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, (C₁-C₆)alkyl, -OR₆, -NR₆R₇, -COR₆, -CO₂R₆, -CONHOH, -CONR₆R₇, -S(O)_mR₆, -S(O)_m-NR₆R₇, -NR₆COR₇, -NR₆SO₂R₇, -N(SO₂R₇)₂, -NR₆-CO-NR₇R₈, C(=N-CN)NR₆R₇, NR₈-C(=N-CN)NR₆R₇ and tetrazolyl optionally substituted with a (C₁-C₄)alkyl, wherein:
 - ✓ m is an integer from 0 to 2 inclusive,
- 10
- 15 ✓ R₆ and R₇, identical or different, independently of each other, represent a hydrogen atom or a group of formula -X₂-R_b wherein:
- X₂ represents a single bond or a (C₁-C₆)alkylene group,
 - R_b represents a group selected from (C₁-C₆)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, (C₁-C₆)alkoxy, (C₁-C₆)alkyl, amino, mono(C₁-C₆)alkylamino, di(C₁-C₆)alkylamino (each alkyl being identical or different, independently of each other), carboxy, (C₁-C₆)alkoxycarbonyl, and benzyl,
 - R₈ represents a hydrogen atom or a (C₁-C₆)alkyl group,
- 20
- 25 optionally the racemics forms thereof, isomers thereof, N-oxides thereof, and the pharmaceutically acceptable acid or base salts thereof.

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

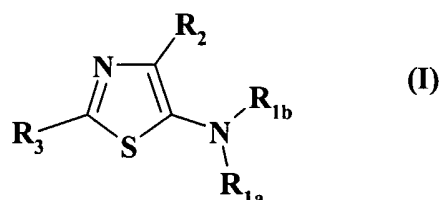
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wherein R_{1a} , R_{1b} , R_2 and R_3 are as defined above, with the exclusion of the following compounds:

- (4-Methyl-2-phenyl-thiazol-5-yl)-phenyl-amine,
- 5 (2,4-diphenyl-thiazol-5-yl)-phenyl-amine,
- (2,4-diphenyl-thiazol-5-yl)-(3-fluoro-phenyl)-amine,
- (2,4-diphenyl-thiazol-5-yl)-(4-fluoro-phenyl)-amine,
- (4-chloro-phenyl)- (2,4-diphenyl-thiazol-5-yl)-amine,
- (2-chloro-phenyl)- (2,4-diphenyl-thiazol-5-yl)-amine,
- 10 (2,4-diphenyl-thiazol-5-yl)-*p*-tolyl-amine, and,
- (2,4-diphenyl-thiazol-5-yl)-(4-methoxy-phenyl)-amine.

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



- wherein R_{1a} , R_{1b} , R_2 and R_3 are as defined above, with the exclusion of the following
- 15 compounds:

- (4-Methyl-2-phenyl-thiazol-5-yl)-phenyl-amine,
- (2,4-diphenyl-thiazol-5-yl)-phenyl-amine,
- (2,4-diphenyl-thiazol-5-yl)-(3-fluoro-phenyl)-amine,
- (2,4-diphenyl-thiazol-5-yl)-(4-fluoro-phenyl)-amine,
- 20 (4-chloro-phenyl)- (2,4-diphenyl-thiazol-5-yl)-amine,
- (2-chloro-phenyl)- (2,4-diphenyl-thiazol-5-yl)-amine,
- (2,4-diphenyl-thiazol-5-yl)-*p*-tolyl-amine, and,
- (2,4-diphenyl-thiazol-5-yl)-(4-methoxy-phenyl)-amine,

- and with the proviso that R_{1b} is other than a substituted pyrimidine or a substituted
- 25 pyrimidine fused to one or several other cycles.

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The substituent R_{1a} that is preferred according to the invention is the hydrogen atom or a (C₁-C₆)alkyl group, and the substituent R_{1b} 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, -CO₂R₄, -OR₄, and
5 tetrazolyl, in which R₄ represents a hydrogen atom or a (C₁-C₆)alkyl group.

More particularly, the substituent R_{1a} that is preferred according to the invention is the hydrogen atom, and the substituent R_{1b} 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 -CO₂R₄ group in which R₄ represents
10 a hydrogen atom or a (C₁-C₆)alkyl group.

The substituent R₂ that is preferred according to the invention is a (C₁-C₆)alkyl group.

More particularly, the substituent R₂ that is preferred according to the invention is the methyl group.

15 The substituent R₃ that is preferred according to the invention is a group selected 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 R₃ that is preferred according to the invention is a
20 group selected from phenyl, pyridyl, thienyl, isoxazolyl, pyrazolyle, pyrazinyl, quinolyl, quinoxaliny, 1*H*-quinoxaliny-2-one, quinazolinyl, 3*H*-quinazolinyl-4-one, 1*H*-quinazolinyl-2,4-dione, indolyle, benzisoxazolyl, phtalazinyl, and benzo[1,3]dioxolyle, 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
25 (I).

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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:

- 5 ✓ 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,
 - 10 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.
- 15 In another preferred embodiment, the substituent R_3 that is particularly interesting for the invention is the group selected from quinoxaliny, 1*H*-quinoxaliny-2-one, quinazolinyl, 3*H*-quinazolinyl-4-one, and 1*H*-quinazolinyl-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:
 - 20 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
 - 25 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_{1a} represents a hydrogen atom,

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- R_{1b} represents a cyclohexyl group optionally substituted by one hydroxy group, or a phenyl group optionally substituted by one tetrazolyl group or one $-\text{CO}_2R_4$ group in which R_4 represents a hydrogen atom or a (C_1-C_6) alkyl group,
 - R_2 represents a methyl group,
- 5 • R_3 represents a phenyl group substituted by one to three groups, identical or different, selected independently of each other from halogen, $-\text{OR}_6$, $-\text{CO}_2R_6$, $-\text{CONR}_6R_7$, $-\text{S(O)}_mR_6$, $-\text{S(O)}_m-\text{NR}_6R_7$, $-\text{NR}_6\text{COR}_7$, 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
- 10 atom or a group of formula $-\text{X}_2-\text{R}_b$ 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,
- 15 (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 amino being identical or different, independently of each other), carboxy, (C_1-C_6) alkoxycarbonyl, and benzyl.

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

- 20 • R_{1a} represents a hydrogen atom,
- R_{1b} represents a cyclohexyl group optionally substituted by one hydroxy group, or a phenyl group optionally substituted by one tetrazolyl group or one $-\text{CO}_2R_4$ group in which R_4 represents a hydrogen atom or a (C_1-C_6) alkyl group,
 - R_2 represents a methyl group,

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- R₃ 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, (C₁-C₆)alkyl, -OR₆, and -NR₆R₇, wherein R₆ and R₇, identical or different, independently of each other, represent a hydrogen atom or a group of formula -X₂-R_b wherein:
 - X₂ represents a single bond,
 - R_b represents a (C₁-C₆)alkyl group, which is optionally substituted by one group selected from hydroxy, (C₁-C₆)alkoxy, amino, mono(C₁-C₆)alkylamino, and di(C₁-C₆)alkylamino (each alkyl amino being identical or different, independently of each other).

The preferred compounds of the invention are:

- *N*-{4-[5-(cyclohexylamino)-4-methyl-1,3-thiazol-2-yl]phenyl}acetamide,
- *N*-{4-[5-[(3-hydroxycyclohexyl)amino]-4-methyl-1,3-thiazol-2-yl]phenyl}acetamide,
- 7-[5-(cyclohexylamino)-4-methyl-1,3-thiazol-2-yl]quinazolin-4-amine,
- and 7-[5-[(3-hydroxycyclohexyl)amino]-4-methyl-1,3-thiazol-2-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 (C₁-C₆)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 (C₁-C₆)alkylene group denotes a (C₁-C₆)alkyl group as defined hereinbefore which is comprised between two groups ; example of such groups, without implying any limitation are methylene (-(CH₂)-), ethylene (-(CH₂)₂-), ...
- a (C₂-C₆)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

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without implying any limitation are vinyl, allyl, 3-buten-1-yl, 2-methyl-buten-1-yl, hexenyl, ...

- a (C₂-C₆)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-butyn-1-yl, 2-methyl-butyn-1-yl, hexynyl, ...

- a (C₁-C₆)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(C₁-C₆)alkylamino denotes an amino group substituted by one (C₁-C₆)alkyl group as defined hereinbefore ; example of such groups, without implying any limitation are methylamino, isobutylamino, ethylamino, ...

- a di(C₁-C₆)alkylamino denotes an amino group substituted by two (C₁-C₆)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, ...

15 - 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, benzisoxazolyl, phtalazinyl, benzodioxolyl, benzodioxinyl, benzo[1,2,5]thiadiazolyl, benzo[1,2,5]oxadiazolyl, benzopyrrolinyl, quinoxalinyl, 1*H*-quinoxalinyl, quinazolinyl, 3*H*-quinazolinyl-4-one, 1*H*-quinazolinyl-2,4-dione,...

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- 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 form a link; examples of such groups without implying any limitation
5 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,
- 10 - a acyl group denotes a (C₁-C₆)alkyl group or an aryl group as defined above bound through a carbonyl group ; examples of such groups without implying any limitation are acetyl, ethylcarbonyl, benzoyl, ...
- a (C₁-C₆)alkoxycarbonyl denotes a (C₁-C₆)alkoxy group as defined hereinbefore bound through a carbonyl group ; examples of such groups without implying any limitation
15 are methoxycarbonyl, ethoxycarbonyl, tert-butyloxycarbonyl,...
- optical isomers refer to racemates, enantiomers and diastereoisomers.

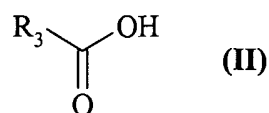
The invention also relates to the pharmaceutically acceptable salts of the compounds of formula (I). A review of the pharmaceutically acceptable salts will be found in *J. Pharm. Sci.*, 1977, 66, 1-19.

- 20 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,
25 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, dibenzylethylenediamine, piperidine, pyrrolidine, benzylamine, quaternary ammonium
30 hydroxides, etc...

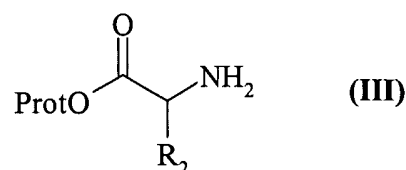
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The invention also relates to a process for the preparation of compounds of formula (I), which uses as starting material a compound of formula (II):

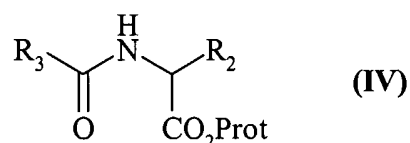


wherein R₃ is as defined in the compound of formula (I),

- 5 compound of formula (II) reacting under peptidic coupling conditions with a compound of formula (III):

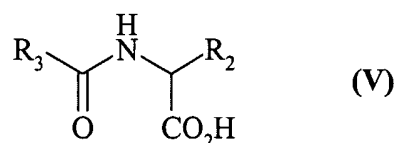


- wherein R₂ is as defined in the compound of formula (I), and Prot represents a protective group of carboxylic group usually used in organic synthesis, like for example and without
10 any limitation a methyl group or a *tert*-butyl group,
to give the compound of formula (IV):



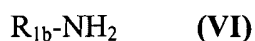
wherein R₂, R₃ and Prot are as defined hereinbefore,

- compound of formula (IV) being deprotected in a first step by treatment with an acid or a
15 base depending on the nature of the protecting group, to give the corresponding free carboxylic acid compound of formula (V):



wherein R₂ and R₃ are as defined hereinbefore,

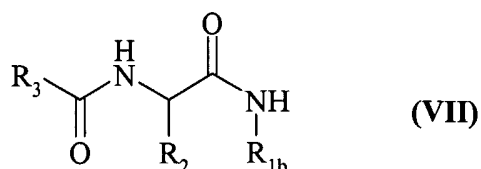
- and then in a second step reacting in peptidic coupling condition, using a coupling agent
20 like for example dicyclohexylcarbodiimide or 1,1'-carbonyldiimidazole, and a primary amine of formula (VI):



wherein R_{1b} is as defined in the compound of formula (I),

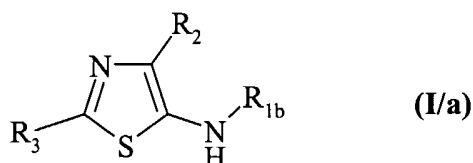
- 12 -

to give the compound of formula (VII):



wherein R_{1b} , R_2 and R_3 are as defined hereinbefore,

compound of formula (VII) being treated with Lawesson's reagent in basic medium, for example using pyridine, to give the compound of formula (I/a), which is a particular case of compounds of formula (I):

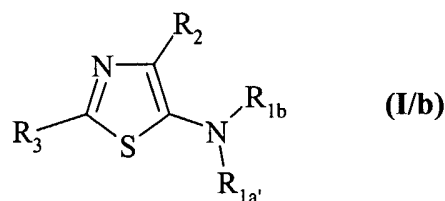


in which R_{1b} , R_2 and R_3 are as defined hereinbefore,

compound of formula (I/a) being treated optionally under alkaline medium, with a compound of formula (VIII):



wherein $R_{1a'}$ has the same definition of the group R_{1a} in the compound of formula (I) except the definition of hydrogen atom, and L_1 represents a leaving group like for example and without any limitations, chloride, bromide, iodide, tosylate, triflate or mesylate group, to give the compound of formula (I/b) which is a particular case of compounds of formula (I):



in which $R_{1a'}$, R_{1b} , R_2 and R_3 are as defined hereinbefore,

compounds of formulae (I/a) and (I/b) 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

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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), (VI) and (VIII) are commercially available or are obtained easily by using classical reactions of organic synthesis well known by the
5 man skilled in the art.

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
10 phosphodiesterase inhibitors, and more particularly inhibitors of the enzyme PDE7.

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
15 excipients or carriers.

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
20 is relevant.

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.

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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.

5 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.

10 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.

15 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.

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.

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

25 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 etc...

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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
5 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.

10 "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,
15 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.

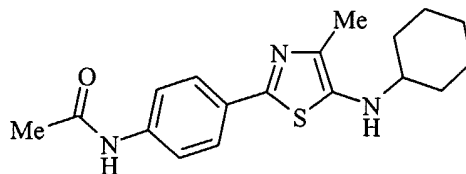
The starting materials used are products that are known or that are prepared
20 according to known operating procedures.

The reactions are monitored by thin layer chromatography (T.L.C.).

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

25 EXAMPLES

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Example 1: *N*-{4-[5-(cyclohexylamino)-4-methyl-1,3-thiazol-2-yl]phenyl}acetamide**Step 1: *tert*-Butyl (2*S*)-2-[(4-nitrobenzoyl)amino]-propanoate**

To a solution of *para*-nitrobenzoic acid in tetrahydrofuran, 1.2 equivalents of 1,1'-carbonyldiimidazole are added and the mixture is stirred for 30 minutes. Then, 1.1 equivalents of the (*S*)-L-alanine *tert*-butyl ester are added and the mixture is stirred for 24 hours at room temperature. The solvent is removed under reduced pressure and the crude is diluted in chloroform and brine. The organic layer is washed with water and dried over MgSO₄. The filtrate is concentrated under vacuum and the residue is purified by column chromatography to give the desired compound.

Step 2: (2*S*)-2-[(4-Nitrobenzoyl)amino]-propanoic acid

The compound obtained in the preceding Step 1 is added to a solution of 5% of trifluoroacetic acid in dichloromethane and the mixture is stirred for 3 hours until reaction completion. Then, the solvent is distilled under reduced pressure. The crude is washed several times with toluene and then used without further purification in the next step.

Step 3: *N*-[(1*S*)-2-(cyclohexylamino)-1-methyl-2-oxoethyl]-4-nitrobenzamide

To a solution of the compound, obtained in the preceding Step 2, in tetrahydrofuran, 1.2 equivalents of 1,1'-carbonyldiimidazole are added and the mixture is stirred for 30 minutes. Then, the cyclohexylamine is added and the mixture is stirred for 24 hours at room temperature. The solvent is removed under reduced pressure and the crude is diluted in chloroform and brine. The organic layer is washed with water and dried over MgSO₄. The filtrate is concentrated and the residue is purified by column chromatography to give the desired product.

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

To a solution of the compound, obtained in the preceding Step 3, in pyridine is added Lawesson's reagent and the mixture is heated at 100°C for 6 hours until disappearance of starting material. After being cooled to room temperature, saturated aqueous sodium
5 hydrogen carbonate solution is added to the reaction mixture, and the product is extracted with chloroform/methanol. The organic layer is washed with water and brine, and dried over MgSO₄. The filtrate is concentrated and the residue is purified by column chromatography to give the desired product.

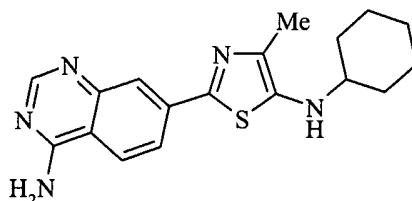
Step 5: *2-(4-Aminophenyl)-N-cyclohexyl-4-methyl-1,3-thiazol-5-amine*

10 Tin chloride dihydrate is added to a solution of the compound, obtained in the preceding Step 4, in ethanol at 70°C and the mixture is refluxed for 3 hours until disappearance of starting material. The mixture is then filtered through a pad of celite and the filtrate is evaporated 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
15 brine, dried over MgSO₄, filtered and evaporated to dryness. The residue is chromatographed through silica gel to give the pure desired product.

Step 6: *N-{4-[5-(cyclohexylamino)-4-methyl-1,3-thiazol-2-yl]phenyl}acetamide*

To a solution of the compound, obtained in the preceding Step 5, and triethylamine (1.1 equivalents) in tetrahydrofuran at 0°C, 1 equivalent of acetyl chloride is added and after 15
20 minutes of stirring the mixture is allowed to warm-up to room temperature for 5 hours until reaction completion. The mixture is concentrated under reduced pressure and the residue is purified by chromatography on silica gel to give the expected compound.

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Example 2: 7-[5-(Cyclohexylamino)-4-methyl-1,3-thiazol-2-yl]quinazolin-4-amine**Step 1: *tert*-Butyl (2*S*)-2-[[4-oxo-3,4-dihydroquinazolin-7-yl]carbonyl]amino} propanoate**

5

To a solution of 4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid in tetrahydrofuran, 1.2 equivalents of 1,1'-carbonyldiimidazole are added and the mixture is stirred for 30 minutes. Then, the (*S*)-L-Alanine *tert*-butyl ester is added and the mixture is stirred for 24 hours until disappearance of starting material. The solvent is removed under reduced pressure and the crude is diluted in chloroform and brine. The organic layer is washed with water and dried over MgSO₄. The filtrate is concentrated and the residue is purified by column chromatography to give the desired compound.

Step 2: (2*S*)-2-[[4-Oxo-3,4-dihydroquinazolin-7-yl]carbonyl]amino}propanoic acid

15 The compound, obtained in the preceding Step 1, is added to a solution of 5% trifluoroacetic acid in dichloromethane and the mixture is stirred for 3 hours until reaction completion. Then, the solvent is distilled under reduced pressure. The crude is washed several times with toluene and then used without further purification in the next step.

Step 3: *N*-[(1*S*)-2-(Cyclohexylamino)-1-methyl-2-oxoethyl]-4-oxo-3,4-dihydroquinazoline-7-carboxamide

20

To a solution of the compound, obtained in the preceding Step 2, in tetrahydrofuran, 1.2 equivalents of 1,1'-carbonyldiimidazole are added and the mixture is stirred for 30 minutes. Then, the cyclohexylamine is added and the mixture is stirred for 24 hours until disappearance of starting material. The solvent is removed under reduced pressure and the crude is diluted in chloroform and brine. The organic layer is washed with water and dried

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over MgSO₄. The filtrate is concentrated and the residue is purified by column chromatography to give the desired compound.

Step 4: 7-[5-(Cyclohexylamino)-4-methyl-1,3-thiazol-2-yl]quinazoline-4(3H)-thione

To a solution of the compound, obtained in the preceding Step 3, in pyridine is added
5 Lawesson's reagent and the mixture is heated to 100°C for 6 hours until disappearance of starting material. After being cooled to room temperature, saturated aqueous sodium hydrogen carbonate solution is added to the reaction mixture, and the product is extracted with chloroform/methanol. The organic layer is washed with water and brine, and dried over MgSO₄. The filtrate is concentrated and the residue is purified by column
10 chromatography to give the desired compound.

Step 5: N-cyclohexyl-4-methyl-2-[4-(methylthio)quinazolin-7-yl]-1,3-thiazol-5-amine

To a stirring solution of the compound, obtained in the preceding Step 4, and potassium carbonate (1.2 equivalents) in methanol is added methyl iodide. After 30 minutes the solvent is removed by rotary evaporation and the residue purified via column
15 chromatography to give a powder corresponding to the desired compound.

Step 6: 7-[5-(Cyclohexylamino)-4-methyl-1,3-thiazol-2-yl]quinazolin-4-amine

A solution of the compound, obtained in the preceding Step 5, in saturated butanolic ammonia is sealed in a steel bomb and heated at 100°C for 2 days. The solvent is removed by rotary evaporation and the residue purified via column chromatography to give the title
20 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 IC₅₀ (concentration necessary to inhibit
25 the enzymatic activity by 50 %).

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

5 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 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
10 Nucleotide Research, Vol. 10 : 69-92, ed. G. Brooker et al. Raven Press, NY.

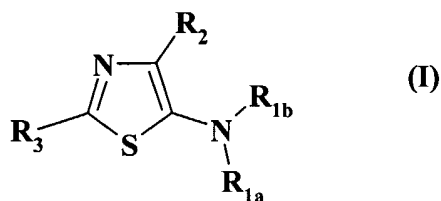
The substrate used is cGMP for PDE1 and PDE5 and cAMP for PDE 3, PDE 4 and PDE 7. The substrate concentration is 0.2 μ M for PDE 1, PDE 3 and PDE 5, 0,25 μ M for PDE 4 and 50nM for PDE 7.

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

In order to determine their IC₅₀, compounds of the invention are assayed at 8 to 11 concentrations ranging from 0.02nM to 100 μ M for PDE 4 and PDE 7 and at least at 6 concentrations ranging from 0,1 μ M to 30 μ M for PDE 1, 3 and 5.

CLAIMS

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



wherein:

- 5 • R_{1a} represents a group selected from hydrogen, (C_1-C_6) alkyl, and aryl (C_1-C_6) alkyl,
- R_{1b} 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
- 10 which is optionally substituted by 1 to 3 groups, identical or different, selected 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:
- 15 - X_1 represent a single bond or a (C_1-C_6) alkylene group,
- 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,
- 20 • 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, $-OR_6$, $-NR_6R_7$, $-COR_6$, $-CO_2R_6$, $-CONHOH$, $-CONR_6R_7$, $-S(O)_mR_6$,

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$-S(O)_m-NR_6R_7$, $-NR_6COR_7$, $-NR_6SO_2R_7$, $-N(SO_2R_7)_2$, $-NR_6-CO-NR_7R_8$, $C(=N-CN)NR_6R_7$, $NR_8-C(=N-CN)NR_6R_7$ and tetrazolyl optionally substituted with a (C_1-C_4) alkyl, wherein:

- ✓ 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 amino being identical or different, independently of each other), carboxy, (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, with the exclusion of the following compounds:
 - (4-Methyl-2-phenyl-thiazol-5-yl)-phenyl-amine,
 - (2,4-diphenyl-thiazol-5-yl)-phenyl-amine,
 - (2,4-diphenyl-thiazol-5-yl)-(3-fluoro-phenyl)-amine,
 - (2,4-diphenyl-thiazol-5-yl)-(4-fluoro-phenyl)-amine,
 - (4-chloro-phenyl)- (2,4-diphenyl-thiazol-5-yl)-amine,
 - (2-chloro-phenyl)- (2,4-diphenyl-thiazol-5-yl)-amine,
 - (2,4-diphenyl-thiazol-5-yl)-*p*-tolyl-amine, and,
 - (2,4-diphenyl-thiazol-5-yl)-(4-methoxy-phenyl)-amine;
 it being understood that:
 - 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,

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- 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 character and it being understood that in the case of a polycyclic system each cycle could be fused together or form a link,
 - 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 with the proviso that R_{1b} is other than a substituted pyrimidine or a substituted pyrimidine fused to one or several other cycles.
3. A compound of formula (I) according to claim 1 or 2 characterized in that :
- R_{1a} represents a hydrogen atom or a (C₁-C₆)alkyl group,
 - R_{1b} represents a group selected from cycloalkyl and aryl, each of these groups being optionally substituted by 1 to 3 groups selected from halogen, trifluoromethyl, -CO₂R₄, -OR₄, and tetrazolyl, in which R₄ represents a hydrogen atom or a (C₁-C₆)alkyl group,
 - R₂ and R₃ 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 anyone of claims 1 to 3, characterized in that:
- R_{1a} represents a hydrogen atom,
 - R_{1b} represents :
 - a cyclohexyl group optionally substituted by one hydroxy group,
 - or a phenyl group optionally substituted by one tetrazolyl group or one -CO₂R₄ in which R₄ represents a hydrogen atom or a (C₁-C₆)alkyl group,
 - R₂ and R₃ 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 or 2 characterized in that R_2 represents a (C_1-C_6) alkyl group,
 R_{1a} , R_{1b} and R_3 being as described in the compound of formula (I),
optionally the racemics forms thereof, isomers thereof, N-oxides thereof, and the
5 pharmaceutically acceptable acid or base salts thereof.
6. A compound of formula (I) according to claim 1 or 2 characterized in that R_2 represents a methyl group,
 R_{1a} , R_{1b} and R_3 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.
7. A compound of formula (I) according to claim 1 or 2 characterized in that R_3 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_1-C_6) alkyl, $-OR_6$, $-NR_6R_7$, $-COR_6$, $-CO_2R_6$, $-CONHOH$,
15 $-CONR_6R_7$, $-S(O)_mR_6$, $-S(O)_m-NR_6R_7$, $-NR_6COR_7$, $-NR_6SO_2R_7$, $-N(SO_2R_7)_2$, $-NR_6-CO-NR_7R_8$, 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:
20
 - 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
25 (each alkyl amino being identical or different, independently of each other), carboxy, (C_1-C_6) alkoxycarbonyl, and benzyl,
 - ✓ R_8 represents a hydrogen atom or a (C_1-C_6) alkyl group
- R_{1a} , R_{1b} and R_2 being as described in the compound of formula (I),

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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 or 7 characterized in that R_3 represents a group selected from phenyl, pyridyl, thienyl, isoxazolyl, pyrazolyle, pyrazinyl, quinolyl, quinoxaliny, 1*H*-quinoxaliny-2-one, quinazolinyl, 3*H*-quinazolinyl-4-one, 1*H*-quinazolinyl-2,4-dione, indolyle, benzisoxazolyl, phtalazinyl, 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_1-C_6) alkyl, $-OR_6$, $-NR_6R_7$, $-COR_6$, $-CO_2R_6$, $-CONHOH$, $-CONR_6R_7$, $-S(O)_mR_6$, $-S(O)_m-NR_6R_7$, $-NR_6COR_7$, $-NR_6SO_2R_7$, $-N(SO_2R_7)_2$, $-NR_6-CO-NR_7R_8$, 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 amino being identical or different, independently of each other), carboxy, (C_1-C_6) alkoxycarbonyl, and benzyl,
- ✓ R_8 represents a hydrogen atom or a (C_1-C_6) alkyl group

R_{1a} , R_{1b} and R_2 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.

9. A compound of formula (I) according to anyone of claims 1, 2, 7 and 8, characterized in that R_3 represents a 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,

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- ✓ R₆ and R₇, identical or different, independently of each other, represent a hydrogen atom or a group of formula -X₂-R_b wherein:
- X₂ represents a single bond or a (C₁-C₆)alkylene group,
 - R_b represents a group selected from (C₁-C₆)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, (C₁-C₆)alkoxy, (C₁-C₆)alkyl, amino, mono(C₁-C₆)alkylamino, di(C₁-C₆)alkylamino (each alkyl amino being identical or different, independently of each other), carboxy, (C₁-C₆)alkoxycarbonyl, and benzyl,
- optionally the racemics forms thereof, isomers thereof, N-oxides thereof, and the pharmaceutically acceptable acid or base salts thereof.

- 10.** A compound of formula (I) according to anyone of claims 1, 2, 7 and 8, characterized in that R₃ 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, (C₁-C₆)alkyl, -OR₆, and -NR₆R₇, wherein:

R₆ and R₇, identical or different, independently of each other, represent a hydrogen atom or a group of formula -X₂-R_b wherein:

- X₂ represents a single bond,
- R_b represents a group (C₁-C₆)alkyl, which is optionally substituted by one group selected from hydroxy, (C₁-C₆)alkoxy, amino, mono(C₁-C₆)alkylamino, and di(C₁-C₆)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.

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

- R_{1a} represents a hydrogen atom,

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- R_{1b} represents a cyclohexyl group optionally substituted by one hydroxy group, or a phenyl group optionally substituted by one tetrazolyl group or one $-CO_2R_4$ group in which R_4 represents a hydrogen atom or a (C_1-C_6) alkyl group,
 - R_2 represents a methyl group,
- 5 • R_3 represents a 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
- 10 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,
- 15 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 amino being identical or different, independently of each other), carboxy, (C_1-C_6) alkoxycarbonyl, and benzyl,
- optionally the racemics forms thereof, isomers thereof, N-oxides thereof, and the pharmaceutically acceptable acid or base salts thereof.
- 20 **12.** A compound of formula (I) according to anyone of claims 1 to 10, characterized in that :
- R_{1a} represents a hydrogen atom,
 - R_{1b} represents a cyclohexyl group optionally substituted by one hydroxy group, or a phenyl group optionally substituted by one tetrazolyl group or one $-CO_2R_4$ group in which
- 25 R_4 represents a hydrogen atom or a (C_1-C_6) alkyl group,
- R_2 represents a methyl group,

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• R₃ 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, (C₁-C₆)alkyl, -OR₆, and -NR₆R₇, wherein R₆ and R₇, identical or different, independently of each other, represent a hydrogen atom or a group of formula -X₂-R_b wherein:

- X₂ represents a single bond,
- R_b represents a (C₁-C₆)alkyl group, which is optionally substituted by one group selected from hydroxy, (C₁-C₆)alkoxy, amino, mono(C₁-C₆)alkylamino, and di(C₁-C₆)alkylamino (each alkyl amino being identical or different, independently of each other),

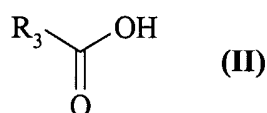
optionally the racemics forms thereof, isomers thereof, N-oxides thereof, and the pharmaceutically acceptable acid or base salts thereof.

13. A compound according to claim 1, which is selected from:

- *N*-{4-[5-(cyclohexylamino)-4-methyl-1,3-thiazol-2-yl]phenyl}acetamide,
- *N*-{4-[5-[(3-hydroxycyclohexyl)amino]-4-methyl-1,3-thiazol-2-yl]phenyl}acetamide,
- 7-[5-(cyclohexylamino)-4-methyl-1,3-thiazol-2-yl]quinazolin-4-amine,
- and 7-[5-[(3-hydroxycyclohexyl)amino]-4-methyl-1,3-thiazol-2-yl]quinazolin-4-amine,

optionally its racemics forms, its isomers, and its pharmaceutically acceptable acid or base salts.

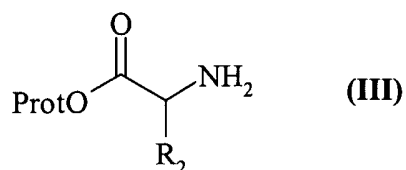
14. A process for the preparation of compounds of formula (I) according to claim 1 characterized in that it is used as starting material a compound of formula (II):



wherein R₃ is as defined in the compound of formula (I),

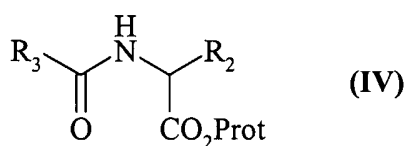
compound of formula (II) reacting under peptidic coupling conditions with a compound of formula (III):

- 29 -



wherein R_2 is as defined in the compound of formula (I), and Prot represents a protective group of a carboxylic group,

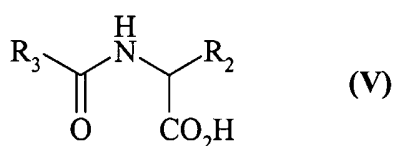
to give the compound of formula (IV):



5

wherein R_2 , R_3 and Prot are as defined hereinbefore,

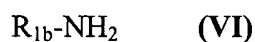
compound of formula (IV) being deprotected in a first step by treatment with an acid or a base depending on the nature of the protecting group, to give the corresponding free carboxylic acid compound of formula (V):



10

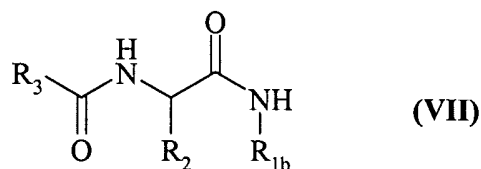
wherein R_2 and R_3 are as defined hereinbefore,

and then in a second step reacting in peptidic coupling condition, in the presence of a coupling agent and a primary amine of formula (VI):

15

wherein R_{1b} is as defined in the compound of formula (I),

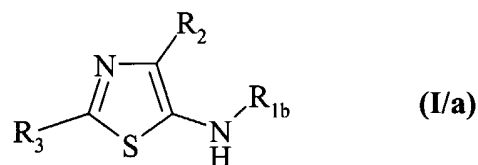
to give the compound of formula (VII):



wherein R_{1b} , R_2 and R_3 are as defined hereinbefore,

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compound of formula (VII) being treated with Lawesson's reagent in basic medium, to give the compound of formula (I/a), which is a particular case of the compounds of formula (I):



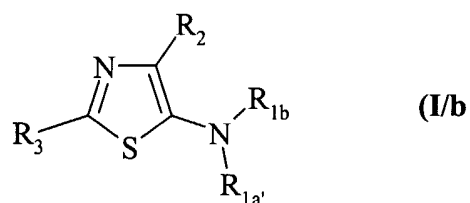
5 in which R_{1b} , R_2 and R_3 are as defined hereinbefore,

compound of formula (I/a) being treated optionally under alkaline medium, with a compound of formula (VIII):



wherein $R_{1a'}$ has the same definition of the group R_{1a} in the compound of formula (I)
 10 except the hydrogen atom definition, and L_1 represents a leaving group,

to give the compound of formula (I/b) which is a particular case of the compound of formula (I):



in which $R_{1a'}$, R_{1b} , R_2 and R_3 are as defined hereinbefore,

15 compounds of formulae (I/a) and (I/b) 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.

20

15. A pharmaceutical composition comprising as active ingredient an effective amount of a compound as claim in anyone of claims 1 to 13, alone or in combination with one or more pharmaceutically acceptable excipients or carriers.

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16. A pharmaceutical composition according to claim 15 comprising as active principle an effective amount of a compound as claimed in anyone of claim 1 to 13 useful for the treatment of a disease for which treatment by PDE7 inhibitor is relevant.

17. A pharmaceutical composition according to claim 16 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.

18. A pharmaceutical composition according to claim 16 in which the disease to be treated
is selected from visceral pain, inflammatory bowel disease, osteoarthritis, multiple
10 sclerosis, osteoporosis, chronic obstructive pulmonary disease (COPD), allergic rhinitis, asthma, cancer, acquired immune deficiency syndrome (AIDS) and graft rejection.

INTERNATIONAL SEARCH REPORT

Inte | Application No
PCT/EP 03/02287

A. CLASSIFICATION OF SUBJECT MATTER

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

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 A61K

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, BIOSIS, 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.
A	WO 98 08844 A (BYK GULDEN LOMBERG CHEM FAB ;BAER THOMAS (DE); ULRICH WOLF RUEDIGE) 5 March 1998 (1998-03-05) claim 1 page 21	1-18
A	WO 01 46184 A (ICOS CORP) 28 June 2001 (2001-06-28) claim 1 page 52	1-18
A	WO 01 64674 A (BRABANDER MARC DE ;VANDERMAESEN NELE (BE); WAUWE JEAN PIERRE FRANS) 7 September 2001 (2001-09-07) page 51 -page 78; examples claim 1	1-18
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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.
- *G* document member of the same patent family

Date of the actual completion of the international search

21 May 2003

Date of mailing of the international search report

28/05/2003

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INTERNATIONAL SEARCH REPORT

Inter Application No
PCT/EP 03/02287

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	CASTRO A ET AL: "CoMFA of benzyl derivatives of 2,1,3-benzo and benzothieno'3,2-a!thiadiazine 2,2-dioxides: clues for the design of phosphodiesterase 7 inhibitors" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, FR, vol. 36, no. 4, May 2001 (2001-05), pages 333-338, XP004255695 ISSN: 0223-5234 the whole document ---	1-18
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A	OSAMU UCHIKAWA: "Aminothiazole derivatives. I. A convenient synthesis of monocyclic and condensed 5-aminothiazole derivatives" JOURNAL OF HETEROCYCLIC CHEMISTRY, HETEROCORPORATION. PROVO, US, vol. 31, no. 4, July 1994 (1994-07), pages 877-887, XP002137194 ISSN: 0022-152X page 880; example 19A -----	1

INTERNATIONAL SEARCH REPORT

Inter Application No
PCT/EP 03/02287

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